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(54) SUBSTITUTED 2-AZABICYCLES AND THEIR USE AS OREXIN RECEPTOR MODULATORS

SUBSTITUIERTE 2-AZABICYCLEN UND DEREN VERWENDUNG ALS OREXINREZEPTORMODULATOREN

2-AZABICYCLES SUBSTITUÉS ET LEUR UTILISATION COMME MODULATEURS DE RÉCEPTEURS DE L'OREXINE

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(56) References cited:
WO-A1-2008/150364 WO-A1-2009/104155

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Description

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 61/780,378, filed March 13, 2013.

TECHNICAL FIELD

[0002] The present invention is directed to substituted 2-azabicyclic compounds, pharmaceutical compositions comprising them, methods of making them, and methods of using them for the modulation of the orexin receptor for the treatment of disease states, disorders, and conditions mediated by orexin receptor activity.

BACKGROUND

[0003] Orexin/hypocretin signaling is mediated by two receptors and two peptide agonists. The peptides (orexin-A and orexin-B) are cleavage products of the same gene, pre-pro orexin. In the central nervous system, neurons producing pre-pro orexin are found solely in the perifornical nucleus, the dorsal hypothalamus, and the lateral hypothalamus (Peyron et al., 1998, J. Neurosci. 18: 9996-10015). Orexigenic cells in these regions project to many areas of the brain, extending rostrally to the olfactory bulbs and caudally to the spinal cord (Van den Pol, 1999, J. Neurosci. 19: 3171-3182).

[0004] The orexins bind to two high affinity receptors, referred to as orexin-1 and orexin-2 receptors. Orexin-1 and orexin-2 receptors are G-protein-coupled, seven transmembrane receptors that share over 64% amino acid sequence identity with one another. Both receptors are generally excitatory, the common cellular response to orexin-induced receptor activation being increases in intracellular calcium. Homology between the species orthologs is high and there are no known pharmacological differences. Orexin-A and -B are usually considered equal ligands for orexin-2 receptor but orexin-B is thought to be 5- to 100-fold weaker ligand than orexin-A at the orexin-1 receptor (Sakurai et al., 1998, Cell 92: 573-585; Ammoun et al., 2003, J. Pharmacol. Exp. Ther. 305: 507-514).

[0005] Many regions of the brain have fairly selective expression of the orexin-1 or orexin-2 receptors (Marcus et al., 2001, J. Comp Neurology 435, 6-25; Trivedi et al., 1998, FEBS Letters, 438, 71-75). Orexin-1 receptors are selective for the limbic system (bed nucleus of the stria terminalis and amygdala), cingulate cortex and noradrenergic neurons in the locus coeruleus. Conversely, the orexin-2 receptor is almost the exclusive orexin receptor in the histaminergic neurons in the tuberomammilary nucleus which play a critical role in wake promotion; in paraventricular neurons and the parabrachial nucleus. In other brain regions like the dorsal raphe, the ventral tegmental area or the prefontal cortex both receptors are coexpressed.

[0006] The broad CNS distribution of cells producing orexin, as well as cells expressing the orexin receptors, suggests involvement of orexin in a number of physiological functions, including feeding and metabolism, regulation of wakefulness and sleep, sympathetic activation and stress response (de Lecea, 2012, Progress in Brain Research, 198, 15-24; Kukkonen, 2013, Am J. Physiol. Cell Physiol., 304, C2-C32). Orexin also plays a key role regulating motivation and reward associated with food intake and with drugs of abuse (Mahler et al., 2012, Progress in Brain Research, 198, 79-121).

[0007] Several lines of evidence indicate that the orexin system is an important modulator of arousal. Rodents administered orexin intracerebroventricularly spend more time awake (Piper et al., 2000, J. Neurosci. 12: 726-730. Orexin-mediated effects on arousal have been linked to orexin neuronal projections to histaminergic neurons in the tuberomammillary nucleus (Yamanaka et al., 2002, Biochem. Biophys. Res. Comm. 290: 1237-1245). Rodents whose pre-pro orexin gene has been knocked out, or whose orexigenic neurons have been killed, display altered sleep/wake cycles similar to narcolepsy (Chemelli et al., 1999, Cell 98: 437-451; Hara et al., 2001, Neuron 30: 345-354). Dog models of narcolepsy have been shown to have mutant or non-functional orexin-2 receptors (Lin et al., 1999, Cell 98: 365-376). Orexin signaling as a target for sleep-promoting therapies was further validated clinically by findings of attenuated orexin levels and loss of orexinergic neurons in human narcoleptic patients (Mignot et al., 2001, Am. J. Hum. Genet. 68: 686-699; Minot & Thorsby, 2001, New England J. Med. 344: 692) or, in rare cases, to mutations in the orexin-2 gene (Peyron et al., 2000, Nature Med. 6: 991-997). Disorders of the sleep-wake cycle are therefore likely targets for orexin-2 receptor modulator activity. Examples of sleep-wake disorders that may be treated by agonists or other modulators that up-regulate orexin-2 receptor-mediated processes include narcolepsy, jet lag (sleepiness) and sleep disorders secondary to neurological disorders such as depression. Examples of disorders that may be treated by antagonists or other modulators that down-regulate orexin-2 receptor-mediated processes include insomnia, restless leg syndrome, jet lag (wakefulness) and sleep disorders secondary to neurological disorders such as mania, schizophrenia, pain syndromes and the like.

[0008] Evidence has accumulated to demonstrate a clear involvement of orexin signaling in reward pathways associated with drug dependence (Mahler et al., 2012, Progress in Brain Research, 198, 79-121). Orexinergic neurons send projections to the ventral tegmental area and other brain regions involved in reward processing. Orexin ligands mediate reward behavior, and antagonizing these effects with a selective orexin-1 receptor antagonist in various preclinical model

of addiction has suggested that these actions are mediated through orexin-1 receptor. Specifically, a selective orexin-1 antagonist attenuates morphine conditioned place preference and reinstatement (Harris et al., 2005, Nature, 437, 556-5599; Narita et al., 2006, J Neurosci.,26, 398-405; Harris et al., 2007, Behav Brain Res, 183, 43-51), stress-induced cocaine reinstatement, cocaine-induced behavioral and synaptic plasticity (Borgland et al., 2006, Neuron, 49, 589-601), and intake and cue and stress-induced reinstatement of ethanol (Lawrence et al., 2006, Br J Pharmacol, 148, 752-759), in addition to attenuating precipitated morphine withdrawal (Sharf et al., 2008, Biol Psychiatry, 64, 175-183) and nicotine self-administration (Hollander et al., 2008, Proc Natl Acad Sci USA., 105, 19480-19485). Another recent study has also suggested a role for OX2R (Shoblock et al., 2011, Psychopharmacology, 215, 191-203).

[0009] Orexin's role in more complex emotional behavior is also emerging (Johnson et al., 2012, Progress in Brain Research, 198, 133-161). Changes in orexin levels in patients with panic and posttraumatic stress disorders have been noted as have changes in the prevalence of anxiety behaviors in narcoleptic patients (Johnson et al., 2010, Nature Medicine, 16, 111-115; Fortuyn et al., 2010, General Hospital Psychiatry, 32, 49-56; Strawn et al., 2010, Psychoneuroendocrinology, 35, 1001-1007). Lactate infusion or acute hypercapnia, which causes panic in humans, and are used as an animal model of panic, activates orexin neurons in the perifornical hypothalamus. This activation correlates with anxiety in the social interaction test or open field test. Blocking orexin signaling with either siRNA or selective orexin-1 receptor antagonists attenuates panic-like responses to lactate (Johnson et al., 2010, Nature Medicine, 16, 111-115; Johnson et al., 2012, Neuropsychopharmacology, 37, 1911, 1922).

[0010] Cerebral spinal fluid (CSF) levels of orexin are lower in depressed or suicidal patients, and the level of orexin inversely correlates with illness severity (Brundin et al., 2007, European Neuropsychopharmacology, 17, 573-579; Salomon et al., 2003, Biol Psychiatry,54, 96-104). A positive correlation between orexin-1 receptor mRNA in the amygdala and depressive behavior in the forced swim test in mice has been reported (Arendt, 2013, Behavioral Neuroscience, 127, 86-94).

[0011] The orexin system also interacts with brain dopamine systems. Intracerebroventricular injections of orexin in mice increase locomotor activity, grooming and stereotypy; these behavioral effects are reversed by administration of D2 dopamine receptor antagonists (Nakamura et al., 2000, Brain Res. 873: 181-187). Therefore, orexin receptor modulators may be useful to treat various neurological disorders; e.g., agonists or up-regulators to treat catatonia, antagonists or down-regulators to treat Parkinson's disease, Tourette's syndrome, anxiety, delerium and dementias.

[0012] Orexins and their receptors have been found in both the myenteric and submucosal plexus of the enteric nervous system, where orexins have been shown to increase motility *in vitro* (Kirchgessner & Liu, 1999, Neuron 24: 941-951) and to stimulate gastric acid secretion *in vitro* (Takahashi et al., 1999, Biochem. Biophys. Res. Comm. 254: 623-627). Orexin effects on the gut may be driven by a projection via the vagus nerve (van den Pol, 1999, *supra*), as vagotomy or atropine prevent the effect of an intracerebroventricular injection of orexin on gastric acid secretion (Takahashi et al., 1999, *supra*). Orexin receptor antagonists or other down-regulators of orexin receptor-mediated systems are therefore potential treatments for ulcers, irritable bowel syndrome, diarrhea and gastroesophageal reflux.

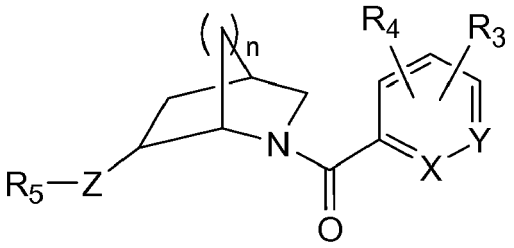
[0013] Body weight may also be affected by orexin-mediated regulation of appetite and metabolism. Some effects of orexin on metabolism and appetite may be mediated in the gut, where, as mentioned, orexins alter gastric motility and gastric acid secretion. Orexin antagonists therefore are likely to be useful in treatment of overweight or obesity and conditions related to overweight or obesity, such as insulin resistance/type II diabetes, hyperlipidemia, gallstones, angina, hypertension, breathlessness, tachycardia, infertility, sleep apnea, back and joint pain, varicose veins and osteoarthritis. Conversely, orexin agonists are likely to be useful in treatment of underweight and related conditions such as hypotension, bradycardia, ammenorrhea and related infertility, and eating disorders such as anorexia and bulimia.

[0014] Intracerebroventricularly administered orexins have been shown to increase mean arterial pressure and heart rate in freely moving (awake) animals (Samson et al., 1999, Brain Res. 831: 248-253; Shirasaka et al., 1999, Am. J. Physiol. 277: R1780-R1785) and in urethane-anesthetized animals (Chen et al., 2000, Am. J. Physiol. 278: R692-R697), with similar results. Orexin receptor agonists may therefore be candidates for treatment of hypotension, bradycardia and heart failure related thereto, while orexin receptor antagonists may be useful for treatment of hypertension, tachycardia and other arrhythmias, angina pectoris and acute heart failure.

[0015] From the foregoing discussion, it can be seen that the identification of orexin receptor modulators, will be of great advantage in the development of therapeutic agents for the treatment of a wide variety of disorders that are mediated through these receptor systems.

SUMMARY

[0016] The present invention is directed to compounds of Formula I, for use in therapy,



I

wherein X is N or CR_1; Y is N or CR_2; R_1 is H, alkoxy, halo, triazolyl, thiazolyl, pyridazinyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl, pyridyl, phenyl or pyrazolyl, wherein triazolyl, thiazolyl, pyridazinyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl, pyridyl, phenyl or pyrazolyl is optionally substituted with up to two substituents selected from halo and alkyl; R_2 is H, alkyl, alkoxy, or halo; Z is NH, N-CH_3, N-CH_2CH_3, N-CH_2-cyclopropyl, N-C(=O)CH_3, N-$CH_2CH_2OCH_3$ or O; R_3 is H, alkyl, alkoxy, halo, triazolyl, thiazolyl, pyridazinyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl, pyridyl, phenyl or pyrazolyl, wherein triazolyl, thiazolyl, pyridazinyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl, pyridyl, phenyl or pyrazolyl is optionally substituted with up to two substituents selected from halo and alkyl; R_4 is H or alkyl; or R_3 and R_4, together with the atoms to which they are attached, form a 6- membered aryl ring or a 5-membered or 6-membered heteroaryl ring; R_5 is pyridyl, pyrazinyl, benzoxazolyl, pyridazinyl, naphthyridinyl or pyrimidinyl, wherein the pyridyl, pyrazinyl, benzoxazolyl, pyridazinyl, naphthyridinyl or pyrimidinyl is optionally substituted with up to two groups selected from halo, alkoxy, hydroxymethyl and alkyl; and n is 1 or 2. Enantiomers and diastereomers of the compounds of Formula I are also described, as well as the pharmaceutically acceptable salts.

[0017] Compositions for use in therapy comprising the compounds of the invention as well as these compositions for use in the treatment of specific diseases, as defined in the claims, are also within the scope of the invention.

BRIEF DESCRIPTION OF DRAWINGS

[0018]

Figure 1 depicts an Oak Ridge Thermal Ellipsoid Plot Program (ORTEP), shown at 40% probability level, of one embodiment of the invention, Example 13.

Figure 2 depicts an ORTEP, shown at 40% probability level, of one embodiment of the invention, Example 14.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

[0019] The invention may be more fully appreciated by reference to the following description, including the following glossary of terms and the concluding examples.

[0020] The term "alkyl" refers to a straight- or branched-chain alkyl group having from 1 to 12 carbon atoms in the chain. In some embodiments, an alkyl group is a C_1-C_6 alkyl group. In some embodiments, an alkyl group is a C_1-C_4 alkyl group. Examples of alkyl groups include methyl (Me) ethyl (Et), n-propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl (tBu), pentyl, isopentyl, tert-pentyl, hexyl, isohexyl, and groups that in light of the ordinary skill in the art and the teachings provided herein would be considered equivalent to any one of the foregoing examples. Alkyl groups of the invention can be substituted with, for example, halogen atoms. One exemplary substitutent is fluoro. Preferred substituted alkyl groups of the invention include trihalogenated alkyl groups such as trifluoromethyl groups.

[0021] Alkyl groups of the invention can also refer to "cycloalkyl" moieties. Cycloalkyl refers to monocyclic, non-aromatic hydrocarbon groups having from 3 to 7 carbon atoms. Examples of cycloalkyl groups include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-methylcyclopropyl, 2-methylcyclopentyl, and the like.

[0022] The term "alkoxy" includes a straight chain or branched alkyl group with a terminal oxygen linking the alkyl group to the rest of the molecule. In some embodiments, an alkoxy group is a C_1-C_6 alkoxy group. In some embodiments, an alkoxy group is a C_1-C_4 alkoxy group. Alkoxy includes methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy, pentoxy and so on.

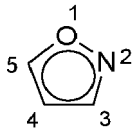
[0023] The term "aryl ring" represents" a mono- or bi-cyclic aromatic, hydrocarbon ring structure. Aryl rings can have 6 or 10 carbon atoms in the ring.

[0024] The term "halogen" represents chlorine, fluorine, bromine, or iodine. The term "halo" represents chloro, fluoro, bromo, or iodo.

[0025] The term "heteroaryl ring" represents a mono-or bicyclic aromatic ring structure including carbon atoms as well as up to four heteroatoms selected from nitrogen, oxygen, and sulfur. Heteroaryl rings can include a total of 5, 6, 9, or 10 ring atoms.

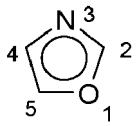
[0026] The term "isoxazolyl" represents the following moiety:

[0027] The term "isoxazolyl" represents the following moiety:



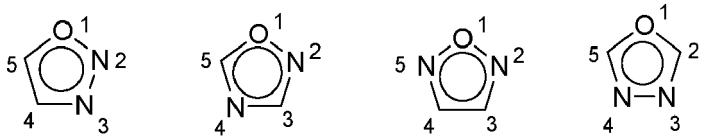
[0028] The isoxazolyl moiety can be attached through any one of the 3-, 4-, or 5-position carbon atoms. Isoxazolyl groups of the invention can be optionally substituted with, for example, one or two alkyl groups, for example, one or two methyl groups.

[0029] The term "oxazolyl" represents the following moiety:



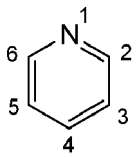
[0030] The oxazolyl moiety can be attached through any one of the carbon atoms.

[0031] The term "oxadiazolyl" represents a 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole, or 1,3,4-oxadiazole moiety:



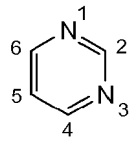
[0032] The oxadiazolyl moieties can be attached through any one of the carbon or nitrogen atoms. Within the scope of the invention, "oxadiazolyl" groups can be substituted with an alkyl or halo group, preferably a methyl group.

[0033] The term "pyridyl" represents the following moiety:



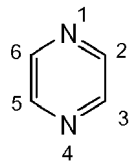
[0034] The pyridyl moiety can be attached through any one of the 2-, 3-, 4-, 5-, or 6-position carbon atoms.

[0035] The term "pyrimidinyl" represents the following moiety:



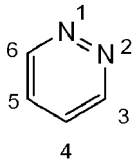
[0036] The pyrimidinyl moiety can be attached through any one of the 2-, 4-, 5-, or 6-position carbon atoms. Within the scope of the invention, "pyrimidinyl" groups of the invention can be substituted with halogen, for example fluoro, or alkyl, for example methyl.

[0037] The term "pyrazinyl" represents the following moiety:



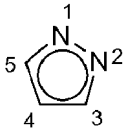
[0038] The pyrazinyl moiety can be attached through any one of the 2-, 3-, 5-, or 6-position carbon atoms.

[0039] The term "pyridazinyl" represents the following moiety:



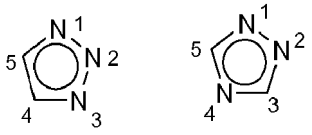
[0040] The pyridazinyl moiety can be attached through any one of the 3-, 4-, 5-, or 6-position carbon atoms.

[0041] The term "pyrazolyl" represents the following moiety:



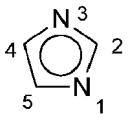
[0042] The pyrazolyl moiety can be attached through any one of the 1-, 2-, 3-, 4-, or 5-position carbon atoms. Pyrazolyl groups of the invention can be optionally substituted with, for example, one or two alkyl groups, for example, one or two methyl groups.

[0043] The term "triazolyl" represents a 1,2,3-triazole or a 1,2,4-triazole moiety:



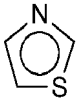
[0044] The triazolyl moieties can be attached through any one of their atoms.

[0045] The term "imidazolyl" represents the following moiety:



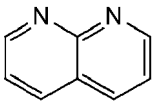
[0046] The imidazolyl moiety can be attached through any one of the 2-, 4-, or 5-position carbon atoms, or via the N-1 nitrogen atom. Imidazolyl groups of the invention can be optionally substituted with, for example, one or two alkyl groups, for example, one or two methyl groups.

[0047] The term "thiazolyl" represents the following moiety:



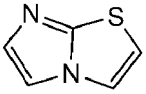
[0048] The thiazolyl moiety can be attached through any one of the carbon atoms. Thiazolyl groups of the invention can be optionally substituted with, for example, one or two alkyl groups, for example, one or two methyl groups.

[0049] The term "naphthyridinyl" represents the following moiety:



[0050] The naphthyridinyl moiety can be attached through any one of the carbon atoms. Naphthyridinyl groups of the invention can be optionally substituted with, for example, one or two alkyl groups, for example, one or two methyl groups, or halo groups.

[0051] The term "imidazothiazolyl" represents the following moiety:



[0052] The imidazothiazolyl moiety can be attached through any one of the carbon atoms. imidazothiazolyl groups of the invention can be optionally substituted with, for example, one or two alkyl groups, for example, one or two methyl groups.

[0053] "Pharmaceutically acceptable" means approved or approvable by a regulatory agency of the Federal or a state government or the corresponding agency in countries other than the United States, or that is listed in the U.S. Pharmacopoeia or other generally recognized pharmacopoeia for use in animals, and more particularly, in humans.

[0054] "Pharmaceutically acceptable salt" refers to a salt of a compound of the invention that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. In particular, such salts are non-toxic may be inorganic or organic acid addition salts and base addition salts. Specifically, such salts include: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylic acid, glucoheptonic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like; or (2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, N-methylglucamine and the like. Salts further include, by way of example only, sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium, and the like; and when the compound contains a basic functionality, salts of non toxic organic or inorganic acids, such as hydrochloride, hydrobromide, tartrate, mesylate, acetate, maleate, oxalate and the like.

[0055] "Pharmaceutically acceptable vehicle" refers to a diluent, adjuvant, excipient or carrier with which a compound of the invention is administered. A "pharmaceutically acceptable excipient" refers to a substance that is non-toxic, biologically tolerable, and otherwise biologically suitable for administration to a subject, such as an inert substance, added to a pharmacological composition or otherwise used as a vehicle, carrier, or diluent to facilitate administration of a agent and that is compatible therewith. Examples of excipients include calcium carbonate, calcium phosphate, various sugars and types of starch, cellulose derivatives, gelatin, vegetable oils, and polyethylene glycols.

[0056] "Subject" includes humans. The terms "human," "patient," and "subject" are used interchangeably herein.

[0057] "Treating" or "treatment" of any disease or disorder refers, in one embodiment, to ameliorating the disease or disorder (i.e., arresting or reducing the development of the disease or at least one of the clinical symptoms thereof). In another embodiment "treating" or "treatment" refers to ameliorating at least one physical parameter, which may not be discernible by the subject. In yet another embodiment, "treating" or "treatment" refers to modulating the disease or disorder, either physically, (e.g., stabilization of a discernible symptom), physiologically, (e.g., stabilization of a physical parameter), or both. In yet another embodiment, "treating" or "treatment" refers to delaying the onset of the disease or disorder.

[0058] In treatment methods according to the invention, a therapeutically effective amount of a pharmaceutical agent according to the invention is administered to a subject suffering from or diagnosed as having such a disease, disorder, or condition. A "therapeutically effective amount" means an amount or dose sufficient to generally bring about the desired therapeutic or prophylactic benefit in patients in need of such treatment for the designated disease, disorder, or condition. Effective amounts or doses of the compounds of the present invention may be ascertained by routine methods such as modeling, dose escalation studies or clinical trials, and by taking into consideration routine factors, e.g., the mode or

route of administration or drug delivery, the pharmacokinetics of the compound, the severity and course of the disease, disorder, or condition, the subject's previous or ongoing therapy, the subject's health status and response to drugs, and the judgment of the treating physician. An example of a dose is in the range of from about 0.001 to about 200 mg of compound per kg of subject's body weight per day, preferably about 0.05 to 100 mg/kg/day, or about 1 to 35 mg/kg/day, in single or divided dosage units (e.g., BID, TID, QID). For a 70-kg human, an illustrative range for a suitable dosage amount is from about 0.05 to about 7 g/day, or about 0.2 to about 2.5 g/day.

[0059] "Compounds of the present invention," and equivalent expressions, are meant to embrace compounds of the Formula (I) as described herein, which expression includes the pharmaceutically acceptable salts, and the solvates, e.g., hydrates, where the context so permits. Similarly, reference to intermediates, whether or not they themselves are claimed, is meant to embrace their salts, and solvates, where the context so permits.

[0060] As used herein, the term "isotopic variant" refers to a compound that contains unnatural proportions of isotopes at one or more of the atoms that constitute such compound. For example, an "isotopic variant" of a compound can be radiolabeled, that is, contain one or more non-radioactive or radioactive isotopes, such as for example, deuterium (^{2}H or D), carbon-13 (^{13}C), nitrogen-15 (^{15}N), or the like. It will be understood that, in a compound where such isotopic substitution is made, the following atoms, where present, may vary, so that for example, any hydrogen may be ^{2}H/D, any carbon may be ^{13}C, or any nitrogen may be ^{15}N, and that the presence and placement of such atoms may be determined within the skill of the art. Likewise, the invention may include the preparation of isotopic variants with radioisotopes, in the instance for example, where the resulting compounds may be used for drug and/or substrate tissue distribution studies. Radiolabeled compounds of the invention can be used in diagnostic methods such as Single-photon emission computed tomography (SPECT). The radioactive isotopes tritium, *i.e.* ^{3}H, and carbon-14, *i.e.* ^{14}C, are particularly useful for their ease of incorporation and ready means of detection. Further, compounds may be prepared that are substituted with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, and would be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

[0061] All isotopic variants of the compounds of the invention, radioactive or not, are intended to be encompassed within the scope of the invention. In one aspect, provided herein are deuterated analogs of compounds of Formula I as described in the Examples section. In one embodiment, deuterated analogs of compounds of Formula I comprise deuterium atoms attached to one or more positions on the 2-azabicyclic ring, such as bridgehead carbons, or non-bridgehead carbons of the 2-azabicyclic ring, and preferably comprise one or more deuterium atoms attached to non-bridgehead carbons of the 2-azabicyclic ring. Also contemplated within the scope of embodiments described herein are compounds in which a single proton in compounds of Formula I is replaced with a deuterium, or 2 protons in compounds of Formula I are replaced with deuterium, or more than 2 protons in compounds of Formula I are replaced with deuterium. Deuteration of a compound of Formula I may also be effected on one or more substituents (such as e.g., ring A, R^1, R^2, or R^5) present on the 2-azabicyclic ring.

[0062] It is also to be understood that compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed "isomers." Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers."

[0063] Stereoisomers that are not mirror images of one another are termed "diastereomers" and those that are non-superimposable mirror images of each other are termed "enantiomers." When a compound has an asymmetric center, for example, it is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the R-and *S*-sequencing rules of Cahn and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (*i.e.,* as (+) or (-)-isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a "racemic mixture."

[0064] "Tautomers" refer to compounds that are interchangeable forms of a particular compound structure, and that vary in the displacement of hydrogen atoms and electrons. Thus, two structures may be in equilibrium through the movement of π electrons and an atom (usually H). For example, enols and ketones are tautomers because they are rapidly interconverted by treatment with either acid or base. Another example of tautomerism is the aci-and nitro-forms of phenyl nitromethane, that are likewise formed by treatment with acid or base.

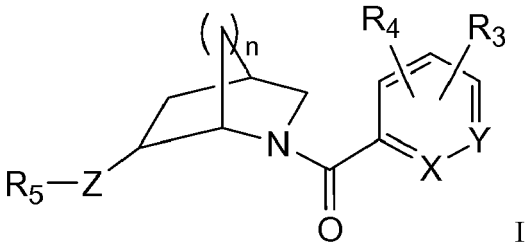
[0065] Tautomeric forms may be relevant to the attainment of the optimal chemical reactivity and biological activity of a compound of interest.

[0066] Compounds of the invention may also exist as "rotamers," that is, conformational isomers that occur when the rotation leading to different conformations is hindered, resulting a rotational energy barrier to be overcome to convert from one conformational isomer to another.

[0067] The compounds of this invention may possess one or more asymmetric centers; such compounds can therefore be produced as individual (*R*)-or (*S*)-stereoisomers or as mixtures thereof.

[0068] Unless indicated otherwise, the description or naming of a particular compound in the specification and claims is intended to include both individual enantiomers and mixtures, racemic or otherwise, thereof. The methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art.

[0069] The present invention is directed to compounds of Formula I:

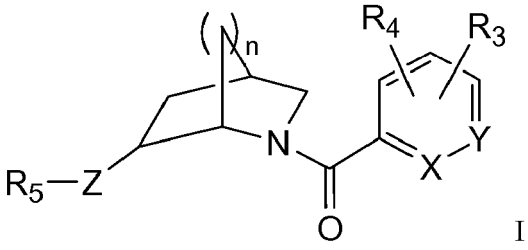


I

wherein

X is N or CR_1
Y is N or CR_2
R_1 is H, alkoxy, halo, triazolyl, thiazolyl, pyridazinyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl, pyridyl, phenyl or pyrazolyl, wherein triazolyl, thiazolyl, pyridazinyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl, pyridyl, phenyl or pyrazolyl is optionally substituted with up to two substituents selected from halo and alkyl;
R_2 is H, alkyl, alkoxy, or halo;
Z is NH, N-CH_3, N-CH_2CH_3, N-CH_2-cyclopropyl, N-C(=O)CH_3, N-$CH_2CH_2OCH_3$ or O; R_3 is H, alkyl, alkoxy, halo, triazolyl, thiazolyl, pyridazinyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl, pyridyl, phenyl or pyrazolyl, wherein triazolyl, thiazolyl, pyridazinyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl, pyridyl, phenyl or pyrazolyl is optionally substituted with up to two substituents selected from halo and alkyl;
R_4 is H or alkyl;
or R_3 and R_4, together with the atoms to which they are attached, form a 6-membered aryl ring or a 5- or 6-membered heteroaryl ring;
R_5 is phenyl, pyridyl, pyrazinyl, benzoxazolyl, pyridazinyl, naphthyridinyl or pyrimidinyl, wherein the pyridyl, pyrazinyl, benzoxazolyl, pyridazinyl, naphthyridinyl or pyrimidinyl is optionally substituted with up to two groups selected from halo, alkoxy, hydroxymethyl and alkyl; and
n is 1 or 2.

[0070] In one aspect, the invention is directed to compounds of Formula I:



I

wherein

X is N or CR_1
Y is N or CR_2
R_1 is H, alkoxy, halo, triazolyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl, or pyrazolyl;
R_2 is H, alkyl, alkoxy, or halo;
Z is NH, or O;
R_3 is H, alkyl, alkoxy, halo, or triazolyl;
R_4 is H or alkyl;

or R_3 and R_4, together with the atoms to which they are attached, form a 6-membered aryl ring or a 5- or 6-membered heteroaryl ring;

R_5 is pyridyl, pyrazinyl, or pyrimidinyl, wherein the pyridyl, pyrazinyl, or pyrimidinyl is optionally substituted with halo or alkyl; and

n is 1 or 2.

[0071] Enantiomers and diastereomers of the compounds of Formula I are also within the scope of the invention. Also within the scope of the invention are the pharmaceutically acceptable salts of the compounds of Formula I, as well as the pharmaceutically acceptable salts of the enantiomers and diastereomers of the compounds of Formula I. Also within the scope of the invention are isotopic variations of compounds of Formula I, such as, e.g., deuterated compounds of Formula I.

[0072] In preferred embodiments, Z is NH. In other embodiments, Z is O. In yet other embodiments, Z is NH, N-CH_3, N-CH_2CH_3, N-CH_2-cyclopropyl, N-C(=O)CH_3, or N-$CH_2CH_2OCH_3$.

[0073] In preferred embodiments, X is CR_1 and Y is CR_2.

[0074] In other embodiments, X is CR_1 and Y is N.

[0075] In yet other embodiments, X is N and Y is CR_2.

[0076] In those embodiments wherein X is CR_1, for example, where X is CR_1 and Y is CR_2 or X is CR_1 and Y is N, R_1 is H. In other embodiments, R_1 is alkoxy, for example, $C_{1\text{-}6}$alkoxy such as methoxy or ethoxy.

[0077] In those embodiments wherein X is CR_1, for example, where X is CR_1 and Y is CR_2 or X is CR_1 and Y is N, R_1 is halo, preferably F, Cl, or Br.

[0078] In those embodiments wherein X is CR_1, for example, where X is CR_1 and Y is CR_2 or X is CR_1 and Y is N, R_1 is triazolyl, optionally substituted with up to two substituents selected from halo and alkyl, with 1,2,3-triazolyl being preferred. In preferred embodiments, the 1,2,3-triazolyl is attached through the 2-position nitrogen atom. In other embodiments, the 1,2,3-triazolyl is attached through the 1-position nitrogen atom.

[0079] In those embodiments wherein X is CR_1, for example, where X is CR_1 and Y is CR_2 or X is CR_1 and Y is N, R_1 is pyrimidinyl, optionally substituted with up to two substituents selected from halo and alkyl, which can be attached through any available atom.

[0080] In those embodiments wherein X is CR_1, for example, where X is CR_1 and Y is CR_2 or X is CR_1 and Y is N, R_1 is oxazolyl, optionally substituted with up to two substituents selected from halo and alkyl, which can be attached through any available atom.

[0081] In those embodiments wherein X is CR_1, for example, where X is CR_1 and Y is CR_2 or X is CR_1 and Y is N, R_1 is isoxazolyl, optionally substituted with up to two substituents selected from halo and alkyl, which can be attached through any available atom.

[0082] In those embodiments wherein X is CR_1, for example, where X is CR_1 and Y is CR_2 or X is CR_1 and Y is N, R_1 is oxadiazolyl, optionally substituted with up to two substituents selected from halo and alkyl, which can be attached through any available atom. The oxadiazolyl group can optionally be substituted with alkyl, for example methyl. In exemplary embodiments, the substituted oxadiazolyl moiety is 1,2,4-oxadiazolyl substituted with methyl.

[0083] In those embodiments wherein X is CR_1, for example, where X is CR_1 and Y is CR_2 or X is CR_1 and Y is N, R_1 is pyridyl, optionally substituted with up to two substituents selected from halo and alkyl, which can be attached through any available atom. The pyridyl group can optionally be substituted with alkyl, for example methyl or halo.

[0084] In those embodiments wherein X is CR_1, for example, where X is CR_1 and Y is CR_2 or X is CR_1 and Y is N, R_1 is imidazolyl, optionally substituted with up to two substituents selected from halo and alkyl, which can be attached through any available atom. The imidazolyl group can optionally be substituted with alkyl, for example methyl or halo.

[0085] In those embodiments wherein X is CR_1, for example, where X is CR_1 and Y is CR_2 or X is CR_1 and Y is N, R_1 is phenyl, optionally substituted with up to two substituents selected from halo and alkyl, which can be attached through any available atom. The phenyl group can optionally be substituted with alkyl, for example methyl or halo.

[0086] In those embodiments wherein X is CR_1, for example, where X is CR_1 and Y is CR_2 or X is CR_1 and Y is N, R_1 is pyrazolyl, optionally substituted with up to two substituents selected from halo and alkyl, which can be attached through any available atom. The pyrazolyl group can optionally be substituted with one or two $C_{1\text{-}6}$alkyl, for example methyl.

[0087] In those embodiments wherein X is CR_1, for example, where X is CR_1 and Y is CR_2 or X is CR_1 and Y is N, R_1 is thiazolyl, optionally substituted with up to two substituents selected from halo and alkyl, which can be attached through any available atom.

[0088] In those embodiments wherein X is CR_1, for example, where X is CR_1 and Y is CR_2 or X is CR_1 and Y is N, R_1 is pyridazinyl, optionally substituted with up to two substituents selected from halo and alkyl, which can be attached through any available atom.

[0089] In preferred embodiments wherein Y is CR_2, for example, X is CR_1 and Y is CR_2 or X is N and Y is CR_2, R_2 is H. In other embodiments, R_2 is alkyl, for example $C_{1\text{-}6}$alkyl such as methyl.

[0090] In those embodiments wherein Y is CR_2, for example, X is CR_1 and Y is CR_2 or X is N and Y is CR_2, R_2 is alkoxy, for example, $C_{1\text{-}6}$alkoxy such as methoxy or ethoxy.

[0091] In those embodiments wherein Y is CR_2, for example, X is CR_1 and Y is CR_2 or X is N and Y is CR_2, R_2 is halo, preferably one of F, Cl, or Br.

[0092] In preferred embodiments, R_3 is H. In other embodiments, R_3 is alkyl, for example, $C_{1\text{-}6}$alkyl such as methyl.

[0093] In yet other embodiments, R_3 is alkoxy, for example, $C_{1\text{-}6}$alkoxy such as methoxy or ethoxy.

[0094] In still other embodiments, R_3 is halo, preferably F, Cl, or Br.

[0095] In other embodiments, R_3 is triazolyl, with 1,2,3-triazolyl being preferred. In preferred embodiments, the 1,2,3-triazolyl is attached through the 2-position nitrogen atom. In other embodiments, the 1,2,3-triazolyl is attached through the 1-position nitrogen atom.

[0096] In preferred embodiments, R_4 is H. In other embodiments, R_3 is alkyl, for example $C_{1\text{-}6}$alkyl such as methyl.

[0097] In alternative embodiments, R_3 and R_4, together with the atoms to which they are attached, form a 6- membered aryl ring.

[0098] In other embodiments, R_3 and R_4, together with the atoms to which they are attached, form a 5-membered heteroaryl ring. Preferably, the 5-membered heteroaryl ring includes one nitrogen atom.

[0099] In other embodiments, R_3 and R_4, together with the atoms to which they are attached, form a 6-membered heteroaryl ring. Preferably, the 6-membered heteroaryl ring includes one nitrogen atom.

[0100] In some embodiments of the invention, R_5 is a phenyl ring optionally substituted with a one or two substituents independently selected from the group consisting of alkyl, cyano, alkoxy, and halo, or from the group consisting of alkyl and halo. In some embodiments of the invention, R_5 is a heteroaryl ring. In some of such embodiments, R_5 is a heteroaryl optionally substituted with a one or two substituents independently selected from the group consisting of alkyl, cyano, alkoxy, and halo, or from the group consisting of alkyl and halo. In preferred embodiments, R_5 is pyridyl, which can be attached through any available atom, optionally substituted with halo (preferably F, Cl, or Br) or alkyl. In some embodiments, the alkyl is substituted with one or more halogen atoms. A preferred substituted alkyl group is trihaloalkyl such as trifluoromethyl. Other substituted alkyl groups include difluoromethyl or monofluoromethyl. Preferably, R_5 is pyridyl substituted at any available position with trifluoromethyl.

[0101] In preferred embodiments, R_5 is pyrazinyl, which can be attached through any available atom, optionally substituted with halo (preferably F, Cl, or Br) or alkyl. In some embodiments, the alkyl is substituted with one or more halogen atoms. A preferred substituted alkyl group is trihaloalkyl such as trifluoromethyl. Other substituted alkyl groups include difluoromethyl or monofluoromethyl. Preferably, R_5 is pyrazinyl substituted at any available position with trifluoromethyl.

[0102] In preferred embodiments, R_5 is pyrimidinyl, which can be attached through any available atom, optionally substituted with halo (preferably F, Cl, or Br) or alkyl. In some embodiments, the alkyl is substituted with one or more halogen atoms. A preferred substituted alkyl group is trihaloalkyl such as trifluoromethyl. Other substituted alkyl groups include difluoromethyl or monofluoromethyl. Preferably, R_5 is pyrimidinyl substituted at any available position with trifluoromethyl.

[0103] In other embodiments, R_5 is benzoxazolyl which can be attached through any available atom, optionally substituted with halo (preferably F, Cl, or Br) or alkyl. In some embodiments, the alkyl is substituted with one or more halogen atoms. A preferred substituted alkyl group is trifluoromethyl. Other substituted alkyl groups include difluoromethyl or monofluoromethyl. Preferably, R_5 is benzoxazolyl, pyridazinyl, or naphthyridinyl substituted at any available position with trifluoromethyl.

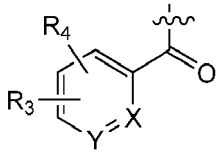
[0104] In other embodiments, R_5 is pyridazinyl which can be attached through any available atom, optionally substituted with halo (preferably F, Cl, or Br) or alkyl. In some embodiments, the alkyl is substituted with one or more halogen atoms. A preferred substituted alkyl group is trifluoromethyl. Other substituted alkyl groups include difluoromethyl or monofluoromethyl. Preferably, R_5 is benzoxazolyl, pyridazinyl, or naphthyridinyl substituted at any available position with trifluoromethyl.

[0105] In other embodiments, R_5 is naphthyridinyl which can be attached through any available atom, optionally substituted with halo (preferably F, Cl, or Br) or alkyl. In some embodiments, the alkyl is substituted with one or more halogen atoms. A preferred substituted alkyl group is trifluoromethyl. Other substituted alkyl groups include difluoromethyl or monofluoromethyl. Preferably, R_5 is benzoxazolyl, pyridazinyl, or naphthyridinyl substituted at any available position with trifluoromethyl.

[0106] In preferred embodiments, n is 1. In other embodiments, n is 2.

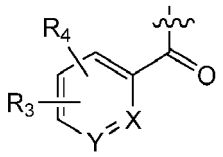
[0107] In some embodiments of Formula I, R_1 is H and R_3 is as defined above for Formula I, preferably R_3 is triazolyl, oxazolyl, pyridyl or pyrimidinyl. In other embodiments of Formula I, R_3 is H and R_1 is as defined above for Formula I, preferably R_1 is triazolyl, oxazolyl, isoxazolyl, oxadiazolyl, pyridyl or pyrimidinyl.

[0108] In some embodiments of Formula I, the group



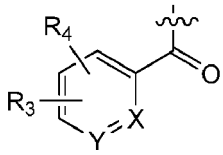
is a pyridyl group, preferably X is N, R_3 is a ring selected from triazolyl, thiazolyl, pyridazinyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl, pyridyl, phenyl or pyrazolyl; preferably triazolyl or pyridyl or pyrimidinyl; R_4 is H or alkyl, preferably methyl; Z is NH or O, preferably O; preferably NH, R_5 is a heteroaryl, preferably pyridyl or pyrazinyl. In some of such embodiments, R_3 is a ring at the ortho position relative to the carbonyl group in Formula I, and R_4 is at the ortho, meta or para position on the relative to the carbonyl group in Formula I, preferably R_4 is at the meta position adjacent to R_3. In some other such embodiments, R_3 is a ring at the ortho position relative to the carbonyl group in Formula I, and R_4 is at the ortho, meta or para position relative to the carbonyl group in Formula I, preferably R_4 is at the meta position not adjacent to R_3. R_3 and R_5 are optionally substituted as described above.

[0109] In some embodiments of Formula I, the group



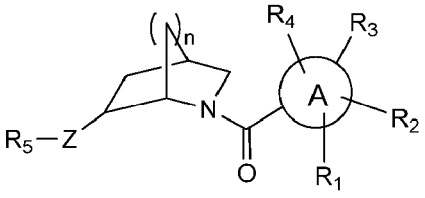
is a pyridyl group, preferably Y is N, R_1 is a ring selected from triazolyl, thiazolyl, pyridazinyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl, pyridyl, phenyl or pyrazolyl; preferably triazolyl or pyridyl or pyrimidinyl; R_4 is H or alkyl, preferably methyl; Z is NH or O, preferably O; preferably NH, R_5 is a heteroaryl, preferably pyridyl or pyrazinyl. In some of such embodiments, R_1 is a ring at the ortho position relative to the carbonyl group in Formula I, and R_4 is at the ortho, meta or para position on the relative to the carbonyl group in Formula I, preferably R_4 is at the meta position adjacent to R_1. In some other such embodiments, R_1 is a ring at the ortho position relative to the carbonyl group in Formula I, and R_4 is at the ortho, meta or para position relative to the carbonyl group in Formula I, preferably R_4 is at the meta position not adjacent to R_1. R_1 and R_5 are optionally substituted as described above.

[0110] In some embodiments of Formula I, the group



is a phenyl group, R_3 is a ring selected from triazolyl, thiazolyl, pyridazinyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl, pyridyl, phenyl or pyrazolyl; preferably triazolyl or pyridyl or pyrimidinyl at the ortho position; R_4 is H or alkyl, preferably methyl; Z is NH or O, preferably O; preferably NH, R_5 is a heteroaryl, preferably pyridyl or pyrazinyl. In some of such embodiments, R_3 is a ring at the ortho position relative to the carbonyl group in Formula I, and R_4 is at the ortho, meta or para position on the relative to the carbonyl group in Formula I, preferably R_4 is at the meta position adjacent to R_3. In some other such embodiments, R_3 is a ring at the ortho position relative to the carbonyl group in Formula I, and R_4 is at the ortho, meta or para position relative to the carbonyl group in Formula I, preferably R_4 is at the meta position not adjacent to R_3. R_3 and R_5 are optionally substituted as described above.

[0111] Also provided herein is a compound of Formula IA:



IA

wherein

ring A is a heteroaryl ring selected from furanyl, thiazolyl, imidazothiazolyl, and pyrazinyl;

R_1 is H, alkoxy, halo, triazolyl, thiazolyl, pyridazinyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl, pyridyl, phenyl, or pyrazolyl, wherein triazolyl, thiazolyl, pyridazinyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl, pyridyl, phenyl or pyrazolyl is optionally substituted with up to two substituents selected from halo and alkyl;

R_2 is H, alkyl, alkoxy, or halo;

Z is NH, N-CH_3, N-CH_2CH_3, N-CH_2-cyclopropyl, N-C(=O)CH_3, N-$CH_2CH_2OCH_3$ or O;

R_3 is H, alkyl, alkoxy, halo, triazolyl, thiazolyl, pyridazinyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl, pyridyl, phenyl, or pyrazolyl, wherein triazolyl, thiazolyl, pyridazinyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl, pyridyl, phenyl or pyrazolyl is optionally substituted with up to two substituents selected from halo and alkyl;
R_4 is H or alkyl;
or R_3 and R_4, together with the atoms to which they are attached, form a 6-membered aryl ring or a 5- or 6-membered heteroaryl ring;
R_5 is pyridyl, pyrazinyl, benzoxazolyl, pyridazinyl, naphthyridinyl or pyrimidinyl, wherein the pyridyl, pyrazinyl, benzoxazolyl, pyridazinyl, naphthyridinyl or pyrimidinyl is optionally substituted with up to two substituents selected from halo, alkoxy, hydroxymethyl and alkyl; and
n is 1 or 2.

[0112] Enantiomers and diastereomers of the compounds of Formula IA are also within the scope of the invention. Also within the scope of the invention are the pharmaceutically acceptable salts of the compounds of Formula IA, as well as the pharmaceutically acceptable salts of the enantiomers and diastereomers of the compounds of Formula IA. Also within the scope of the invention are isotopic variations of compounds of Formula IA, such as, e.g., deuterated compounds of Formula IA.

[0113] In some embodiments, ring A is a furanyl ring. In some embodiments, ring A is a thiazolyl ring. In some embodiments, ring A is a imidazothiazolyl ring. In other embodiments, ring A is a pyrazinyl ring.

[0114] All of the embodiments described for Formula I above, with respect to the variables R_1, R_2, Z, R_3, R_4, R_5 and n, also apply for Formula IA, and are expressly contemplated herein.

[0115] The invention relates to methods of using the compounds described herein to treat subjects diagnosed with or suffering from a disease, disorder, or condition mediated by orexin receptor activity. These methods are accomplished by administering to the subject a compound of the invention. In some embodiments, the compounds described herein are selective for orexin-1 receptor activity. In some embodiments, the compounds described herein are selective for orexin-1 receptor activity over orexin-2 receptor activity.

[0116] Diseases, disorders, and conditions mediated by orexin receptor activity include disorders of the sleep-wake cycle, insomnia, restless legs syndrome, jet-lag, disturbed sleep, sleep disorders secondary to neurological disorders, mania, depression, manic depression, schizophrenia, pain syndromes, fibromyalgia, neuropathic pain, catatonia, Parkinson's disease, Tourette's syndrome, anxiety, delirium, dementia, overweight, obesity, or conditions related to overweight or obesity, insulin resistance, type II diabetes, hyperlipidemia, gallstones, angina, hypertension, breathlessness, tachycardia, infertility, sleep apnea, back and joint pain, varicose veins, osteoarthritis, hypertension, tachycardia, arrhythmias, angina pectoris, acute heart failure, ulcers, irritable bowel syndrome, diarrhea gastroesophageal reflux, mood disorders, post-traumatic stress disorder, panic disorders, attention deficit disorders, cognitive deficiencies, or substance abuse.

[0117] Compounds of the invention are particularly suited for the treatment of mood disorders, post-traumatic stress disorder, panic disorders, attention deficit disorders, cognitive deficiencies, or substance abuse.

[0118] In one aspect, compounds of the invention are particularly suited for the treatment of mood disorders. Non-limiting examples of mood disorders include anxiety-related mood disorders, depression, panic-related mood disorders, stress related mood disorders and the like. In another aspect, compounds of the invention are suitable for the treatment of post-traumatic stress disorder, panic disorders, attention deficit disorders, cognitive deficiencies, or substance abuse (e.g., morphine abuse, cocaine abuse, alcohol abuse and the like). It will be understood that certain disorders such as, for example, depression and/or schizophrenia and/or substance abuse and/or cognitive impairments also have elements of anxiety and/or panic and/or stress associated with them and the treatment of such conditions and/or combinations of conditions are also contemplated within the scope of embodiments presented herein. In some embodiments, advantageously, compounds of the invention treat a mood disorder (e.g., anxiety) with reduced concomitant sedation and/or with reduced effect on sleep (e.g. attenuated arousal effects). In one embodiment, compounds of the invention are particularly suited for the treatment of anxious depression. In another embodiment, compounds of the invention are particularly suited for the treatment of panic, schizophrenia, and substance abuse.

[0119] Sleep disorders include, but are not limited to, sleep-wake transition disorders, insomnia, restless legs syndrome, jet-lag, disturbed sleep, and sleep disorders secondary to neurological disorders (e.g., manias, depressions, manic depression, schizophrenia, and pain syndromes (e.g., fibromyalgia, neuropathic).

[0120] Metabolic disorders include, but are not limited to, overweight or obesity and conditions related to overweight or obesity, such as insulin resistance, type II diabetes, hyperlipidemia, gallstones, angina, hypertension, breathlessness, tachycardia, infertility, sleep apnea, back and joint pain, varicose veins and osteoarthritis.

[0121] Neurological disorders include, but are not limited to, Parkinson's disease, Alzheimer's disease, Tourette's Syndrome, catatonia, anxiety, delirium and dementias.

[0122] In treatment methods according to the invention, a therapeutically effective amount of a pharmaceutical agent according to the invention is administered to a subject suffering from or diagnosed as having such a disease, disorder,

or condition. A "therapeutically effective amount" means an amount or dose sufficient to generally bring about the desired therapeutic or prophylactic benefit in patients in need of such treatment for the designated disease, disorder, or condition. Effective amounts or doses of the compounds of the present invention may be ascertained by routine methods such as modeling, dose escalation studies or clinical trials, and by taking into consideration routine factors, e.g., the mode or route of administration or drug delivery, the pharmacokinetics of the compound, the severity and course of the disease, disorder, or condition, the subject's previous or ongoing therapy, the subject's health status and response to drugs, and the judgment of the treating physician. An example of a dose is in the range of from about 0.001 to about 200 mg of compound per kg of subject's body weight per day, preferably about 0.05 to 100 mg/kg/day, or about 1 to 35 mg/kg/day, in single or divided dosage units (e.g., BID, TID, QID). For a 70-kg human, an illustrative range for a suitable dosage amount is from about 0.05 to about 7 g/day, or about 0.2 to about 2.5 g/day.

[0123] Once improvement of the patient's disease, disorder, or condition has occurred, the dose may be adjusted for preventative or maintenance treatment. For example, the dosage or the frequency of administration, or both, may be reduced as a function of the symptoms, to a level at which the desired therapeutic or prophylactic effect is maintained. Of course, if symptoms have been alleviated to an appropriate level, treatment may cease. Patients may, however, require intermittent treatment on a long-term basis upon any recurrence of symptoms.

[0124] In addition, the compounds of the invention may be used in combination with additional active ingredients in the treatment of the above conditions. The additional active ingredients may be coadministered separately with a compound of the invention or included with such an agent in a pharmaceutical composition according to the invention. In an exemplary embodiment, additional active ingredients are those that are known or discovered to be effective in the treatment of conditions, disorders, or diseases mediated by orexin activity, such as another orexin modulator or a compound active against another target associated with the particular condition, disorder, or disease. The combination may serve to increase efficacy (e.g., by including in the combination a compound potentiating the potency or effectiveness of an active agent according to the invention), decrease one or more side effects, or decrease the required dose of the active agent according to the invention.

[0125] The compounds of the invention are used, alone or in combination with one or more additional active ingredients, to formulate pharmaceutical compositions of the invention. A pharmaceutical composition of the invention comprises: (a) an effective amount of at least one compound in accordance with the invention; and (b) a pharmaceutically acceptable excipient.

[0126] Delivery forms of the pharmaceutical compositions containing one or more dosage units of the active agents may be prepared using suitable pharmaceutical excipients and compounding techniques known or that become available to those skilled in the art. The compositions may be administered in the inventive methods by a suitable route of delivery, e.g., oral, parenteral, rectal, topical, or ocular routes, or by inhalation.

[0127] The preparation may be in the form of tablets, capsules, sachets, dragees, powders, granules, lozenges, powders for reconstitution, liquid preparations, or suppositories. Preferably, the compositions are formulated for intravenous infusion, topical administration, or oral administration.

[0128] For oral administration, the compounds of the invention can be provided in the form of tablets or capsules, or as a solution, emulsion, or suspension. To prepare the oral compositions, the compounds may be formulated to yield a dosage of, e.g., from about 0.05 to about 100 mg/kg daily, or from about 0.05 to about 35 mg/kg daily, or from about 0.1 to about 10 mg/kg daily. For example, a total daily dosage of about 5 mg to 5 g daily may be accomplished by dosing once, twice, three, or four times per day.

[0129] Oral tablets may include a compound according to the invention mixed with pharmaceutically acceptable excipients such as inert diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavoring agents, coloring agents and preservative agents. Suitable inert fillers include sodium and calcium carbonate, sodium and calcium phosphate, lactose, starch, sugar, glucose, methyl cellulose, magnesium stearate, mannitol, sorbitol, and the like. Exemplary liquid oral excipients include ethanol, glycerol, water, and the like. Starch, polyvinylpyrrolidone (PVP), sodium starch glycolate, microcrystalline cellulose, and alginic acid are suitable disintegrating agents. Binding agents may include starch and gelatin. The lubricating agent, if present, may be magnesium stearate, stearic acid or talc. If desired, the tablets may be coated with a material such as glyceryl monostearate or glyceryl distearate to delay absorption in the gastrointestinal tract, or may be coated with an enteric coating.

[0130] Capsules for oral administration include hard and soft gelatin capsules. To prepare hard gelatin capsules, compounds of the invention may be mixed with a solid, semi-solid, or liquid diluent. Soft gelatin capsules may be prepared by mixing the compound of the invention with water, an oil such as peanut oil or olive oil, liquid paraffin, a mixture of mono and di-glycerides of short chain fatty acids, polyethylene glycol 400, or propylene glycol.

[0131] Liquids for oral administration may be in the form of suspensions, solutions, emulsions or syrups or may be lyophilized or presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid compositions may optionally contain: pharmaceutically-acceptable excipients such as suspending agents (for example, sorbitol, methyl cellulose, sodium alginate, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminum stearate gel and the like); non-aqueous vehicles, e.g., oil (for example, almond oil or fractionated coconut oil), propylene glycol,

ethyl alcohol, or water; preservatives (for example, methyl or propyl p-hydroxybenzoate or sorbic acid); wetting agents such as lecithin; and, if desired, flavoring or coloring agents.

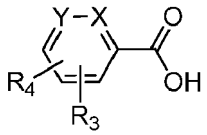
[0132] The active agents of this invention may also be administered by non-oral routes. For example, the compositions may be formulated for rectal administration as a suppository. For parenteral use, including intravenous, intramuscular, intraperitoneal, or subcutaneous routes, the compounds of the invention may be provided in sterile aqueous solutions or suspensions, buffered to an appropriate pH and isotonicity or in parenterally acceptable oil. Suitable aqueous vehicles include Ringer's solution and isotonic sodium chloride. Such forms will be presented in unit-dose form such as ampules or disposable injection devices, in multi-dose forms such as vials from which the appropriate dose may be withdrawn, or in a solid form or pre-concentrate that can be used to prepare an injectable formulation. Illustrative infusion doses may range from about 1 to 1000 .mu.g/kg/minute of compound, admixed with a pharmaceutical carrier over a period ranging from several minutes to several days.

[0133] For topical administration, the compounds may be mixed with a pharmaceutical carrier at a concentration of about 0.1% to about 10% of drug to vehicle. Another mode of administering the compounds of the invention may utilize a patch formulation to affect transdermal delivery.

[0134] Compounds of the invention may alternatively be administered in methods of this invention by inhalation, via the nasal or oral routes, e.g., in a spray formulation also containing a suitable carrier.

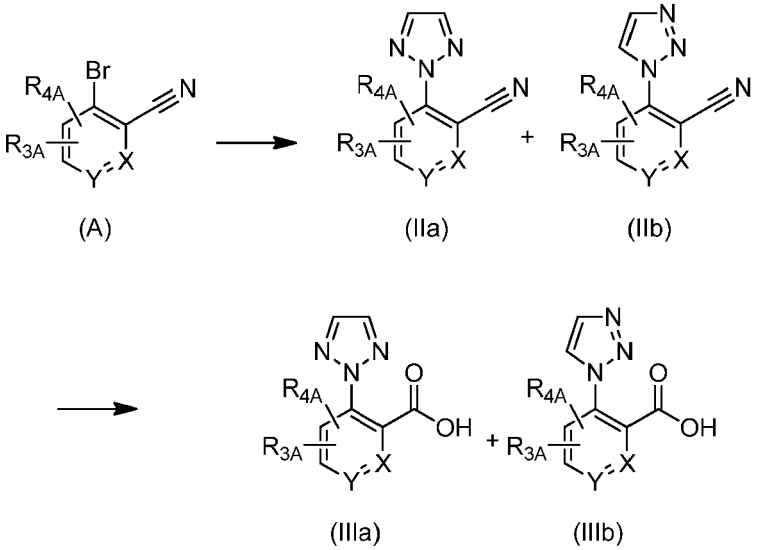
[0135] Exemplary compounds useful in methods of the invention will now be described by reference to the illustrative synthetic schemes for their general preparation below and the specific examples that follow. Artisans will recognize that, to obtain the various compounds herein, starting materials may be suitably selected so that the ultimately desired substituents will be carried through the reaction scheme with or without protection as appropriate to yield the desired product. Alternatively, it may be necessary or desirable to employ, in the place of the ultimately desired substituent, a suitable group that may be carried through the reaction scheme and replaced as appropriate with the desired substituent. Unless otherwise specified, the variables are as defined above in reference to Formula (I). Reactions may be performed between the melting point and the reflux temperature of the solvent, and preferably between 0 °C and the reflux temperature of the solvent. Reactions may be heated employing conventional heating or microwave heating. Reactions may also be conducted in sealed pressure vessels above the normal reflux temperature of the solvent.

[0136] The synthesis of exemplary intermediates having the structure



is described in Schemes 1-6 below and in the Examples section below (Intermediates A-1 to A-59).

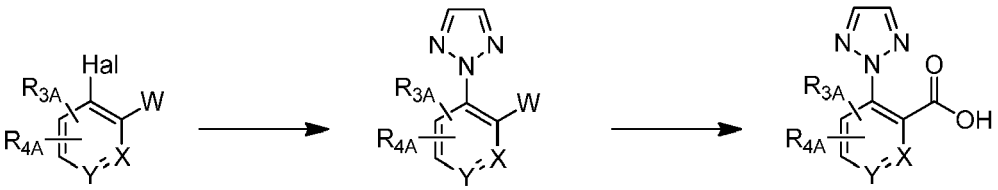
Scheme 1



[0137] Intermediate compounds of formula (IIIa) and (IIIb) can be prepared as outlined in Scheme 1 from commercially

available or synthetically accessible compounds of formula (A) where R_{3A}, R_{4A} are -H, halo, -C_{1-4}alkyl, -C_{1-4}alkoxy or R_{3A} and R_{4A} together with the atoms to which they are attached form a 6- membered aryl or 6 membered heteroaryl ring and X and Y are as defined in formula (1) as above. Compounds of formula (IIa) and (IIb), are obtained by reacting a compound of formula (A), with commercially available 1,2,3-triazole, in the presence K_2CO_3 in DMF or dioxane, at temperatures ranging from about 60 °C to about 100 °C. Compounds of formula (IIIa) and (IIIb) are obtained by reacting compounds of formula (II) in the presence of a base such as NaOH in a solvent such as EtOH at temperatures ranging from about 80 °C to about 100 °C. One skilled in the art will recognize that 1,2,3-triazole can exist in two tautomeric forms defined as 2H-[1,2,3]triazole and 1H-[1,2,3]triazole thus accounting for the formation of (IIIa) and (IIIb).

Scheme 2



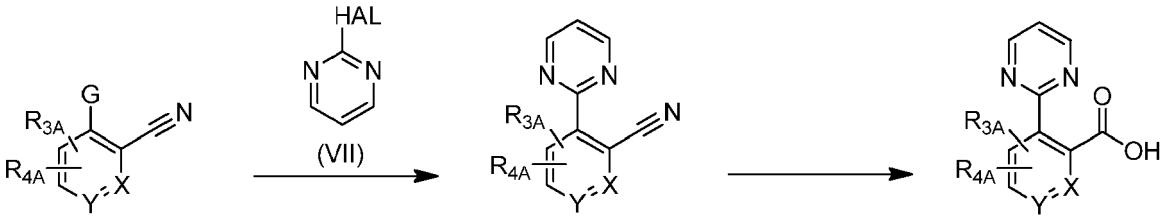
(IVa) W is CN
(IVb) W is CO_2Alkyl
(IVc) W is CO_2H

(Va) W is CN
(Vb) W is CO_2Alkyl

(III)

[0138] Intermediate compounds of formula (III) can be prepared as outlined in Scheme 2 from commercially available or synthetically accessible compounds of formula (IV_{a-c}). Compounds of formula (Va) and (Vb) are obtained by reacting compounds of formula (IVa), (IVb) and (IVc) where Hal is -Br, or -I; W is CO_2H, CO_2Alkyl, or CN and R_{3A} and R_{4A} are -H, halo, -C_{1-4}alkyl, -C_{1-4}alkoxy or R_{3A} and R_{4A} together with the atoms to which they are attached form a 6- membered aryl or 6 membered heteroaryl ring, and X and Y are as defined in Formula I above, with commercially available 1,2,3-triazole, in the presence of, for example, copper(I)iodide, Cs_2CO_3 and trans-N,N'-dimethyl-1,2-cyclohexanediamine in, for example, DMF or dioxane, at temperatures ranging from about 60 °C to about 120 °C. Compounds of formula (IVc) can be converted to the corresponding esters (Vb) by treatment with, for example, alkyl iodide in the presence of a base such as K_2CO_3 in a solvent such as DME Compounds of formula (III) are obtained by reacting a compound of formula (Va) and (Vb) in the presence of a base such as NaOH in a solvent such as EtOH at temperatures ranging from about 80 °C to about 100 °C. One skilled in the art will recognize that 1,2,3-triazole can exist in two tautomeric forms defined as 2H-[1,2,3]triazole and 1H-[1,2,3]triazole thus compounds of formula (Va), (Vb), and (III) can also exist as the N1 linked variant (structure not shown). It will be understood that the heterocycle in (Va) and (Vb) is not limited to triazole and may be any other suitable heterocycle.

Scheme 3



(VI)

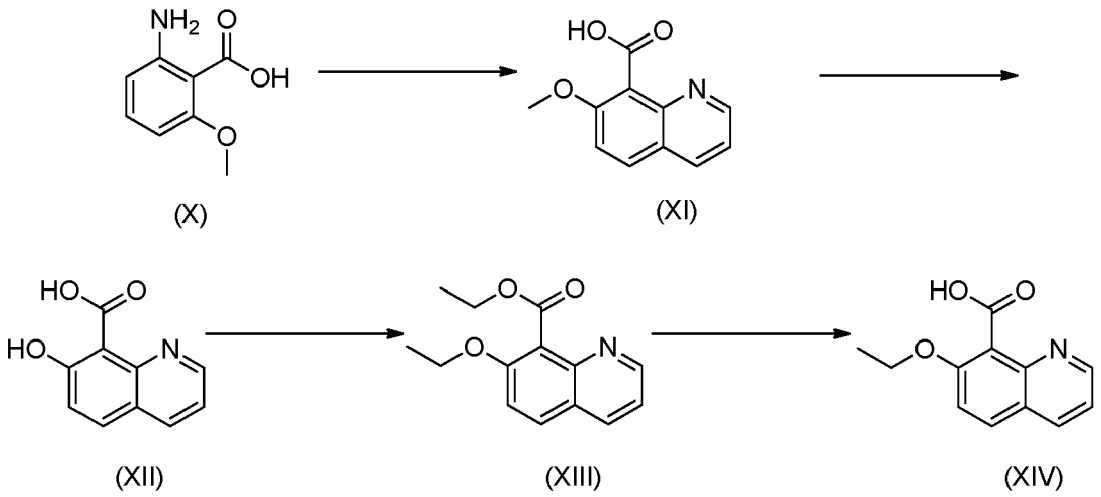
(VIII)

(IX)

[0139] Intermediate compounds of formula (IX) can be prepared as outlined in Scheme 3 from commercially available or synthetically accessible compounds of formula (VI) where R_{3A}, R_{4A} are - H, halo, -C_{1-4}alkyl, -C_{1-4}alkoxy or R_{3A} and R_{4A} together with the atoms to which they are attached form a 6- membered aryl or 6 membered heteroaryl ring, and X and Y are as defined in formula (I) as above, G is $SnBu_3$, or 4,4,5,5 tetramethyl-1,dioxaboralane, and HAL is Cl, or Br, preferably Br. Compounds of formula (VIII) are obtained by reacting a compound of formula (VI) with commercially available (VII) in the presence of a catalyst such as 1,1'-Bis(di-tert-butylphosphino)ferrocene palladium dichloride and a base such as Na_2CO_3 in a solvent such as 2-MeTHF or THF at temperatures ranging from about 60 °C to about 90 °C. Compounds of formula (IX) are obtained by reacting a compound of formula (VIII) in the presence of a base such as NaOH in a solvent such as MeOH at temperatures ranging from about 80 °C to about 100°C or acids such as H_2SO_4

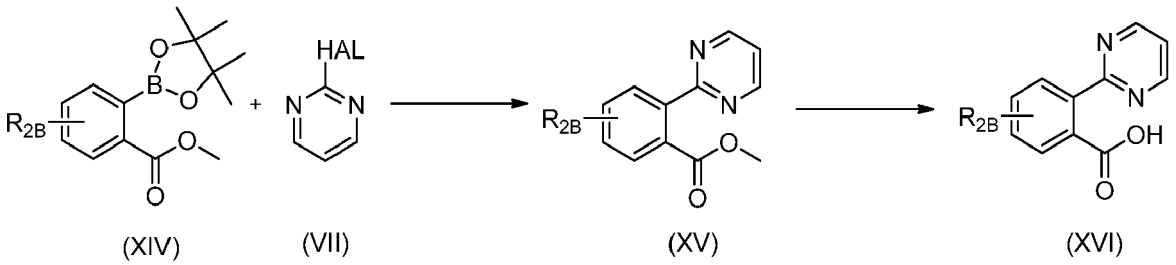
in solvents such as H_2O at temparatures ranging from about 80 °C to about 100 °C. It will be understood that the heterocycle in (VII) is not limited to pyrimidine and may be any other suitable heterocycle.

Scheme 4



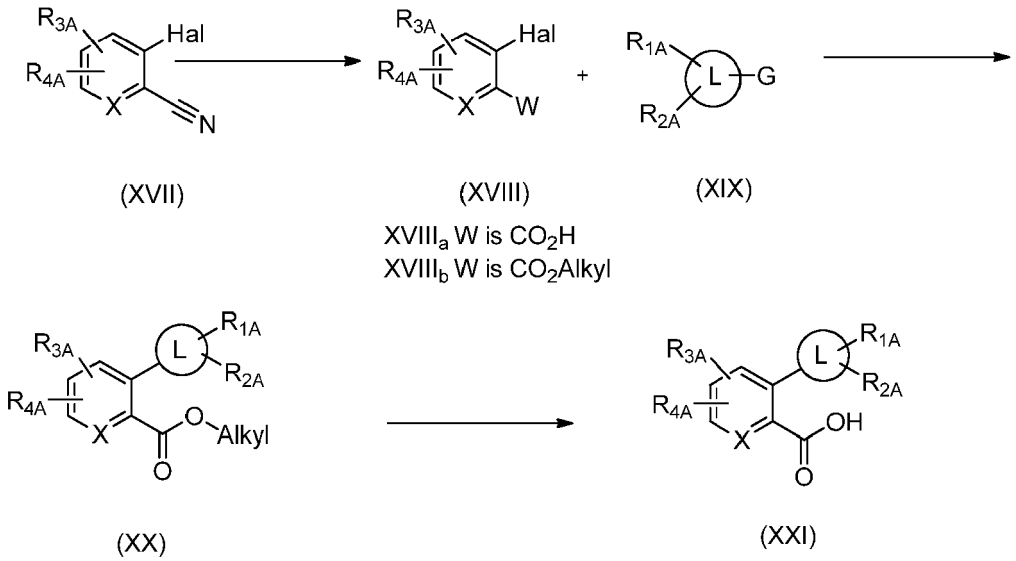
[0140] Intermediate compound of formula (XIV) can be prepared as outlined in Scheme 4 from commercially available compound (X). Compound (XI) is obtained by reacting compound (X) with commercially available acrolein in a solvent such as 1,4 dioxane at temperatures of about 200 °C in, for example, a microwave reactor. Compound (XII) can be prepared from compound (XI) by treatment with an acid such as HBr in a solvent such as toluene at a temperature of about 90 °C. Compound (XIII) can be obtained by treatment of compound (XII) with, for example, commercially available iodoethane and a base such as K_2CO_3 in a solvent such as DMF at temperatures ranging from about 45 °C to about 65 °C. Compound (XIV) is obtained by treating compound (XIII) with a base such as NaOH in a solvent such as MeOH at temperatures ranging from about 80 °C to about 100 °C.

Scheme 5



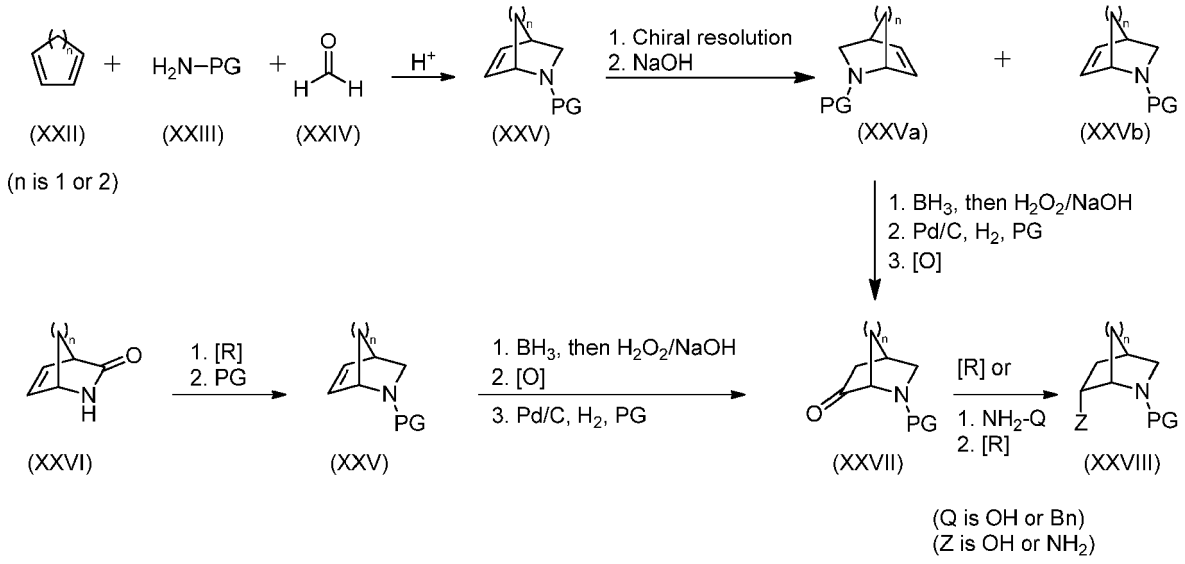
[0141] Intermediate compounds of formula (XVI) are prepared as outlined in Scheme 5 from commercially available or synthetically accessible compounds of formula (XIV) where R_{2B} is -H, - C_{1-4}alkyl, or -C_{1-4}alkoxy, or R_{2B} is -H, halo, -C_{1-4}alkyl, or -C_{1-4}alkoxy,and HAL is halo, preferably Cl, or Br. Compounds of formula (XV) are obtained by reacting a compound of formula (XIV) with commercially available (VII) in the presence of a catalyst such as $Pd(dppf)Cl_2$ and a base such as Na_2CO_3 in a solvent such as 2-MeTHF at temperatures ranging from about 75 °C to about 150 °C. Compounds of formula (XVI) are obtained by reacting a compound of formula (XV) in the presence of a base such as NaOH in a solvent such as MeOH at temperatures ranging from about 80 °C to about 100 °C. It will be understood that the heterocycle in (VII) is not limited to pyrimidine and may be any other suitable heterocycle.

Scheme 6



[0142] Intermediate compounds of formula (XXI) can be prepared as outlined in Scheme 6 from commercially available or synthetically accessible compounds of formula (XVII) where Hal is Br or I; and where R_{3A} and R_{4A} are -H, halo, -C_{1-4}alkyl, -C_{1-4}alkoxy, or R_{3A} and R_{4A} together with the atoms to which they are attached form a 6- membered aryl or 6 membered heteroaryl ring. Compounds of formula (XVIIIa) can be converted to the corresponding ester (XVIIIb) by treatment with, for example, thionyl chloride in a solvent such as MeOH. Compounds of the formula (XX) are obtained by reacting compounds of formula (XVIIIb) with commercially available compounds of the formula XIX where L is a heterocycle such as pyrazole, pyridyl, or oxazole or any other heterocycle described herein; G is $SnBu_3$ or 4,4,5,5 tetramethyl-1,dioxaboralane and R_{1A} and R_{2A} are -H, -C_{1-4}alkyl,or -C_{1-4}alkoxy, or R_{1A} and R_{2A} are -H, halo, -C_{1-4}alkyl,or -C_{1-4}alkoxy; in the presence of a catalyst such as $Pd(Ph_3P)_4$ and a base such as Na_2CO_3 in a mixture of solvents such as DME and H_2O at temperatures ranging from about 100 °C to about 150 °C. Compounds of formula (XXI) are obtained by reacting a compound of formula (XX) in the presence of a base such as NaOH in a solvent such as MeOH at temperatures ranging from about 80 °C to about 100 °C.

Scheme 7



[0143] According to Scheme 7, compound (XXV), where n is 1 or 2, is obtained by reaction of (XXII), (XXIII) where PG of H_2N-PG is H, benzyl (Bn), methyl benzyl, and the like, and (XXIV) in an aqueous medium where H^+ is HCl, AcOH and the like as described in C. Chiu et al. Synthetic Communications 1996, 26, 577-584 and S. Larsen et al. J. Am.

Chem. Soc. 1985, 107, 1768-1769. In a particularly preferred embodiment, a compound of formula (XXV), where n is 1, is obtained by reacting, for example, commercially available cyclopentadiene, (+)-α-methyl-benzylamine and formaldehyde in an aqueous medium with AcOH. Enantio-enriched compounds of formula (XXVa) and (XXVb) are obtained by chiral resolution of (XXV) using a chiral acid, such as commercially available L or D-dibenzoyl tartaric acid and the like, followed by formation of the free base using a base such as aqueous NaOH and the like, as described in C. Chiu et al. Synthetic Communications 1996, 26, 577-584. In a preferred embodiment, a compound of formula (XXV) is treated with, for example, D-dibenzoyl tartaric acid followed by a base such as aqueous NaOH to afford an enantio-enriched compound of formula (XXVa). Compound (XXVII) is obtained from (XXVa) through a hydroboration/oxidation sequence of the olefin to install the hydroxyl group; followed by, for example, an optional one-pot palladium-mediated hydrogenolysis and PG "swap" (*i.e.* methyl benzyl to Boc); and subsequent oxidation of the hydroxyl group using an oxidant such as IBX, SO_3-pyridine, Swern conditions [$(COCl)_2$, DMSO, Et_3N], and the like, in a solvent such as EtOAc, DMSO, DCM, and the like, at temperatures ranging from about -78 °C to room temperature (about 23 °C). In a preferred embodiment, a compound of formula (XXVa) where PG is methyl benzyl, is treated with, for example, BH_3 followed by H_2O_2 and NaOH to install the hydroxyl group, and, for example, a one-pot palladium mediated hydrogenolysis using hydrogen gas (1 atm), Pd/C, and Boc_2O, in EtOH at room temperature (23 °C) exchanges the methyl benzyl for a Boc group. The Boc-protected intermediate is oxidized with, for example, IBX in refluxing such as, for example, EtOAc to afford a compound of formula (XXVII). Compound (XXVb) could also be subjected to the same set of transformations as compound (XXVa) to obtain the corresponding opposite enantiomer (structure not shown).

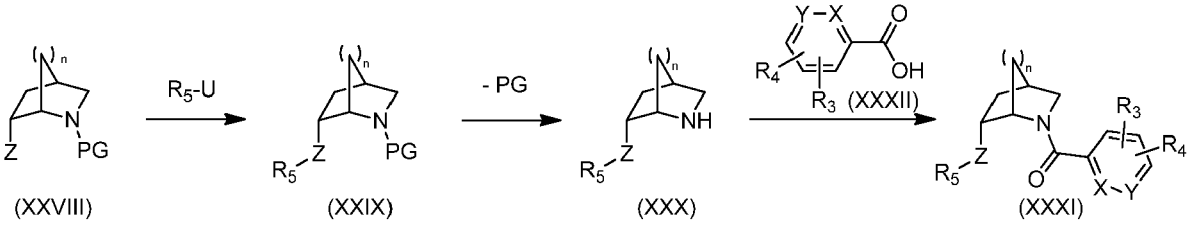
[0144] A compound of formula (XXVIII) where Z is OH, is obtained from reduction ([R]) of the ketone in a compound of formula (XXVII), with a reducing agent such as L-Selectride, $NaBH_4$ and the like, in a solvent such as THF, MeOH and the like at temperatures ranging from about -78 °C to room temperature (about 23 °C). Alternatively, the racemic form of a compound of formula (XXVIII) can be obtained from reduction of commercially available (R/S)-tert-butyl 6-oxo-2-azabicyclo[2.2.1]heptane-2-carboxylate as described in R. Nencka et al. Tetrahedron 2012, 68, 1286-1298.

[0145] An alternative route to a compound of formula (XXVII) can be prepared from commercially available (1S,4R)-2-azabicyclo[2.2.1]hept-5-en-3-one (XXVI). A compound of formula (XXV) is obtained from treatment of compound (XXVI) with a reducing agent such as $LiAlH_4$ and the like, followed by protection of the free amine with a suitable protecting group. A compound of formula (XXVII) is obtained from a compound of formula (XXV) by a hydroboration/oxidation sequence of the olefin to install the hydroxyl group; followed by oxidation of the hydroxyl group using an oxidant such as IBX, SO_3-pyridine, Swern conditions [$(COCl)_2$, DMSO, Et_3N], and the like, in a solvent such as EtOAc, DMSO, DCM, and the like at temperatures ranging from about -78 °C to room temperature (about 23 °C); and, optionally, a one-pot palladium mediated hydrogenolysis and PG "swap" (*i.e.* Bn to Boc). In a preferred embodiment, a compound of formula (XXV) where PG is Bn is subjected to the conditions described in F. Carroll et al. J. of Med. Chem. 1992, 35, 2184-2191, followed by PG swap (Bn to Boc) to obtain a compound of formula (XXVII) where PG is Boc.

[0146] A compound of formula (XXVIII) where Z is NH_2, is obtained by reacting a compound of formula (XXVII) with an amine NH_2-Q, where Q is OH or Bn, followed by reduction of the corresponding oxime or imine with a suitable reducing agent such as $NaBH_4$ (with or without a metal salt additive such as $NiCl_2$ and the like), Raney Ni (H_2 atm), $Zn(BH_4)_2$, and the like in a solvent such as MeOH and the like. In a particular embodiment, the oxime intermediate from reaction of a compound of formula (XXVII) with an amine NH_2-Q, where Q is OH, is obtained by reacting a compound of formula (XXVII) with commercially available hydroxylamine hydrochloride and triethylamine in EtOH at temperatures ranging from room temperature (about 23 °C) to reflux. The oxime intermediate is reduced with $NaBH_4$ in combination with $NiCl_2$ in MeOH to give a compound of formula (XXVIII) where Z is NH_2. Alternatively, the imine intermediate from reaction of a compound of formula (XXVII) with an amine NH_2-Q, where Q is Bn, is obtained by reacting a compound of formula (XXVII) with commercially available benzylamine. *In-situ* reduction of the imine intermediate with a reducing agent such as sodium triacetoxyborohydride and the like, followed by debenzylation under, for example, palladium mediated hydrogenolysis affords a compound of formula (XXVIII) where Z is NH_2.

[0147] Referring to Scheme 7, the synthesis of compounds wherein n is 2 is described in the Examples section, for instance in Intermediates C-1 - C-11, and in Examples 248 - 283.

Scheme 8



[0148] According to Scheme 8, a compound of formula (XXIX), where Z is O or NH, is obtained from a compound of formula (XXVIII), by a S_NAr reaction or metal mediated cross-coupling reaction with a compound R_5-U; where R_5-U is a suitable commercially available or synthetically accessible halogen-substituted heteroaryl compound, where R_5 is defined in formula (I) as above and W is F, Cl, Br, I, or OTf. A compound of formula (XXIX) where Z is O, is obtained from a compound of formula (XXVIII), where Z is OH, by S_NAr coupling with a compound R_5-W as described above, in the presence of a base, such as NaH, K_2CO_3 and the like, in a solvent such as DMF at temperatures ranging from room temperature (about 23 °C) to about 90 °C. In a preferred embodiment the base is NaH and the solvent is DMF. A compound of formula (XXIX), where Z is NH, is obtained from a compound of formula (XXVIII), where Z is NH_2, by metal mediated cross-coupling with a compound R_5-W as described above, in the presence of a palladium catalyst, a phosphine ligand such as BINAP and the like, a base such as NaOtBu and the like, in a solvent such as toluene, DME, and DMF, at temperatures ranging from room temperature (about 23 °C) to about 100 °C. In a preferred embodiment the palladium catalyst is $Pd(OAc)_2$, the ligand is BINAP, the base is NaO*t*Bu, and the solvent is toluene. Alternatively, a compound of formula (XXIX) where Z is NH, is obtained from a compound of formula (XXVIII), where Z is NH_2, by S_NAr coupling with a compound R_5-W as described above, in the presence of a base, such as NaH, K_2CO_3 in a solvent such as DMF at temperatures ranging from room temperature (about 23 °C) to about 90 °C. In a preferred embodiment the base is K_2CO_3 and the solvent is DMF. Removal of PG (where PG is Boc, Bn, methyl benzyl, and the like) in compounds of formula (XXIX) is accomplished using methods known to one skilled in the art to give compounds of formula (XXX). In a preferred embodiment, where PG is Boc in a compound of formula (XXIX) and Z is O or NH, is treated with, for example, HCl in dioxane to afford a compound of formula (XXX).

[0149] A compound of formula (XXXI) is obtained from a compound of formula (XXX), by reaction of a compound of formula (XXX) with a compound of formula (XXXII), under amide bond formation conditions. Compounds of formula (XXXII), where X, Y, R_3, and R_4 are as defined in formula (I), are commercially available, as described, or synthetically accessible appropriately substituted aryl or heteroaryl carboxylic acids or acid salts. A compound of formula (XXX), either as a free base or as an acid salt, is reacted with a compound of formula (XXXII) in the presence of a dehydrating agent such as HOBt/EDAC, CDI, HATU, HOAT, T_3P; a suitably selected base such as DIPEA, TEA; in an organic solvent or mixture thereof, such as toluene, MeCN, EtOAc, DMF, THF, DCM to afford a compound of formula (XXXI). In a particularly preferred embodiment a compound of formula (XXXI) is obtained using, for example, the dehydrating agent HATU, the base DIPEA, and the solvent DMF; or the dehydrating agent T_3P, the base Et_3N, and the solvent mixture of DCM/DMF. Alternatively, one skilled in the art can transform a compound of formula (XXXII) to the corresponding acid chloride or an activated ester before amide formation with a compound of formula (XXX).

[0150] Referring to Scheme 8, the synthesis of compounds wherein n is 2 is described in the Examples section, for instance in Intermediates C-1 - C-11, and in Examples 248-283.

[0151] In one group of embodiments, provided herein is a compound of Formula I of Examples 1-84 with structures and names as set forth in the Examples section. In another group of embodiments, provided herein is a compound of Formula I of Examples 1-4, 7-92, 94-204, 206, 208-660 with structures and names as set forth in the Examples section below. In yet another embodiment, provided herein is a compound of Formula I of Examples 85-92, 94-204, 206, 208-660 with structures and names as set forth in the Examples section below. In one group of embodiments, provided herein is a compound of Formula IA selected from Examples 5, 6, 93, 205, and 207 having the structures and names as set forth in the Examples section below. In one group of embodiments, provided herein is a compound of Formula I or Formula IA having structures and names as set forth in Table 2 below.

EXAMPLES

Abbreviations:

[0152]

Term	Acronym
Acetic Acid	HOAc
Acetonitrile	ACN
Apparent	app
Aqueous	aq
Atmosphere	atm
2-(1H-9-Azobenzotriazole-1-yl)-1,1,3,3-tetramethylaminium hexafluorophosphate	HATU
Benzyl	Bn
2,2' -bis(diphenylphosphino)-1,1' -binaphthalene	BINAP
[1,1'-Bis(di-*tert*-butylphosphino)ferrocene]dichloropalladium(II)	$PdCl_2$(dtbpf)
Broad	br
tert-Butylcarbamoyl	Boc/Boc
Dichloromethane	DCM
Diisopropylethylamine	DIPEA
1,2-Dimethoxyethane	DME
N,N-Dimethylformamide	DMF
Dimethylsulfoxide	DMSO
Doublet	d
Electrospray ionization	ESI
Enantiomeric excess	ee
Ethanol	EtOH
Ethyl Acetate	EtOAc, or EA
Grams	g
Hertz	Hz
High-pressure liquid chromatography	HPLC
Hours	h
Liquid chromatography and mass spectrometry	LCMS
Mass spectrometry	MS
Mass to charge ratio	m/z
Methanol	MeOH
Microliter	μL
Milligrams	mg
Milliliter	mL
Millimoles	mmol
Minute	min
Molar	M

(continued)

Term	Acronym
Multiplet	m
Normal	N
Nuclear magnetic resonance	NMR
Palladium on carbon	Pd/C
Palladium hydroxide on carbon	$Pd(OH)_2/C$
Parts per million	ppm
Phenyl	Ph
Propylphosphonic anhydride	T_3P
Retention time	R_t
Room temperature	rt
Quartet	q
Singlet	S
Supercritical Fluid Chromatography	SFC
Temperature	T
Thin layer chromatography	TLC
Times	X
Triethylamine	TEA
Trifluoroacetic acid	TFA
Triplet	t

Chemistry:

[0153] In obtaining the compounds described in the examples below and the corresponding analytical data, the following experimental and analytical protocols were followed unless otherwise indicated.

[0154] Unless otherwise stated, reaction mixtures were magnetically stirred at room temperature (rt) under a nitrogen atmosphere. Where solutions were "dried," they were generally dried over a drying agent such as Na_2SO_4 or $MgSO_4$. Where mixtures, solutions, and extracts were "concentrated", they were typically concentrated on a rotary evaporator under reduced pressure. Reactions under microwave irradiation conditions were carried out in a Biotage Initiator or CEM Discover instrument.

[0155] Where compounds were "purified via silica gel chromatography" normal-phase flash column chromatography was performed on silica gel (SiO_2) using prepackaged cartridges, eluting with the indicated solvents.

[0156] Where compounds were purified by "Shimadzu Method X" the method employed was either:

Preparative reverse-phase high performance liquid chromatography (HPLC) was performed on a Shimadzu LC-8A Series HPLC with an Inertsil ODS-3 column (3 μm, 30 × 100mm, T = 45 °C), mobile phase of 5% ACN in H_2O (both with 0.05% TFA) was held for 1 min, then a gradient of 5-99% ACN over 6 min, then held at 99% ACN for 3 min, with a flow rate of 80 mL/min.

or

Preparative reverse-phase high performance liquid chromatography (HPLC) was performed on a Shimadzu LC-8A Series HPLC with an XBridge C18 OBD column (5 μm, 50 × 100mm), mobile phase of 5% ACN in H_2O (both with 0.05% TFA) was held for 1 min, then a gradient of 5-99% ACN over 14 min, then held at 99% ACN for 10 min, with a flow rate of 80 mL/min.

[0157] Where compounds were purified by "Agilent Prep Method X" the method employed was either:

Preparative reverse-phase high performance liquid chromatography (HPLC) was performed on a Agilent 1100 Series HPLC with an XBridge C18 OBD column (5 μm, 30 × 100mm), mobile phase of 5% ACN in 20mM NH_4OH was held for 2 min, then a gradient of 5-99% ACN over 15 min, then held at 99% ACN for 5 min, with a flow rate of 40 mL/min. or

Preparative reverse-phase high performance liquid chromatography (HPLC) was performed on a Agilent 1100 Series HPLC with an XBridge C18 OBD column (5 μm, 50 × 100mm), mobile phase of 5% ACN in 20mM NH_4OH was held for 2min, then a gradient of 5-99% ACN over 15 min, then held at 99% ACN for 5 min, with a flow rate of 80 mL/min.

[0158] Where compounds were purified by "Gilson Prep Method X" the method employed was: Preparative reverse-phase high performance liquid chromatography (HPLC) was performed on a Gilson HPLC with an XBridge C18 column (5μm, 100 × 50mm), mobile phase of 5-99% ACN in 20 mM NH_4OH over 10 min and then hold at 99 ACN for 2 min, at a flow rate of 80 mL/min.

[0159] Mass spectra (MS) were obtained on an Agilent series 1100 MSD using electrospray ionization (ESI) in positive mode unless otherwise indicated. Calculated (calcd.) mass corresponds to the exact mass.

[0160] Where acids are employed for amide bond coupling the free acid or acid salt may be used interchangeably.

[0161] Nuclear magnetic resonance (NMR) spectra were obtained on Bruker model DRX spectrometers. The format of the ^1H NMR data below is: chemical shift in ppm downfield of the tetramethylsilane reference (multiplicity, coupling constant J in Hz, integration). Definitions for multiplicity are as follows: s = singlet, d = doublet, t= triplet, q = quartet, m = multiplet, br = broad. For compounds that are present as a mixture of rotamers the ratio is represented so that the total is 1, e.g. 0.80:0.20. Alternatively, ^1H NMR data may be reported for only the major rotamer as indicated, or the data may be reported for one or more rotamers such that the total is less than 1. It will be understood that for compounds comprising an exchangeable proton, said proton may or may not be visible on an NMR spectrum depending on the choice of solvent used for running the NMR spectrum and the concentration of the compound in the solution.

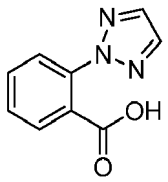
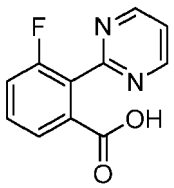
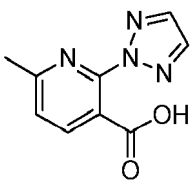
[0162] Chemical names were generated using ChemDraw Ultra 12.0 (CambridgeSoft Corp., Cambridge, MA) or ACD/Name Version 10.01 (Advanced Chemistry).

[0163] Compounds designated (R/S) are racemic compounds where the relative stereochemistry is as drawn.

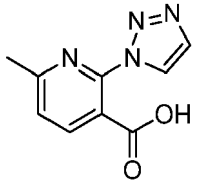
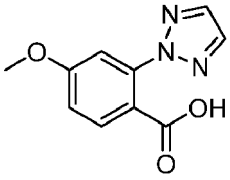
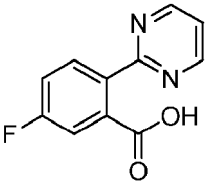
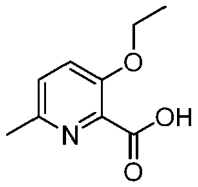
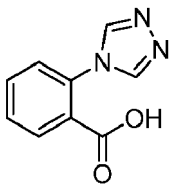
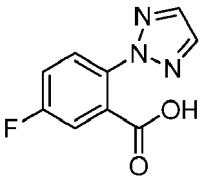
[0164] Examples 63-65, 68-72, 75, 78-79, 81-82, 84, 164-165, 303-419, 421-660 are suitable for preparation using methods analogous to the methods described in the synthetic schemes and in the Examples section.

INTERMEDIATES

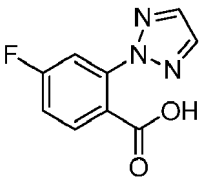
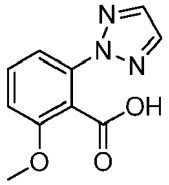
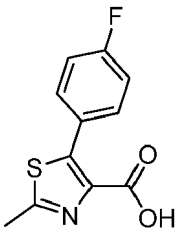
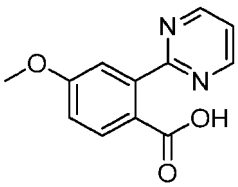
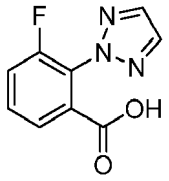
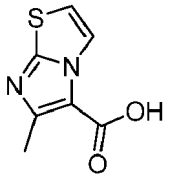
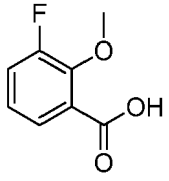
[0165]

Intermediate	Name	Structure	Reference
A-1	2-(2H-1,2,3-triazol-2-yl)benzoic acid		Prepared according to WO 2011/050198 Intermediate 2
A-2	3-fluoro-2-(pyrimidin-2-yl) benzoic acid		Prepared according to WO 2011/050198 Intermediate 50
A-3	6-methyl-2-(2H-1,2,3-triazol-2-yl)nicotinic acid		Prepared according to WO 2011/050198 Intemediate 70

(continued)

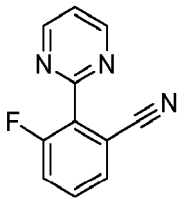
Intermediate	Name	Structure	Reference
A-4	6-methyl-2-(1H-1,2,3-triazol-1-yl)nicotinic acid		Prepared according to WO 2011/050198 Intemediate 71
A-5	4-methoxy-2-(2H-1,2,3-triazol-2-yl)benzoic acid		Prepared according to WO 2011/050198 Intemediate 54
A-6	2-fluoro-6-(pyrimidin-2-yl) benzoic acid		Prepared according to WO 2011/050198 Intermediate 14
A-7	5-fluoro-2-(pyrimidin-2-yl) benzoic acid.		Prepared according to WO 2011/050198 Intermediate 13
A-8	3-ethoxy-6-methylpicolinic acid		WO 2010/063663 Description 39
A-9	2-(4H-1,2,4-triazol-4-yl)benzoic acid		Commercially available, CAS 167626-65-5
A-10	5-fluoro-2-(2H-1,2,3-triazol-2-yl)benzoic acid		Prepared according to WO 2011/050198 Intermediate 1
A-11	2-fluoro-6-(2H-1,2,3-triazol-2-yl)benzoic acid		Prepared according to WO 2011/050198 Intermediate 12

(continued)

Intermediate	Name	Structure	Reference
A-12	4-fluoro-2-(2H-1,2,3-triazol-2-yl)benzoic acid		Prepared according to WO 2011/050198 Intermediate 4
A-13	2-methoxy-6-(2H-1,2,3-triazol-2-yl)benzoic acid		Prepared analogous to Intermediate A-X using 2-bromo-6-(2H-1,2,3-triazol-2-yl)benzoic acid
A-14	5-(4-fluorophenyl)-2-methylthiazole-4-carboxylic acid		Commercially available, CAS 433283-22-8
A-15	4-methoxy-2-(pyrimidin-2-yl) benzoic acid		Prepared according to WO 2011/050198 Intermediate 88
A-16	3-fluoro-2-(2H-1,2,3-triazol-2-yl)benzoic acid		Prepared according to WO 2011/050198 Intermediate 5
A-17	6-methylimidazo[2,1-b] thiazole-5-carboxylic acid		Commercially available, CAS 77628-51-4
A-18	3-fluoro-2-methoxybenzoic acid		Commercially available, CAS 106428-05-1

Synthesis of 3-fluoro-2-(pyrimidin-2-yl)benzonitrile (Intermediate in the synthesis of intermediate A-2)

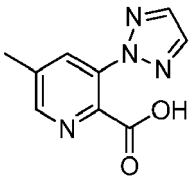
[0166]



[0167] To a solution of 3-fluoro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (4.98 g, 19.1 mmol) and 2-bromopyrimidine (3.85 g, 23 mmol) in THF (96 mL) was added Na_2CO_3 (6 g, 57.4 mmol) followed by water (43 mL). The reaction mixture was degassed with N_2 for 10 minutes. $PdCl_2$(dtbpf) (374 mg, 0.57 mmol) was added and the reaction mixture was stirred at 80 °C for 5h. The solution was cooled to room temperature and a mixture of EtOAc and water was added. The aqueous was extracted twice with EtOAc and the combined organic layers were dried over MgSO4, filtered and evaporated. The title compound was precipitated by dissolving the residue in a minimum amount of EtOAc and then adding hexanes. The solid was filtered, washed with hexanes and dried to afford the title compound (2.46 g, 64%). MS (ESI) mass calcd. for $C_{11}H_6FN_3$, 199.1; m/z found 200.1 $[M+H]^+$. ^{1}H NMR (400 MHz, Chloroform-d) δ 9.02 - 8.91 (m, 2H), 7.65 (dt, *J* = 7.7, 1.0 Hz, 1H), 7.60 - 7.52 (m, 1H), 7.51 - 7.43 (m, 1H), 7.41 (t, *J* = 4.9 Hz, 1H).

Intermediate A-19: 5-methyl-3-(2H-1,2,3-triazol-2-yl)picolinic acid.

[0168]

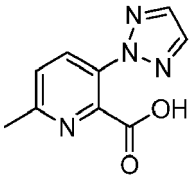


[0169] Step A: 5-methyl-3-(2H-1,2,3-triazol-2-yl)picolinonitrile. To 3-bromo-5-methylpicolinic acid (1.5 g, 7.6 mmol) in DMF (19 mL) was added K_2CO_3 (1.2 g, 8.4 mmol) and 2H-1,2,3-triazole (440 μL, 7.6 mmol). The mixture was heated to 100 °C for 16 h, cooled to room temperature and extracted with EtOAc (2X). The combined organics were dried (Na_2SO_4) and concentrated. Purification via silica gel chromatography (5-60% EtOAc in hexanes) gave the title compound (490 mg, 35%) ^{1}H NMR (500 MHz, Chloroform-d) 8.58 - 8.53 (m, 1H), 8.29 - 8.24 (m, 1H), 7.98 (s, 2H), 2.54 (s, 3H) and 5-methyl-3-(1H-1,2,3-triazol-1-yl)picolinonitrile (387 mg, 27%).

[0170] Step B: (sodium 5-methyl-3-(2H-1,2,3-triazol-2-yl)picolinate). To a solution of the title compound of Step A (489 mg, 2.6 mmol) in EtOH (7 mL) was added 4 N NaOH (660 μL, 2.6 mmol). The mixture was heated at 100°C for 24 h. The reaction mixture was concentrated in vacuo to a white solid which was used without further purification in subsequent steps. MS (ESI) mass calcd. for $C_9H_8N_4O_2$, 204.1; m/z found 205.0 $[M+H]^+$.

Intermediate A-20: 6-methyl-3-(2H-1,2,3-triazol-2-yl)picolinic acid.

[0171]



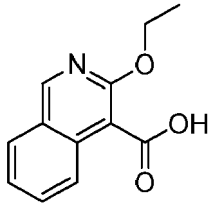
[0172] Step A: 6-methyl-3-(2H-1,2,3-triazol-2-yl)picolinonitrile. To 3-bromo-6-methylpicolinonitrile (2.2 g, 11 mmol) in DMF (28 mL) was added K_2CO_3 (1.7 g, 12 mmol) and 2H-1,2,3-triazole (650 μL, 11 mmol). The mixture was heated to 100 °C for 36 h, cooled to rt and extracted with EtOAc. The combined organics were dried (Na_2SO_4) and concentrated. Purification via silica gel chromatography (10-100% EtOAc in hexanes) gave the title compound (1 g, 48%).

[0173] Step B: 6-methyl-3-(2H-1,2,3-triazol-2-yl)picolinic acid. To a solution of the title compound of Step A (730 mg, 4 mmol) in EtOH (10 mL) was added 4 N NaOH (1 mL, 4 mmol). The mixture was heated at 100°C for 24 h. The reaction mixture was concentrated in vacuo to a white solid which was used without further purification in subsequent steps. MS

(ESI) mass calcd. for $C_9H_8N_4O_2$, 204.1; m/z found 205.1 $[M+H]^+$.

Intermediate A-21: 3-ethoxyisoquinoline-4-carboxylic acid.

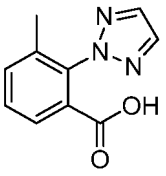
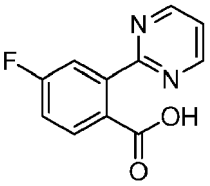
[0174]



[0175] Step A: ethyl 3-hydroxyisoquinoline-4-carboxylate. To a suspension of ethyl 3-aminoisoquinoline-4-carboxylate (583 mg, 2.70 mmol) in 6.8 mL of H_2SO_4 5N cooled to 0 °C was added sodium nitrite (223 mg, 3.24 mmol, dissolved in 1 mL of water). The reaction mixture was stirred at 0 °C for 2.5 h and then $NaOH_{(aq)}$ 1N was added until pH=7. The aqueous phase was extracted twice with DCM and the combined organic phases were dried over $MgSO_4$, filtered and evaporated to give the title compound of Step A which was used without further purification in the next step (583 mg, 99%). MS (ESI) mass calcd. for $C_{12}H_{11}NO_3$, 217.1; m/z found 218.1 $[M+H]^+$.

[0176] Step B: ethyl 3-ethoxyisoquinoline-4-carboxylate. To the title compound of Step A (583 mg, 2.68 mmol) in THF (13 mL) was added triphenylphosphine (1.06 g, 4.03 mmol), ethanol (0.24 mL, 4.03 mmol) and DIAD (0.79 mL, 4.03 mmol). The reaction mixture was stirred at room temperature for 16h and then the solvent was evaporated. The crude was purified via silica gel chromatography (0-30% EtOAc in hexanes) to afford the title compound of Step B (498 mg, 76%). MS (ESI) mass calcd. for $C_{14}H_{15}NO_3$, 245.1; m/z found 246.1 $[M+H]^+$. ^1H NMR (500 MHz, Chloroform-d) δ 8.97 (s, 1H), 7.91 - 7.82 (m, 2H), 7.65 - 7.60 (m, 1H), 7.42 - 7.36 (m, 1H), 4.59 - 4.48 (m, 4H), 1.48 - 1.39 (m, 6H).

[0177] Step C: 3-ethoxyisoquinoline-4-carboxylic acid. The title compound of Step B (492 mg, 2 mmol) dissolved in MeOH (15 mL) was added $NaOH_{(aq)}$ 2M (2.5 mL). The reaction mixture was stirred at 60 °C for 16h and then $NaOH_{(aq)}$ 4M (2 mL) was added and the mixture was stirred at 70 °C for 4h. MeOH was evaporated and the aqueous phase was cooled to 0 °C and acidified with the addition of $HCl_{(aq)}$ 6N. The solid was filtered, washed with cold water and dried to afford the title compound (285 mg, 65%). MS (ESI) mass calcd. for $C_{12}H_{11}NO_3$, 217.1; m/z found 218.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6) δ 13.36 (s, 1H), 9.15 (s, 1H), 8.13 - 8.06 (m, 1H), 7.82 - 7.70 (m, 2H), 7.54 - 7.47 (m, 1H), 4.50 (q, *J* = 7.0 Hz, 2H), 1.35 (t, *J* = 7.0 Hz, 3H).

Intermediate	Name	Structure	Reference
A-22	3-methyl-2-(2H-1,2,3-triazol-2-yl) benzoic acid		Prepared according to WO 2011/050198 Intermediate 82
A-23	4-fluoro-2-(pyrimidin-2-yl)benzoic acid		Prepared according to WO 2011/050198 Intermediate 87

Intermediate A-24: 2-methoxy-6-(pyrimidin-2-yl)benzoic acid

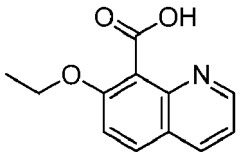
[0178]

[0179] Step A: Methyl 2-methoxy-6-(pyrimidin-2-yl)benzoate. In a microwave vial was dissolved methyl 2-methoxy-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (CAS 1146214-77-8) (500 mg, 1.71 mmol) and 2-bromopyrimidine (344 mg, 2.05 mmol) in THF (8.5 mL). Na_2CO_3 (544 mg, 5.14 mmol) was then added followed by water (4 mL) and the reaction mixture was degassed with N_2 for 10 minutes. $PdCl_2$(dtbpf) (CAS 95408-45-0) (45 mg, 0.069 mmol) was then added and the reaction mixture was heated at 80 °C for 4 h. The mixture was cooled to room temperature and water and EtOAc added. The reaction mixture was extracted with EtOAc (3X). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude was purified via silica gel chromatography (0-70% EtOAc in hexanes) to afford the title compound (265 mg, 63%). MS (ESI) mass calcd. for $C_{13}H_{12}N_2O_3$, 244.1; m/z found 245.1 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d) δ 8.78 (d, J = 4.9 Hz, 2H), 7.99 (dd, J = 7.9, 0.9 Hz, 1H), 7.49 (t, J = 8.1 Hz, 1H), 7.19 (t, J = 4.8 Hz, 1H), 7.09 (dd, J = 8.3, 0.9 Hz, 1H), 3.90 (s, 3H), 3.89 (s, 3H).

[0180] Step B: 2-methoxy-6-(pyrimidin-2-yl)benzoic acid. To a solution of the title compound of Step A (265 mg, 1.09 mmol) in THF (4 mL) was added 2 M NaOH (2 mL). The mixture was heated at 50°C for 72 h. The reaction mixture was cooled to room temperature and concentrated in vacuo to remove THF. Then, 1 M $HCl_{(aq)}$ was added and the aqueous was extracted with 10:1 DCM/2,2,2-trifluoroethanol (3X). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to give intermediate A-24, which was used without further purification in subsequent steps. MS (ESI) mass calcd. for $C_{12}H_{10}N_2O_3$, 230.1; m/z found 231.1 $[M+H]^+$. ^1H NMR (500 MHz, DMSO-d_6) δ 12.63 (s, 1H), 8.86 (d, J = 4.9 Hz, 2H), 7.77 (dd, J = 7.9, 1.0 Hz, 1H), 7.51 (t, J = 8.1 Hz, 1H), 7.45 (t, J = 4.9 Hz, 1H), 7.25 (dd, J = 8.4, 1.0 Hz, 1H), 3.83 (s, 3H).

Intermediate A-25: 7-ethoxyquinoline-8-carboxylic acid

[0181]



[0182] Step A: 7-methoxyquinoline-8-carboxylic acid. In separate batches (1 g) a mixture of 2-amino-6-methoxybenzoic acid (11 g, 66 mmol) and acrolein (4.8 mL, 72 mmol) in 1,4-dioxane (66 mL) was heated in a microwave reactor for 20 min at 200 °C. After combining the reactions, the mixture was concentrated and purified via silica gel chromatography (0-10% MeOH in DCM) to give the title compound (2.8 g, 20%). MS (ESI) mass calcd. for $C_{11}H_{19}NO_3$, 203.1; m/z found 204.0 $[M+H]^+$.

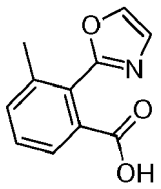
[0183] Step B: 7-hydroxyquinoline-8-carboxylic acid. The title compound of Step A (2.9 g, 14.1 mmol) in HBr (14 mL) was heated at 90 °C for 1 h. The mixture was then concentrated washed with $PhCH_3$ and used without further purification in subsequent steps.

[0184] Step C: ethyl 7-ethoxyquinoline-8-carboxylate. To the title compound of Step B (800 mg, 3.9 mmol) and K_2CO_3 (1.4 g, 10.4 mmol) in DMF (15 mL) was added iodoethane (560 mL, 6.9 mmol). After stirring overnight at room temperature, the reaction was concentrated and purified via silica gel chromatography (0-30% EtOAc in hexanes) to give the title compound. MS (ESI) mass calcd. for $C_{14}H_{15}NO_3$, 245.1; m/z found 246.0 $[M+H]^+$.

[0185] Step D: 7-ethoxyquinoline-8-carboxylic acid. To the title compound of Step C (1.3 g, 5.4 mmol) in THF (22 mL) and H_2O (11 mL) was added LiOH hydrate (675 mg, 16.5 mmol) and MeOH. The mixture was heated at 67 °C for 12 h. Additional LiOH hydrate (675 mg, 16.5 mmol) was added and the heating was continued at 70 °C for 1 day. Additional LiOH hydrate (1.4 g, 33 mmol) was added and the heating was continued at 75 °C for 1 day. The reaction was allowed to cool to room temperature, acidified to pH=3 with 1 N $HCl_{(aq)}$ and concentrated. Purification via prep HPLC gave the title compound (1 g, 84%). MS (ESI) mass calcd. for $C_{12}H_{11}NO_3$, 217.1; m/z found 218.0 $[M+H]^+$.

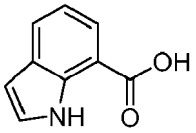
Intermediate A-27: 3-methyl-2-(oxazol-2-yl)benzoic acid

[0186]



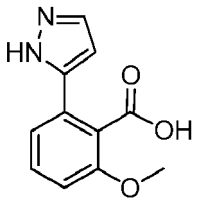
[0187] Step A: ethyl 3-methyl-2-(oxazol-2-yl)benzoate. In a microwave vial was dissolved ethyl 2-iodo-3-methylbenzoate (627 mg, 2.16 mmol) and 2-(tributylstannyl)oxazole (0.54 mL, 0.07 mmol) in DME (2.59 mL). The solution was degassed with N_2 for 5 minutes then CuI (21 mg, 0.11 mmol) and $Pd(PPh_3)_4$ (125 mg, 0.11 mmol) were added. The reaction was purged with N_2 and heated at 150 °C for 1 h. The reaction was cooled to room temperature, filtered through a pad of Celite and purified via silica gel chromatography (0-40% EtOAc in hexanes) to give the title compound of step A (333 mg, 67%). MS (ESI) mass calcd. for $C_{13}H_{13}NO_3$, 231.1; m/z found 232.1 $[M+H]^+$. ^1H NMR (500 MHz, Chloroform-d) δ 7.89 - 7.82 (m, 1H), 7.79 (d, *J* = 0.8 Hz, 1H), 7.48 - 7.43 (m, 2H), 7.30 (d, *J* = 0.9 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 2.27 (s, 3H), 1.18 (t, *J* = 7.1 Hz, 3H).

[0188] Step B: 3-methyl-2-(oxazol-2-yl)benzoic acid. To the title compound of step A (166 mg, 0.72 mmol) was added MeOH (7.2 mL) and 1M $NaOH_{(aq)}$ (7.2 mL). MeOH was evaporated and then 1 M $HCl_{(aq)}$ was added. To the solution was added DCM and the aqueous was extracted with DCM (3X). The combined organic layers were dried over $MgSO_4$, filtered and evaporated to give the title compound (145 mg). MS (ESI) mass calcd. for $C_{11}H_9NO_3$, 203.1; m/z found 204.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.20 (s, 1H), 7.79 - 7.68 (m, 1H), 7.65 - 7.49 (m, 2H), 7.35 (s, 1H), 4.34 (s, 1H), 2.20 (s, 3H).

Intermediate	Name	Structure	Reference
A-28	3-(2H-1,2,3-triazol-2-yl) picolinic acid		Prepared according to WO 2011/050198 Intermediate 72
A-29	1H-indole-7-carboxylic acid		Commercially available, CAS 1670-83-3

Intermediate A-30: 2-methoxy-6-(1H-pyrazol-5-yl)benzoic acid

[0189]



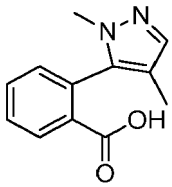
[0190] Step A: Ethyl 2-methoxy-6-(1H-pyrazol-5-yl)benzoate. In a microwave vial was dissolved ethyl 2-bromo-6-methoxybenzoate (500 mg, 1.54 mmol) and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (330 mg, 1.70 mmol) in DME (10 mL) and water (2 mL). Na_2CO_2 (259 mg, 3.09 mmol) was then added followed by $Pd(PPh_3)_4$ (89 mg, 0.077 mmol) and the reaction mixture was degassed with N_2 for 10 minutes. The reaction mixture was then heated at 100 °C for 1 h in the microwave. The mixture was cooled to room temperature, filtered through Celite and washed with

EtOAc and DCM. The crude solution was concentrated in vacuo and directly purified via silica gel chromatography (10-80% EtOAc in hexanes) to afford the title compound (125 mg, 33%). MS (ESI) mass calcd. for $C_{13}H_{14}N_2O_3$, 246.3; m/z found 247.1 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d) δ 7.63 (d, J = 2.2 Hz, 1H), 7.44 - 7.37 (m, 1H), 7.24 (d, J = 8.1 Hz, 1H), 6.94 (dd, J = 8.3, 0.9 Hz, 1H), 6.53 (d, J = 2.3 Hz, 1H), 4.29 (q, J = 7.2 Hz, 2H), 3.88 (s, 3H), 1.25 - 1.16 (m, 3H).

[0191] Step B: 2-methoxy-6-(1H-pyrazol-5-yl)benzoic acid. Prepared analogous to intermediate A-24 step B to give title compound. MS (ESI) mass calcd. for $C_{11}H_{10}N_2O_3$, 218.1; m/z found 219.1 $[M+H]^+$. ^1H NMR (500 MHz, DMSO-d_6) δ 12.85 (br. s, 1H), 7.71 (d, J = 2.2 Hz, 1H), 7.39 (t, J = 8.0 Hz, 1H), 7.35 - 7.28 (m, 1H), 7.04 (dd, J = 8.3, 1.0 Hz, 1H), 6.51 (d, J = 2.3 Hz, 1H), 3.80 (s, 3H).

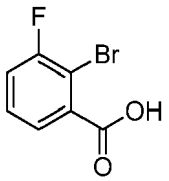
Intermediate A-31: 2-(1,4-dimethyl-1H-pyrazol-5-yl)benzoic acid

[0192]



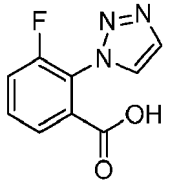
[0193] Step A: Methyl 2-(1,4-dimethyl-1H-pyrazol-5-yl)benzoate. Prepared analogous to intermediate A-30 step A to give title compound. MS (ESI) mass calcd. for $C_{13}H_{14}N_2O_2$, 230.1; m/z found 231.1 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d) δ 8.04 (dd, J = 7.8, 1.5 Hz, 1H), 7.61 (td, J = 7.5, 1.5 Hz, 1H), 7.53 (td, J = 7.7, 1.4 Hz, 1H), 7.35 (s, 1H), 7.28 (dd, J = 7.6, 1.4 Hz, 1H), 3.71 (s, 3H), 3.58 (s, 3H), 1.84 (s, 3H).

[0194] Step B: 2-(1,4-dimethyl-1H-pyrazol-5-yl)benzoic acid. To a solution of the title compound of Step A (680 mg, 2.95 mmol) in MeOH (15 mL) was added 4 M LiOH (4 mL). The mixture was heated at 50°C overnight. MeOH was removed and HCl added until pH=2. White solids precipitated from the reaction mixture and the precipitate was filtered, washed with EtOAc and collected to give intermediate A-31, which was used without further purification in subsequent steps. MS (ESI) mass calcd. for $C_{12}H_{12}N_2O_2$, 216.1; m/z found 217.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 12.87 (s, 1H), 7.95 (dd, J = 7.8, 1.5 Hz, 1H), 7.67 (td, J = 7.5, 1.5 Hz, 1H), 7.59 (td, J = 7.6, 1.4 Hz, 1H), 7.33 (dd, J = 7.6, 1.4 Hz, 1H), 7.25 (s, 1H), 3.48 (s, 3H), 1.77 (s, 3H).

Intermediate	Name	Structure	Reference
A-33	2-bromo-3-fluorobenzoic acid		Commercially available, CAS 132715-69-6

Intermediate A-33: 3-fluoro-2-(1H-1,2,3-triazol-1-yl)benzoic acid

[0195]

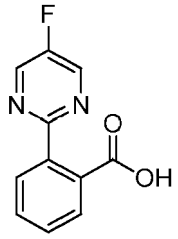


[0196] To 3-fluoro-2-iodobenzoic acid (4.5 g, 16.9 mmol) dissolved in dioxane (33.8 mL) and H_2O (0.09 mL) was added Cs_2CO_3 (11.02 g, 33.8 mmol), CuI (161 mg, 0.85 mmol), 2H-1,2,3-triazole (1.96 mL, 33.8 mmol), and trans-N,N-dimethyl-1,2-cyclohexanediamine (0.53 mL, 3.38 mmol). The mixture was then heated to 100 °C overnight, cooled to room temperature, diluted with H_2O, and extracted with EtOAc. The aqueous layer was then acidified and extracted with EtOAc. The combined organics were dried and concentrated. From this concentrate a solid precipitated to provide

intermediate A-33 (285 mg, 8%). MS (ESI) mass calcd for $C_9H_6FN_3O_2$, 207.0; m/z found 208.1 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4) δ 6.81 - 6.77 (m, 1H), 6.46 - 6.40 (m, 2H), 6.30 - 6.23 (m, 1H), 6.18 - 6.12 (m, 1H).

Intermediate A-34: 2-(5-fluoropyrimidin-2-yl)benzoic acid.

[0197]



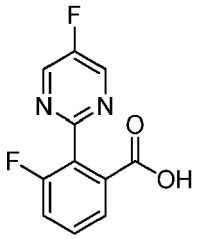
[0198] Step A: 5-fluoro-2-iodopyrimidine. To a solution of 2-chloro-5-fluoropyrimidine (4 mL, 32 mmol) in propionitrile (33 mL) was added chlorotrimethylsilane (12 mL, 97 mmol) and sodium iodide (15 g, 97 mmol), and the reaction mixture was heated to 150 °C for 1 h. Upon completion of the reaction, the reaction mixture was cooled to room temperature and the solvent removed. The residue was taken up in EtOAc and a solution of saturated $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered and evaporated. Purification via silica gel chromatography (0-20% EtOAc in hexanes) gave the title compound (2.82 g, 39%).

[0199] Step B: 2-(5-fluoropyrimidin-2-yl)benzonitrile. In a microwave vial was dissolved 2-cyanophenylboronic acid (500 mg, 3.40 mmol) in THF (15 mL), and the reaction mixture was degassed with N_2. Then, the title compound of step A (915 mg, 4.08 mmol), Na_2CO_3 (1.08 g, 10.2 mmol), water (5 mL), and $PdCl_2$(dtbpf) (CAS 95408-45-0) (89 mg, 0.14 mmol) were added, and the reaction mixture was stirred at room temperature for 1 h and then heated via microwave heating to 75 °C for 2 h. The mixture was cooled to room temperature and water and EtOAc added. The reaction mixture was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude was purified via silica gel chromatography (0-30% EtOAc in hexanes) to afford the title compound (280 mg, 41%). MS (ESI) mass calcd. for $C_{11}H_6FN_3$, 199.1; m/z found 200.0 $[M+H]^+$.

[0200] Step C: 2-(5-fluoropyrimidin-2-yl)benzoic acid. A solution of the title compound of step B (1.24 g, 6.22 mmol) in H_2SO_4 (6 mL) and water (6 mL) was stirred at 80 °C for 1 h. Then, the reaction mixture was cooled to 0 °C and the aqueous phase extracted with DCM (2X). A solution of 20 M NaOH (11 mL) was added to the aqueous layer until pH ~3-4. The aqueous layer was extracted again with EtOAc and DCM. The combined organic layers were dried over $MgSO_4$, filtered and concentrated to afford the title compound (672 mg, 50%). MS (ESI) mass calcd. for $C_{11}H_7FN_2O_2$, 218.1; m/z found 219.1 $[M+H]^+$.

Intermediate A-35: 3-fluoro-2-(5-fluoropyrimidin-2-yl)benzoic acid.

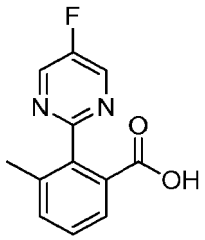
[0201]



[0202] Prepared analogous to Intermediate A-34, substituting 2-cyanophenylboronic acid with (2-cyano-6-fluorophenyl)boronic acid (CAS 656235-44-8). MS (ESI) mass calcd. for $C_{11}H_6F_2N_2O_2$, 236.0; m/z found 237.1 $[M+H]^+$.

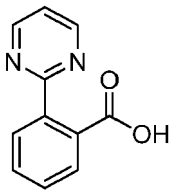
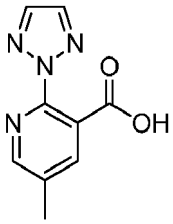
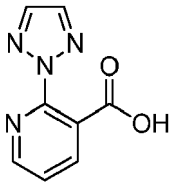
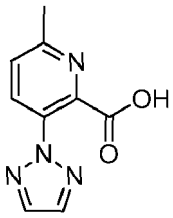
Intermediate A-36: 2-(5-fluoropyrimidin-2-yl)-3-methylbenzoic acid

[0203]

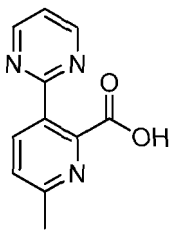
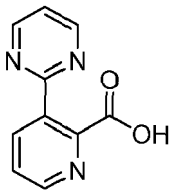
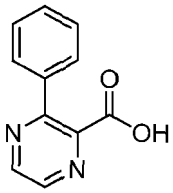
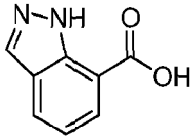
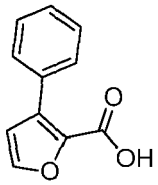


[0204] Step A: Methyl 2-(5-fluoropyrimidin-2-yl)-3-methylbenzoate. A solution of methyl 3-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (CAS 887234-98-2) (3 g, 11 mmol) in THF (30 mL) was degassed with N_2. Then, 2-chloro-5-fluoropyrimidine (1.6 mL, 13.04 mmol), Na_2CO_3 (3.45 g, 32.6 mmol), water (10 mL), and $Pd(dppf)Cl_2$ (354 mg, 0.434 mmol) were added, and the reaction mixture was stirred at 100 °C overnight. The mixture was cooled to room temperature and water and EtOAc added. The reaction mixture was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude was purified via silica gel chromatography (0-40% EtOAc in hexanes) to afford the title compound (1.07 g, 40%).

[0205] Step B: 2-(5-fluoropyrimidin-2-yl)-3-methylbenzoic acid. To a solution of the title compound of Step A (1.46 g, 5.93 mmol) in MeOH (20 mL) was added 1 M NaOH (12 mL), and the reaction mixture was stirred at room temperature overnight. The solvent was removed and the crude was diluted with water until pH = 10. The aqueous layer was extracted with EtOAc. The aqueous layer was further acidified with 12 M $HCl_{(aq)}$ until pH = 2 and extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated to afford the title compound (1.19 g, 83%). MS (ESI) mass calcd. for $C_{12}H_9FN_2O_2$, 232.1; m/z found 233.1 $[M+H]^+$.

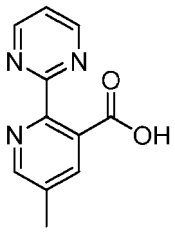
Intermediate	Name	Structure	Reference
A-37	2-(pyrimidin-2-yl)benzoic acid		Commercially available, CAS 400892-62-8
A-38	5-methyl-2-(2H-1,2,3-triazol-2-yl) nicotinic acid		Prepared analogous to WO 2011/050200 Intermediate 47, Example 160
A-39	2-(2H-1,2,3-triazol-2-yl)nicotinic acid		Commercially available, CAS 1369497-44-8
A-40	6-methyl-3-(2H-1,2,3-triazol-2-yl) picolinic acid		2012/089606 Intermediate D40.

(continued)

Intermediate	Name	Structure	Reference
A-41	6-methyl-3-(pyrimidin-2-yl)picolinic acid		WO 2010/122151 Intermediate D28
A-42	3-(pyrimidin-2-yl)picolinic acid		WO 2010/122151 Intermediate D105
A-43	3-phenylpyrazine-2-carboxylic acid		Commercially available, CAS 2881-85--8
A-44	1H-indazole-7-carboxylic acid		Commercially available, CAS 677304-69-7
A-45	3-phenylfuran-2-carboxylic acid		Commercially available, CAS169772-63-8

Intermediate A-46: 5-methyl-2-(pyrimidin-2-yl)nicotinic acid.

[0206]

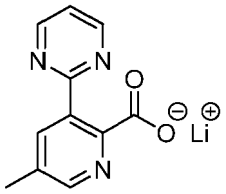


[0207] Step A: Methyl 5-methyl-2-(pyrimidin-2-yl)nicotinate. To a sealed tube containing methyl 2-chloro-5-methylnicotinate (CAS 65169-43-9) (745 mg, 4.01 mmol), CuI (38 mg, 0.2 mmol), LiCl (169 mg, 4.01 mmol), and $Pd(PPh_3)_4$ (231 mg, 0.2 mmol) in toluene (15 mL) was added 2-(tributylstannyl)pyrimidine (1.5 mL, 4.4 mmol), and the reaction mixture was heated at 120 °C overnight. The reaction mixture was diluted with water and extracted with DCM. The combined organic layers were dried over $MgSO_4$, filtered and evaporated. Purification via silica gel chromatography (0-50% EtOAc in hexanes) gave the title compound (494 mg, 52%). MS (ESI) mass calcd. for $C_{12}H_{11}N_3O_2$, 229.1; m/z found 229.99.

[0208] Step B: 5-methyl-2-(pyrimidin-2-yl)nicotinic acid. To a solution of the title compound of step A (466 mg, 2.03 mmol) in MeOH (10 mL) was added 10 M NaOH (1 mL), and the reaction mixture was stirred at room temperature for 2 h. The solvent was removed and the crude was diluted with water and acidified with 6 M $HCl_{(aq)}$ until pH = 3. The aqueous layer was saturated with solid NaCl and extracted with 20% *i*PrOH in $CHCl_3$ (3X). The combined organic layers were dried over $MgSO_4$, filtered and concentrated to afford the title compound (432 mg, 99%). MS (ESI) mass calcd. for $C_{11}H_9N_3O_2$, 215.1; m/z found 216.1 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4) δ 8.90 (br. s, 2H), 8.64 (br. s, 1H), 8.17 (s, 1H), 7.55 (br. s, 1H), 2.51 (s, 3H).

Intermediate A-47: Lithium 5-methyl-3-(pyrimidin-2-yl)picolinate.

[0209]

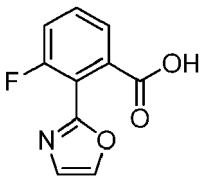


[0210] Step A: Methyl 5-methyl-3-(pyrimidin-2-yl)picolinate. Prepared analogous to intermediate A-46, step A substituting methyl 2-chloro-5-methylnicotinate with methyl 3-bromo-5-methylpicolinate. MS (ESI) mass calcd. for $C_{12}H_{11}N_3O_2$, 229.1; m/z found 230.0 $[M+H]^+$.

[0211] Step B: Lithium 5-methyl-3-(pyrimidin-2-yl)picolinate. To a solution of the title compound of step A (592 mg, 2.58 mmol) in THF (5 mL) was added 4 M LiOH (0.8 mL) and water (1.5 mL), and the reaction mixture was stirred at room temperature for 2.5 h. The solvent was removed and the crude reaction mixture placed under vacuum overnight to give the title compound (591 mg), which was used in the next step without further purification. MS (ESI) mass calcd. for $C_{11}H_9N_3O_2$, 215.1; m/z found 216.1 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4) δ 8.83 (d, *J* = 4.9 Hz, 2H), 8.39 (br. s, 1H), 8.23 - 8.18 (m, 1H), 7.38 (t, *J* = 4.9 Hz, 1H), 2.44 (s, 3H).

Intermediate A-48: 3-fluoro-2-(oxazol-2-yl)benzoic acid.

[0212]



[0213] Step A: 2-bromo-N-(2,2-dimethoxyethyl)-6-fluorobenzamide. To a solution of 2-bromo-6-fluorobenzoic acid (2 g, 9.1 mmol) in DMF (27 mL) was added HBTU (5.20 g, 13.7 mmol) and DIPEA (4.7 mL, 27 mmol), and the reaction mixture was stirred for 10 min. Then, 2,2-dimethoxyethylamine (1.3 mL, 11.9 mmol) was added and the reaction mixture stirred at room temperature for 12 h. The reaction mixture was diluted with EtOAc and washed with saturated aqueous $NaHCO_3$. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Purification via silica gel chromatography (0-25% EtOAc in hexanes) gave the title compound (2.3 g, 82%).

[0214] Step B: 2-(2-bromo-6-fluorophenyl)oxazole. To P_2O_5 (6.4 g, 22.6 mmol) was added methanesulfonic acid (52 mL, 801 mmol), and the reaction mixture was stirred at room temperature for 1 h. Then, the title compound of step A (2.3 g, 7.54 mmol) was added to the reaction mixture, and the mixture heated to 140 °C for 2 h. DCM was added and the mixture was slowly poured into a saturated solution of aqueous $NaHCO_3$ on ice. The mixture was extracted with DCM. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Purification via silica gel chromatography (0-10% EtOAc in hexanes) gave the title compound (1.5 g, 82%). MS (ESI) mass calcd. for C_9H_5BrFNO, 240.95; m/z found 242.0 $[M+H]^+$.

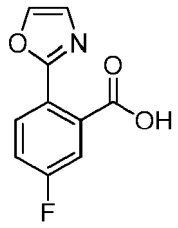
[0215] Step C: Methyl 3-fluoro-2-(oxazol-2-yl)benzoate. A solution of the title compound of step B (2.18 g, 8.99 mmol), $Pd(OAc)_2$ (40 mg, 0.18 mmol), 1,1'-bis(diphenylphosphino)ferrocene (199 mg, 0.36 mmol), and Et_3N (3.7 mL, 27 mmol) in 1:1 MeOH/1,4-dioxane (36 mL) was degassed with N_2 for 15 min. Then, the mixture was stirred at 95 °C under an atmosphere of carbon monoxide overnight. The reaction mixture was diluted with EtOAc and washed with a solution of

$NaHCO_3$. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated. Purification via silica gel chromatography (0-12% EtOAc in hexanes) gave the title compound (1.7 g, 83%). MS (ESI) mass calcd. for $C_{11}H_8FNO_3$, 221.1; m/z found 222.0 $[M+H]^+$.

[0216] Step D: 3-fluoro-2-(oxazol-2-yl)benzoic acid. To a solution of the title compound of step C (1.65 g, 7.46 mmol) in MeOH (22 mL) was added 2 M NaOH (7.5 mL), and the reaction mixture was stirred at room temperature overnight. The reaction mixture was acidified with 1 M $HCl_{(aq)}$ and the solvents evaporated in vacuo. The mixture was diluted with water and extracted with DCM. The combined organic were dried over $MgSO_4$, filtered and concentrated to afford the title compound (905 mg, 58%). MS (ESI) mass calcd. for $C_{10}H_6FNO_3$, 207.0; m/z found 208.0 $[M+H]^+$. MP = 182 °C.

Intermediate A-49: 5-fluoro-2-(oxazol-2-yl)benzoic acid.

[0217]

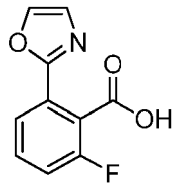


[0218] Step A: Methyl 5-fluoro-2-(oxazol-2-yl)benzoate. To a solution of methyl 2-bromo-5-fluorobenzoate (1.1 g, 4.8 mmol) and 2-(tri-n-butylstannyl)oxazole (1.3 mL, 6.2 mmol) in toluene (14 mL) was added $Pd(PPh_3)_4$ (550 mg, 0.476 mmol), and the reaction mixture was heated via microwave heating to 150 °C for 30 min. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Purification via silica gel chromatography (0-40% EtOAc in hexanes, followed by a second column 0-10% EtOAc in hexanes) gave the title compound (553 mg, 52%). MS (ESI) mass calcd. for $C_{11}H_6FNO_3$, 221.1; m/z found 222.1 $[M+H]^+$.

[0219] Step B: 5-fluoro-2-(oxazol-2-yl)benzoic acid. Prepared analogous to intermediate 48, step D, to give the title compound (858 mg, 99%). MS (ESI) mass calcd. for $C_{10}H_6FNO_3$, 207.0; m/z found 208.1 $[M+H]^+$.

Intermediate A-50: 2-fluoro-6-(oxazol-2-yl)benzoic acid.

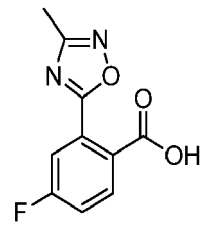
[0220]



[0221] Prepared analogous to intermediate 48, substituting 2-bromo-6-fluorobenzoic acid with 2-bromo-3-fluorobenzoic acid. MS (ESI) mass calcd. for $C_{10}H_6FNO_3$, 207.0; m/z found 208.0 $[M+H]^+$.

Intermediate A-51: 4-fluoro-2-(3-methyl-1,2,4-oxadiazol-5-yl)benzoic acid

[0222]



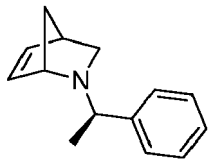
[0223] Step A: 5-(2-bromo-5-fluorophenyl)-3-methyl-1,2,4-oxadiazole. To a solution of bromo-5-fluorobenzoyl chloride (2.17 g, 9.13 mmol) in THF (18 mL) was added DIPEA (1.7 mL, 10 mmol). Then, acetamide oxime (676 mg, 9.13 mmol) was added portionwise, and the reaction mixture was stirred at 70 °C for 16 h. The reaction mixture was diluted with EtOAc and washed with a saturated solution of $NaHCO_3$. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Purification via silica gel chromatography (0-20% EtOAc in hexanes) gave the title compound (2.35 g, 57%). MS (ESI) mass calcd. for $C_9H_6BrFN_2O$, 255.96; m/z found 257.0 $[M+H]^+$.

[0224] Step B: 4-fluoro-2-(3-methyl-1,2,4-oxadiazol-5-yl)benzoic acid. Prepared analogous to intermediate 48, steps C and D, to give the title compound. MS (ESI) mass calcd. for $C_{10}H_7FN_2O_3$, 222.0; m/z found 223.0 $[M+H]^+$.

Enantiopure Route A (2-azabicyclo[2.2.1]heptan-6-ol):

Intermediate B-1: (1S,4R)-2-((R)-1-phenylethyl)-2-azabicyclo[2.2.1]hept-5-ene

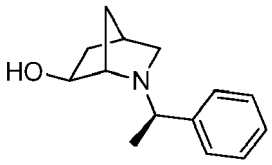
[0225]



[0226] Intermediate B-1 was prepared according to the procedure of C. Chiu et al. [Synthetic Communications 1996, 26, 577-584] with the substitution of (+)-α-Methyl-benzylamine for (-)-α-Methyl-benzylamine and D-dibenzoyl tartaric acid for L- dibenzoyl tartaric acid. MS (ESI) mass calcd. for $C_{14}H_{17}N$, 199.1; m/z found 200.1 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d) δ 7.36 - 7.25 (m, 4H), 7.23 - 7.17 (m, 1H), 6.35 - 6.30 (m, 1H), 6.11 (dd, *J* = 5.7, 2.0 Hz, 1H), 4.16 - 4.12 (m, 1H), 3.05 (q, *J* = 6.5 Hz, 1H), 2.89 (dd, *J* = 8.9, 3.1 Hz, 1H), 2.85 - 2.81 (m, 1H), 1.65 - 1.59 (m, 1H), 1.48 - 1.43 (m, 1H), 1.37 - 1.31 (m, 4H).

Intermediate B-2: (1S,4R,6S)-2-((R)-1-phenylethyl)-2-azabicyclo[2.2.1]heptan-6-ol

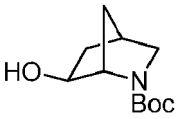
[0227]



[0228] Intermediate B-2 was synthesized according to the procedure of F. Carroll et al. [J. Med. Chem. 1992, 35, 2184-2191] on a similar substrate. A 1 M solution of BH_3-THF (1 M BH_3-THF in THF, 359.3 mL, 359.3 mmol) was added dropwise via addition funnel to a stirred solution of intermediate B-1 (35.8 g, 179.6 mmol) in THF (359 mL) at 0 °C. Upon complete addition of BH_3-THF, the reaction mixture was stirred at 0 °C for 2 h. Then, excess BH_3 was quenched with a solution of THF-H_2O. A 3 MNaOH (132 mL) solution was added followed by the dropwise addition of H_2O_2 (30% w/w in H_2O, 140 mL), and the reaction mixture was warmed to 40 °C and stirred for 1.5 h. The biphasic mixture was then cooled to room temperature and K_2CO_3 (17 g) added in one portion. The resulting mixture was concentrated under reduced pressure to remove THF and re-dissolved in DCM. The crude reaction mixture was washed with H_2O and the aqueous phase extracted with DCM (3X). The combined organics were then washed with brine, dried with Na_2SO_4, filtered, and concentrated to give a clear oil, which was further purified by silica gel chromatography (5-10% MeOH (with 10% 2 M NH_3) in DCM) to give intermediate B-2 as a clear oil (20.2 g, 93.0 mmol, 52%). MS (ESI) mass calcd. for $C_{14}H_{19}NO$, 217.2; m/z found 218.1 $[M+H]^+$. ^1H NMR (500 MHz, Chloroform-d) δ 7.34 - 7.27 (m, 4H), 7.24 - 7.19 (m, 1H), 4.03 (d, *J* = 6.9 Hz, 1H), 3.46 (q, *J* = 6.5 Hz, 1H), 3.01 (s, 1H), 2.56 - 2.48 (m, 1H), 2.42 - 2.33 (m, 1H), 2.25 (dd, *J* = 8.8, 1.3 Hz, 1H), 1.82 (ddd, *J* = 13.1, 6.9, 2.2 Hz, 1H), 1.53 - 1.43 (m, 2H), 1.33 - 1.28 (m, 1H), 1.27 (d, *J* = 6.5 Hz, 3H).

Intermediate B-3: (1S,4R,6S)-tert-butyl 6-hydroxy-2-azabicyclo[2.2.1]heptane-2-carboxylate

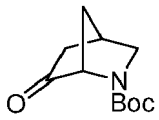
[0229]



[0230] To a solution of intermediate B-2 (500 mg, 2.3 mmol) in EtOH (11.5 mL) was added Boc_2O (603 mg, 2.76 mmol) and 10 wt% Pd/C wet Degussa (490 mg, 0.46 mmol). The reaction mixture was stirred under an atmosphere of H_2 (balloon) at room temperature for 22 h. Then, the reaction mixture was filtered through a pad of Celite and washed with EtOAc. The filtrate was concentrated to a clear oil to give the title compound in quantitative yield, which was used without further purification. MS (ESI) mass calcd. for $C_{11}H_{19}NO_3$, 213.1; m/z found 158.1 $[M+2H-t\text{Bu}]^+$. ^{1}H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers) δ 4.08 - 3.99 (m, 1H), 3.99 - 3.92 (m, 1H), 3.18 - 3.09 (m, 1H), 2.80 (dd, *J* = 28.1, 9.2 Hz, 1H), 2.18 - 1.37 (m, 14H).

Intermediate B-4: (1S,4R)-tert-butyl 6-oxo-2-azabicyclo[2.2.1]heptane-2-carboxylate

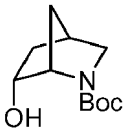
[0231]



[0232] To a solution of intermediate B-3 (7 g, 33 mmol) in EtOAc (219 mL) was added IBX (24.5 g, 39.4 mmol), and the heterogeneous reaction mixture was stirred at 80 °C overnight. Upon completion, the reaction mixture was then filtered through Celite, washed with EtOAc and concentrated to a white solid. The crude reaction mixture was re-dissolved in EtOAc and washed once with a 5% aqueous Na_2CO_3 solution. The aqueous layer was further extracted with EtOAc (2X) and the combined organics were washed with brine, dried with Na_2SO_4, filtered, and concentrated to afford intermediate B-4 as a light yellow solid (6.12 g, 28.9 mmol, 88%), which was used in the next step without further purification. MS (ESI) mass calcd. for $C_{11}H_{17}NO_3$, 211.1; m/z found 156.1 $[M+2H-t\text{Bu}]^+$. ^{1}H NMR (400 MHz, Chloroform-d) δ 4.32 - 4.04 (m, 1H), 3.45 (ddd, *J* = 9.6, 3.1, 1.8 Hz, 1H), 3.25 - 3.04 (m, 1H), 2.89 - 2.77 (m, 1H), 2.21 (ddd, *J* = 18.0, 4.6, 1.8 Hz, 1H), 2.04 - 1.96 (m, 1H), 1.95 - 1.82 (m, 1H), 1.75 - 1.66 (m, 1H), 1.45 (s, 9H).

Intermediate B-5: (1S,4R,6R)-tert-butyl 6-hydroxy-2-azabicyclo[2.2.1]heptane-2-carboxylate

[0233]



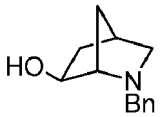
[0234] A 1 M solution of L-Selectride (1 M in THF, 19.8 mL, 19.8 mmol) was added to a solution of intermediate B-4 (1.67 g, 7.91 mmol) in dry THF (40 mL) at -78 °C, and the reaction mixture was stirred at that temperature for 3 h. Then, the reaction mixture was warmed to 0 °C and a 3 M NaOH (8.4 mL) solution was added followed by a solution of H_2O_2 (30% w/w in H_2O, 4.3 mL). The resulting mixture was warmed to room temperature and stirred for 2 h. The biphasic mixture was then concentrated in vacuo to remove THF and the aqueous layer extracted with DCM (3X). The combined organics were washed with brine, dried with Na_2SO_4, filtered, and concentrated to an oil, which was further purified by silica gel chromatography (10-90% EtOAc in hexanes), to give intermediate B-2 as a white solid (1.16 g, 5.44 mmol, 67%). MS (ESI) mass calcd. for $C_{11}H_{19}NO_3$, 213.1; m/z found 158.1 $[M+2H-t\text{Bu}]^+$. ^{1}H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers) δ 4.38 - 4.10 (m, 2H), 3.36 (br. s, 1H), 3.09 (dd, *J* = 9.6, 1.4 Hz, 1H), 2.54 - 1.38 (m, 14H), 1.16 - 1.00 (m, 1H).

Intermediate B-5 can also be prepared from commercially available (1S,4R)-2-azabicyclo[2.2.1]hept-5-en-3-one. The procedure is as follows:

Enantiopure Route B (2-azabicyclo[2.2.1]heptan-6-ol):

Intermediate B-6: (1S,4R,6S)-2-benzyl-2-azabicyclo[2.2.1]heptan-6-ol

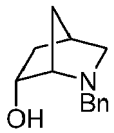
[0235]



[0236] To a round bottom flask containing commercially available, (1S,4R)-2-azabicyclo[2.2.1]hept-5-en-3-one (2.0 g, 18.3 mmol), in THF (100 mL) at 0 °C was added a solution of $LiAlH_4$ (1 M in THF, 40.3 mL, 40.3 mmol), and the reaction mixture was refluxed overnight. The reaction mixture was then cooled to 0 °C and carefully quenched by the dropwise addition of H_2O (15 mL). Celite and solid Na_2CO_3 were added to the slurry and the reaction mixture was vigorously stirred at room temperature for 3 h. The slurry was then filtered and the solids washed with THF. Benzyl bromide (2.4 mL, 20.2 mmol) and an aqueous solution of Na_2CO_3 (3.2 g in 30 mL H_2O) were added to the filtrate and the reaction mixture stirred at room temperature overnight. Upon completion of the reaction, the reaction mixture was extracted with EtOAc (3X). The combined organics were washed with H_2O, brine, dried with $MgSO_4$, filtered, and concentrated to provide crude (1S,4R)-2-benzyl-2-azabicyclo[2.2.1]hept-5-ene as a yellow oil, which was directly hydroborated according to the procedure of F. Carroll et al. [J. Med. Chem. 1992, 35, 2184-2191]. The crude alcohol was purified by silica gel chromatography (0-15% MeOH (with 5% NH_4OH) in DCM) to give intermediate B-6 as a clear oil (2.66 g, 13.1 mmol, 71% over 3 steps). MS (ESI) mass calcd for $C_{13}H_{17}NO$, 203.1; m/z found 204.1 $[M+H]^+$. ^1H NMR (500 MHz, Chloroform-d) δ 7.39 - 7.28 (m, 4H), 7.26 - 7.21 (m, 1H), 4.18 - 4.09 (m, 1H), 3.76 - 3.66 (m, 2H), 3.06 (br. s, 1H), 2.51 (dt, *J* = 9.0, 3.0 Hz, 1H), 2.44 - 2.35 (m, 2H), 1.90 - 1.81 (m, 1H), 1.68 - 1.53 (m,2H), 1.38 - 1.30 (m, 1H).

Intermediate B-7: (1S,4R,6R)-2-benzyl-2-azabicyclo[2.2.1]heptan-6-ol

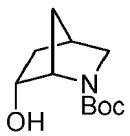
[0237]



[0238] Intermediate B-7 was prepared from intermediate B-6 according to the procedure of F. Carroll et al. [J. Med. Chem. 1992, 35, 2184-2191]. MS (ESI) mass calcd for $C_{13}H_{17}NO$, 203.1; m/z found 204.1 $[M+H]^+$. ^1H NMR (500 MHz, Chloroform-d) δ 7.37 - 7.22 (m, 5H), 4.56 (s, 1H), 4.05 - 3.94 (m, 1H), 3.80 (d, *J* = 13.0 Hz, 1H), 3.62 (d, *J* = 12.9 Hz, 1H), 3.20 - 3.11 (m, 1H), 2.77 (d, *J* = 9.2 Hz, 1H), 2.45 - 2.34 (m, 2H), 1.88 - 1.79 (m, 1H), 1.76 - 1.64 (m, 1H), 1.30 (d, *J*= 10.4 Hz, 1H), 0.99 (dt, *J*= 13.3, 2.9 Hz, 1H).

Intermediate B-5: (1S,4R,6R)-tert-butyl 6-hydroxy-2-azabicyclo[2.2.1]heptane-2-carboxylate

[0239]



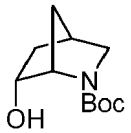
[0240] To a solution of intermediate B-7 (3.41 g, 16.8 mmol) in EtOH (168 mL) was added Boc_2O (5.49 g, 25.2 mmol) and 20 wt% $Pd(OH)_2/C$ (2.36 g, 3.36 mmol). The reaction mixture was stirred under an atmosphere of H_2 (balloon) at room temperature overnight. Then, the reaction mixture was filtered through a pad of Celite and washed with EtOAc.

The filtrate was concentrated to a clear oil, which was further purified by silica gel chromatography (10-60% EtOAc in hexanes), to give intermediate B-5 as a white solid (3.1 g, 1.5 mmol, 87%). $[\alpha]^{D}_{20}$ -11.2 (c 0.0065, MeOH). MS (ESI) mass calcd. for $C_{11}H_{19}NO_3$, 213.1; m/z found 158.1 $[M+2H-t\text{Bu}]^+$. ^{1}H NMR (500 MHz, Chloroform-d, Compound present as a mixture of rotamers) δ 4.39 - 4.12 (m, 2H), 3.35 (br. s, 1H), 3.08 (dd, *J* = 9.4, 1.4 Hz, 1H), 2.56 - 1.39 (m, 14H), 1.15-0.99 (m, 1H).

Racemic Route (2-azabicyclo[2.2.1]heptan-6-ol):

Intermediate B-8: (R/S)-tert-butyl 6-hydroxy-2-azabicyclo[2.2.1]heptane-2-carboxylate

[0241]

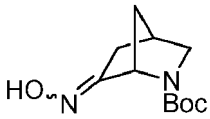


[0242] Intermediate B-8 was prepared from commercially available (R/S)-tert-butyl 6-oxo-2-azabicyclo[2.2.1]heptane-2-carboxylate following the procedure of R. Nencka et. al. [Tetrahedron 2012, 68, 1286-1298]. MS (ESI) mass calcd. for $C_{11}H_{19}NO_3$, 213.1; m/z found 158.1 $[M+2H-t\text{Bu}]^+$. ^{1}H NMR (400 MHz, Chloroform-d) δ 4.39 - 4.08 (m, 2H), 3.36 (br.s, 1H), 3.10 (dd, *J*= 9.6, 1.4 Hz, 1H), 2.56-1.41 (m, 14H), 1.17 - 1.01 (m, 1H).

Enantiopure Route (2-azabicyclo[2.2.1]heptan-6-amine):

Intermediate B-9: (1S,4R)-tert-butyl 6-(hydroxyimino)-2-azabicyclo[2.2.1]heptane-2-carboxylate

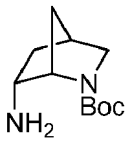
[0243]



[0244] To a flask containing Intermediate B-4 (1.0 g, 4.7 mmol) dissolved in EtOH (20 mL) was added NEt_3 (2.0 ml, 14.4 mmol), and hydroxylamine hydrochloride (789 mg, 2.40 mmol) and the reaction mixture was brought to reflux. Upon completion, the reaction mixture was concentrated, diluted with H_2O, and the aqueous layer extracted with EtOAc (3X). The combined organics were then washed with H_2O, brine, dried with $MgSO_4$, filtered, and concentrated to provide intermediate B-9 as an off-white solid (1.018 g) which was used without further purification. MS (ESI) mass calcd. for $C_{11}H_{18}N_2O_3$, 226.1; m/z found 171.1 $[M+2H-t\text{Bu}]^+$. ^{1}H NMR (500 MHz, Chloroform-d) δ 7.71 and 7.41 (2s, 1H), 4.62 and 4.48 (2s, 1H), 3.40 - 3.33 (m, 1H), 3.15 - 2.96 (m, 1H), 2.79 - 2.70 (m, 1H), 2.54 - 2.43 (m, 1H), 2.29-2.19 (m, 1H), 1.87 - 1.64 (m, 1H), 1.61 - 1.53 (m, 1H), 1.45 (s, 9H).

Intermediate B-10: (1S,4S,6R)-tert-butyl 6-amino-2-azabicyclo[2.2.1]heptane-2-carboxylate

[0245]



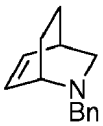
[0246] A mixture of $NiCl_2$ (1.15 g, 8.84 mmol) and intermediate B-9 (1.0 g, 4.4 mmol) in MeOH (30 mL) was cooled to -35 °C and $NaBH_4$ (3.34 g, 88.4 mmol) was added portion wise to the reaction mixture over 30 min. Upon complete addition of $NaBH_4$, the reaction mixture was stirred for an additional 25 min and then warmed to room temperature. After 30 min at room temperature the reaction mixture was quenched with H_2O and concentrated under reduced pressure to a dark brown residue, which was re-dissolved in a mixture of DCM and 15% aqueous NaOH solution, and the aqueous

layer extracted with DCM (3X). The combined organics were dried with $MgSO_4$, filtered, and concentrated to provide intermediate B-10 (209 mg). 5 N NH_4OH solution was then added to the aqueous layer along with DCM, NaCl, and Celite and after several minutes of stirring the mixture was filtered to remove solids. The filtrate was then transferred to a separatory funnel, the layers separated, and the aqueous layer extracted with DCM (2X). The combined organics were dried with $MgSO_4$, filtered, and concentrated to provide additional intermediate B-10 (582 mg) which was combined with the above fraction to provide intermediate B-10 (791 mg) as a brown oil which was used without further purification. MS (ESI) mass calcd. for $C_{11}H_{20}N_2O_2$, 212.2; m/z found 213.1 $[M+H]^+$. ^1H NMR (500 MHz, Chloroform-d) δ 4.13 - 3.92 (m, 1H), 3.41 - 3.27 (m, 2H), 2.99 (dd, *J*= 24.3, 9.6 Hz, 1H), 2.51 - 2.39 (m, 1H), 2.16 - 2.05 (m, 1H), 1.68 - 1.57 (m, 1H), 1.47 (s, 10H), 1.22 - 1.07 (m, 2H), 0.85 - 0.74 (m, 1H).

Route A (2-azabicyclo[2.2.1]heptan-6-ol and 2-azabicyclo[2.2.2]octan-6-amine):

Intermediate C-1: (R/S)-2-benzyl-2-azabicyclo[2.2.2]oct-5-ene

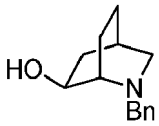
[0247]



[0248] Intermediate C-1 was prepared according to the procedure of S. Larsen et al. [J. Am. Chem. Soc. 1985, 107, 1768-1769]. To a solution of phenylmethanamine (3.92 g, 27.3 mmol) in H_2O (5 mL) was added aqueous formaldehyde (2.03 mL, 27.3 mmol, 37 wt. % in H_2O). After 2 minutes, 1,3-cyclohexadiene (2 mL, 21 mmol) was added and the reaction mixture was heated to 55 °C for 4 days. The reaction mixture was cooled to room temperature and diluted with H_2O and extracted with Et_2O (2X). The organic layer was discarded and the aqueous layer was basified with solid KOH and further extracted with Et_2O (2X). The organic layer was washed with brine, dried with $MgSO_4$, filtered, and concentrated. The concentrate was further purified by silica gel chromatography (100% DCM to 100% MeOH (with 10% 2 M NH_3) in DCM) to give intermediate C-1 as a brown oil, which contained minor impurities. Intermediate C-1 was used without further purification. MS (ESI) mass calcd. for $C_{14}H_{17}N$, 199.1; m/z found 200.1 $[M+H]^+$.

Intermediate C-2: (R/S)-2-benzyl-2-azabicyclo[2.2.2]octan-6-ol

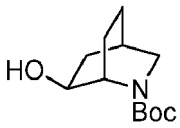
[0249]



[0250] Intermediate C-2 was synthesized according to the procedure of F. Carroll et al. [J. Med. Chem. 1992, 35, 2184-2191] on a similar substrate. A 1 M solution of BH_3-THF (1 M BH_3-THF in THF, 1.11 L, 1.11 mol) was added dropwise via addition funnel to a stirred solution of intermediate C-1 (37 g, 186 mmol) in THF (250 mL) at 0 °C. Upon complete addition of BH_3-THF, the reaction mixture was stirred at 0 °C for 3 h. Then, excess BH_3 was quenched with a solution of THF-H_2O. A 4 M NaOH (100 mL) solution was added followed by the dropwise addition of H_2O_2 (30% w/w in H_2O, 100 mL), and the reaction mixture was warmed to 40 °C and stirred overnight. The biphasic mixture was then cooled to room temperature and K_2CO_3 added portionwise. The resulting mixture was concentrated under reduced pressure to remove THF. Solid NaCl was added to the remaining aqueous layer and the crude mixture extracted with EtOAc (3X). The combined organics were then washed with brine, dried with Na_2SO_4, filtered, and concentrated to give a yellow-orange oil, which was further purified by silica gel chromatography (0-100% EtOAc in hexanes followed by 10% MeOH (with 10% 2 M NH_3) in DCM) to give intermediate C-2 as a yellow oil (20.7 g, 95.3 mmol, 51%), which contained minor impurities. Intermediate C-2 was used without further purification. MS (ESI) mass calcd. for $C_{14}H_{19}NO$, 217.2; m/z found 218.2 $[M+H]^+$.

Intermediate C-3: (R/S)-tert-Butyl 6-hydroxy-2-azabicyclo[2.2.2]octane-2-carboxylate

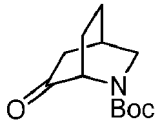
[0251]



[0252] To a solution of intermediate C-2 (20.7 g, 95.3 mmol) in EtOH (477 mL) was added Boc_2O (27.1 g, 124 mmol) and 10 wt% Pd/C wet Degussa (5 g, 4.77 mmol). The reaction mixture was stirred under an atmosphere of H_2 (balloon) at room temperature for 48 h. Analysis of the crude reaction mixture showed that the majority of the mixture was the deprotected amine, 2-azabicyclo[2.2.2]octan-6-ol. An additional equivalent of Boc_2O (27.1 g, 124 mmol) was added, and the reaction mixture was stirred at room temperature overnight. Then, the reaction mixture was filtered through a pad of Celite and washed with EtOAc. The filtrate was concentrated to a yellow oil to give intermediate C-3, which was used without further purification. MS (ESI) mass calcd. for $C_{12}H_{21}NO_3$, 227.2; m/z found 172.2 $[M+2H-t\text{Bu}]^+$.

Intermediate C-4A: (R/S)-tert-Butyl 6-oxo-2-azabicyclo[2.2.2]octane-2-carboxylate

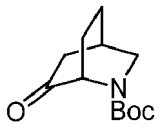
[0253]



[0254] To a solution of intermediate C-3 (21.6 g, 95.0 mmol) in EtOAc (380 mL) was added IBX (31.9 g, 114 mmol), and the heterogeneous reaction mixture was stirred at 80 °C overnight. Upon completion, the reaction mixture was then filtered through Celite, washed with EtOAc and concentrated. The crude reaction mixture was re-dissolved in EtOAc and washed once with a 5% aqueous Na_2CO_3 solution. The aqueous layer was further extracted with EtOAc (2X) and the combined organics were washed with brine, dried with Na_2SO_4, filtered, and concentrated to a brown residue. The concentrate was further purified by silica gel chromatography (0-35% EtOAc in hexanes), to give intermediate C-4A as a yellow solid. MS (ESI) mass calcd. for $C_{12}H_{19}NO_3$, 225.1; m/z found 170.1 $[M+2H-t\text{Bu}]^+$. Analytical HPLC using a XBridge C18 column (5μm, 100 × 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 2min and then hold at 100% ACN for 2 min, at a flow rate of 2.5 mL/min (Temperature = 45 °C). R_t = 1.91 min at 280 nm.

Intermediate C-4B: (1S,4R)-tert-butyl 6-oxo-2-azabicyclo[2.2.2]octane-2-carboxylate

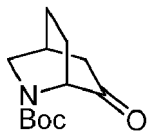
[0255]



[0256] The title compound was obtained as a single enantiomer by Chiral SFC purification of Intermediate C-4A performed using a Chiralpak IC column (5μm, 250 × 20 mm), mobile phase of 20% iPrOH: 80% CO_2, and a flow rate of 80 mL/min (Temperature = 35 °C). Elution was monitored following absorbance at 250nm. The enantiomeric purity was confirmed by analytical SFC using a Chiralpak IC column (5μm, 150 × 4.6 mm), mobile phase of 20% iPrOH+(0.3% $iPrNH_2$): 80% CO_2, and a flow rate of 3 mL/min over 7 minutes (Temperature = 35°C). Elution was monitored following absorbance at 250nm. Enantiopurity 100%, which elutes at one peak (1.56 min retention time). MS (ESI) mass calcd. for $C_{12}H_{19}NO_3$, 225.1; m/z found 170.1 $[M+2H-t\text{Bu}]^+$. ^1H NMR (500 MHz, Chloroform-d, Compound present as a mixture of rotamers) δ 4.42 - 4.15 (m, 1H), 3.62 - 3.34 (m, 2H), 2.49 - 2.32 (m, 3H), 2.21 - 2.06 (m, 1H), 1.97 - 1.85 (m, 1H), 1.79 - 1.68 (m, 1H), 1.66 - 1.56 (m, 1H), 1.45 (s, 9H).

Intermediate C-4C: (1R,4S)-tert-butyl 6-oxo-2-azabicyclo[2.2.2]octane-2-carboxylate

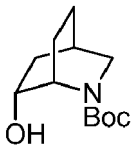
[0257]



[0258] The title compound was obtained as a single enantiomer by Chiral SFC purification of Intermediate C-4A performed using a Chiralpak IC column (5μm, 250 × 20 mm), mobile phase of 20% iPrOH: 80% CO_2, and a flow rate of 80 mL/min (Temperature = 35 °C). Elution was monitored following absorbance at 250nm. The enantiomeric purity was confirmed by analytical SFC using a Chiralpak IC column (5μm, 150 × 4.6 mm), mobile phase of 20% iPrOH+(0.3% $iPrNH_2$): 80% CO_2, and a flow rate of 3 mL/min over 7 minutes (Temperature = 35°C). Elution was monitored following absorbance at 250nm. Enantiopurity 100%, which elutes at one peak (2.18 min retention time). MS (ESI) mass calcd. for $C_{12}H_{19}NO_3$, 225.1; m/z found 170.1 $[M+2H-t\text{Bu}]^+$. ^1H NMR (500 MHz, Chloroform-d, Compound present as a mixture of rotamers) δ 4.41 - 4.13 (m, 1H), 3.57 - 3.31 (m, 2H), 2.46 - 2.31 (m, 3H), 2.22 - 2.08 (m, 1H), 1.96 - 1.86 (m, 1H), 1.83 - 1.68 (m, 1H), 1.67 - 1.56 (m, 1H), 1.45 (s, 9H).

Intermediate C-5A: (R/S)-tert-Butyl 6-hydroxy-2-azabicyclo[2.2.2]octane-2-carboxylate

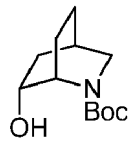
[0259]



[0260] A 1 M solution of L-Selectride (1 M in THF, 1.7 mL, 1.7 mmol) was added to a solution of intermediate C-4A (150 mg, 0.666 mmol) in dry THF (3 mL) at -78 °C, and the reaction mixture was stirred at that temperature for 3 h. Then, the reaction mixture was warmed to 0 °C and a 3 M NaOH (0.71 mL) solution was added followed by a solution of H_2O_2 (30% w/w in H_2O, 0.37 mL). The resulting mixture was warmed to room temperature and stirred for 2 h. The biphasic mixture was then concentrated in vacuo to remove THF and the aqueous layer extracted with DCM (3X). The combined organics were washed with brine, dried with Na_2SO_4, filtered, and concentrated to an oil, which was further purified by silica gel chromatography (10-100% EtOAc in hexanes), to give intermediate C-5A as a white solid (114 mg, 0.502 mmol, 75%). MS (ESI) mass calcd. for $C_{12}H_{21}NO_3$, 227.2; m/z found 172.2 $[M+2H-t\text{Bu}]^+$. ^1H NMR (500 MHz, Methanol-d_4) δ 3.97 - 3.86 (m, 2H), 3.38 - 3.20 (m, 2H), 2.09 - 2.00 (m, 1H), 1.96 - 1.87 (m, 1H), 1.87 - 1.79 (m, 1H), 1.62 - 1.48 (m, 3H), 1.46 (d, *J* = 4.9 Hz, 9H), 1.43 - 1.37 (m, 1H).

Intermediate C-5B: (1S,4R,6R)-tert-butyl 6-hydroxy-2-azabicyclo[2.2.2]octane-2-carboxylate

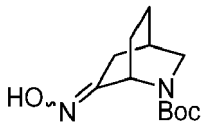
[0261]



[0262] Intermediate C-5B was prepared analogous to Intermediate C-5A substituting racemic Intermediate C-4A for enantiopure Intermediate C-4B. MS (ESI) mass calcd. for $C_{12}H_{21}NO_3$, 227.2; m/z found 172.1 $[M+2H-t\text{Bu}]^+$.

Intermediate C-6A: (R/S)-tert-butyl 6-(hydroxyimino)-2-azabicyclo[2.2.2]octane-2-carboxylate

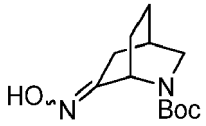
[0263]



[0264] To a flask containing Intermediate C-4A (324 mg, 1.44 mmol) dissolved in EtOH (5 mL) was added NEt_3 (1 ml, 7.2 mmol), and hydroxylamine hydrochloride (300 mg, 4.32 mmol) and the reaction mixture was heated to 70 °C overnight. Upon completion, the reaction mixture was cooled to room temperature, concentrated, diluted with H_2O, and the aqueous layer extracted with EtOAc (3X). The combined organics were then dried with $MgSO_4$, filtered, and concentrated to provide intermediate C-6A as a light purple solid (351 mg) which was used without further purification. MS (ESI) mass calcd. for $Cl_2H_{20}N_2O_3$, 240.2; m/z found 184.1 $[M+2H-t\text{Bu}]^+$.

Intermediate C-6B: (1S,4R)-tert-butyl 6-(hydroxyimino)-2-azabicyclo[2.2.2]octane-2-carboxylate

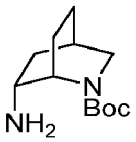
[0265]



[0266] Intermediate C-6B was prepared analogous to Intermediate C-6A substituting racemic Intermediate C-4A for enantiopure Intermediate C-4B. MS (ESI) mass calcd. for $C_{12}H_{20}N_2O_3$, 240.2; m/z found 241.2 $[M+H]^+$.

Intermediate C-7A: (R/S)-tert-butyl 6-amino-2-azabicyclo[2.2.2]octane-2-carboxylate

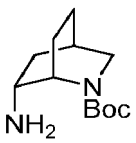
[0267]



[0268] A mixture of $NiCl_2$ (373 mg, 2.88 mmol) and intermediate C-6A (346 mg) in MeOH (12 mL) was cooled to -35 °C and $NaBH_4$ (1.09 g, 28.8 mmol) was added portion wise to the reaction mixture. Upon complete addition of $NaBH_4$, the reaction mixture was warmed to room temperature. After 2 h at room temperature the reaction mixture was quenched with H_2O. Celite was added and the crude reaction mixture was stirred for 30 min. The crude reaction mixture was filtered and the filtrate concentrated under reduced pressure to a dark brown residue, which was re-dissolved in a mixture of DCM and 15% aqueous NaOH solution. The aqueous layer was extracted with DCM (3X). The combined organics were filtered through Celite, dried with $MgSO_4$, filtered, and concentrated to provide intermediate C-7A (308 mg) as a brown oil which was used without further purification. MS (ESI) mass calcd. for $C_{12}H_{22}N_2O_2$, 226.2; m/z found 227.2 $[M+H]^+$.

Intermediate C-7B: (1S,4R,6R)-tert-butyl 6-amino-2-azabicyclo[2.2.2]octane-2-carboxylate

[0269]

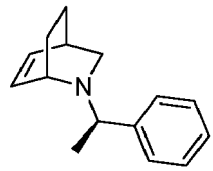


[0270] Intermediate C-7B was prepared analogous to Intermediate C-7A substituting racemic Intermediate C-6A for enantiopure Intermediate C-6B. MS (ESI) mass calcd. for $C_{12}H_{22}N_2O_2$, 226.2; m/z found 227.2 $[M+H]^+$.

Alternative routes (2-azabicyclo[2.2.1]heptan-6-ol):

Intermediate C-8: (R/S)-2-((R)-1-phenylethyl)-2-azabicyclo[2.2.2]oct-5-ene

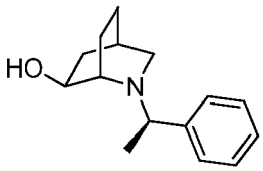
[0271]



[0272] Intermediate C-8 was prepared according to the procedure of C. Chiu et al. [Synthetic Communications 1996, 26, 577-584] on a similar substrate. To a solution of H_2O (5.4 mL) and 12 M HCl (5 mL) was added (+)-α-methylbenzylamine (6.95 mL, 54.6 mmol), and the reaction mixture was stirred at room temperature for 5 minutes. Then, aqueous formaldehyde (4.06 mL, 54.6 mmol, 37 wt. % in H_2O) and 1,3-cyclohexadiene (4 mL, 42 mmol) were added and the reaction mixture heated to 55 °C for 4 days. The reaction mixture was cooled to room temperature and diluted with H_2O and the crude reaction mixture extracted with Et_2O (2X). The aqueous phase was basified with KOH, extracted with Et_2O (2X), saturated with solid NaCl, and extracted once more with Et_2O. The combined organics were dried with Na_2SO_4, filtered, and concentrated to give an orange oil, which was further purified by silica gel chromatography (0-10% MeOH (with 10% 2 M NH_3) in DCM) to give intermediate C-8 as a yellow-orange oil (*ca.* 3:1 dr). Intermediate C-8 was carried forward as a mixture of diastereoisomers. MS (ESI) mass calcd. for $C_{15}H_{19}N$, 213.2; m/z found 214.2 $[M+H]^+$.

Intermediate C-9: (R/S)-2-((R)-1-phenylethyl)-2-azabicyclo[2.2.2]octan-6-ol

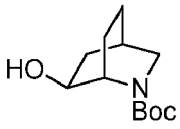
[0273]



[0274] Intermediate C-9 was synthesized according to the procedure of F. Carroll et al. [J. Med. Chem. 1992, 35, 2184-2191] on a similar substrate. A 1 M solution of BH_3-THF (1 M BH_3-THF in THF, 68 mL, 68 mmol) was added dropwise via addition funnel to a stirred solution of intermediate C-8 (2.88 g, 13.5 mmol) in THF (42 mL) at 0 °C. Upon complete addition of BH_3-THF, the reaction mixture was stirred at 0 °C for 2 h. Then, excess BH_3 was quenched with a solution of THF-H_2O. A 4 M NaOH (8 mL) solution was added followed by the dropwise addition of H_2O_2 (30% w/w in H_2O, 8 mL), and the reaction mixture was warmed to 40 °C and stirred for 2 h. The biphasic mixture was then cooled to room temperature and K_2CO_3 added in one portion. The resulting mixture was concentrated under reduced pressure to remove THF and re-dissolved in DCM. The crude reaction mixture was washed with H_2O and the aqueous phase extracted with DCM (3X). The combined organics were then washed with brine, dried with Na_2SO_4, filtered, and concentrated and the concentrate was further purified by silica gel chromatography (0-10% MeOH (with 10% 2 M NH_3) in DCM) to give intermediate C-9 as an orange-brown foam (1.35 g, 5.84 mmol, 43%). MS (ESI) mass calcd. for $C_{15}H_{21}NO$, 231.2; m/z found 232.2 $[M+H]^+$.

Intermediate C-10: (R/S)-tert-butyl 6-hydroxy-2-azabicyclo[2.2.2]octane-2-carboxylate

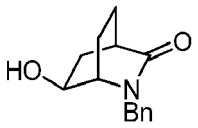
[0275]



[0276] Intermediate C-10 was prepared analogous to Intermediate C-3 substituting racemic Intermediate C-2 for schlemic Intermediate C-9. MS (ESI) mass calcd. for $C_{12}H_{21}NO_3$, 227.2; m/z found 172.2 $[M+2H-t\text{Bu}]^+$. Intermediate C-10 can be carried forward to Intermediate C-4A, which can be obtained as a single enantiomer (Intermediate C-4B or C-4C) by Chiral SFC purification as described above.

Intermediate C-11: (R/S)-2-benzyl-6-hydroxy-2-azabicyclo[2.2.2]octan-3-one

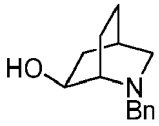
[0277]



[0278] Intermediate C-11 was synthesized according to the procedure in US3674793. A mixture of 7-oxabicyclo[4.1.0]heptane-3-carboxylic acid methyl ester (268.0 g, 1.72 mol) and benzylamine (170.0 g, 1.58 mol) in ethanol (1.3 L) was heated to reflux for 20 h and the reaction mixture was evaporated. The oily residue was stirred at 200 °C for 2 h to distill off low-boiling byproducts. The resulting oil was cooled to room temperature, diluted with a solution of sodium hydroxide (51.0 g, 1.27 mol) in methanol (1.0 L) and heated to reflux for 10 min. The reaction mixture was cooled to room temperature and diluted with a mixture of brine (1.5 L) and water (750 mL). The aqueous layer was extracted with dichloromethane (3X) and the combined organic layers were dried with $MgSO_4$, filtered, and concentrated. The oily residue was triturated with diisopropyl ether (400 mL) to give intermediate C-11 (190.0 g, 0.82 mol, 48%) as a white solid. MS (ESI) mass calcd. for $C_{14}H_{17}NO_2$, 231.1; m/z found 232.1 $[M+H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.43 - 7.12 (m, 5H), 4.99 (d, J = 3.3 Hz, 1H), 4.48 (d, J = 14.7 Hz, 1H), 4.39 (d, J = 14.7 Hz, 1H), 3.76 - 3.61 (m, 1H), 3.31-3.23 (m, 1H), 2.38 - 2.24 (m, 1H), 2.15 - 1.91 (m, 2H), 1.79 - 1.51 (m, 2H), 1.45 - 1.16 (m, 2H).

Intermediate C-2: 2-benzyl-2-azabicyclo[2.2.2]octan-6-ol

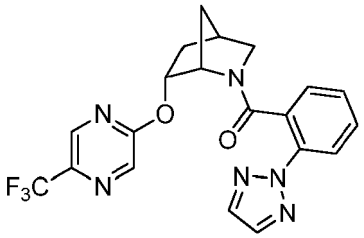
[0279]



[0280] To a suspension of lithium aluminum hydride (54.4 g, 1.43 mol) in THF (180 mL) under argon at 0 °C was added a solution of intermediate C-11 (170.0 g, 716.4 mmol) dropwise as a solution in THF (720 mL). The reaction mixture was allowed to warm to room temperature, then carefully heated to 60 °C and stirred for 2 h. The resulting suspension was cooled to 0 °C and diluted with diethyl ether (540 mL). To this suspension was added sodium sulfate decahydrate (450 g) in small portions. The mixture was stirred at room temperature for 16 h. The suspension was filtered and the filtrate evaporated. The residue was triturated with hexane (100 mL) to give intermediate C-2 (130.2 g, 0.60 mol, 84%) as a white solid. MS (ESI) mass calcd. for $C_{14}H_{19}NO$, 217.2; m/z found 218.3 $[M+H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.41 - 7.25 (m, 4H), 7.25 - 7.10 (m, 1H), 4.50 (d, J = 3.6 Hz, 1H), 3.97 - 3.86 (m, 1H), 3.71 (d, J = 14.7 Hz, 1H), 3.66 (d, J = 14.4 Hz, 1H), 2.61 (d, J = 9.3 Hz, 1H), 2.48 - 2.32 (m, 2H), 1.94 (t, J = 11.1 Hz, 1H), 1.82 - 1.66 (m, 2H), 1.66 - 1.56 (m, 1H), 1.52 - 1.37 (m, 2H), 1.32 - 1.15 (m, 1H). Intermediate C-2 can be carried forward to Intermediate C-4A, which can be obtained as a single enantiomer (Intermediate C-4B or C-4C) by Chiral SFC purification as described above.

Example 1: (R/S)-(2-(2H-1,2,3-triazol-2-yl)phenyl)(6-((5-(trifluoromethyl)pyrazin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

[0281]



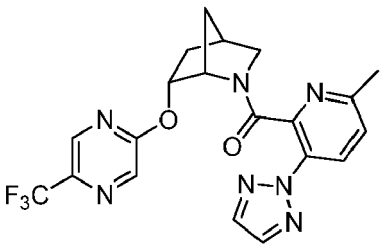
[0282] Step A: (R/S)-tert-butyl 6-((5-(trifluoromethyl)pyrazin-2-yl)oxy)-2-azabicyclo[2.2.1]heptane-2-carboxylate. To intermediate B-8 (100 mg, 0.469 mmol) dissolved in DMF (3 mL) was added NaH (28 mg, 0.70 mmol, 60% dispersion in mineral oil). After 5 minutes 2-chloro-5-(trifluoromethyl)pyrazine (0.087 mL, 0.70 mmol) was then added and the mixture heated to 90 °C. After heating at 90 °C for 3.5 h, the mixture was cooled to room temperature, quenched with saturated NH_4Cl solution, and diluted with EtOAc and H_2O. The aqueous layer was extracted with EtOAc (3X). The combined organics were washed with H_2O, brine, dried with $MgSO_4$, filtered and concentrated. Purification via silica gel chromatography (0-20% EtOAc in hexanes) gave the title compound (151 mg, 0.420 mmol, 90%). MS (ESI) mass calcd. for $C_{16}H_{20}F_3N_3O_3$, 359.1; m/z found 304.1 $[M+2H-tBu]^+$. ^1H NMR (400 MHz, Chloroform-d. compound present as a mixture of rotamers) δ 8.46 - 8.41 (m, 1H), 8.27 - 8.24 and 8.16 - 8.12 (2m, 1H), 5.45 - 5.30 (m, 1H), 4.63 - 4.48 (m, 1H), 3.48 - 3.33 (m, 1H), 3.28 - 3.13 (m, 1H), 2.67 - 2.54 (m, 1H), 2.32 - 2.19 (m, 1H), 1.85 - 1.04 (m, 12H).

[0283] Step B: (R/S)-6-((5-(trifluoromethyl)pyrazin-2-yl)oxy)-2-azabicyclo[2.2.1]heptane · xHCl. To the title compound of step A (151 mg, 0.42 mmol) in EtOAc (1 mL) was added 4 M HCl in dioxane (6 mL). After 3.25 h, the reaction was concentrated to give the title compound of step B which was used without further purification. MS (ESI) mass calcd. for $C_{11}H_{12}F_3N_3O$, 259.1; m/z found 260.1 $[M+H]^+$.

[0284] Step C: (R/S)-(2-(2H-1,2,3-triazol-2-yl)phenyl)(6-((5-(trifluoromethyl)pyrazin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone. To the title compound of step B (43 mg) and intermediate A-1 (24 mg, 0.13 mmol) in DMF (1.5 mL) was added DIPEA (0.4 mL, 2.32 mmol) and HATU (48 mg, 0.13 mmol). Upon completion of the reaction, purification was performed using Agilent Prep Method X to give the title compound (9 mg). MS (ESI) mass calcd. for $C_{20}H_{17}F_3N_6O_2$, 430.1; m/z found 431.1 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.80:0.20), major rotamer reported) δ 8.25 (s, 1H), 8.02 - 7.98 (m, 1H), 7.87 - 7.79 (m, 3H), 7.32 (ddd, *J* = 8.2, 7.4, 1.5 Hz, 1H), 7.04 (dd, *J* = 7.7, 1.5 Hz, 1H), 6.81 (t, *J* = 7.5 Hz, 1H), 4.97 (dt, *J* = 10.2, 3.3 Hz, 1H), 4.03 - 3.96 (m, 1H), 3.62 (dt, *J* = 11.0, 3.2 Hz, 1H), 3.44 (dd, *J* = 10.9, 1.5 Hz, 1H), 2.68 - 2.63 (m, 1H), 2.27 - 2.18 (m, 1H), 1.48 (dt, *J* = 13.6, 3.6 Hz, 1H), 1.40 (d, *J* = 10.6 Hz, 1H), 1.33 - 1.25 (m, 1H).

Example 2: (R/S)-(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)(6-((5-(trifluoromethyl)pyrazin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

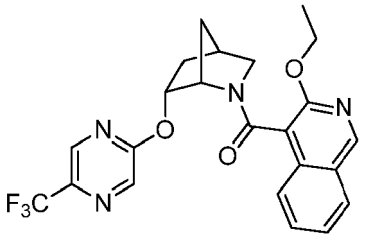
[0285]



[0286] Prepared analogous to Example 1 substituting intermediate A-1 with intermediate A-20. MS (ESI) mass calcd. for $C_{20}H_{18}F_3N_7O_2$, 445.1; m/z found 446.2 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.78:0.22), major rotamer reported) δ 8.30 - 8.27 (m, 1H), 8.05 - 8.00 (m, 2H), 7.83 (s, 2H), 7.11 - 7.07 (m, 1H), 5.01 (dt, *J* = 10.2, 3.2 Hz, 1H), 4.27 - 4.23 (m, 1H), 3.70 (dt, *J* = 11.0, 3.2 Hz, 1H), 3.49 (dd, *J* = 11.0, 1.4 Hz, 1H), 2.72 - 2.67 (m, 1H), 2.30-2.21 (m, 4H), 1.60 - 1.48 (m, 3H).

Example 3: (R/S)-(3-ethoxyisoquinolin-4-yl)((5-(trifluoromethyl)pyrazin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

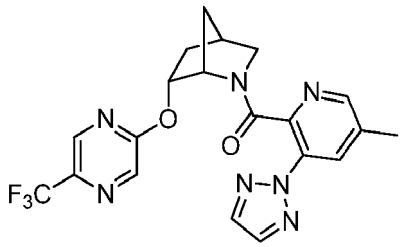
[0287]



[0288] Prepared analogous to Example 1 substituting intermediate A-1 with intermediate A-21. MS (ESI) mass calcd. for $C_{23}H_{21}F_3N_4O_3$, 458.2; m/z found 459.2 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers, major rotamer reported) δ 8.72 (d, *J* = 0.8 Hz, 1H), 7.77 - 7.72 (m, 1H), 7.71 - 7.68 (m, 1H), 7.64 - 7.58 (m, 2H), 7.52 - 7.47 (m, 1H), 7.30 (ddd, *J* = 8.1, 6.8, 1.1 Hz, 1H), 4.87 (dt, *J* = 10.2, 3.4 Hz, 1H), 4.68 - 4.39 (m, 3H), 3.87 (dt, *J* = 11.1, 3.2 Hz, 1H), 3.56 (dd, *J* = 11.1, 1.6 Hz, 1H), 2.83 - 2.77 (m, 1H), 2.35 - 2.26 (m, 1H), 2.01 - 1.95 (m, 1H), 1.84 - 1.75 (m, 1H), 1.56 - 1.38 (m, 4H).

Example 4: (R/S)-5-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)(6-((5-(trifluoromethyl)pyrazin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

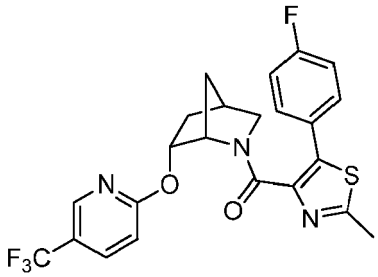
[0289]



[0290] Prepared analogous to Example 1 substituting intermediate A-1 with intermediate A-19. MS (ESI) mass calcd. for $C_{20}H_{18}F_3N_7O_2$, 445.1; m/z found 446.1 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.88:0.12), major rotamer reported) δ 8.34 (d, *J* = 1.3 Hz, 1H), 8.00 - 7.95 (m, 2H), 7.84 - 7.80 (m, 2H), 7.62 - 7.59 (m, 1H), 5.10 (dt, *J* = 10.3, 3.2 Hz, 1H), 4.27 - 4.24 (m, 1H), 3.71 (dt, *J* = 11.0, 3.2 Hz, 1H), 3.49 (dd, *J* = 11.0, 1.5 Hz, 1H), 2.76 - 2.70 (m, 1H), 2.34 - 2.22 (m, 4H), 1.71 - 1.54 (m, 3H).

Example 5: (R/S)-(5-(4-fluorophenyl)-2-methylthiazol-4-yl)(6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[0291]



[0292] Step A: (R/S)-tert-butyl 6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptane-2-carboxylate. To intermediate B-8 (200 mg, 0.94 mmol) dissolved in DMF (5 mL) was added NaH (56 mg, 1.41 mmol, 60% dispersion in mineral oil). After 5 minutes 2-chloro-5-(trifluoromethyl)pyridine (340 mg, 1.87 mmol) was then added and the mixture heated to 80 °C. After heating at 80 °C for 5.75 h, the mixture was cooled to room temperature, quenched with saturated NH_4Cl solution, diluted with H_2O, and the aqueous layer extracted with EtOAc (3X). The combined organics were washed with H_2O, brine, dried with $MgSO_4$, filtered and concentrated. Purification via silica gel chromatography (0-30% EtOAc in hexanes) gave the title compound (300 mg, 0.84 mmol, 89%). MS (ESI) mass calcd. for $C_{17}H_{21}F_3N_2O_3$, 358.2; m/z

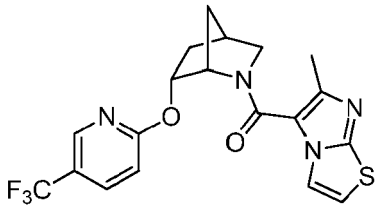
found 359.2 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d) δ 8.47 - 8.37 (m, 1H), 7.84 - 7.69 (m, 1H), 6.87 - 6.68 (m, 1H), 5.45 - 5.29 (m, 1H), 4.63 - 4.52 (m, 1H), 3.47 - 3.34 (m, 1H), 3.26 - 3.11 (m, 1H), 2.66 - 2.52 (m, 1H), 2.31-2.16 (m, 1H), 1.80 - 1.09 (series of m, 12H).

[0293] Step B: (R/S)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptane · xHCl. To the title compound of step A (300 mg, 0.84 mmol) in EtOAc (1 mL) was added 4 M HCl in dioxane (5 mL). After 7 h, the reaction was concentrated to give the title compound of step B (243 mg) which was used without further purification. MS (ESI) mass calcd. for $C_{12}H_{13}F_3N_2O$, 258.1; m/z found 259.1 $[M+H]^+$.

[0294] Step C: (R/S)-(5-(4-fluorophenyl)-2-methylthiazol-4-yl)(6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone. To the title compound of step B (30 mg) and intermediate A-14 (24 mg, 0.10 mmol) in DMF (1 mL) was added DIPEA (0.1 mL, 0.58 mmol) and HATU (38 mg, 0.10 mmol). Upon completion, the reaction was diluted with H2O and the aqueous layer extracted with EtOAc (3X). The combined organics were washed with H2O, brine, dried with MgSO4, filtered, and concentrated. Purification of the concentrate was performed using Agilent Prep Method X to give the title compound (40.3 mg). MS (ESI) mass calcd. for $C_{23}H_{19}F4N_3O_2S$, 477.1 m/z found 478.1 [M+H]+. 1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.85:0.15), major rotamer reported) δ 8.19 - 8.14 (m, 1H), 7.63 - 7.57 (m, 1H), 7.49 - 7.41 (m, 2H), 7.12 - 7.01 (m, 2H), 6.61 - 6.54 (m, 1H), 5.03 (dt, *J* = 10.3, 3.2 Hz, 1H), 4.64 - 4.58 (m, 1H), 3.56 - 3.51 (m, 2H), 2.66 - 2.58 (m, 1H), 2.44 (s, 3H), 2.26 - 2.15 (m, 1H), 1.53 (d, *J* = 10.8 Hz, 1H), 1.45 - 1.35 (m, 2H).

Example 6: (R/S)-(6-methylimidazo[2,1 -b]thiazol-5-yl)(6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

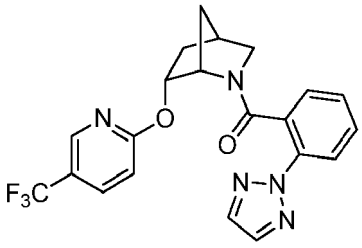
[0295]



[0296] Prepared analogous to Example 5 substituting intermediate A-14 with intermediate A-17. MS (ESI) mass calcd. for $C_{19}H_{17}F_3N_4O_2S$, 422.1; m/z found 423.1 $[M+H]^+$.^1H NMR (400 MHz, Chloroform-d) δ 8.08 (br.s, 1H), 7.54 - 7.37 (m, 2H), 6.68 (d, *J* = 4.5 Hz, 1H), 6.53 - 6.41 (m, 1H), 5.22 - 5.08 (m, 1H), 4.98 - 4.85 (m, 1H), 3.87 - 3.65 (m, 1H), 3.57 - 3.46 (m, 1H), 2.77 - 2.71 (m, 1H), 2.39 (s, 3H), 2.36 - 2.24 (m, 1H), 2.04 - 1.95 (m, 1H), 1.85 (d, *J* = 10.5 Hz, 1H), 1.49 (dt, *J* = 13.6, 3.5 Hz, 1H).

Example 7: (R/S)-(2-(2H-1,2,3-triazol-2-yl)phenyl)(6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

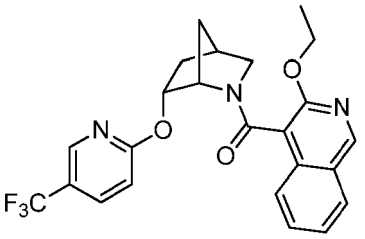
[0297]



[0298] Prepared analogous to Example 5 using intermediate A-1. MS (ESI) mass calcd. for $C_{21}H_{18}F_3N_5O_2$, 429.2; m/z found 430.1 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers, major rotamer reported) δ 8.02 - 7.99 (m, 1H), 7.87 - 7.74 (m, 4H), 7.35 - 7.29 (m, 1H), 7.03 (dd, *J* = 7.7, 1.5 Hz, 1H), 6.84 - 6.78 (m, 2H), 5.00 (dt, *J* = 10.1, 3.3 Hz, 1H), 4.07 - 4.03 (m, 1H), 3.61 (dt, *J* = 11.0, 3.2 Hz, 1H), 3.40 (dd, *J* = 10.9, 1.5 Hz, 1H), 2.65 - 2.60 (m, 1H), 2.25 - 2.16 (m, 1H), 1.45 - 1.37 (m, 2H), 1.33 - 1.25 (m, 1H).

Example 8: (R/S)-(3-ethoxyisoquinolin-4-yl)(6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

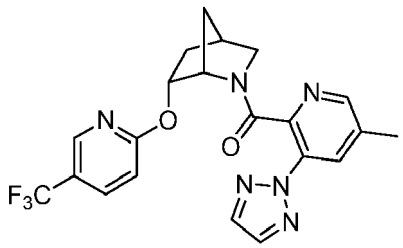
[0299]



[0300] Prepared analogous to Example 5 using intermediate A-21 and additional purification using Shimadzu Prep Method X. MS (ESI) mass calcd. for $C_{24}H_{22}F_3N_3O_3$, 457.2; m/z found 458.2 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d) δ 8.71 (s, 1H), 7.81 - 7.76 (m, 1H), 7.71 - 7.68 (m, 1H), 7.61 (d, *J* = 8.2 Hz, 1H), 7.46 (ddd, *J* = 8.4, 6.8, 1.3 Hz, 1H), 7.29 - 7.23 (buried m, 1H), 7.10 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.11 (d, *J* = 8.6 Hz, 1H), 4.91 (dt, *J* = 10.3, 3.4 Hz, 1H), 4.68 - 4.66 (m, 1H), 4.65 - 4.58 (m, 1H), 4.49 - 4.40 (m, 1H), 3.86 (dt, *J* = 11.2, 3.2 Hz, 1H), 3.58 (dd, *J* = 11.1, 1.7 Hz, 1H), 2.84 - 2.76 (m, 1H), 2.36 - 2.24 (m, 1H), 1.99 - 1.94 (m, 1H), 1.80 (d, *J* = 10.4 Hz, 1H), 1.50 (dt, *J* = 13.7, 3.8 Hz, 1H), 1.44 (t, *J* = 7.1 Hz, 3H).

Example 9: (R/S)-(5-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)(6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

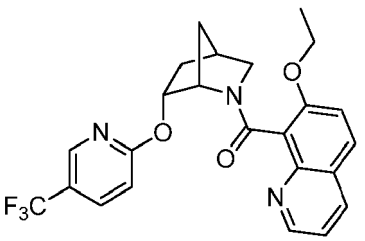
[0301]



[0302] Prepared analogous to Example 5 using intermediate A-19. MS (ESI) mass calcd. for $C_{21}H_{19}F_3N_6O_2$, 444.2; m/z found 445.2 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.93:0.07), major rotamer reported) δ 7.98 - 7.95 (m, 1H), 7.95 - 7.92 (m, 1H), 7.82 (s, 2H), 7.71 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.67 - 7.64 (m, 1H), 6.88 - 6.83 (m, 1H), 5.02 (dt, *J* = 10.2, 3.2 Hz, 1H), 4.28 - 4.21 (m, 1H), 3.68 (dt, *J* = 10.9, 3.2 Hz, 1H), 3.45 (dd, *J* = 11.0, 1.2 Hz, 1H), 2.71 - 2.64 (m, 1H), 2.28 (s, 3H), 2.28 - 2.17 (m, 1H), 1.59 - 1.46 (m, 3H).

Example 10: (R/S)-(7-ethoxyquinolin-8-yl)(6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

[0303]

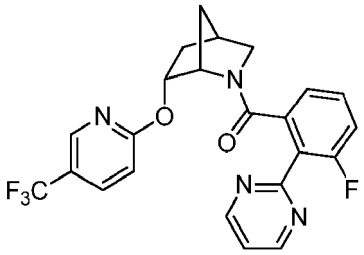


[0304] Prepared analogous to Example 5 using intermediate A-25. MS (ESI) mass calcd. for $C_{24}H_{22}F_3N_3O_3$, 457.2; m/z found 458.2 $[M+H]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5um,

100 × 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 30 °C). R_t = 6.49 min (major rotamer) at 254 nm.

Example 11: (R/S)-(3-fluoro-2-(pyrimidin-2-yl)phenyl)(6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

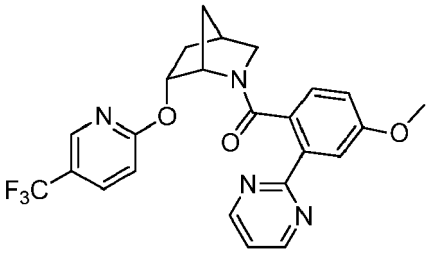
[0305]



[0306] Prepared analogous to Example 5 using intermediate A-2. MS (ESI) mass calcd. for $C_{23}H_{18}F_4N_4O_2$, 458.1; m/z found 459.2 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.82:0.18), major rotamer reported) δ 8.86 (d, *J* = 4.9 Hz, 2H), 8.14 - 8.10 (m, 1H), 7.79 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.30 - 7.26 (m, 1H), 7.10 - 7.03 (m, 1H), 6.95 - 6.81 (m, 3H), 5.06 (dt, *J* = 10.2, 3.4 Hz, 1H), 4.27 - 4.23 (m, 1H), 3.34 - 3.30 (m, 2H), 2.57 - 2.51 (m, 1H), 2.25 - 2.14 (m, 1H), 1.46 - 1.40 (m, 1H), 1.36 (dt, *J* = 13.6, 3.6 Hz, 1H), 0.94 - 0.87 (m, 1H).

Example 12: (R/S)-(4-methoxy-2-(pyrimidin-2-yl)phenyl)(6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

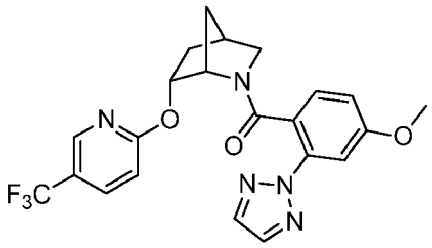
[0307]



[0308] To the title compound of Example 5 step B (20 mg) and intermediate A-15 (15 mg, 0.066 mmol) was added DCM (0.8 mL) and DIPEA (0.05 mL, 0.29 mmol). T_3P (0.11 mL, 0.18 mmol, 50% solution in DMF) was then added dropwise and the mixture heated to 45 °C. Upon completion the reaction was quenched with saturated $NaHCO_3$ solution and the aqueous layer extracted with EtOAc (3X). The combined organics were washed saturated $NaHCO_3$ solution, brine, dried with $MgSO_4$, filtered, and concentrated. Purification of the concentrate was performed using Agilent Prep Method X to give the title compound (9.3 mg). MS (ESI) mass calcd. for $C_{24}H_{21}F_3N_4O_3$, 470.2; m/z found 471.2 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.82:0.18), major rotamer reported) δ 8.78 (d, *J* = 4.8 Hz, 2H), 8.11 - 8.09 (m, 1H), 7.83 - 7.77 (m, 1H), 7.70 (d, *J* = 2.6 Hz, 1H), 7.20 (t, *J* = 4.9 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 1H), 6.87 - 6.80 (m, 1H), 6.45 (dd, *J* = 8.4, 2.7 Hz, 1H), 5.03 (dt, *J* = 10.1, 3.3 Hz, 1H), 4.16 - 4.12 (m, 1H), 3.81 (s, 3H), 3.62 (dt, *J* = 10.9, 3.2 Hz, 1H), 3.40 (dd, *J* = 10.8, 1.4 Hz, 1H), 2.66 - 2.60 (m, 1H), 2.26 - 2.16 (m, 1H), 1.45 - 1.35 (m, 2H), 1.29 - 1.17 (m, 1H).

Example 13: (R/S)-4-methoxy-2-(2H-1,2,3-triazol-2-yl)phenyl)(6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

[0309]

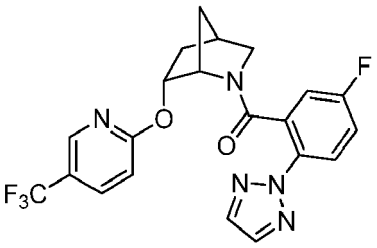


[0310] Prepared analogous to Example 5 using intermediate A-5. MS (ESI) mass calcd. for $C_{22}H_{20}F_3N_5O_3$, 459.1; m/z found 460.2 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.88:0.12), major rotamer reported) δ 8.11 - 8.07 (m, 1H), 7.84 - 7.75 (m, 3H), 7.37 (d, *J* = 2.5 Hz, 1H), 6.96 (d, *J* = 8.5 Hz, 1H), 6.81 (d, *J* = 8.7 Hz, 1H), 6.37 (dd, *J* = 8.5, 2.5 Hz, 1H), 5.01 (dt, *J* = 10.1, 3.3 Hz, 1H), 4.08 - 4.01 (m, 1H), 3.80 (s, 3H), 3.58 (dt, *J* = 10.9, 3.2 Hz, 1H), 3.39 (dd, *J* = 10.9, 1.4 Hz, 1H), 2.65 - 2.58 (m, 1H), 2.25 - 2.14 (m, 1H), 1.45 - 1.35 (m, 2H), 1.30 - 1.22 (m, 1H).

[0311] An ORTEP of Example 13 is depicted in Figure 1.

Example 14: (R/S)-(5-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)(6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

[0312]

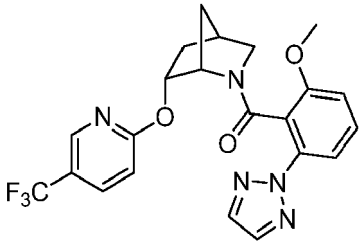


[0313] Prepared analogous to Example 5 using intermediate A-10. MS (ESI) mass calcd. for $C_{21}H_{17}F_4N_5O_2$, 447.1; m/z found 448.1 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.85:0.15), major rotamer reported) δ 8.09 - 8.05 (m, 1H), 7.85 - 7.78 (m, 4H), 7.00 (ddd, *J* = 9.0, 7.6, 2.9 Hz, 1H), 6.82 (d, *J* = 8.7 Hz, 1H), 6.78 (dd, *J* = 8.1, 2.9 Hz, 1H), 5.02 (dt, *J* = 10.2, 3.3 Hz, 1H), 4.06 - 4.01 (m, 1H), 3.59 (dt, *J* = 10.9, 3.2 Hz, 1H), 3.40 (dd, *J* = 10.9, 1.5 Hz, 1H), 2.66 - 2.60 (m, 1H), 2.28 - 2.17 (m, 1H), 1.47 - 1.37 (m, 2H), 1.34 - 1.27 (m, 1H).

[0314] An ORTEP of Example 14 is depicted in Figure 2.

Example 15: (R/S)-2-methoxy-6-(2H-1,2,3-triazol-2-yl)phenyl)(6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

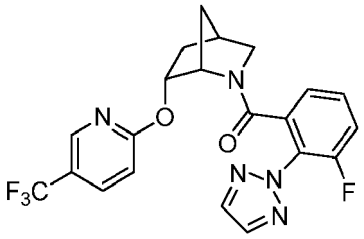
[0315]



[0316] Prepared analogous to Example 5 using intermediate A-13. MS (ESI) mass calcd. for $C_{22}H_{20}F_3N_5O_3$, 459.2; m/z found 460.2 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers, major rotamer reported) δ 8.00 - 7.95 (m, 1H), 7.82 (s, 2H), 7.73 (d, *J* = 10.6 Hz, 1H), 7.46 (dd, *J* = 8.2, 0.9 Hz, 1H), 7.28 - 7.21 (m, 1H), 6.75 - 6.71 (m, 1H), 6.42 (dd, *J* = 8.4, 0.9 Hz, 1H), 4.82 (dt, *J* = 10.2, 3.4 Hz, 1H), 4.18 - 4.12 (m, 1H), 3.63 - 3.58 (m, 1H), 3.57 (s, 3H), 3.37 (dd, *J* = 11.0, 1.5 Hz, 1H), 2.58 - 2.52 (m, 1H), 2.19 - 2.09 (m, 1H), 1.74 - 1.66 (m, 1H), 1.45 - 1.37 (m, 1H), 1.32 - 1.23 (m, 1H).

Example 16: (R/S)-(3-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)(6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

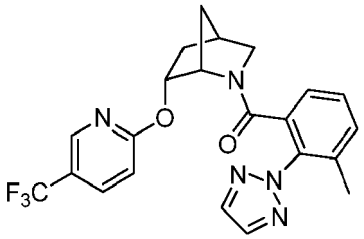
[0317]



[0318] Prepared analogous to Example 5 using intermediate A-16. MS (ESI) mass calcd. for $C_{21}H_{17}F_4N_5O_2$, 447.1; m/z found 448.1[M+H]$^+$. ^{1}H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.86:0.14), major rotamer reported) δ 8.14 - 8.09 (m, 1H), 7.89 (s, 2H), 7.83 - 7.78 (m, 1H), 7.16 (ddd, *J* = 9.9, 8.1, 1.6 Hz, 1H), 6.98 - 6.81 (m, 3H), 5.06 (dt, *J* = 10.1, 3.3 Hz, 1H), 4.19 - 4.15 (m, 1H), 3.38 - 3.30 (m, 2H), 2.59 - 2.53 (m, 1H), 2.26 - 2.16 (m, 1H), 1.50 - 1.43 (m, 1H), 1.39 - 1.30 (m, 1H), 1.19 - 1.10 (m, 1H).

Example 17: (R/S)-(3-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)(6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

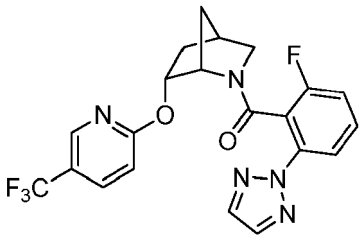
[0319]



[0320] Prepared analogous to Example 5 using intermediate A-22. MS (ESI) mass calcd. for $C_{22}H_{20}F_3N_5O_2$, 443.2 m/z found 444.2 [M+H]$^+$. ^{1}H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.85:0.15), major rotamer reported) δ 8.15 - 8.11 (m, 1H), 7.86 - 7.77 (m, 3H), 7.24 - 7.19 (m, 1H), 6.99 - 6.82 (m, 3H), 5.09 (dt, *J* = 10.1, 3.3 Hz, 1H), 4.25 - 4.19 (m, 1H), 3.31 - 3.23 (m, 2H), 2.57 - 2.50 (m, 1H), 2.27 - 2.11 (m, 4H), 1.53 - 1.47 (m, 1H), 1.37 - 1.28 (m, 1H), 1.27 - 1.21 (m, 1H).

Example 18: (R/S)-(2-fluoro-6-(2H-1,2,3-triazol-2-yl)phenyl)(6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

[0321]

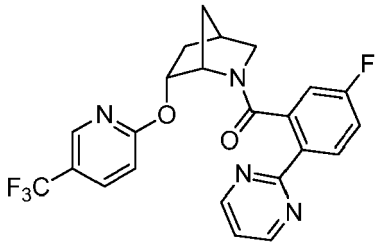


[0322] Prepared analogous to Example 5 using intermediate A-11. MS (ESI) mass calcd. for $C_{21}H_{17}F_4N_5O_2$, 447.1; m/z found 448.1 [M+H]$^+$. ^{1}H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers, major rotamer reported) δ 8.04 - 8.02 (m, 1H), 7.85 - 7.72 (m, 4H), 7.32 - 7.26 (m, 1H), 6.92 - 6.88 (m, 1H), 6.61 (td, *J* = 8.4, 1.0 Hz, 1H), 5.00 - 4.94 (m, 1H), 4.03 - 4.00 (m, 1H), 3.65 (dt, *J* = 11.0, 3.2 Hz, 1H), 3.44 (dd, *J* = 10.9, 1.5 Hz, 1H), 2.68 - 2.60

(m, 1H), 2.28 - 2.17 (m, 1H), 1.46 - 1.37 (m, 2H), 1.31 - 1.25 (m, 1H).

Example 19: (R/S)-(5-fluoro-2-(pyrimidin-2-yl)phenyl)(6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

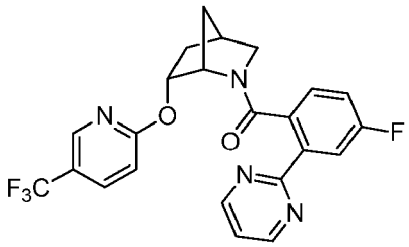
[0323]



[0324] Prepared analogous to Example 5 using intermediate A-7. MS (ESI) mass calcd. for $C_{23}H_{18}F_4N_4O_2$, 458.1 m/z found 459.2 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.88:0.12), major rotamer reported) δ 8.77 (d, *J* = 4.9 Hz, 2H), 8.22 (dd, *J* = 8.8, 5.6 Hz, 1H), 8.11 - 8.06 (m, 1H), 7.82 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.19 (t, *J* = 4.9 Hz, 1H), 6.98 (ddd, *J* = 8.8, 7.9, 2.7 Hz, 1H), 6.85 (d, *J*= 8.8 Hz, 1H), 6.77 (dd, *J* = 8.6, 2.7 Hz, 1H), 5.03 (dt, *J* = 10.1, 3.4 Hz, 1H), 4.16 - 4.11 (m, 1H), 3.66 (dt, *J* = 10.8, 3.2 Hz, 1H), 3.42 (dd, *J* = 10.8, 1.5 Hz, 1H), 2.70 - 2.63 (m, 1H), 2.30 - 2.19 (m, 1H), 1.50 - 1.39 (m, 2H), 1.35 - 1.27 (m, 1H).

Example 20: (R/S)-(4-fluoro-2-(pyrimidin-2-yl)phenyl)(-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

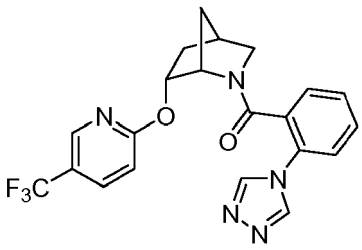
[0325]



[0326] Prepared analogous to Example 5 using intermediate A-23. MS (ESI) mass calcd. for $C_{23}H_{18}F_4N_4O_2$, 458.1 m/z found 459.2 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.84:0.16), major rotamer reported) δ 8.80 (d, *J* = 4.8 Hz, 2H), 8.12 - 8.09 (m, 1H), 7.93 (dd, *J* = 9.9, 2.6 Hz, 1H), 7.83 - 7.78 (m, 1H), 7.25 - 7.21 (m, 1H), 7.01 (dd, *J* = 8.4, 5.6 Hz, 1H), 6.85 - 6.81 (m, 1H), 6.63 - 6.55 (m, 1H), 5.03 (dt, *J* = 10.1, 3.3 Hz, 1H), 4.16 - 4.09 (m, 1H), 3.65 (dt, *J* = 10.8, 3.3 Hz, 1H), 3.46 - 3.36 (m, 1H), 2.69 - 2.62 (m, 1H), 2.29 - 2.17 (m, 1H), 1.48 - 1.37 (m, 2H), 1.31-1.23 (m, 1H).

Example 21: (R/S)-(2-(4H-1,2,4-triazol-4-yl)phenyl)(6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

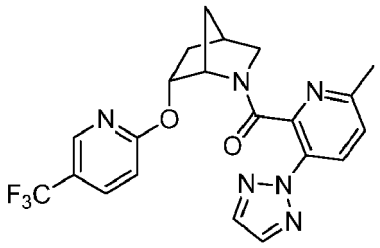
[0327]



[0328] Prepared analogous to Example 5 using intermediate A-9. MS (ESI) mass calcd. for $C_{21}H_{18}F_3N_5O_2$, 429.1 m/z found 430.2 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.84:0.16), major rotamer reported) δ 8.44 (s, 2H), 8.03 - 7.95 (m, 1H), 7.80 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.44 - 7.34 (m, 1H), 7.30 - 7.24 (m, 1H), 7.08 - 6.92 (m, 2H), 6.83 (d, *J* = 8.7 Hz, 1H), 5.04 - 4.94 (m, 1H), 3.90 (br.s, 1H), 3.47 - 3.32 (m, 2H), 2.65 - 2.57 (m, 1H), 2.26 - 2.13 (m, 1H), 1.52 - 1.33 (m, 2H), 1.05 - 0.86 (m, 1H).

Example 22: (R/S)-(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)(6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

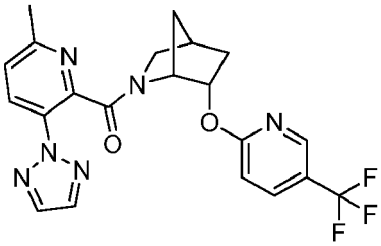
[0329]



[0330] Prepared analogous to Example 5 using intermediate A-20. MS (ESI) mass calcd. for $C_{21}H_{19}F_3N_6O_2$, 444.2; m/z found 445.1 $[M+H]^+$.^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.82:0.18), major rotamer reported) δ 8.05 - 7.98 (m, 2H), 7.83 (s, 2H), 7.71 - 7.66 (m, 1H), 7.10 - 7.05 (m, 1H), 6.86 - 6.80 (m, 1H), 5.01 - 4.93 (m, 1H), 4.28 - 4.22 (m, 1H), 3.68 (dt, *J* = 10.9, 3.2 Hz, 1H), 3.46 (dd, *J* = 10.9, 1.2 Hz, 1H), 2.67 - 2.62 (m, 1H), 2.28 - 2.16 (m, 4H), 1.53 - 1.42 (m, 3H).

Example 23: (6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)((1R,4S,6S)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

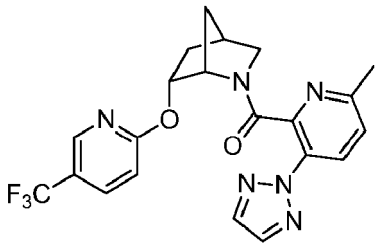
[0331]



[0332] The title compound, absolute configuration confirmed by Example 25, was obtained as a single enantiomer by Chiral SFC purification of Example 22 performed using a Chiralpak IC column (Sum 250 × 21 mm), mobile phase of 20% EtOH: 80% CO_2, and a flow rate of 40 mL/min (Temperature = 40 °C). Elution was monitored following absorbance at 270nm. The enantiomeric purity was confirmed by analytical SFC using a Chiralpak IC column (Sum 250 × 4.6 mm), mobile phase of 20% EtOH: 80% CO_2, and a flow rate of 2 mL/min over 45 minutes (Temperature = 40 °C). Elution was monitored following absorbance at 270nm. (enantiopurity >98%) which elutes as two peaks with an initial minor peak followed by a second major peak (due to rotamers), 6.77 min and 23.40 min retention time). MS (ESI) mass calcd. for $C_{21}H_{19}F_3N_6O_2$, 444.2; m/z found 445.2 $[M+H]^+$. ^1H NMR data is in agreement with Example 22.

Example 24: (6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

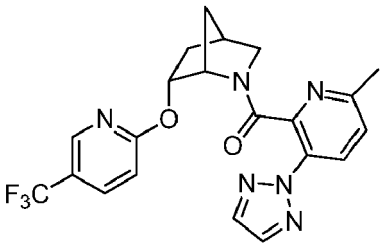
[0333]



[0334] The title compound, absolute configuration confirmed by Example 25, was obtained as a single enantiomer by Chiral SFC purification of Example 22 performed using a Chiralpak IC column (Sum 250 × 21 mm), mobile phase of 20% EtOH: 80% CO_2, and a flow rate of 40 mL/min (Temperature = 40 °C). Elution was monitored following absorbance at 270nm. The enantiomeric purity was confirmed by analytical SFC using a Chiralpak IC column (Sum 250 × 4.6 mm), mobile phase of 20% EtOH: 80% CO_2, and a flow rate of 2 mL/min over 45 minutes (Temperature = 40 °C). Elution was monitored following absorbance at 270nm. (enantiopurity >98%) which elutes as two peaks with an initial minor peak followed by a second major peak (due to rotamers), 7.75 min and 11.79 min retention time). MS (ESI) mass calcd. for $C_{21}H_{19}F_3N_6O_2$, 444.2; m/z found 445.2 $[M+H]^+$. ^1H NMR data is in agreement with Example 22.

Example 25: (6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

[0335]



[0336] Step A: (1S,4R,6R)-tert-butyl 6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptane-2-carboxylate. To intermediate B-5 (422 mg, 1.98 mmol) dissolved in DMF (8 mL) was added NaH (119 mg, 2.97 mmol, 60% dispersion in mineral oil). After 5 minutes 2-chloro-5-(trifluoromethyl)pyridine (718 mg, 3.96 mmol) was then added and the mixture heated to 80 °C. After heating at 80 °C for 4.75h, the mixture was cooled to room temperature, quenched with saturated NH_4Cl solution, diluted with H_2O, and the aqueous layer extracted with EtOAc (3X).The combined organics were washed with H_2O, brine, dried with $MgSO_4$, filtered and concentrated. Purification via silica gel chromatography (0-25% EtOAc in hexanes) gave the title compound (622 mg, 1.74 mmol, 88%). MS (ESI) mass calcd. for $C_{17}H_{21}F_3N_2O_3$, 358.2; m/z found 359.2 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, compound present as a mixture of rotamers (0.75:0.25)) δ 8.44 - 8.37 (m, 1H), 7.80 - 7.74 (m, 0.75H), 7.73 - 7.66 (m, 0.25H), 6.82 - 6.77 (m, 0.75H), 6.73 - 6.68 (m, 0.25H), 5.44 - 5.37 (m, 0.25H), 5.34 (dt, *J* = 10.1, 3.2 Hz, 0.75H), 4.58 - 4.53 (m, 1H), 3.44 - 3.34 (m, 1H), 3.20 (dd, *J* = 9.6, 1.3 Hz, 0.75H), 3.13 (d, *J* = 9.5 Hz, 0.25H), 2.61 - 2.52 (m, 1H), 2.29 - 2.15 (m, 1H), 1.79 - 1.58 (m, 2H), 1.47 - 1.23 (m, 3H), 1.12 (s, 7H).

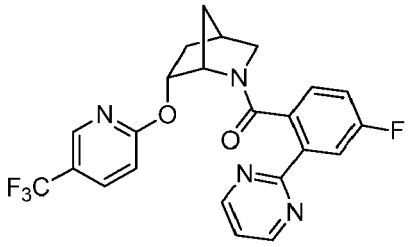
[0337] Step B: (1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptane · xHCl. To the title compound of step A (622 mg, 1.74 mmol) in EtOAc (1 mL) was added 4M HCl in dioxane (10 mL). After 2h, the reaction was concentrated to give the title compound of step B (507 mg) which was used without further purification. MS (ESI) mass calcd. for $C_{12}H_{13}F_3N_2O$, 258.1; m/z found 259.1 $[M+H]^+$.

[0338] Step C: (6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone To the title compound of step B (100 mg) and intermediate A-20 (84 mg, 0.37 mmol) in DMF (4 mL) was added DIPEA (0.3 mL, 1.74 mmol) and HATU (142 mg, 0.37 mmol). Upon completion, the reaction was diluted with H_2O and the aqueous layer extracted with EtOAc (3X). The combined organics were washed with H_2O, brine, dried with $MgSO_4$, filtered, and concentrated. Purification of the concentrate was performed using Agilent Prep Method X to give the title compound (112 mg). The enantiomeric purity was confirmed by analytical SFC using a Chiralpak IC column (Sum 250 × 4.6 mm), mobile phase of 20% EtOH: 80% CO_2, and a flow rate of 2 mL/min over 45 minutes (Temperature = 40 °C). Elution was monitored following absorbance at 270nm. (100% single enantiomer) which elutes as two peaks with an initial minor peak followed by a second major peak (due to rotamers), 7.69 min and 11.90 min retention time). MS (ESI) mass calcd. for $C_{21}H_{19}F_3N_6O_2$, 444.2; m/z found 445.2 $[M+H]^+$. ^1H NMR data is in agreement

with Example 22.

Example 26: (4-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

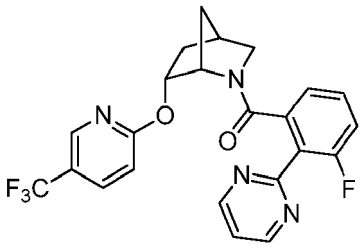
[0339]



[0340] Prepared analogous to Example 25 substituting intermediate A-20 with intermediate A-23. MS (ESI) mass calcd. for $C_{23}H_{18}F_4N_4O_2$, 458.1 m/z found 459.1 $[M+H]^+$. ^{1}H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.85:0.15), major rotamer reported) δ 8.80 (d, *J* = 4.8 Hz, 2H), 8.13 - 8.07 (m, 1H), 7.95 - 7.90 (m, 1H), 7.84 - 7.78 (m, 1H), 7.23 (t, *J* = 4.8 Hz, 1H), 7.01 (dd, *J* = 8.4, 5.6 Hz, 1H), 6.87 - 6.81 (m, 1H), 6.59 (ddd, *J* = 8.5, 7.9,2.7 Hz, 1H), 5.03 (dt, *J* = 10.1, 3.3 Hz, 1H), 4.15 - 4.10 (m, 1H), 3.65 (dt, *J* = 10.8, 3.2 Hz, 1H), 3.44 - 3.38 (m, 1H), 2.69 - 2.62 (m, 1H), 2.29 - 2.18 (m, 1H), 1.48 - 1.37 (m, 2H), 1.34 - 1.23 (m, 1H).

Example 27: (3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

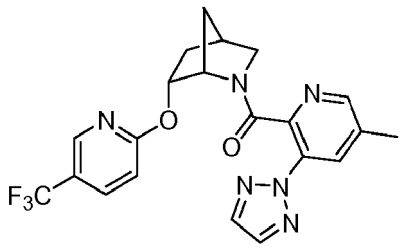
[0341]



[0342] Prepared analogous to Example 25 substituting intermediate A-20 with intermediate A-2. MS (ESI) mass calcd. for $C_{23}H_{18}F_4N_4O_2$, 458.1 m/z found 459.2 $[M+H]^+$. ^{1}H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.88:0.12), major rotamer reported) δ 8.86 (d, *J* = 4.9 Hz, 2H), 8.14 - 8.08 (m, 1H), 7.79 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.30 - 7.26 (m, 1H), 7.10 - 7.02 (m, 1H), 6.95 - 6.80 (m, 3H), 5.06 (dt, *J* = 10.3, 3.4 Hz, 1H), 4.28 - 4.22 (m, 1H), 3.34 - 3.30 (m, 2H), 2.56 - 2.51 (m, 1H), 2.25 - 2.15 (m, 1H), 1.45 - 1.40 (m, 1H), 1.36 (dt, *J* = 13.6, 3.6 Hz, 1H), 0.95 - 0.86 (m, 1H).

Example 28: (5-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

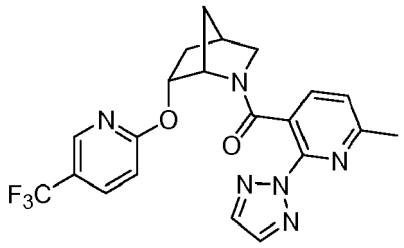
[0343]



[0344] Prepared analogous to Example 25 substituting intermediate A-20 with intermediate A-19. MS (ESI) mass calcd. for $C_{21}H_{19}F_3N_6O_2$, 444.2 m/z found 445.2 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.86:0.14), major rotamer reported) δ 7.98 - 7.92 (m, 2H), 7.83 (s, 2H), 7.75 - 7.69 (m, 1H), 7.67 - 7.63 (m, 1H), 6.89 - 6.83 (m, 1H), 5.02 (dt, *J* = 10.3, 3.2 Hz, 1H), 4.27 - 4.21 (m, 1H), 3.69 (dt, *J* = 10.9, 3.2 Hz, 1H), 3.51 - 3.42 (m, 1H), 2.70 - 2.64 (m, 1H), 2.33 - 2.16 (m, 4H), 1.58 - 1.46 (m, 3H).

Example 29: (6-methyl-2-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

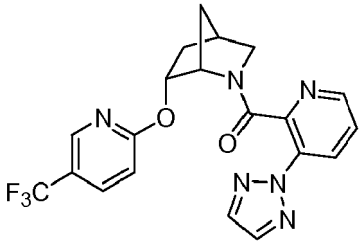
[0345]



[0346] Prepared analogous to Example 25 substituting intermediate A-20 with intermediate A-3. MS (ESI) mass calcd. $C_{21}H_{19}F_3N_6O_2$, 444.2 m/z found 445.2 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.83:0.17), major rotamer reported) δ 8.06 - 8.02 (m, 1H), 7.88 (s, 2H), 7.80 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.31 - 7.24 (m, 1H), 6.82 (d, *J* = 8.7 Hz, 1H), 6.61 (d, *J* = 7.8 Hz, 1H), 4.98 (dt, *J* = 10.1, 3.3 Hz, 1H), 4.06 - 4.02 (m, 1H), 3.62 (dt, *J* = 11.0, 3.2 Hz, 1H), 3.41 (dd, *J* = 10.9, 1.5 Hz, 1H), 2.68 - 2.61 (m, 1H), 2.56 (s, 3H), 2.27 - 2.14 (m, 1H), 1.48 - 1.40 (m, 2H), 1.37 - 1.29 (m, 1H).

Example 30: (3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

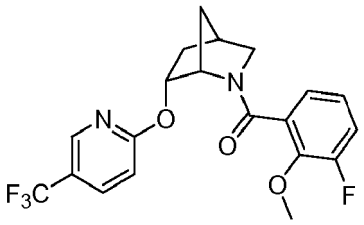
[0347]



[0348] Prepared analogous to Example 25 substituting intermediate A-20 with intermediate A-28. MS (ESI) mass calcd. $C_{20}H_{17}F_3N_6O_2$, 430.1 m/z found 431.2 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.80:0.20), major rotamer reported) δ 8.17 (dd, *J* = 8.4, 1.5 Hz, 1H), 7.95 - 7.91 (m, 1H), 7.88 - 7.81 (m, 3H), 7.72 (dd, *J* = 8.7, 2.6 Hz, 1H), 7.20 (dd, *J* = 8.3, 4.7 Hz, 1H), 6.86 (d, *J* = 8.8 Hz, 1H), 5.03 (dt, *J* = 10.2, 3.2 Hz, 1H), 4.27 - 4.23 (m, 1H), 3.74 - 3.68 (m, 1H), 3.47 (dd, *J* = 11.0, 1.3 Hz, 1H), 2.71 - 2.66 (m, 1H), 2.29 - 2.19 (m, 1H), 1.64 - 1.48 (m, 3H).

Example 31: (3-fluoro-2-methoxyphenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

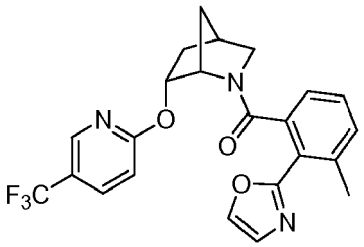
[0349]



[0350] Prepared analogous to Example 25 substituting intermediate A-20 with intermediate A-18. MS (ESI) mass calcd. $C_{20}H_{18}F_4N_2O_3$, 410.1 m/z found 411.1 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.83:0.17), major rotamer reported) δ 8.01 - 7.97 (m, 1H), 7.74 -7.71 (m, 1H), 6.92 (ddd, J = 11.5, 8.1, 1.7 Hz, 1H), 6.79 (d, 8.7 Hz, 1H), 6.67 - 6.49 (m, 2H), 5.07 (dt, *J* = 10.1, 3.2 Hz, 1H), 4.43 - 4.38 (m, 1H), 3.90 (d, *J* = 1.7 Hz, 3H), 3.69 (dt, *J* = 11.1, 3.3 Hz, 1H), 3.45 (dd, *J* = 11.1, 1.5 Hz, 1H), 2.76 - 2.70 (m, 1H), 2.33 - 2.21 (m, 1H), 1.90 - 1.83 (m, 1H), 1.75 - 1.69 (m, 1H), 1.44 (dt, *J* = 13.5, 3.6 Hz, 1H).

Example 32: (3-methyl-2-(oxazol-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

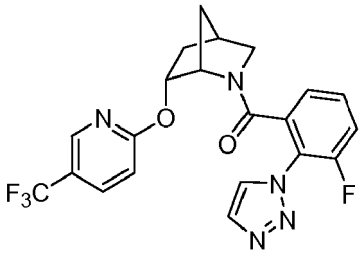
[0351]



[0352] Prepared analogous to Example 25 substituting intermediate A-20 with intermediate A-27. MS (ESI) mass calcd. $C_{23}H_{20}F_3N_3O_3$, 443.1 m/z found 444.2 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.81:0.19), major rotamer reported) δ 8.07 - 8.03 (m, 1H), 7.81 - 7.73 (m, 2H), 7.30 - 7.25 (m, 1H), 7.18 - 7.13 (m, 1H), 6.91 - 6.80 (m, 3H), 5.04 (dt, *J* = 10.2, 3.2 Hz, 1H), 4.22 - 4.17 (m, 1H), 3.49 - 3.41 (m, 1H), 3.40 - 3.33 (m, 1H), 2.63 - 2.57 (m, 1H), 2.44 (s, 3H), 2.26 - 2.16 (m, 1H), 1.49 (d, *J* = 10.4 Hz, 1H), 1.41 - 1.26 (m, 2H).

Example 33: (3-fluoro-2-(1H-1,2,3-triazol-1-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

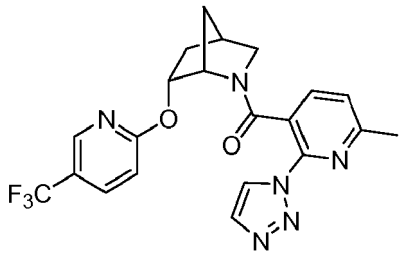
[0353]



[0354] Prepared analogous to Example 25 substituting intermediate A-20 with intermediate A-33. MS (ESI) mass calcd. $C_{21}H_{17}F_4N_5O_2$, 447.1 m/z found 448.2 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.76:0.24), major rotamer reported) δ 8.20 - 8.15 (m, 1H), 7.92 - 7.88 (m, 1H), 7.87 - 7.80 (m, 2H), 7.24 - 7.16 (m, 1H), 7.07 - 6.99 (m, 1H), 6.92 - 6.85 (m, 2H), 5.14 (dt, *J* = 9.9, 3.2 Hz, 1H), 4.28 - 4.24 (m, 1H), 3.37 - 3.31 (m, 1H), 3.30 - 3.24 (m, 1H), 2.62 - 2.56 (m, 1H), 2.32 - 2.21 (m, 1H), 1.42 - 1.31 (m, 2H), 0.94 - 0.89 (m, 1H).

Example 34: (6-methyl-2-(1H-1,2,3-triazol-1-yl)pyridin-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

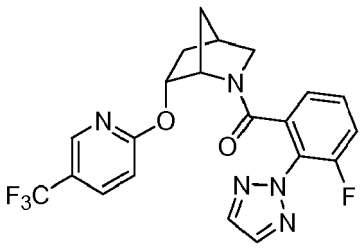
[0355]



[0356] Prepared analogous to Example 25 substituting intermediate A-20 with intermediate A-4. MS (ESI) mass calcd. $C_{21}H_{19}F_3N_6O_2$, 444.2 m/z found 445.2 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.87:0.13), major rotamer reported) δ 8.44 (d, *J* = 1.2 Hz, 1H), 8.09 - 8.05 (m, 1H), 7.84 - 7.78 (m, 2H), 7.28 (d, *J* = 7.8 Hz, 1H), 6.88 - 6.83 (m, 1H), 6.65 (d, *J* = 7.8 Hz, 1H), 5.05 (dt, *J* = 10.1, 3.3 Hz, 1H), 4.13 - 4.06 (m, 1H), 3.73 (dt, *J* = 11.0, 3.2 Hz, 1H), 3.38 (dd, *J* = 10.9, 1.5 Hz, 1H), 2.72 - 2.65 (m, 1H), 2.50 (s, 3H), 2.31 - 2.21 (m, 1H), 1.73 - 1.67 (m, 1H), 1.51 - 1.40 (m, 2H).

Example 35: (3-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

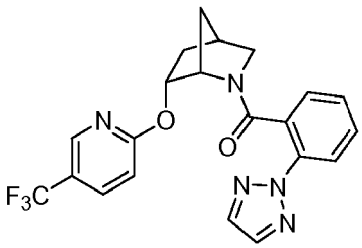
[0357]



[0358] Prepared analogous to Example 25 substituting intermediate A-20 with intermediate A-16. MS (ESI) mass calcd. $C_{21}H_{17}F_4N_5O_2$, 447.1 m/z found 448.2 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.85:0.15), major rotamer reported) δ 8.14 - 8.08 (m, 1H), 7.89 (s, 2H), 7.80 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.16 (ddd, *J* = 9.9, 8.2, 1.6 Hz, 1H), 6.98 - 6.81 (m, 3H), 5.06 (dt, *J* = 10.1, 3.3 Hz, 1H), 4.21 - 4.13 (m, 1H), 3.39 - 3.30 (m, 2H), 2.60 - 2.52 (m, 1H), 2.26 - 2.15 (m, 1H), 1.51 - 1.43 (m, 1H), 1.39 - 1.30 (m, 1H), 1.20 - 1.10 (m, 1H).

Example 36: (2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

[0359]

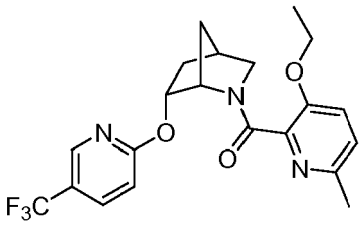


[0360] Prepared analogous to Example 25 substituting intermediate A-20 with intermediate A-1. MS (ESI) mass calcd. $C_{21}H_{18}F_3N_5O_2$, 429.1 m/z found 430.2 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of

rotamers (0.87:0.13), major rotamer reported) δ 8.04 - 7.98 (m, 1H), 7.89 - 7.74 (m, 4H), 7.36 - 7.28 (m, 1H), 7.02 (dd, *J* = 7.7, 1.5 Hz, 1H), 6.85 - 6.77 (m, 2H), 4.99 (dt, *J* = 10.2, 3.3 Hz, 1H), 4.10 - 4.00 (m, 1H), 3.61 (dt, *J* = 10.9, 3.3 Hz, 1H), 3.40 (dd, *J* = 10.9, 1.5 Hz, 1H), 2.67 - 2.58 (m, 1H), 2.26 - 2.15 (m, 1H), 1.47 - 1.23 (m, 3H).

Example 37: (3-ethoxy-6-methylpyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

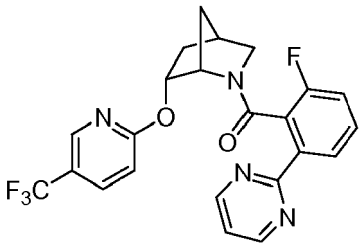
[0361]



[0362] Prepared analogous to Example 25 substituting intermediate A-20 with intermediate A-8. MS (ESI) mass calcd. $C_{21}H_{22}F_3N_3O_3$, 421.2 m/z found 422.2 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.83:0.17), major rotamer reported) δ 7.92 - 7.88 (m, 1H), 7.71 - 7.66 (m, 1H), 6.92 (d, *J* = 8.5 Hz, 1H), 6.87 - 6.82 (m, 2H), 5.00 (dt, *J* = 10.2, 3.3 Hz, 1H), 4.68 - 4.63 (m, 1H), 4.05 - 3.85 (m, 2H), 3.72 (dt, *J* = 11.0, 3.2 Hz, 1H), 3.51 (dd, *J* = 11.0, 1.6 Hz, 1H), 2.74 - 2.68 (m, 1H), 2.31 - 2.16 (m, 4H), 1.96 - 1.88 (m, 1H), 1.78 - 1.70 (m, 1H), 1.48 (dt, *J* = 13.5, 3.6 Hz, 1H), 1.43 - 1.35 (m, 3H).

Example 38: (2-fluoro-6-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

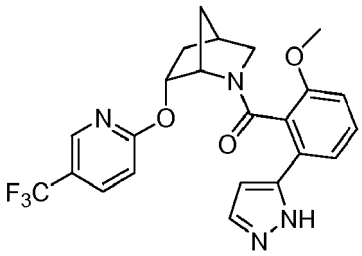
[0363]



[0364] Prepared analogous to Example 25 substituting intermediate A-20 with intermediate A-6 and substituting purification by Agilent Prep Method X by silica gel chromatography (15-80% EtOAc (with 10% MeOH) in hexanes). MS (ESI) mass calcd. $C_{23}H_{18}F_4N_4O_2$, 458.1; m/z found 459.1 $[M+H]^+$. ^1H NMR (500 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.78:0.22), major rotamer reported) δ 8.81 (d, *J* = 4.9 Hz, 2H), 8.11 - 8.05 (m, 1H), 8.05 - 8.00 (m, 1H), 7.77 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.31 - 7.27 (m, 1H), 7.23 (t, *J* = 4.8 Hz, 1H), 6.91 (d, *J* = 8.7 Hz, 1H), 6.72 - 6.64 (m, 1H), 4.97 (dt, *J* = 10.1, 3.4 Hz, 1H), 4.14 - 4.09 (m, 1H), 3.68 (dt, *J* = 10.9, 3.2 Hz, 1H), 3.46 (dd, *J* = 10.9, 1.5 Hz, 1H), 2.65 (s, 1H), 2.28 - 2.18 (m, 1H), 1.48 - 1.38 (m, 2H), 1.25 - 1.18 (m, 1H).

Example 39: (2-methoxy-6-(1H-pyrazol-5-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

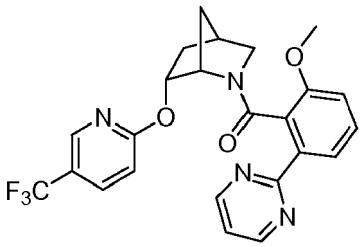
[0365]



[0366] Prepared analogous to Example 25 substituting intermediate A-20 with intermediate A-30. MS (ESI) mass calcd. $C_{23}H_{21}F_3N_4O_3$, 458.2; m/z found 459.3 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers, major rotamer reported) δ 8.00 (s, 1H), 7.75 (dd, *J* = 8.7, 2.6 Hz, 1H), 7.62 - 7.57 (m, 1H), 7.34 - 7.26 (m, 1H), 7.25 - 7.21 (m, 1H), 6.76 (d, *J* = 8.7 Hz, 1H), 6.53 (d, *J* = 2.0 Hz, 1H), 6.46 (d, *J* = 8.4 Hz, 1H), 4.84 (dt, *J* = 10.2, 3.4 Hz, 1H), 4.15 (s, 1H), 3.54 - 3.46 (m, 4H), 3.34 (d, *J* = 10.8 Hz, 1H), 2.49 (s, 1H), 2.19 - 2.07 (m, 1H), 1.55 - 1.22 (m, 3H).

Example 40: (2-methoxy-6-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

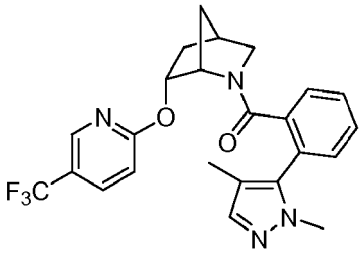
[0367]



[0368] Prepared analogous to Example 25 substituting intermediate A-20 with intermediate A-24. MS (ESI) mass calcd. $C_{24}H_{21}F_3N_4O_3$, 470.2; m/z found 471.1 $[M+H]^+$. Analytical HPLC using a XBridge C18 column (5um, 100 × 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 2min and then hold at 100% ACN for 2 min, at a flow rate of 2.5 mL/min (Temperature = 45 °C). R_t = 2.01 and 2.24 min (major rotamers) at 254 nm.

Example 41: (2-(1,4-dimethyl-1H-pyrazol-5-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

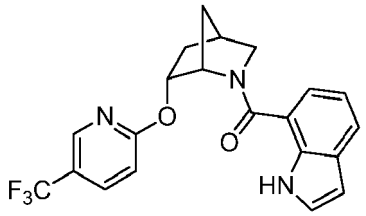
[0369]



[0370] Prepared analogous to Example 25 substituting intermediate A-20 with intermediate A-31. MS (ESI) mass calcd. $C_{24}H_{23}F_3N_4O_2$, 456.2; m/z found 457.2 $[M+H]^+$. ^1H NMR (500 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.74:0.26), major rotamer reported) δ 7.95 - 7.90 (m, 1H), 7.75 (dd, *J* = 9.0, 1.7 Hz, 1H), 7.39 (s, 1H), 7.30 - 7.27 (m, 1H), 7.13 (dd, *J* = 7.7, 0.7 Hz, 1H), 7.03 (dd, *J* = 7.7, 0.8 Hz, 1H), 6.91 - 6.87 (m, 1H), 6.80 (d, *J* = 8.8 Hz, 1H), 4.96 - 4.91 (m, 1H), 4.05 - 4.03 (m, 1H), 3.61 (s, 3H), 3.39 - 3.35 (m, 1H), 3.34 - 3.29 (m, 1H), 2.54 - 2.49 (m, 1H), 2.19 - 2.10 (m, 1H), 2.08 (s, 3H), 1.44 - 1.34 (m, 2H), 0.95 - 0.89 (m, 1H).

Example 42: (1H-indol-7-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

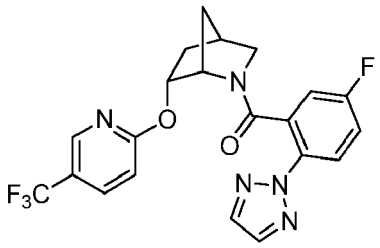
[0371]



[0372] Prepared analogous to Example 25 substituting intermediate A-20 with intermediate A-29 and substituting purification by Agilent Prep Method X by silica gel chromatography (0-60% EtOAc (with 10% MeOH) in hexanes). MS (ESI) mass calcd. $C_{21}H_{18}F_3N_3O_2$, 401.1; m/z found 402.1 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.82 (s, 1H), 7.92 (br. s, 1H), 7.62 (dd, *J* = 8.9, 2.7 Hz, 1H), 7.32 (d, *J* = 7.9 Hz, 1H), 7.21 (t, *J* = 2.8 Hz, 1H), 6.93 (d, *J* = 7.3 Hz, 1H), 6.69 (t, *J* = 7.5 Hz, 1H), 6.57 (d, *J* = 8.7 Hz, 1H), 6.32 - 6.25 (m, 1H), 5.06 (dt, *J* = 10.0, 3.1 Hz, 1H), 4.67 (br. s, 1H), 3.60 - 3.53 (m, 1H), 3.52 - 3.44 (m, 1H), 2.70 - 2.62 (m, 1H), 2.29 - 2.17 (m, 1H), 2.06 - 1.99 (m, 1H), 1.73 (d, *J* = 10.2 Hz, 1H), 1.30 (dt, *J* = 13.4, 3.5 Hz, 1H).

Example 43: (5-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

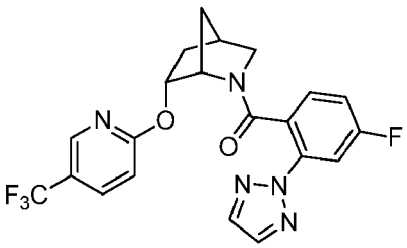
[0373]



[0374] Prepared analogous to Example 25 substituting intermediate A-20 with intermediate A-10. MS (ESI) mass calcd. for $C_{21}H_{17}F_4N_5O_2$, 447.2; m/z found 448.2 $[M+H]^+$. ^{1}H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.91:0.09), major rotamer reported) δ 8.09 - 8.03 (m, 1H), 7.84 - 7.81 (m, 1H), 7.81 - 7.78 (m, 3H), 7.05 - 6.95 (m, 1H), 6.82 (d, *J* = 8.7 Hz, 1H), 6.78 (dd, *J* = 8.1, 2.9 Hz, 1H), 5.01 (dt, *J* = 10.1, 3.3 Hz, 1H), 4.07 - 3.99 (m, 1H), 3.58 (dt, *J* = 11.0, 3.2 Hz, 1H), 3.40 (dd, *J* = 10.9, 1.5 Hz, 1H), 2.67 - 2.60 (m, 1H), 2.29 - 2.17 (m, 1H), 1.46 - 1.37 (m, 2H), 1.33 - 1.27 (m, 1H).

Example 44: (4-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

[0375]

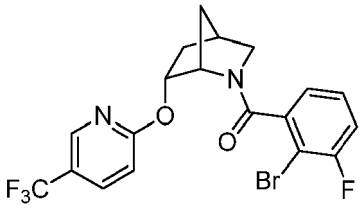


[0376] Prepared analogous to Example 25 substituting intermediate A-20 with intermediate A-12. MS (ESI) mass calcd. for $C_{21}H_{17}F_4N_5O_2$, 447.2; m/z found 448.2 $[M+H]^+$.^{1}H NMR (400 MHz, Chloroform-d, Compound present as a

mixture of rotamers (0.88:0.12), major rotamer reported) δ 8.13 - 8.07 (m, 1H), 7.83 (s, 2H), 7.81 - 7.78 (m, 1H), 7.63 (dd, *J* = 9.5, 2.5 Hz, 1H), 7.02 (dd, *J* = 8.5, 5.9 Hz, 1H), 6.82 (d, *J* = 8.7 Hz, 1H), 6.52 (td, *J* = 8.1, 2.5 Hz, 1H), 5.01 (dt, *J* = 10.2, 3.3 Hz, 1H), 4.03 (s, 1H), 3.63 (dt, *J* = 11.0, 3.2 Hz, 1H), 3.40 (dd, *J* = 10.9, 1.4 Hz, 1H), 2.68 - 2.61 (m, 1H), 2.28 - 2.16 (m, 1H), 1.46 - 1.38 (m, 2H), 1.38 - 1.28 (m, 1H).

Example 45: (2-bromo-3-fluorophenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

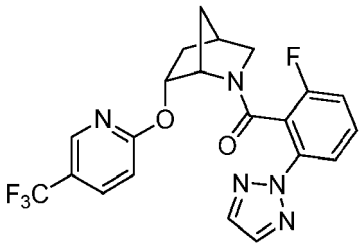
[0377]



[0378] Prepared analogous to Example 25 substituting intermediate A-20 with intermediate A-32. MS (ESI) mass calcd. for $C_{19}H_{15}BrF_4N_2O_2$, 458.0; m/z found 459.1 $[M+H]^+$.^{1}H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.82:0.18), major rotamer reported) δ 8.03 (s, 1H), 7.78 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.94 (td, *J* = 8.3, 1.5 Hz, 1H), 6.87 - 6.81 (m, 1H), 6.73 (br. s, 1H), 6.63 (br. s, 1H), 5.15 - 5.06 (m, 1H), 4.23 (br. s, 1H), 3.73 (dt, *J* = 11.1, 3.3 Hz, 1H), 3.45 (dd, *J* = 11.0, 1.6 Hz, 1H), 2.80 - 2.71 (m, 1H), 2.37 - 2.25 (m, 1H), 1.99 - 1.89 (m, 1H), 1.84 - 1.71 (m, 1H), 1.46 (dt, *J* = 13.6, 3.6 Hz, 1H).

Example 46: (2-fluoro-6-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

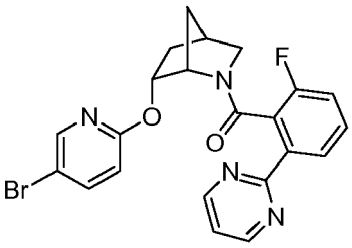
[0379]



[0380] Prepared analogous to Example 25 substituting intermediate A-20 with intermediate A-11. MS (ESI) mass calcd. for $C_{21}H_{17}F_4N_5O_2$, 447.2; m/z found 448.2 $[M+H]^+$.^{1}H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.81:0.19), major rotamer reported) δ 8.05 - 8.00 (m, 1H), 7.83 (s, 2H), 7.80 - 7.77 (m, 1H), 7.77 - 7.72 (m, 1H), 7.32 - 7.27 (m, 1H), 6.89 (d, *J* = 8.8 Hz, 1H), 6.60 (td, *J* = 8.4, 1.0 Hz, 1H), 4.96 (dt, *J* = 10.1, 3.4 Hz, 1H), 4.06 - 3.96 (m, 1H), 3.64 (dt, *J* = 10.9, 3.2 Hz, 1H), 3.44 (dd, *J* = 10.9, 1.5 Hz, 1H), 2.69 - 2.60 (m, 1H), 2.28 - 2.16 (m, 1H), 1.51 - 1.34 (m, 2H), 1.30 - 1.22 (m, 1H).

Example 47: ((1S,4R,6R)-6-((5-bromopyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)(2-fluoro-6-(pyrimidin-2-yl)phenyl)methanone

[0381]



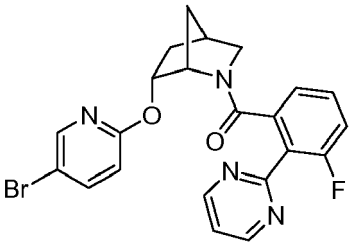
[0382] Step A: (1S,4R,6R)-tert-butyl 6-((5-bromopyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptane-2-carboxylate. To intermediate B-5 (101 mg, 0.474 mmol) dissolved in DMF (3 mL) was added NaH (38 mg, 0.95 mmol, 60% dispersion in mineral oil). After 5 minutes the sides of the flask were rinsed with additional DMF (1.0 mL) and 5-bromo-2-fluoropyridine (0.078 mL, 0.76 mmol) was then added and the mixture heated to 70 °C. After heating at 70 °C for 3.25h, the mixture was cooled to room temperature, quenched with saturated NH_4Cl solution, diluted with H_2O, and the aqueous layer extracted with EtOAc (3X).The combined organics were washed with H_2O, brine, dried with $MgSO_4$, filtered and concentrated. Purification via silica gel chromatography (0-25% EtOAc in hexanes) gave the title compound (149 mg, 0.40 mmol, 85%). MS (ESI) mass calcd. for $C_{16}H_{21}BrN_2O_3$, 368.1; m/z found 369.1 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, compound is present a mixture of rotamers (0.75:0.25)) δ 8.20 - 8.11 (m, 1H), 7.63 (dd, *J* = 8.8, 2.6 Hz, 0.75H), 7.58 (dd, *J* = 8.8, 2.6 Hz, 0.25H), 6.63 (dd, *J* = 8.8, 0.7 Hz, 0.75H), 6.57 - 6.52 (m, 0.25H), 5.29 (dt, *J* = 9.8, 3.0 Hz, 0.25H), 5.22 (dt, *J* = 10.1, 3.2 Hz, 0.75H), 4.57 - 4.49 (m, 1H), 3.43 - 3.31 (m, 1H), 3.19 (dd, *J* = 9.5, 1.3 Hz, 0.75H), 3.15 - 3.09 (m, 0.25H), 2.59 - 2.50 (m, 1H), 2.26 - 2.13 (m, 1H), 1.77 - 1.66 (m, 1H), 1.65 - 1.56 (m, 1H), 1.43 (s, 2H), 1.41 - 1.23 (m, 1H), 1.16 (s, 7H).

[0383] Step B: (1S,4R,6R)-6-((5-bromopyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptane · xHCl. To the title compound of step A (149 mg, 0.404 mmol) in EtOAc (1.5 mL) was added 4M HCl in dioxane (5 mL). After 3.25h, the reaction was concentrated to give the title compound of step B (128 mg) which was used without further purification. MS (ESI) mass calcd. for $C_{11}H_{13}BrN_2O$, 268.0; m/z found 269.0 $[M+H]^+$.

[0384] Step C: ((1S,4R,6R)-6-((5-bromopyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)(2-fluoro-6-(pyrimidin-2-yl)phenyl)methanone. To the title compound of step B (30 mg) and intermediate A-6 (24 mg, 0.11 mmol) in DMF (1.5 mL) was added DIPEA (0.25 mL, 1.45 mmol) and HATU (41 mg, 0.11 mmol). Upon completion the reaction was diluted with H_2O and the aqueous layer extracted with EtOAc (3X). The combined organics were washed with H_2O, brine, dried with $MgSO_4$, filtered, and concentrated. Purification of the concentrate was performed using Agilent Prep Method X to give the title compound (20 mg). MS (ESI) mass calcd. $C_{22}H_{18}BrFN_4O_2$, 468.1; m/z found 469.1 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.79:0.21), major rotamer reported) δ 8.80 (d, *J* = 4.8 Hz, 2H), 8.08 (d, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 2.5 Hz, 1H), 7.64 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.39 - 7.30 (m, 1H), 7.23 (t, *J* = 4.9 Hz, 1H), 6.81 - 6.72 (m, 2H), 4.86 (dt, *J* = 10.1, 3.3 Hz, 1H), 4.11 - 4.02 (m, 1H), 3.65 (dt, *J* = 10.9, 3.1 Hz, 1H), 3.44 (dd, *J* = 10.8, 1.5 Hz, 1H), 2.66 - 2.59 (m, 1H), 2.25 - 2.15 (m, 1H), 1.42 - 1.34 (m,2H), 1.22 - 1.13 (m, 1H).

Example 48: ((1S,4R,6R)-6-((5-bromopyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)(3-fluoro-2-(pyrimidin-2-yl)phenyl)methanone

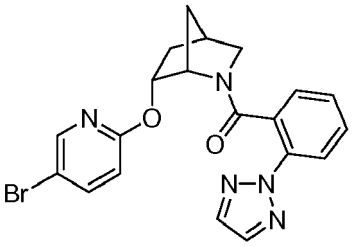
[0385]



[0386] Prepared analogous to Example 47 substituting intermediate A-6 with intermediate A-2. MS (ESI) mass calcd. $C_{22}H_{18}BrFN_4O_2$, 468.1; m/z found 469.1 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.88:0.12), major rotamer reported) ^1H NMR (400 MHz, Chloroform-d) δ 8.85 (d, *J* = 4.9 Hz, 2H), 7.90 - 7.83 (m, 1H), 7.66 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.29 - 7.26 (m, 1H), 7.16 - 7.07 (m, 1H), 7.05 - 6.96 (m, 1H), 6.91 (dd, *J* = 7.5, 1.3 Hz, 1H), 6.67 (d, *J* = 8.7 Hz, 1H), 4.96 (dt, *J* = 10.1, 3.3 Hz, 1H), 4.27 - 4.16 (m, 1H), 3.34 - 3.24 (m, 2H), 2.52 (s, 1H), 2.23 - 2.11 (m, 1H), 1.40 (d, *J* = 10.8 Hz, 1H), 1.31 (dt, *J* = 13.5, 3.6 Hz, 1H), 0.98 - 0.87 (m, 1H).

Example 49: (2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((5-bromopyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

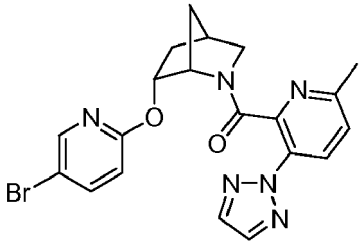
[0387]



[0388] Prepared analogous to Example 47 substituting intermediate A-6 with intermediate A-1. MS (ESI) mass calcd. $C_{20}H_{18}BrN_5O_2$, 439.1; m/z found 440.1 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.89:0.11), major rotamer reported) δ 7.85 (dd, *J*= 8.2, 1.1 Hz, 1H), 7.81 (s, 2H), 7.75 (dd, *J*= 2.5, 0.7 Hz, 1H), 7.64 (dd, *J*= 8.7, 2.6 Hz, 1H), 7.41 - 7.35 (m, 1H), 7.05 (dd, *J*= 7.7, 1.5 Hz, 1H), 6.91 (td, *J*= 7.6, 1.2 Hz, 1H), 6.65 (d, *J*= 8.7 Hz, 1H), 4.89 (dt, *J*= 10.2, 3.3 Hz, 1H), 4.05 - 3.97 (m, 1H), 3.59 (dt, *J*= 10.9, 3.2 Hz, 1H), 3.38 (dd, *J*= 10.9, 1.4 Hz, 1H), 2.63 - 2.56 (m, 1H), 2.23 - 2.12 (m, 1H), 1.41 - 1.33 (m, 2H), 1.29 - 1.23 (m, 1H).

Example 50: ((1S,4R,6R)-6-((5-bromopyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)(6-methyl-3 -(2H-1,2,3-triazol-2-yl)pyridin-2-yl)methanone

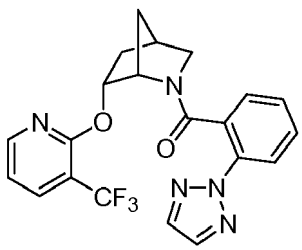
[0389]



[0390] Prepared analogous to Example 47 substituting intermediate A-6 with intermediate A-20. MS (ESI) mass calcd. $C_{20}H_{19}BrN_6O_2$, 454.1; m/z found 455.1 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.85: 0.15), major rotamer reported) δ 8.03 (d, *J*= 8.4 Hz, 1H), 7.82 (s, 2H), 7.70 (dd, *J*= 2.6, 0.7 Hz, 1H), 7.56 (dd, *J*= 8.8, 2.6 Hz, 1H), 7.14 (d, *J*= 8.4 Hz, 1H), 6.66 (dd, *J*= 8.6, 0.7 Hz, 1H), 4.82 (dt, *J*= 10.2, 3.3 Hz, 1H), 4.23 - 4.16 (m, 1H), 3.65 (dt, *J*= 11.0, 3.2 Hz, 1H), 3.43 (dd, *J*= 10.9, 1.5 Hz, 1H), 2.63 - 2.58 (m, 1H), 2.30 (s, 3H), 2.23 - 2.11 (m, 1H), 1.48 - 1.33 (m, 3H).

Example 51: (2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((3-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

[0391]



[0392] Step A: (1S,4R,6R)-tert-butyl 6-((3-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptane-2-carboxylate. To intermediate B-5 (101 mg, 0.474 mmol) dissolved in DMF (3 mL) was added NaH (38 mg, 0.95 mmol, 60%

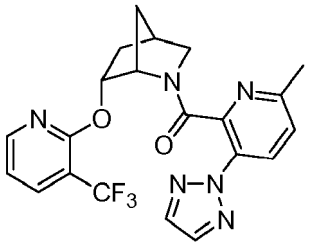
dispersion in mineral oil). After 5 minutes the sides of the flask were rinsed with additional DMF (1.0 mL) and 2-fluoro-3-(trifluoromethyl)pyridine (0.091 mL, 0.76 mmol) was then added and the mixture heated to 70 °C. After heating at 70 °C for 3 h, the mixture was cooled to room temperature, quenched with saturated NH_4Cl solution, diluted with EtOAc and H_2O. The aqueous layer was extracted with EtOAc (3X). The combined organics were washed with H_2O, 5% aqueous LiCl, brine, dried with Na_2SO_4, filtered, and concentrated. Purification via silica gel chromatography (0-35% EtOAc in hexanes) gave the title compound (87 mg, 0.24 mmol, 51%) as a white solid. MS (ESI) mass calcd. for $C_{17}H_{21}F_3N_2O_3$, 358.2; m/z found 303.1 $[M+2H-t\text{Bu}]^+$. ^{1}H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers, (0.68:.0.32), major rotamer reported) δ 8.35 - 8.25 (m, 1H), 7.90 - 7.82 (m, 1H), 6.96 (dd, *J*= 7.5, 5.0 Hz, 1H), 5.32 (dt, *J*= 10.1, 3.1 Hz, 1H), 4.64 - 4.58 (m, 1H), 3.42 (dt, *J*= 9.5, 3.1 Hz, 1H), 3.15 (d, *J*= 9.5 Hz, 1H), 2.61 - 2.56 (m, 1H), 2.27 - 2.15 (m, 1H), 1.76 - 1.66 (m, 1H), 1.63 (br. s, 1H), 1.48 (dt, *J*= 13.5, 3.5 Hz, 1H), 1.08 (s, 9H).

[0393] Step B: (1S,4R,6R)-6-((3-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptane · xHCl. To the title compound of step A (86 mg, 0.24 mmol) in EtOAc (1 mL) was added 4M HCl in dioxane (3 mL). After 2h, the reaction was concentrated to give the title compound of step B (76.5 mg) as a white solid and used without further purification. MS (ESI) mass calcd. for $C_{12}H_{13}F_3N_2O$, 258.1; m/z found 259.1 $[M+H]^+$.

[0394] Step C: (2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((3-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone. To the title compound of step B (25 mg) and intermediate A-1 (18 mg, 0.093 mmol) in DMF (0.8 mL) was added DIPEA (75 μL, 0.44 mmol) and HATU (36 mg, 0.093 mmol), and the reaction mixture was stirred at room temperature for 1 h. The reaction was quenched by the addition of H_2O and the aqueous layer was extracted with EtOAc (3X). The combined organics were washed with H_2O, 5% aqueous LiCl, brine, dried with Na_2SO_4, filtered, and concentrated. Purification via silica gel chromatography (0-60% EtOAc in hexanes) gave the title compound (29 mg). MS (ESI) mass calcd. $C_{21}H_{18}F_3N_5O_2$, 429.1; m/z found 430.1 $[M+H]^+$. ^{1}H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers, (0.76:0.24), major rotamer reported) δ 7.93 - 7.82 (m, 4H), 7.81 (s, 2H), 7.07 (dd, J = 7.7, 1.5 Hz, 1H), 6.93 - 6.86 (m, 1H), 6.75 (td, J = 7.6, 1.2 Hz, 1H), 5.04 (dt, J = 10.2, 3.4 Hz, 1H), 4.15 - 4.04 (m, 1H), 3.66 (dt, J = 10.9, 3.3 Hz, 1H), 3.38 (dd, J = 10.9, 1.4 Hz, 1H), 2.66 - 2.60 (m, 1H), 2.27 - 2.15 (m, 1H), 1.48 (dt, J = 13.3, 3.6 Hz, 1H), 1.44 - 1.37 (m, 1H), 1.36 - 1.28 (m, 1H).

Example 52: (6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((3-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

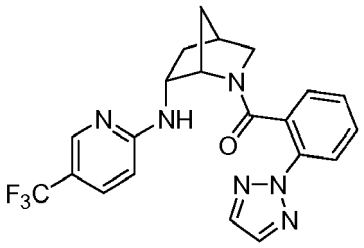
[0395]



[0396] Prepared analogous to Example 51 substituting intermediate A-1 with intermediate A-20. MS (ESI) mass calcd. $C_{21}H_{19}F_3N_6O_2$, 444.2; m/z found 445.0 $[M+H]^+$. ^{1}H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers, (0.72:0.28), major rotamer reported) δ 8.01 (d, *J*= 8.5 Hz, 1H), 7.83 - 7.78 (m, 4H), 7.05 (d, *J*= 8.4 Hz, 1H), 6.85 - 6.78 (m, 1H), 4.97 (dt, *J*= 10.4, 3.3 Hz, 1H), 4.31 (br. s, 1H), 3.70 (dt, *J*= 10.9, 3.3 Hz, 1H), 3.42 (d, *J*= 10.9 Hz, 1H), 2.66 - 2.62 (m, 1H), 2.23 - 2.14 (m, 1H), 2.10 (s, 3H), 1.58 - 1.15 (m, 3H).

Example 53: (2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

[0397]



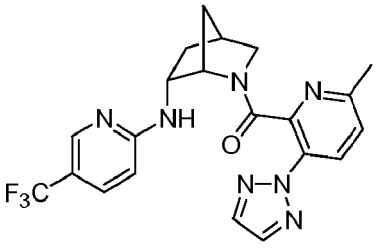
[0398] Step A: (1S,4S,6R)-tert-butyl 6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptane-2-carboxylate. To a microwave vial containing degassed toluene (9 mL) was added $Pd(OAc)_2$ (24 mg, 0.035 mmol) and racemic BINAP (22 mg, 0.035 mmol) at room temperature and the reaction mixture was purged with N_2 for 5 min. Then, 2-chloro-5-(trifluoromethyl)pyridine (159 mg, 0.874 mmol), intermediate B-10 (204 mg), and sodium tert-butoxide (121 mg, 1.22 mmol) were added and the reaction mixture heated to 70 °C overnight. Upon completion of the reaction, the mixture was cooled to room temperature, filtered through Celite and the filter pad washed with EtOAc. The filtrate was concentrated in vacuo and the crude residue subjected directly to silica gel chromatography (0-50% EtOAc in hexanes) to give the title compound of step A (198 mg, 0.554 mmol, 63%). MS (ESI) mass calcd. for $C_{17}H_{22}F_3N_3O_2$, 357.2; m/z found 358.2 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers, major rotamer reported) δ 8.33 (s, 1H), 7.55 (d, *J*= 8.8 Hz, 1H), 6.37 (d, *J*= 8.8 Hz, 1H), 5.11 - 4.97 (m, 1H), 4.41 (s, 1H), 4.27 - 4.18 (m, 1H), 3.44 - 3.36 (m, 1H), 3.08 (d, *J*= 9.7 Hz, 1H), 2.62 - 2.55 (m, 1H), 2.39 - 2.26 (m, 1H), 1.68 - 1.61 (m, 1H), 1.45 - 1.43 (m, 1H), 1.48 and 1.22 (two s, 9H).

[0399] Step B: Step B: (1S,4R,6R)-N-(5-(trifluoromethyl)pyridin-2-yl)-2-azabicyclo[2.2.1]heptan-6-amine · xHCl. To the title compound of step A (198 mg, 0.554 mmol) in EtOAc (3 mL) was added 4M HCl in dioxane (14 mL). After 1h, the reaction was concentrated to give the title compound of step B (183 mg), which was used without further purification. MS (ESI) mass calcd. for $C_{12}H_{14}F_3N_3$, 257.1; m/z found 258.1 $[M+H]^+$.

[0400] Step C: (2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone. To the title compound of step B (30 mg) and intermediate A-1 (19 mg, 0.10 mmol) in DMF (1 mL) was added DIPEA (94 μL, 0.55 mmol) and HATU (38 mg, 0.10 mmol), and the reaction mixture was stirred at room temperature for 1 h. The reaction was quenched by the addition of H_2O and the aqueous layer was extracted with 4:1 EtOAc/hexanes (3×X). The combined organics were washed with H_2O, 5% aqueous LiCl, brine, dried with Na_2SO_4, filtered, and concentrated. Purification via silica gel chromatography (25-100% EtOAc (with 10% MeOH) in hexanes) gave the title compound (20 mg). MS (ESI) mass calcd. $C_{21}H_{19}F_3N_6O$, 428.2; m/z found 429.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6, Compound presents as a mixture of rotamers, major rotamer reported) δ 8.10 (s, 2H), 7.94 - 7.77 (m, 1H), 7.70 (d, *J*= 8.1 Hz, 1H), 7.67 - 7.49 (m, 2H), 7.28 (td, *J*= 7.7, 1.5 Hz, 1H), 6.96 - 6.82 (m, 1H), 6.77 - 6.56 (m, 2H), 3.96 (br. s, 1H), 3.64 (br. s, 1H), 3.33 - 3.25 (m, 1H), 3.23 - 3.14 (m, 1H), 2.15 - 2.00 (m, 1H), 1.44 - 1.33 (m, 1H), 1.23 - 1.03 (m, 2H), *1 H buried under DMSO-d_6 peak.

Example 54: (6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

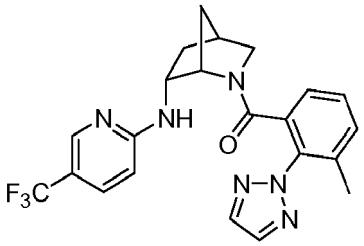
[0401]



[0402] Prepared analogous to Example 53 substituting intermediate A-1 with intermediate A-20 and substituting purification by silica gel chromatography with Agilent Prep Method X. MS (ESI) mass calcd. $C_{21}H_{20}F_3N_7O$, 443.2; m/z found 444.2 $[M+H]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5um, 100 × 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 30 °C). R_t = 5.92 min (major rotamer) at 254 nm.

Example 55: (3-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

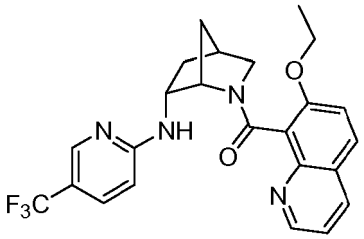
[0403]



[0404] Prepared analogous to Example 53 substituting intermediate A-1 with intermediate A-22 and substituting purification by silica gel chromatography with Agilent Prep Method X. MS (ESI) mass calcd. $C_{22}H_{21}F_3N_6O$, 442.2; m/z found 443.2 $[M+H]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5um, 100 × 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 30 °C). R_t = 6.85 min (major rotamer) at 254 nm.

Example 56: (7-ethoxyquinolin-8-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

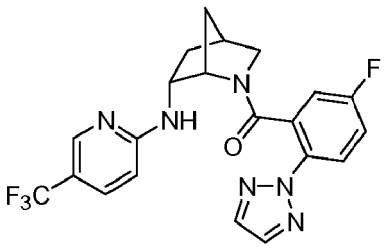
[0405]



[0406] Prepared analogous to Example 53 substituting intermediate A-1 with intermediate A-25 and substituting purification by silica gel chromatography with Agilent Prep Method X. MS (ESI) mass calcd. $C_{24}H_{23}F_3N_4O_2$, 456.2; m/z found 457.2 $[M+H]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5um, 100 × 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 30 °C). R_t = 6.45 min (major rotamer) at 254 nm.

Example 57: (5-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

[0407]

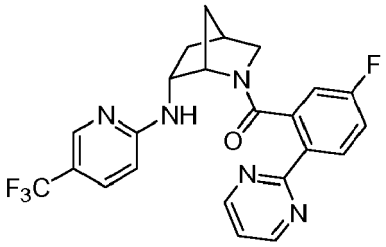


[0408] Prepared analogous to Example 53 substituting intermediate A-1 with intermediate A-10. MS (ESI) mass calcd. $C_{21}H_{18}F_4N_6O$, 446.1; m/z found 447.1 $[M+H]^+$. ^1H NMR (400 MHz, Methanol-d_4) δ 7.95 (s, 2H), 7.91 - 7.84 (m, 1H), 7.81 (dd, *J*= 9.0, 4.7 Hz, 1H), 7.56 (d, *J*= 8.1 Hz, 1H), 7.12 - 7.02 (m, 1H), 6.78 - 6.67 (m, 1H), 6.67 - 6.47 (m, 1H), 4.02 - 3.91 (m, 1H), 3.85 (br. s, 1H), 3.42 (dt, *J* = 11.1, 3.2 Hz, 1H), 3.30 - 3.27 (m, 1H), 2.63 - 2.55 (m, 1H), 2.26 - 2.14 (m,

1H), 1.51-1.40 (m, 1H), 1.28-1.16 (m, 2H).

Example 58: (5-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

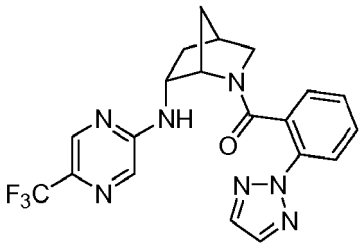
[0409]



[0410] Prepared analogous to Example 53 substituting intermediate A-1 with intermediate A-7 and substituting purification by silica gel chromatography with Agilent Prep Method X. MS (ESI) mass calcd. $C_{23}H_{19}F_4N_5O$, 457.2; m/z found 458.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6, Compound presents as a mixture of rotamers (0.90:0.10), major rotamer reported) δ 8.87 (d, *J*= 4.9 Hz, 2H), 8.03 (dd, *J*= 8.8, 5.6 Hz, 1H), 7.88 (br. s, 1H), 7.64 - 7.49 (m, 2H), 7.45 (t, *J*= 4.9 Hz, 1H), 7.04 (td, *J*= 8.6, 2.8 Hz, 1H), 6.70 - 6.53 (m, 2H), 3.96 (br. s, 1H), 3.73 (br. s, 1H), 3.23 - 3.13 (m, 1H), 2.15 - 2.02 (m, 1H), 1.37 (d, *J*= 9.7 Hz, 1H), 1.21 - 0.99 (m, 3H). *1 H buried under DMSO-d_6 peak.

Example 59: (2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

[0411]



[0412] Step A: (1S,4S,6R)-tert-butyl 6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptane-2-carboxylate. To intermediate B-10 (44 mg) and 2-chloro-5-(trifluoromethyl)pyrazine (45 mg, 0.25 mmol) dissolved in DMF (2 mL) was added K_2CO_3 (43 mg, 0.31 mmol) and the mixture heated to 70 °C. After heating at 70 °C for 3.5 h, the mixture was cooled to room temperature, diluted with H_2O, and the aqueous layer extracted with EtOAc (3X).The combined organics were washed with H_2O, brine, dried with $MgSO_4$, filtered and concentrated. Purification via silica gel chromatography (0-45% EtOAc in hexanes) gave the title compound (31 mg, 0.087 mmol, 42%). MS (ESI) mass calcd. for $C_{16}H_{21}F_2N_4O_2$, 358.2; m/z found 303.1 $[M+2H-tBu]^+$. ^1H NMR (500 MHz, Chloroform-d) δ 8.38 - 8.25 (m, 1H), 7.93 - 7.76 (m, 1H), 6.25 - 6.12 and 5.57 - 5.44 (2m, 1H), 4.50 - 4.38 (m, 1H), 4.34 - 4.11 (m, 1H), 3.46 - 3.33 (m, 1H), 3.16 - 3.01 (m, 1H), 2.66 - 2.57 (m, 1H), 2.42 - 2.29 (m, 1H), 1.95 - 0.80 (m, 12H).

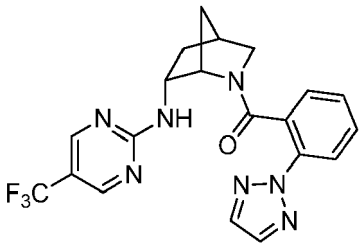
[0413] Step B: (1S,4R,6R)-N-(5-(trifluoromethyl)pyrazin-2-yl)-2-azabicyclo[2.2.1]heptan-6-amine · xHCl. To the title compound of step A (31 mg, 0.087 mmol) in EtOAc (0.5 mL) was added 4M HCl in dioxane (4 mL). After 1.5 h additional 4 M HCl in dioxane (2 mL) was added. After an additional 1.25 h, the reaction was concentrated to give the title compound of step B (31 mg) which was used without further purification. MS (ESI) mass calcd. for $C_{11}H_{13}F_3N_4$, 258.1; m/z found 259.1 $[M+H]^+$.

[0414] Step C: (2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone. To the title compound of step B (29 mg) and intermediate A-1 (18 mg, 0.096 mmol) in DMF (2.0 mL) was added DIPEA (0.1 mL, 0.58 mmol) and HATU (37 mg, 0.096 mmol). Upon completion the reaction was diluted with H_2O and the aqueous layer extracted with EtOAc (3X). The combined organics were washed with H_2O, brine, dried with $MgSO_4$, filtered, and concentrated. Purification of the concentrate was performed using Agilent Prep Method X to give the title compound (8 mg). MS (ESI) mass calcd. $C_{20}H_{18}F_3N_7O$, 429.2; m/z found 430.2 $[M+H]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5um, 100 × 4.6mm), mobile

phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 30 °C). R_t = 6.27 min (major rotamer) at 254 nm.

Example 60: (2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrimidin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

[0415]



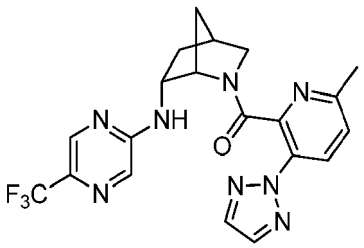
[0416] Step A: (1S,4S,6R)-tert-butyl 6-((5-(trifluoromethyl)pyrimidin-2-yl)amino)-2-azabicyclo[2.2.1]heptane-2-carboxylate. To a microwave vial containing intermediate B-10 (218 mg, 1.03 mmol) in MeCN (5 mL) was added 2-chloro-5-(trifluoromethyl)pyrimidine (225 mg, 1.23 mmol) and Et_3N (0.21 mL, 1.54 mmol), and the reaction mixture was sealed and heated to 90 °C overnight. Upon completion of the reaction, the mixture was cooled to room temperature and diluted with H_2O. The reaction mixture was extracted with EtOAc (3X). The combined organics were concentrated and the concentrate subjected directly to silica gel chromatography (0-50% EtOAc in hexanes) to give the title compound of step A (263 mg, 0.734 mmol, 71%). MS (ESI) mass calcd. for $C_{16}H_{21}F_3N_4O_2$; 358.2, m/z found 303.1 $[M+2H-tBu]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers) δ 8.54-8.36 (m, 2H), 6.18 - 6.09 and 5.82-5.71 (two m, 1H), 4.49-4.36 (m, 1H), 4.34-4.23 (m, 1H), 3.45 - 3.31 (m, 1H), 3.12 (3.00, 1H), 2.63-2.55 (m, 1H), 2.38-2.27 (m, 1H), 1.77 - 1.18 (m, 12H), 1.12-1.02 (m, 1H).

[0417] Step B: (1S,4R,6R)-N-(5-(trifluoromethyl)pyrimidin-2-yl)-2-azabicyclo[2.2.1]heptan-6-amine · xHCl. To the title compound of step A (263 mg, 0.73 mmol) in EtOAc (2 mL) was added 4M HCl in dioxane (6 mL), and the reaction mixture was stirred at room temperature for 5h. The reaction was concentrated to give the title compound of step B (230 mg), which was used without further purification. MS (ESI) mass calcd. for $C_{11}H_{13}F_3N_4$, 258.1; m/z found 259.1 $[M+H]^+$.

[0418] Step C: (2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrimidin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone. To the title compound of step B (35 mg) and intermediate A-1 (25 mg, 0.13 mmol) in DMF (1 mL) was added DIPEA (0.1 mL, 0.58 mmol) and HATU (50 mg, 0.13 mmol), and the reaction mixture was stirred at room temperature for 1 h. The reaction was quenched by the addition of H_2O and the aqueous layer was extracted with EtOAc (2X). The combined organics were concentrated and the concentrate subjected directly to purification via Agilent Prep Method X to give the title compound (34 mg). MS (ESI): mass calcd. for $C_{20}H_{18}F_3N_7O$, 429.2; m/z found, 430.9 $[M+H]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5μm, 100 $\times$ 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 30 °C). R_t = 6.18 min (major rotamer) at 254 nm.

Example 61: (6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[0419]

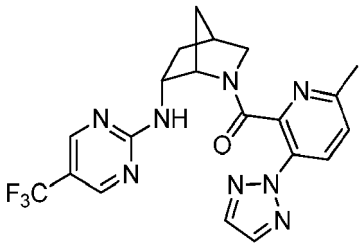


[0420] Prepared analogous to Example 59 substituting intermediate A-1 with intermediate A-40. MS (ESI): mass calcd. for $C_{20}H_{19}F_3N_8O$, 444.2; m/z found, 445.2 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.88:0.12), major rotamer reported) δ 8.23 (s, 1H), 8.16 (d, *J*= 8.4 Hz, 1H), 7.92 (s, 1H), 7.86 (s, 2H), 7.73

(s, 1H), 7.32 (d, *J*= 8.4 Hz, 1H), 4.34 - 4.29 (m, 1H), 4.19 - 4.11 (m, 1H), 3.72 (dt, *J*= 11.0, 3.2 Hz, 1H), 3.33 (dd, *J* = 11.1, 1.6 Hz, 1H), 2.83 - 2.77 (m, 1H), 2.60 (s, 3H), 2.49 - 2.39 (m, 1H), 2.00 - 1.93 (m, 1H), 1.75 - 1.69 (m, 1H), 1.21 (dt, *J*= 13.2, 3.6 Hz, 1H).

Example 62: (6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)((1S,4S,6R)-6-((5-(trifhioromethyl)pyrimidin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

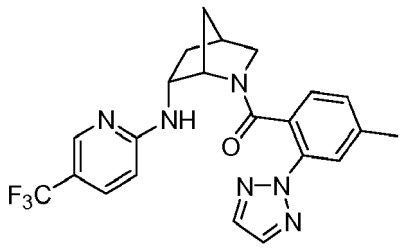
[0421]



[0422] Prepared analogous to Example 60 substituting intermediate A-1 with intermediate A-40. MS (ESI): mass calcd. for $C_{20}H_{19}F_3N_8O$, 444.2; m/z found, 445.9 $[M+H]^+$. ^1H NMR (400 MHz, Methanol-d_4, Compound present as a mixture of rotamers (0.73:0.27), major rotamer reported) δ 8.52 - 8.44 (m, 1H), 8.36 - 8.30 (m, 1H), 8.21 (d, *J*= 8.5 Hz, 1H), 7.99 (s, 2H), 7.39 (d, *J*= 8.5 Hz, 1H), 4.24 - 4.15 (m, 1H), 4.12 - 4.00 (m, 1H), 3.60 (dt, *J*= 11.1, 3.3 Hz, 1H), 3.35 - 3.32 (m, 1H), 2.75 - 2.70 (m, 1H), 2.48 (s, 3H), 2.43 - 2.30 (m, 1H), 1.76 - 1.62 (m, 2H), 1.39 - 1.29 (m, 1H).

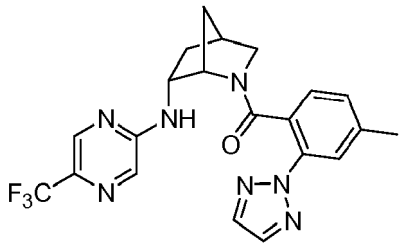
Example 63: (4-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

[0423]



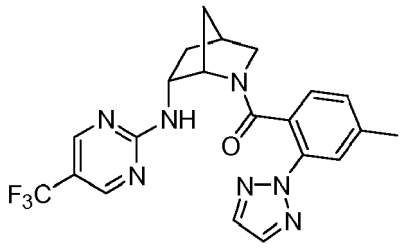
Example 64: (4-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

[0424]



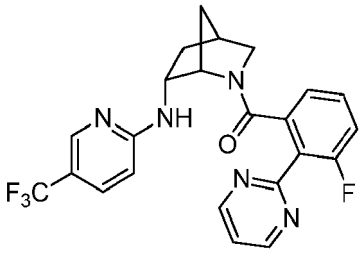
Example 65: (4-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrimidin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

[0425]



Example 66: (3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

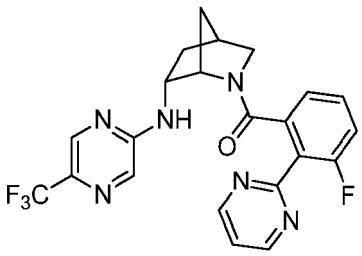
[0426]



[0427] Prepared analogous to Example 53 substituting intermediate A-1 with intermediate A-2. MS (ESI): mass calcd. for $C_{23}H_{19}F_4N_5O$, 457.2; m/z found, 458.1 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers (0.93:0.07), major rotamer reported) δ 8.90 (d, *J* = 5.0 Hz, 2H), 7.93 (s, 1H), 7.57 (dd, J = 8.9, 2.5 Hz, 1H), 7.49 (t, J = 5.0 Hz, 1H), 7.10 - 7.03 (m, 1H), 6.91 - 6.83 (m, 1H), 6.84 - 6.76 (m, 1H), 6.60 - 6.52 (m, 1H), 4.17 (s, 1H), 4.14 - 4.03 (m, 1H), 3.23 (s, 2H), 2.57 - 2.49 (m, 1H), 2.27 - 2.17 (m, 1H), 1.54 (d, J = 11.3 Hz, 1H), 1.26 - 1.17 (m, 1H), 1.04 (d, J = 10.0 Hz, 1H).

Example 67: (3 -fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

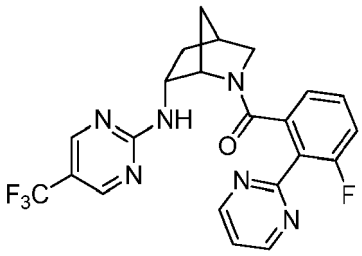
[0428]



[0429] Prepared analogous to Example 59 substituting intermediate A-1 with intermediate A-2. MS (ESI): mass calcd. for $C_{22}H_{18}F_4N_6O$, 458.1; m/z found, 459.2 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.83:0.17), major rotamer reported) δ 8.89 (d, *J* = 4.9 Hz, 2H), 8.12 (s, 1H), 7.72 (d, *J* = 1.4 Hz, 1H), 7.37 (t, *J*= 5.0 Hz, 1H), 7.18 - 7.11 (m, 1H), 7.07 (d, *J* = 7.5 Hz, 1H), 4.52 (s, 1H), 4.41 - 4.28 (m, 1H), 3.59 - 3.48 (m, 1H), 3.24 (d, *J* = 11.6 Hz, 1H), 2.79 - 2.69 (m, 1H), 2.49 - 2.38 (m, 1H), 1.81 - 1.71 (m, 2H), 1.15 - 1.05 (m, 1H). 1H buried under solvent.

Example 68: (3 -fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrimidin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

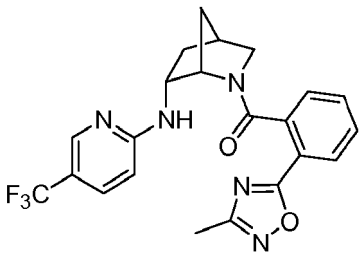
[0430]



[0431] Prepared analogous to Example 60 substituting intermediate A-1 with intermediate A-2. MS (ESI): mass calcd. for $C_{22}H_{18}F_4N_6O$, 458.1; m/z found, 459.9 $[M+H]^+$. ^1H NMR (600 MHz, Methanol-d_4, Compound present as a mixture of rotamers (0.89:0.11), major rotamer reported) δ 8.91 (d, *J*= 4.9 Hz, 2H), 8.55 - 8.50 (m, 1H), 8.24 - 8.19 (m, 1H), 7.49 (t, *J*= 5.0 Hz, 1H), 7.16 - 7.08 (m, 1H), 7.06 - 6.96 (m, 1H), 6.89 (d, *J*= 7.8 Hz, 1H), 4.16 (s, 1H), 4.14 - 4.07 (m, 1H), 3.28 - 3.26 (m, 1H), 3.26 - 3.21 (m, 1H), 2.58 - 2.52 (m, 1H), 2.24 - 2.14 (m, 1H), 1.54 (d, *J*= 10.0 Hz, 1H), 1.34 - 1.28 (m, 1H), 1.09 - 1.01 (m, 1H).

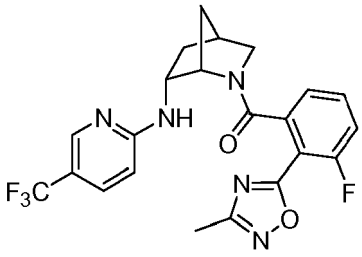
Example 69: (2-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

[0432]



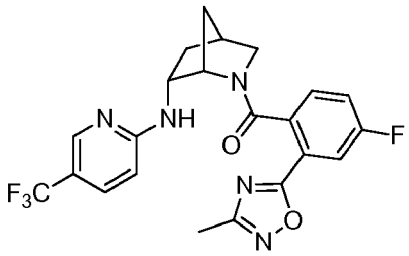
Example 70: (3-fluoro-2-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

[0433]



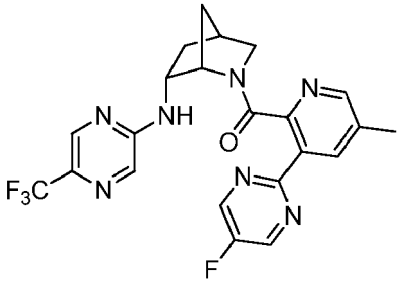
Example 71: (4-fluoro-2-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

[0434]



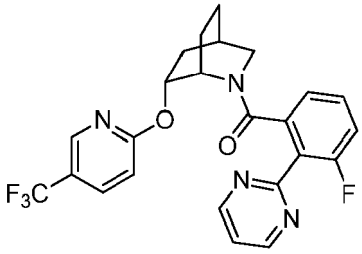
Example 72: (3-(5-fluoropyrimidin-2-yl)-5-methylpyridin-2-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[0435]



Example 73: (3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

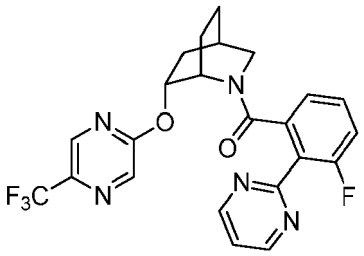
[0436]



[0437] Prepared analogous to Example 76 substituting intermediate A-40 with intermediate A-2. The enantiomeric purity of the title compound was confirmed by analytical SFC using a Chiralpak AZ-H column (5μm, 250 × 4.6 mm), mobile phase of 35% EtOH+(0.2%TEA): 65% CO_2, and a flow rate of 2 mL/min over 45 minutes (Temperature = 40 °C). Elution was monitored following absorbance at 220nm. Enantiopurity 100%, which elutes as a major peak (R_t = 10.8 min). MS (ESI): mass calcd. for $C_{24}H_{20}F_4N_4O_2$, 472.2; m/z found, 473.2 $[M+H]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5μm, 100 × 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 30 °C). R_t = 7.18 min (major rotamer) at 254 nm.

Example 74: (3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone

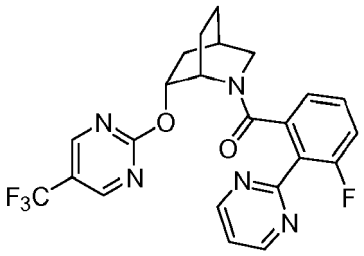
[0438]



[0439] Prepared analogous to Example 77 substituting intermediate A-40 with intermediate A-2. MS (ESI): mass calcd. for $C_{23}H_{19}F_4N_5O_2$, 473.2; m/z found, 474.1 $[M+H]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5μm, 100 × 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 30 °C). R_t = 6.39 min (major rotamer) at 254 nm.

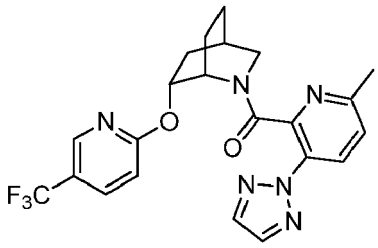
Example 75: (3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrimidin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone

[0440]



Example 76: (6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[0441]



[0442] Step A: (1S,4R,6R)-tert-butyl 6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octane-2-carboxylate. To intermediate C-5B (196 mg, 0.862 mmol) dissolved in DMF (7 mL) was added NaH (69 mg, 1.7 mmol, 60% dispersion in mineral oil). After 5 minutes 2-chloro-5-(trifluoromethyl)pyridine (250 mg, 1.38 mmol) was then added and the mixture stirred at room temperature for 90 min. The reaction mixture was quenched with saturated NH_4Cl solution, and diluted with EtOAc and H_2O. The aqueous layer was extracted with EtOAc (3X). The combined organics were washed with H_2O, brine, dried with $MgSO_4$, filtered and concentrated. Purification via silica gel chromatography (0-50% EtOAc in hexanes) gave the title compound (250 mg, 0.671 mmol, 78%). MS (ESI) mass calcd. for $C_{18}H_{23}F_3N_2O_3$, 372.2; m/z found 373.0 $[M+H]^+$.

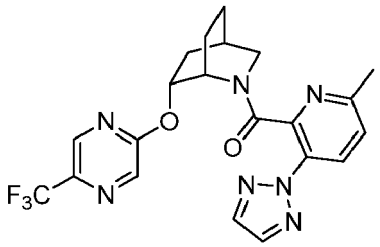
[0443] Step B: (1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octane · xHCl. To the title compound of step A (250 mg, 0.671 mmol) in EtOAc (8 mL) was added 4 M HCl in dioxane (0.84 mL), and the reaction mixture was stirred at room temperature overnight. The reaction was then concentrated to give the title compound of step B which was used without further purification. MS (ESI) mass calcd. for $C_{13}H_{15}F_3N_2O$, 272.1; m/z found 273.1 $[M+H]^+$.

[0444] Step C: (6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone. To the title compound of step B (35 mg) and intermediate A-40 (75 mg, 0.15

mmol, 42% purity) in DMF (1 mL) was added DIPEA (0.13 mL, 0.77 mmol) and HATU (54 mg, 0.14 mmol), and the reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with MeOH and subjected directly to purification using Agilent Prep Method X to give the title compound (28 mg). MS (ESI): mass calcd. for $C_{22}H_{21}F_3N_6O_2$, 458.2; m/z found, 459.2 $[M+H]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5μm, 100 × 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 30 °C). R_t = 7.14 min (major rotamer) at 254 nm.

Example 77: (6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone

[0445]



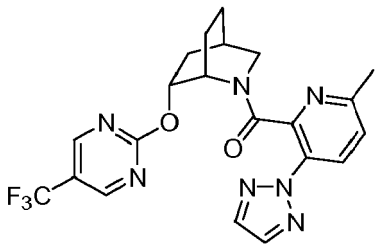
[0446] Step A: (1S,4R,6R)-tert-butyl 6-((5-(trifluoromethyl)pyrazin-2-yl)oxy)-2-azabicyclo[2.2.2]octane-2-carboxylate. To intermediate C-5B (52 mg, 0.23 mmol) dissolved in DMF (2 mL) was added NaH (18 mg, 0.46 mmol, 60% dispersion in mineral oil). After 5 minutes 2-chloro-5-(trifluoromethyl)pyrazine (45 μL, 0.37 mmol) was then added and the mixture stirred at room temperature for 1 h. The reaction mixture was quenched with saturated NH_4Cl solution, and diluted with EtOAc and H_2O. The aqueous layer was extracted with EtOAc (3X). The combined organics were washed with H_2O, brine, dried with $MgSO_4$, filtered, and concentrated. Purification via silica gel chromatography (0-50% EtOAc in hexanes) gave the title compound (75 mg, 0.20 mmol, 88%). MS (ESI) mass calcd. for $C_{17}H_{22}F_3N_3O_3$, 373.1; m/z found 317.9 $[M+2H\text{-}tBu]^+$.

[0447] Step B: (1S,4R,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)oxy)-2-azabicyclo[2.2.2]octane · xHCl. To the title compound of step A (75 mg, 0.20 mmol) in EtOAc (3 mL) was added 4M HCl in dioxane (0.25 mL), and the reaction mixture was stirred at room temperature overnight. Analysis of the reaction mixture showed unreacted starting material. An additional equivalent of 4M HCl in dioxane (0.25 mL) was added and the reaction mixture stirred at room temperature overnight. The reaction was concentrated to give the title compound of step B (55 mg), which was used without further purification. MS (ESI) mass calcd. for $C_{12}H_{14}F_3N_3O$, 273.1; m/z found 274.1 $[M+H]^+$.

[0448] Step C: (6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone. To the title compound of step B (27 mg) and intermediate A-40 (58 mg, 0.12 mmol) in DMF (1 mL) was added DIPEA (0.1 mL, 0.59 mmol) and HATU (41 mg, 0.11 mmol), and the reaction mixture was stirred at room temperature overnight. The reaction was diluted with MeOH and the crude reaction mixture subjected directly to purification via Agilent Prep Method X to give the title compound (5.2 mg). MS (ESI): mass calcd. for $C_{21}H_{20}F_3N_7O_2$, 459.2; m/z found, 460.2 $[M+H]^+$. ^1H NMR (500 MHz, $CDCl_3$) δ 8.28 - 8.24 (m, 1H), 8.15 - 8.11 (m, 1H), 8.08 - 8.02 (m, 1H), 7.83 - 7.79 (s, 2H), 7.13 - 7.09 (d, J = 8.3 Hz, 1H), 5.03 - 4.94 (m, 1H), 3.84 - 3.75 (m, 2H), 3.68 - 3.58 (m, 1H), 2.77 - 2.63 (m, 1H), 2.29 - 2.24 (s, 3H), 2.25 - 2.18 (m, 3H), 1.93 - 1.81 (m, 1H), 1.71 - 1.62 (m, 1H), 1.50 - 1.43 (m, 1H).

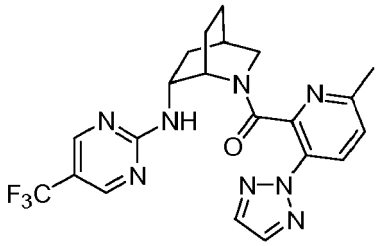
Example 78: (6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrimidin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone

[0449]



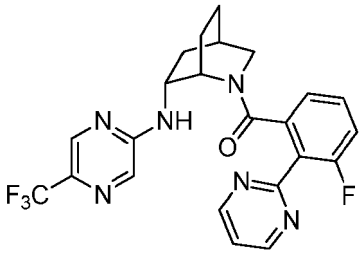
Example 79: (6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrimidin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone

[0450]



Example 80: (3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone

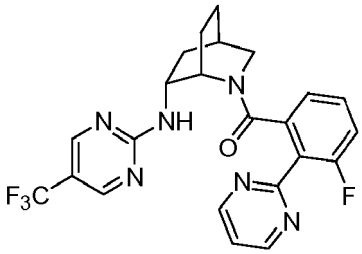
[0451]



[0452] Prepared analogous to Example 83 substituting intermediate A-40 with intermediate A-2. MS (ESI): mass calcd. for $C_{23}H_{20}F_4N_6O$, 472.2; m/z found, 472.9 $[M+H]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5μm, 100 × 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 30 °C). R_t = 6.44 min (major rotamer) at 254 nm.

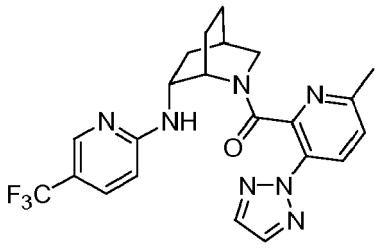
Example 81: (3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrimidin-2-yl)amino)-2-azabicyclo [2.2.2] octan-2-yl)methanone

[0453]



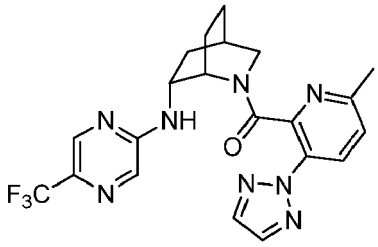
Example 82: (6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone

[0454]



Example 83: (6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone

[0455]



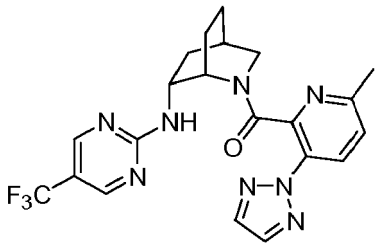
[0456] Step A: (1S,4R,6R)-tert-butyl 6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.2]octane-2-carboxylate. To a microwave vial containing intermediate C-7B (193 mg, 0.853 mmol) in MeCN (4 mL) was added 2-chloro-5-(trifluoromethyl)pyrazine (0.1 mL, 0.82 mmol) and Et_3N (0.14 mL, 1.02 mmol), and the reaction mixture was sealed and heated to reflux bench top overnight. Upon completion of the reaction, the crude reaction mixture was concentrated and subjected directly to silica gel chromatography (0-50% EtOAc in hexanes) to give the title compound of step A (245 mg, 0.658 mmol, 77%) MS (ESI) mass calcd. for $C_{17}H_{23}F_3N_4O_2$; 372.2, m/z found 373.2 $[M+H]^+$.

[0457] Step B: (1S,4R,6R)-N-(5-(trifluoromethyl)pyrazin-2-yl)-2-azabicyclo[2.2.2]octan-6-amine · xHCl. To the title compound of step A (245 mg, 0.658 mmol) in EtOAc (8 mL) was added 4M HCl in dioxane (0.82 mL), and the reaction mixture was stirred at room temperature overnight. The reaction was concentrated to give the title compound of step B (179 mg), which was used without further purification. MS (ESI) mass calcd. for $C_{12}H_{15}F_3N_4$, 272.1; m/z found 273.1 $[M+H]^+$.

[0458] Step C: (6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone. To the title compound of step B (35 mg) and intermediate A-40 (75 mg, 0.15 mmol, 42 % purity) in DMF (1.3 mL) was added DIPEA (0.13 mL, 0.77 mmol) and HATU (54 mg, 0.14 mmol), and the reaction mixture was stirred at room temperature overnight. The reaction was diluted with MeOH and the crude reaction mixture subjected directly to purification via Agilent Prep Method X to give the title compound (26 mg). MS (ESI): mass calcd. for $C_{21}H_{21}F_3N_8O$, 458.2; m/z found, 459.2 $[M+H]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5μm, 100 × 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 30 °C). R_t = 5.97 min (major rotamer) at 254 nm.

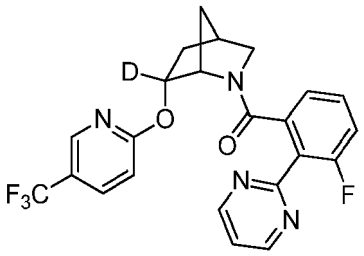
Example 84: (6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrimidin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone

[0459]



Example 85: (3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-(6-^{2}H)-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

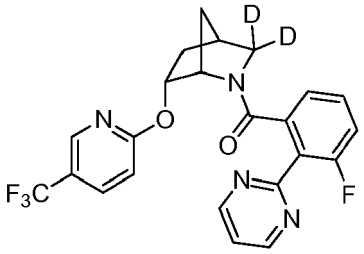
[0460]



[0461] Prepared analogous to Example 27 where the reduction of intermediate B-5 is carried out with $NaBD_4$ instead of L-Selectride. MS (ESI): mass calcd. for $C_{23}H_{17}DF_4N_4O_2$, 459.1; m/z found, 460.1 $[M+H]^+$. ^{1}H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers (0.83:0.17), major rotamer reported) δ 8.91 (d, *J*= 5.0 Hz, 2H), 8.19 - 8.13 (m, 1H), 7.96 (dd, *J*= 8.7, 2.6 Hz, 1H), 7.50 (t, *J*= 5.0 Hz, 1H), 7.18 - 7.13 (m, 1H), 7.06 - 6.97 (m, 2H), 6.88 (dd, *J*= 7.6, 1.1 Hz, 1H), 4.33 - 4.23 (m, 1H), 3.27 - 3.24 (m, 2H), 2.59 - 2.53 (m, 1H), 2.30 - 2.21 (m, 1H), 1.54 (d, *J*= 10.6 Hz, 1H), 1.37 (dd, *J*= 13.5, 3.6 Hz, 1H), 1.01 - 0.91 (m, 1H).

Example 86: (3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]-(3-^{2}H,^{2}H)-heptan-2-yl)methanone.

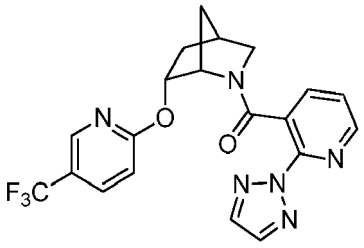
[0462]



[0463] Prepared analogous to Example 27 where the Diels-Alder reaction to intermediate B-1 is carried out with formaldehyde-d_2 instead of formaldehyde. MS (ESI): mass calcd. for $C_{23}H_{16}D_2F_4N_4O_2$, 460.1; m/z found, 461.2 $[M+H]^+$. ^{1}H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.88:0.12), major rotamer reported) δ 8.86 (d, *J*= 4.9 Hz, 2H), 8.15 - 8.09 (m, 1H), 7.79 (dd, *J*= 8.8, 2.5 Hz, 1H), 7.30 - 7.27 (m, 1H), 7.10 - 7.03 (m, 1H), 6.96 - 6.86 (m, 2H), 6.84 (d, *J* = 8.7 Hz, 1H), 5.07 (dt, *J*= 10.1, 3.3 Hz, 1H), 4.31 - 4.19 (m, 1H), 2.56 - 2.48 (m, 1H), 2.27 - 2.12 (m, 1H), 1.46 - 1.40 (m, 1H), 1.36 (dt, *J*= 13.6, 3.6 Hz, 1H), 0.96 - 0.86 (m, 1H).

Example 87: (2-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

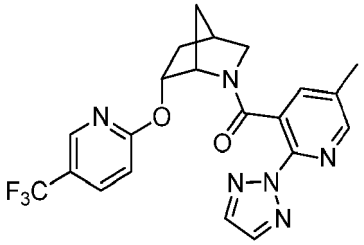
[0464]



[0465] Prepared analogous to Example 25 substituting intermediate A-20 with intermediate A-39. MS (ESI): mass calcd. for $C_{20}H_{17}F_3N_6O_2$, 430.1; m/z found, 431.2 $[M+H]^+$. ^1H NMR (400 MHz, Methanol-d_4, Compound present as a mixture of rotamers (0.88:0.12), major rotamer reported) δ 8.43 (dd, *J* = 4.8, 1.8 Hz, 1H), 8.18 - 8.11 (m, 1H), 8.11 - 8.02 (m, 2H), 7.95 (dd, *J*= 8.6, 2.5 Hz, 1H), 7.71 - 7.55 (m, 1H), 7.12 - 6.90 (m, 2H), 5.08 (dt, *J*= 10.1, 3.2 Hz, 1H), 4.01 (s, 1H), 3.57 (dt, *J*= 11.1, 3.2 Hz, 1H), 3.35 (dd, *J*= 11.1, 1.7 Hz, 1H), 2.75 - 2.64 (m, 1H), 2.37 - 2.24 (m, 1H), 1.57 (d, *J*= 10.4 Hz, 1H), 1.53 - 1.35 (m, 2H).

Example 88: (5-methyl-2-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

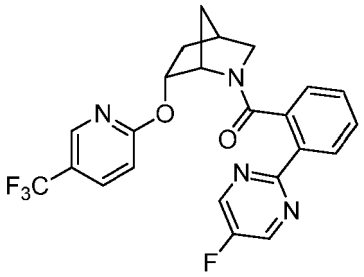
[0466]



[0467] Prepared analogous to Example 25 substituting intermediate A-20 with intermediate A-38. MS (ESI): mass calcd. for $C_{21}H_{19}F_3N_6O_2$, 444.2; m/z found, 445.2 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers (0.90:0.10), major rotamer reported) δ 8.26 - 8.21 (m, 1H), 8.19 - 8.14 (m, 1H), 8.05 (s, 2H), 7.98 (dd, *J* = 8.7, 2.6 Hz, 1H), 7.50 - 7.46 (m, 1H), 6.99 (d, *J*= 8.8 Hz, 1H), 5.06 (dt, *J*= 10.4, 3.2 Hz, 1H), 4.05 - 3.97 (m, 1H), 3.54 (dt, *J*= 11.0, 3.2 Hz, 1H), 3.35 (dd, *J*= 11.1, 1.6 Hz, 1H), 2.68 - 2.62 (m, 1H), 2.32 - 2.19 (m, 1H), 2.08 (s, 3H), 1.56 (d, *J*= 10.7 Hz, 1H), 1.47 - 1.35 (m, 2H).

Example 89: (2-(5-fluoropyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

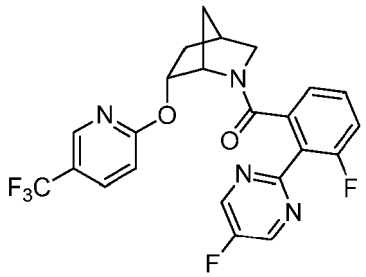
[0468]



[0469] Prepared analogous to Example 25 substituting intermediate A-20 with intermediate A-34. MS (ESI): mass calcd. for $C_{23}H_{18}F_4N_4O_2$, 458.1; m/z found, 459.1 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers, (0.85:0.15), major rotamer reported) δ 8.85 - 8.80 (m, 2H), 8.17 (dd, J = 8.1, 1.3 Hz, 1H), 8.09 - 8.03 (m, 1H), 7.95 (dd, J = 8.8, 2.6 Hz, 1H), 7.39 - 7.31 (m, 1H), 7.05 - 6.96 (m, 2H), 6.92 (td, J = 7.5, 1.2 Hz, 1H), 5.11 (dt, J = 10.2, 3.3 Hz, 1H), 4.16 - 4.10 (m, 1H), 3.61 (dt, J = 10.9, 3.2 Hz, 1H), 3.35 - 3.33 (m, 1H), 2.74 - 2.65 (m, 1H), 2.36 - 2.26 (m, 1H), 1.59 - 1.53 (m, 1H), 1.46 (dt, J = 13.4, 3.7 Hz, 1H), 1.41 - 1.32 (m, 1H).

Example 90: (3-fluoro-2-(5-fluoropyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

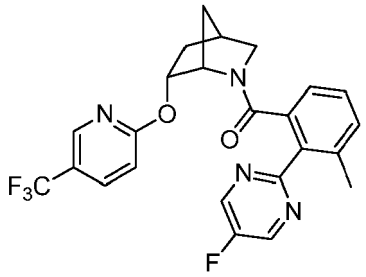
[0470]



[0471] Prepared analogous to Example 25 substituting intermediate A-20 with intermediate A-35. MS (ESI): mass calcd. for $C_{23}H_{17}F_5N_4O_2$, 476.1; m/z found, 477.1 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers, (0.81:0.19), major rotamer reported) δ 8.88 (d, J = 0.7 Hz, 2H), 8.21 - 8.15 (m, 1H), 7.96 (dd, J = 8.8, 2.6 Hz, 1H), 7.19 - 7.13 (m, 1H), 7.07 - 6.99 (m, 2H), 6.91 (dd, J = 7.6, 0.9 Hz, 1H), 5.17 (dt, J = 10.2, 3.3 Hz, 1H), 4.31 - 4.21 (m, 1H), 3.35 - 3.32 (m, 1H), 3.27 - 3.23 (m, 1H), 2.63 - 2.59 (m, 1H), 2.32 - 2.25 (m, 1H), 1.65 - 1.56 (m, 1H), 1.39 (dt, J = 13.6, 3.6 Hz, 1H), 1.20 - 1.05 (m, 1H).

Example 91: (2-(5-fluoropyrimidin-2-yl)-3-methylphenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

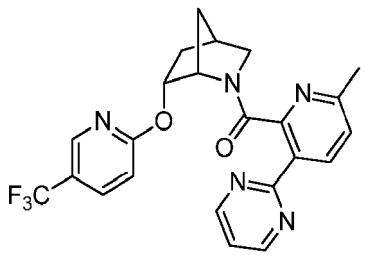
[0472]



[0473] Prepared analogous to Example 25 substituting intermediate A-20 with intermediate A-36. MS (ESI): mass calcd. for $C_{24}H_{20}F_4N_4O_2$, 472.2; m/z found, 473.1 $[M+H]^+$. ^1H NMR (400 MHz, Methanol-d_4, Compound present as a mixture of rotamers, (0.81:0.19), major rotamer reported) δ 8.85 (d, J = 0.8 Hz, 2H), 8.21 - 8.10 (m, 1H), 7.96 (dd, J = 8.8, 2.6 Hz, 1H), 7.25 - 7.18 (m, 1H), 7.08 - 6.96 (m, 1H), 6.96 - 6.79 (m, 2H), 5.17 (dt, J = 10.2, 3.3 Hz, 1H), 4.33 - 4.23 (m, 1H), 3.27 - 3.16 (m, 2H), 2.58 (s, 1H), 2.33 - 2.22 (m, 4H), 1.62 - 1.56 (m, 1H), 1.37 (dt, J = 13.5, 3.6 Hz, 1H), 1.21 - 1.02 (m, 1H).

Example 92: (6-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[0474]

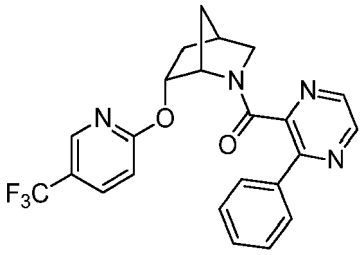


[0475] Prepared analogous to Example 25 substituting intermediate A-20 with intermediate A-41. MS (ESI): mass calcd. for $C_{23}H_{20}F_3N_5O_2$, 455.2; m/z found, 456.2 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers, (0.90:0.10), major rotamer reported) δ 8.87 (d, *J*= 4.9 Hz, 2H), 8.47 (d, *J*= 8.2 Hz, 1H), 8.05 - 7.99 (m, 1H), 7.86 (dd, *J*= 8.8, 2.5 Hz, 1H), 7.42 (t, *J*= 4.9 Hz, 1H), 7.22 (d, *J*= 8.2 Hz, 1H), 6.91 - 6.87 (m, 1H), 4.99 (dt, *J*=

10.3, 3.4 Hz, 1H), 4.32 - 4.25 (m, 1H), 3.66 (dt, *J*= 10.9, 3.2 Hz, 1H), 3.39 (dd, *J*= 10.9, 1.6 Hz, 1H), 2.71 - 2.66 (m, 1H), 2.33 - 2.24 (m, 1H), 2.19 (s, 3H), 1.62 - 1.54 (m, 1H), 1.49 (dt, *J*= 13.4, 3.7 Hz, 1H), 1.44 - 1.32 (m, 1H).

Example 93: (3-phenylpyrazin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

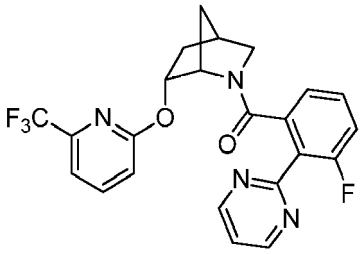
[0476]



[0477] Prepared analogous to Example 25 substituting intermediate A-20 with intermediate A-43. MS (ESI): mass calcd. for $C_{23}H_{19}F_3N_4O_2$, 440.1; m/z found, 441.2 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers, major rotamer reported) δ 8.52 (d, *J*= 2.4 Hz, 1H), 8.04 - 8.01 (m, 1H), 7.93 (d, *J*= 2.5 Hz, 1H), 7.89 (dd, *J*= 8.8, 2.7 Hz, 1H), 7.75 - 7.71 (m, 2H), 7.56 - 7.53 (m, 3H), 6.91 - 6.84 (m, 1H), 4.95 (dt, *J*= 10.3, 3.3 Hz, 1H), 4.11 - 3.99 (m, 1H), 3.38 - 3.34 (m, 2H), 2.57 - 2.52 (m, 1H), 2.27 - 2.12 (m, 1H), 1.45 - 1.35 (m, 2H), 0.68 - 0.59 (m, 1H).

Example 94: (3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((6-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[0478]



[0479] Step A: (1S,4R,6R)-tert-butyl 6-((6-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptane-2-carboxylate. To intermediate B-5 (50 mg, 0.23 mmol) dissolved in DMF (1 mL) was added NaH (19 mg, 0.47 mmol, 60% dispersion in mineral oil). After 5 minutes the sides of the flask were rinsed with additional DMF (1 mL) and 2-fluoro-6-(trifluoromethyl)pyridine (0.045 mL, 0.38 mmol) was then added and the mixture stirred overnight at room temperature. The mixture was quenched with saturated NH_4Cl solution, diluted with EtOAc and H_2O. The aqueous layer was extracted with EtOAc (3X). The combined organics were washed with H_2O, 5% aqueous LiCl, brine, dried with Na_2SO_4, filtered, and concentrated. Purification via silica gel chromatography (0-40% EtOAc in hexanes) gave the title compound (29 mg, 0.080 mmol, 34%) as a clear oil. MS (ESI) mass calcd. for $C_{17}H_{21}F_3N_2O_3$, 358.2; m/z found 303.1 $[M+2H-t\text{Bu}]^+$.

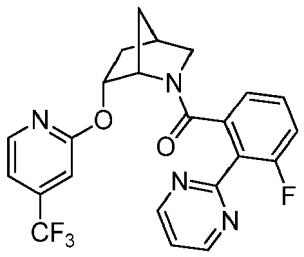
[0480] Step B: (1S,4R,6R)-6-((6-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptane · xHCl. To the title compound of step A (28 mg, 0.078 mmol) in EtOAc (1 mL) was added 4M HCl in dioxane (0.1 mL). After 4h, the reaction was concentrated to give the title compound of step B (23 mg) as a pink solid and used without further purification. MS (ESI) mass calcd. for $C_{12}H_{13}F_3N_2O$, 258.1; m/z found 259.1 $[M+H]^+$.

[0481] Step C: (3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((6-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone. To the title compound of step B (23 mg) and intermediate A-2 (25 mg, 0.094 mmol) in DMF (1.1 mL) was added DIPEA (81 μL, 0.47 mmol) and HATU (33 mg, 0.086 mmol), and the reaction mixture was stirred at room temperature for 1 h. The reaction was quenched by the addition of H_2O and the aqueous layer was extracted with EtOAc (3X). The combined organics were concentrated. Purification of the concentrate was performed using Agilent Prep Method X to give the title compound (15 mg). MS (ESI): mass calcd. for $C_{23}H_{18}F_4N_4O_2$, 458.1; m/z found, 459.1 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers, (0.84:0.16), major

rotamer reported) δ 8.89 (d, J = 4.9 Hz, 2H), 7.95 - 7.88 (m, 1H), 7.48 (t, J = 5.0 Hz, 1H), 7.33 (d, J = 7.5 Hz, 1H), 7.17 - 7.10 (m, 2H), 7.05 - 6.99 (m, 1H), 6.86 (dd, J = 7.9, 1.0 Hz, 1H), 5.12 (dt, J = 10.2, 3.3 Hz, 1H), 4.29 - 4.25 (m, 1H), 3.26 (t, J = 3.0 Hz, 1H), 3.25 (s, 1H), 2.58 (s, 1H), 2.32 - 2.24 (m, 1H), 1.60 (d, J = 10.1 Hz, 1H), 1.38 (dt, J = 13.5, 3.6 Hz, 1H), 1.11-1.05 (m, 1H).

Example 95: (3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((4-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[0482]



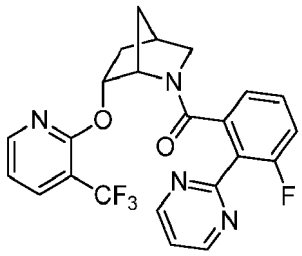
[0483] Step A: (1S,4R,6R)-tert-butyl 6-((4-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptane-2-carboxylate. To intermediate B-5 (101 mg, 0.47 mmol) dissolved in DMF (3 mL) was added NaH (38 mg, 0.95 mmol, 60% dispersion in mineral oil). After 5 minutes the sides of the flask were rinsed with additional DMF (1 mL) and 2-chloro-4-(trifluoromethyl)pyridine (0.10 mL, 0.76 mmol) was then added and the mixture heated to 70 °C. After heating at 70 °C for 3 h, the mixture was cooled to room temperature, quenched with saturated NH_4Cl solution, diluted with EtOAc and H_2O. The aqueous layer was extracted with EtOAc (3X). The combined organics were washed with H_2O, 5% aqueous LiCl, brine, dried with Na_2SO_4, filtered, and concentrated. Purification via silica gel chromatography (0-40% EtOAc in hexanes) gave the title compound (16 mg, 0.045 mmol, 10%) as a yellow-brown solid. MS (ESI) mass calcd. for $C_{17}H_{21}F_3N_2O_3$, 358.2; m/z found 359.1 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d) δ 8.34 - 8.23 (m, 1H), 7.12 - 7.04 (m, 1H), 7.01 - 6.92 (m, 1H), 5.35 (dt, J = 10.1, 3.2 Hz, 1H), 4.56 - 4.49 (m, 1H), 3.41 (dt, J = 9.5, 3.1 Hz, 1H), 3.27 - 3.17 (m, 1H), 2.60 - 2.55 (m, 1H), 2.28 - 2.16 (m, 1H), 1.80 - 1.71 (m, 1H), 1.68 - 1.62 (m, 1H), 1.53 - 0.93 (m, 10H).

[0484] Step B: (1S,4R,6R)-6-((4-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptane · xHCl. To the title compound of step A (16 mg, 0.045 mmol) in EtOAc (0.1 mL) was added 4M HCl in dioxane (0.1 mL). After 3h, the reaction was concentrated to give the title compound of step B (16 mg) and used without further purification. MS (ESI) mass calcd. for $C_{12}H_{13}F_3N_2O$, 258.1; m/z found 259.2 $[M+H]^+$.

[0485] Step C: (3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((4-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone. To the title compound of step B (16 mg) and intermediate A-2 (13 mg, 0.060 mmol) in DMF (0.6 mL) was added DIPEA (56 μL, 0.33 mmol) and HATU (23 mg, 0.060 mmol), and the reaction mixture was stirred at room temperature for 1 h. The reaction was quenched by the addition of H_2O and the aqueous layer was extracted with EtOAc (3X). The combined organics were washed with H_2O, 5% aqueous LiCl, brine, dried with Na_2SO_4, filtered, and concentrated. Purification of the concentrate was performed using Agilent Prep Method X to give the title compound (3.4 mg). MS (ESI): mass calcd. for $C_{23}H_{18}F_4N_4O_2$, 458.1; m/z found, 459.1 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers, (0.80:0.20), major rotamer reported) δ 8.90 (d, J = 5.0 Hz, 2H), 8.07 (d, J = 5.3 Hz, 1H), 7.49 (t, J = 5.0 Hz, 1H), 7.20 - 7.11 (m, 3H), 7.03 - 6.97 (m, 1H), 6.91 - 6.87 (m, 1H), 5.16 (dt, J = 10.2, 3.3 Hz, 1H), 4.28 - 4.23 (m, 1H), 3.28 - 3.24 (m, 2H), 2.61 - 2.54 (m, 1H), 2.32 - 2.20 (m, 1H), 1.56 (d, J = 10.6 Hz, 1H), 1.38 (dt, J = 13.6, 3.6 Hz, 1H), 1.04 - 0.96 (m, 1H).

Example 96: (3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((3-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[0486]



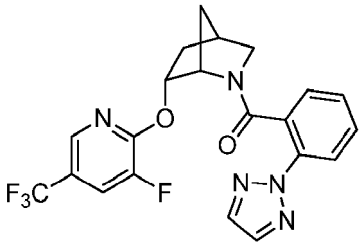
[0487] Step A: (1S,4R,6R)-tert-butyl 6-((3-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptane-2-carboxylate. To intermediate B-5 (101 mg, 0.47 mmol) dissolved in DMF (3 mL) was added NaH (38 mg, 0.95 mmol, 60% dispersion in mineral oil). After 5 minutes the sides of the flask were rinsed with additional DMF (1 mL) and 2-fluoro-3-(trifluoromethyl)pyridine (0.10 mL, 0.76 mmol) was then added and the mixture heated to 70 °C. After heating at 70 °C for 3 h, the mixture was cooled to room temperature, quenched with saturated NH_4Cl solution, diluted with EtOAc and H_2O. The aqueous layer was extracted with EtOAc (3X). The combined organics were washed with H_2O, 5% aqueous LiCl, brine, dried with Na_2SO_4, filtered, and concentrated. Purification via silica gel chromatography (0-35% EtOAc in hexanes) gave the title compound (87 mg, 0.24 mmol, 51%) as a white solid. MS (ESI) mass calcd. for $C_{17}H_{21}F_3N_2O_3$, 358.2; m/z found 303.1 $[M+2H-t\text{Bu}]^+$. ^1H NMR (400 MHz, Chloroform-d) δ 8.35 - 8.25 (m, 1H), 7.90 - 7.82 (m, 1H), 6.96 (dd, *J*= 7.5, 5.0 Hz, 1H), 5.32 (dt, *J*= 10.1, 3.1 Hz, 1H), 4.64 - 4.58 (m, 1H), 3.42 (dt, *J* = 9.5, 3.1 Hz, 1H), 3.15 (d, *J*= 9.5 Hz, 1H), 2.61 - 2.56 (m, 1H), 2.27 - 2.15 (m, 1H), 1.76 - 1.66 (m, 2H), 1.48 (dt, *J*= 13.5, 3.5 Hz, 1H), 1.08 (s, 9H).

[0488] Step B: (1S,4R,6R)-6-((3-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptane · xHCl. To the title compound of step A (86 mg, 0.24 mmol) in EtOAc (0.9 mL) was added 4M HCl in dioxane (3 mL). After 2h, the reaction was concentrated to give the title compound of step B (77 mg) and used without further purification. MS (ESI) mass calcd. for $C_{12}H_{13}F_3N_2O$, 258.1; m/z found 259.1 $[M+H]^+$.

[0489] Step C: (3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((3-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone. To the title compound of step B (28 mg) and intermediate A-2 (23 mg, 0.11 mmol) in DMF (1 mL) was added DIPEA (98 μL, 0.57 mmol) and HATU (40 mg, 0.11 mmol), and the reaction mixture was stirred at room temperature for 1 h. The reaction was quenched by the addition of H_2O and the aqueous layer was extracted with EtOAc (3X). The combined organics were washed with H_2O, 5% aqueous LiCl, brine, dried with Na_2SO_4, filtered, and concentrated. Purification of the concentrate was performed using Agilent Prep Method X to give the title compound (5.4 mg). MS (ESI): mass calcd. for $C_{23}H_{18}F_4N_4O_2$, 458.1; m/z found, 459.1 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers, (0.86:0.14), major rotamer reported) δ 8.90 (d, J = 5.0 Hz, 2H), 8.05 - 8.01 (m, 2H), 7.49 (t, J = 5.0 Hz, 1H), 7.17 - 7.11 (m, 1H), 7.08 - 7.04 (m, 1H), 6.96 - 6.90 (m, 1H), 6.77 (dd, J = 7.6, 1.1 Hz, 1H), 5.20 (dt, J = 10.2, 3.3 Hz, 1H), 4.32 - 4.28 (m, 1H), 3.29 - 3.26 (m, 1H), 3.25 - 3.20 (m, 1H), 2.60 - 2.54 (m, 1H), 2.29 - 2.21 (m, 1H), 1.53 (d, J = 10.4 Hz, 1H), 1.40 (dt, J = 13.6, 3.6 Hz, 1H), 0.95 - 0.89 (m, 1H).

Example 97: (2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((3-fluoro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[0490]



[0491] Step A: (1S,4R,6R)-tert-butyl 6-((3-fluoro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptane-2-carboxylate. To intermediate B-5 (70 mg, 0.33 mmol) and 2,3-difluoro-5-(trifluoromethyl)pyridine (90 mg, 0.49 mmol) dissolved in DMF (3 mL) was added NaH (18 mg, 0.46 mmol, 60% dispersion in mineral oil) and the reaction mixture was stirred overnight at room temperature after which analysis of the reaction mixture showed mainly starting material. Additional 2,3-difluoro-5-(trifluoromethyl)pyridine (0.05 mL) was then added and the reaction mixture heated to 70 °C and stirred overnight after which analysis of the reaction mixture still showed starting material remaining. Additional 2,3-difluoro-5-(trifluoromethyl)pyridine (0.05 mL) was again added and the reaction mixture was heated at 70 °C for an

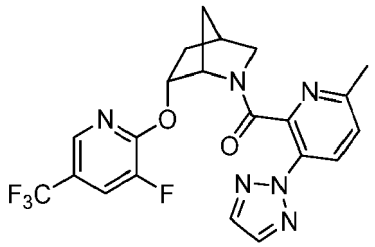
additional 4.5 hours before additional 2,3-difluoro-5-(trifluoromethyl)pyridine (0.05 mL) was added and the reaction stirred overnight. After this time analysis still showed incomplete conversion however the reaction was cooled to room temperature and quenched with H_2O. The aqueous layer was extracted with EtOAc (3X) and the combined organics were washed with 5% aqueous LiCl, brine, dried with Na_2SO_4, filtered, and concentrated. Purification via silica gel chromatography (0-25% EtOAc in hexanes) gave the title compound. MS (ESI) mass calcd. for $C_{17}H_{20}F_4N_2O_3$, 376.1; m/z found 321.1 $[M+2H-t\text{Bu}]^+$.^{1}H NMR (500 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.67:0.33), major rotamer reported) δ 8.21 - 8.18 (m, 1H), 7.51 (dd, *J*= 9.5, 2.1 Hz, 1H), 5.37 (dt, *J*= 10.1, 3.2 Hz, 1H), 4.57 - 4.50 (m, 1H), 3.41 (dt, *J*= 9.5, 3.1 Hz, 1H), 3.22 (dd, *J*= 9.5, 1.4 Hz, 1H), 2.62 - 2.57 (m, 1H), 2.30 - 2.19 (m, 1H), 1.77 - 1.73 (m, 1H), 1.67 - 1.63 (m, 1H), 1.48 (dt, *J*= 13.7, 3.6 Hz, 1H), 1.12 (s, 9H).

[0492] Step B: (1S,4R,6R)-6-((3-fluoro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptane · xHCl. To the title compound of step A (130 mg, 0.345 mmol) in EtOAc (1 mL) was added 4M HCl in dioxane (3 mL) and the reaction mixture was stirred at room temperature overnight. The reaction was concentrated to give the title compound of step B (114 mg) as a yellow oil and used without further purification. MS (ESI) mass calcd. for $C_{12}H_{12}F_4N_2O$, 276.1; m/z found 277.1 $[M+H]^+$.

[0493] Step C: (2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((3-fluoro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone. To the title compound of step B (28.5 mg) and intermediate A-1 (19 mg, 0.1 mmol) in DMF (0.9 mL) was added DIPEA (0.13 mL, 0.73 mmol) and HATU (38 mg, 0.1 mmol), and the reaction mixture was stirred at room temperature for 1 h. The reaction was quenched by the addition of H_2O and the aqueous layer was extracted with EtOAc (3X). The combined organics were concentrated. Purification of the concentrate was performed using Agilent Prep Method X to give the title compound (18 mg). MS (ESI): mass calcd. for $C_{21}H_{17}F_4N_5O_2$, 447.1; m/z found, 448.2 $[M+H]^+$. ^{1}H NMR (500 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.81:0.19), major rotamer reported) δ 7.87 (s, 1H), 7.81 (s, 2H), 7.57 - 7.50 (m, 2H), 7.37 - 7.30 (m, 2H), 6.96 (t, *J*= 7.5 Hz, 1H), 5.05 (dt, *J*= 10.1, 3.4 Hz, 1H), 4.03 (s, 1H), 3.64 (dt, *J*= 11.0, 3.2 Hz, 1H), 3.42 (dd, *J* = 10.9, 1.4 Hz, 1H), 2.72 - 2.62 (m, 1H), 2.36 - 2.20 (m, 1H), 1.51 - 1.36 (m, 3H).

Example 98: (1S,4R,6R)-6-((3-fluoro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)methanone.

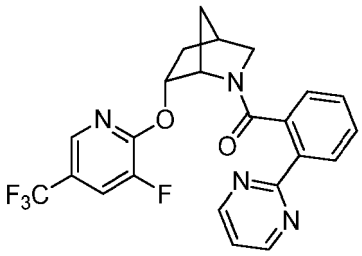
[0494]



[0495] Prepared analogous to Example 97 substituting intermediate A-1 with intermediate A-40. MS (ESI): mass calcd. for $C_{21}H_{18}F_4N_6O_2$, 462.1; m/z found, 463.1 $[M+H]^+$. ^{1}H NMR (500 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.79:0.21), major rotamer reported) δ 8.00 (d, *J* = 8.4 Hz, 1H), 7.81 (s, 2H), 7.72 - 7.69 (m, 1H), 7.39 (dd, *J* = 9.4, 2.1 Hz, 1H), 7.07 (d, J = 8.4 Hz, 1H), 4.96 (dt, *J*= 10.3, 3.3 Hz, 1H), 4.47 - 4.40 (m, 1H), 3.72 (dt, *J*= 11.0, 3.2 Hz, 1H), 3.48 (dd, *J* = 11.0, 1.4 Hz, 1H), 2.72 - 2.64 (m, 1H), 2.29 - 2.21 (m, 4H), 1.66 - 1.61 (m, 1H), 1.57 - 1.50 (m, 2H).

Example 99: ((1S,4R,6R)-6-((3-fluoro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)(2-(pyrimidin-2-yl)phenyl)methanone.

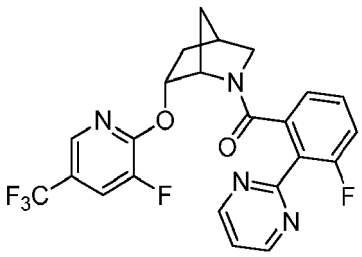
[0496]



[0497] Prepared analogous to Example 97 substituting intermediate A-1 with intermediate A-37. MS (ESI): mass calcd. for $C_{23}H_{18}F_4N_4O_2$, 458.1; m/z found, 459.1 $[M+H]^+$. ^1H NMR (500 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.81:0.19), major rotamer reported) δ 8.79 (d, *J*= 4.8 Hz, 2H), 8.21 - 8.18 (m, 1H), 7.89 - 7.84 (m, 1H), 7.57 - 7.52 (m, 1H), 7.36 - 7.29 (m, 1H), 7.29 - 7.26 (m, 1H), 7.20 (t, *J*= 4.8 Hz, 1H), 7.01 (td, *J*= 7.5, 1.3 Hz, 1H), 5.06 (dt, *J*= 10.0, 3.3 Hz, 1H), 4.17 - 4.11 (m, 1H), 3.69 (dt, *J* = 10.8, 3.2 Hz, 1H), 3.43 (dd, *J*= 10.8, 1.5 Hz, 1H), 2.72 - 2.65 (m, 1H), 2.37 - 2.23 (m, 1H), 1.51 - 1.43 (m, 2H), 1.42 - 1.30 (m, 1H).

Example 100: (3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((3-fluoro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

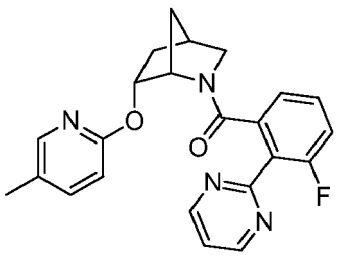
[0498]



[0499] Prepared analogous to Example 97 substituting intermediate A-1 with intermediate A-2. MS (ESI): mass calcd. for $C_{23}H_{17}F_5N_4O_2$, 476.1; m/z found, 477.2 $[M+H]^+$. ^1H NMR (500 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.81:0.19), major rotamer reported) δ 8.85 (d, *J*= 4.8 Hz, 2H), 8.00 - 7.94 (m, 1H), 7.55 (dd, *J*= 9.5, 2.1 Hz, 1H), 7.30 - 7.27 (m, 1H), 7.19 (dd, *J*= 7.1, 1.7 Hz, 1H), 7.13 - 7.03 (m, 2H), 5.10 (dt, *J*= 10.0, 3.3 Hz, 1H), 4.31 - 4.24 (m, 1H), 3.45 - 3.29 (m, 2H), 2.65 - 2.53 (m, 1H), 2.35 - 2.23 (m, 1H), 1.48 (d, *J*= 9.9 Hz, 1H), 1.40 (dt, *J*= 13.6, 3.7 Hz, 1H), 1.18 - 0.99 (m, 1H).

Example 101: (3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-methylpyridin-2-yl)oxy)-2-azabicyclo [2.2.1]heptan-2-yl)methanone.

[0500]



[0501] Step A: (1S,4R,6R)-tert-butyl 6-((5-methylpyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptane-2-carboxylate. To intermediate B-5 (101 mg, 0.47 mmol) dissolved in DMF (3 mL) was added NaH (38 mg, 0.95 mmol, 60% dispersion in mineral oil). After 5 minutes the sides of the flask were rinsed with additional DMF (1 mL) and 2-chloro-5-methylpyridine (0.08 mL, 0.76 mmol) was then added and the mixture heated to 70 °C. After heating at 70 °C for 3 h, the mixture was

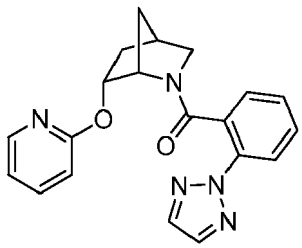
cooled to room temperature, quenched with saturated NH_4Cl solution, diluted with EtOAc and H_2O. The aqueous layer was extracted with EtOAc (3X). The combined organics were washed with H_2O, 5% aqueous LiCl, brine, dried with Na_2SO_4, filtered, and concentrated. Purification via silica gel chromatography (0-35% EtOAc in hexanes) gave the title compound (16 mg, 0.053 mmol, 11%) as a white solid. MS (ESI) mass calcd. for $C_{17}H_{24}N_2O_3$, 304.2; m/z found 305.1 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers, major rotamer reported) δ 7.97 - 7.89 (m, 1H), 7.37 (dd, J = 8.4, 2.5 Hz, 1H), 6.61 (d, J = 8.5 Hz, 1H), 5.25 (dt, J = 10.1, 3.2 Hz, 1H), 4.56 - 4.48 (m, 1H), 3.38 (dt, J = 9.5, 3.1 Hz, 1H), 3.19 (d, J = 9.5 Hz, 1H), 2.59 - 2.52 (m, 1H), 2.23 (s, 3H), 2.20 - 2.14 (m, 1H), 1.76 - 1.68 (m, 1H), 1.65 - 1.60 (m, 1H), 1.35 (dt, J = 13.4, 3.6 Hz, 1H), 1.14 (s, 9H).

[0502] Step B: (1S,4R,6R)-6-((5-methylpyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptane · xHCl. To the title compound of step A (16 mg, 0.053 mmol) in EtOAc (0.1 mL) was added 4M HCl in dioxane (0.1 mL). After 3h, the reaction was concentrated to give the title compound of step B (15 mg) and used without further purification. MS (ESI) mass calcd. for $C_{12}H_{16}N_2O$, 204.1; m/z found 205.2 $[M+H]^+$.

[0503] Step C: (3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-methylpyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone. To the title compound of step B (16 mg) and intermediate A-2 (16 mg, 0.07 mmol) in DMF (1 mL) was added DIPEA (69 μL, 0.40 mmol) and HATU (28 mg, 0.073 mmol), and the reaction mixture was stirred at room temperature for 1 h. The reaction was quenched by the addition of H_2O and the aqueous layer was extracted with EtOAc (3X). The combined organics were washed with H_2O, 5% aqueous LiCl, brine, dried with Na_2SO_4, filtered, and concentrated. Purification of the concentrate was performed using Agilent Prep Method X to give the title compound (6 mg). MS (ESI): mass calcd. for $C_{23}H_{21}FN_4O_2$, 404.2; m/z found, 405.1 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers, (0.85:0.15), major rotamer reported) δ 8.89 (d, J = 4.9 Hz, 2H), 7.69 - 7.65 (m, 1H), 7.52 (dd, J = 8.4, 2.5 Hz, 1H), 7.48 (t, J = 4.9 Hz, 1H), 7.21 - 7.14 (m, 1H), 7.07 - 7.00 (m, 1H), 6.92 (dd, J = 7.6, 1.1 Hz, 1H), 6.74 (d, J = 8.4 Hz, 1H), 5.02 (dt, J = 10.1, 3.3 Hz, 1H), 4.25 - 4.19 (m, 1H), 3.26 - 3.18 (m, 2H), 2.57 - 2.53 (m, 1H), 2.25 (s, 3H), 2.24 - 2.19 (m, 1H), 1.56 - 1.51 (m, 1H), 1.34 - 1.28 (m, 1H), 1.08 - 1.02 (m, 1H).

Example 102: (2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-(pyridin-2-yloxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[0504]



[0505] Step A: (1S,4R,6R)-tert-butyl 6-(pyridin-2-yloxy)-2-azabicyclo[2.2.1]heptane-2-carboxylate. To intermediate B-5 (150 mg, 0.70 mmol) dissolved in DMF (5 mL) was added NaH (37 mg, 0.91 mmol, 60% dispersion in mineral oil). After 5 minutes the sides of the flask were rinsed with additional DMF (1 mL) and 2-fluoropyridine (0.10 mL, 1.13 mmol) was then added and the mixture heated to 70 °C. After heating at 70 °C for 7 h, the mixture was cooled to room temperature, quenched with saturated NH_4Cl solution, diluted with EtOAc and H_2O. The aqueous layer was extracted with EtOAc (3X). The combined organics were washed with H_2O, 5% aqueous LiCl, brine, dried with Na_2SO_4, filtered, and concentrated. Purification via silica gel chromatography (0-30% EtOAc in hexanes) gave the title compound (73 mg, 0.25 mmol, 36%) as a colorless solid. MS (ESI) mass calcd. for $C_{16}H_{22}N_2O_3$, 290.2; m/z found 291.2 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers, major rotamer reported) δ 8.11 (ddd, *J*= 5.1, 2.0, 0.8 Hz, 1H), 7.59 - 7.50 (m, 1H), 6.89 - 6.80 (m, 1H), 6.70 (dt, *J* = 8.4, 0.9 Hz, 1H), 5.29 (dt, *J*= 10.1, 3.2 Hz, 1H), 4.61 - 4.49 (m, 1H), 3.39 (dt, *J*= 9.5, 3.1 Hz, 1H), 3.20 (dd, *J* = 9.5, 1.3 Hz, 1H), 2.59 - 2.50 (m, 1H), 2.26 - 2.15 (m, 1H), 1.76 - 1.69 (m, 1H), 1.67 - 1.63 (m, 1H), 1.38 (dt, *J* = 13.3, 3.6 Hz, 1H), 1.12 (s, 9H).

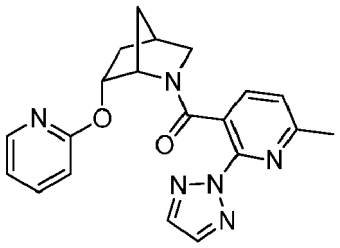
[0506] Step B: (1S,4R,6R)-6-(pyridin-2-yloxy)-2-azabicyclo[2.2.1]heptane · xHCl. To the title compound of step A (73 mg, 0.25 mmol) in EtOAc (1 mL) was added 4M HCl in dioxane (4 mL) and the reaction mixture was stirred overnight. Then, the reaction was concentrated to give the title compound of step B (68 mg) and used without further purification. MS (ESI) mass calcd. for $C_{11}H_{14}N_2O$, 190.1; m/z found 191.1 $[M+H]^+$.

[0507] Step C: (2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-(pyridin-2-yloxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone. To the title compound of step B (23 mg) and intermediate A-1 (18 mg, 0.094 mmol) in DMF (1 mL) was added DIPEA (0.17 mL, 0.99 mmol) and HATU (36 mg, 0.094 mmol), and the reaction mixture was stirred at room temperature for 1 h. The reaction was quenched by the addition of H_2O and the aqueous layer was extracted with EtOAc (3X). The

combined organics were washed with H_2O, 5% aqueous LiCl, brine, dried with Na_2SO_4, filtered, and concentrated. Purification of the concentrate was performed using Agilent Prep Method X to give the title compound (22 mg). MS (ESI): mass calcd. for $C_{20}H_{19}N_5O_2$, 361.2; m/z found, 362.2 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers, (0.90:0.10), major rotamer reported) δ 7.84 (dd, *J*= 8.3, 1.2 Hz, 1H), 7.82 - 7.77 (m, 3H), 7.60 - 7.54 (m, 1H), 7.36 - 7.28 (m, 1H), 7.16 (dd, *J*= 7.8, 1.5 Hz, 1H), 6.88 (td, *J*= 7.6, 1.2 Hz, 1H), 6.82 - 6.77 (m, 1H), 6.74 (d, *J*= 8.3 Hz, 1H), 5.03 (dt, *J*= 10.3, 3.2 Hz, 1H), 4.06 - 3.97 (m, 1H), 3.60 (dt, *J* = 10.9, 3.3 Hz, 1H), 3.39 (dd, *J* = 10.8, 1.4 Hz, 1H), 2.68 - 2.56 (m, 1H), 2.27 - 2.13 (m, 1H), 1.48 - 1.31 (m, 3H).

Example 103: (6-methyl-2-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)((1S,4R,6R)-6-(pyridin-2-yloxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

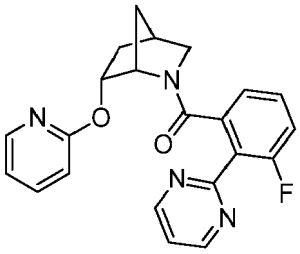
[0508]



[0509] Prepared analogous to Example 102 substituting intermediate A-1 with intermediate A-3. MS (ESI): mass calcd. for $C_{20}H_{20}N_6O_2$, 376.2; m/z found, 377.2 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers, (0.92:0.08), major rotamer reported) δ 7.86 (s, 2H), 7.82 - 7.78 (m, 1H), 7.60 - 7.54 (m, 1H), 7.40 (d, *J*= 7.7 Hz, 1H), 6.85 - 6.79 (m, 1H), 6.74 - 6.64 (m, 2H), 4.98 (dt, *J* = 10.1, 3.2 Hz, 1H), 4.05 - 3.97 (m, 1H), 3.61 (dt, *J*= 10.9, 3.2 Hz, 1H), 3.40 (dd, *J*= 10.8, 1.4 Hz, 1H), 2.65 - 2.59 (m, 1H), 2.56 (s, 3H), 2.25 - 2.15 (m, 1H), 1.48 - 1.33 (m, 3H).

Example 104: (3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-(pyridin-2-yloxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

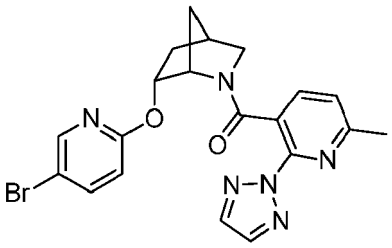
[0510]



[0511] Prepared analogous to Example 102 substituting intermediate A-1 with intermediate A-2. MS (ESI): mass calcd. for $C_{22}H_{19}FN_4O_2$, 390.1; m/z found, 391.2 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers, (0.89:0.11), major rotamer reported) δ 8.84 (d, *J*= 4.9 Hz, 2H), 7.92 - 7.85 (m, 1H), 7.63 - 7.56 (m, 1H), 7.28 - 7.24 (m, 2H), 7.09 - 6.96 (m, 2H), 6.85 - 6.80 (m, 1H), 6.76 (dt, *J*= 8.3, 0.9 Hz, 1H), 5.10 (dt, *J* = 10.0, 3.3 Hz, 1H), 4.26 - 4.15 (m, 1H), 3.34 - 3.30 (m, 2H), 2.59 - 2.48 (m, 1H), 2.27 - 2.15 (m, 1H), 1.45 (d, *J* = 11.0 Hz, 1H), 1.32 (dt, *J*= 13.4, 3.6 Hz, 1H), 1.13 - 1.01 (m, 1H).

Example 105: ((1S,4R,6R)-6-((5-bromopyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)(6-methyl-2-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)methanone.

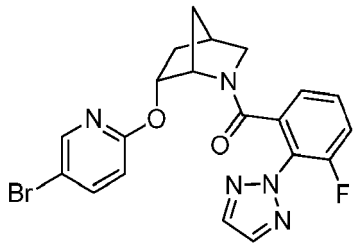
[0512]



[0513] Prepared analogous to Example 47 substituting intermediate A-6 with intermediate A-3. MS (ESI): mass calcd. for $C_{20}H_{19}BrN_6O_2$, 454.1; m/z found, 455.1 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers, (0.93:0.07), major rotamer reported) δ 7.87 (s, 2H), 7.76 (d, *J*= 2.6 Hz, 1H), 7.64 (dd, *J*= 8.7, 2.6 Hz, 1H), 7.29 (d, *J* = 7.8 Hz, 1H), 6.69 (d, *J*= 7.7 Hz, 1H), 6.62 (d, *J*= 8.7 Hz, 1H), 4.83 (dt, *J*= 10.3, 3.3 Hz, 1H), 4.05 - 3.94 (m, 1H), 3.59 (dt, *J*= 11.0, 3.2 Hz, 1H), 3.38 (d, *J*= 11.0 Hz, 1H), 2.66 - 2.56 (m, 4H), 2.23 - 2.10 (m, 1H), 1.44 - 1.33 (m, 2H), 1.32 - 1.23 (m, 1H).

Example 106: ((1S,4R,6R)-6-((5-bromopyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)(3-fluoro-2-(2H-1,2,3 -triazol-2-yl)phenyl)methanone.

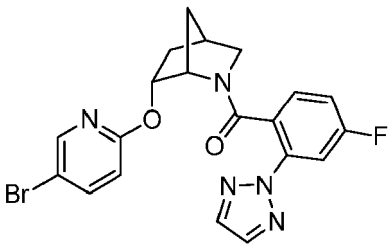
[0514]



[0515] Prepared analogous to Example 47 substituting intermediate A-6 with intermediate A-16. MS (ESI): mass calcd. for $C_{20}H_{17}BrFN_5O_2$, 457.1; m/z found, 458.1$[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers, (0.90:0.10), major rotamer reported) δ 7.87 (s, 2H), 7.85 (dd, *J*= 2.6, 0.7 Hz, 1H), 7.66 (dd, *J*= 8.7, 2.5 Hz, 1H), 7.24 - 7.17 (m, 1H), 7.07 - 6.98 (m, 1H), 6.91 (dt, *J* = 7.7, 1.2 Hz, 1H), 6.66 (dd, *J* = 8.8, 0.7 Hz, 1H), 4.95 (dt, *J* = 10.1, 3.3 Hz, 1H), 4.19 - 4.10 (m, 1H), 3.35 - 3.30 (m, 2H), 2.60 - 2.49 (m, 1H), 2.24 - 2.12 (m, 1H), 1.48 - 1.41 (m, 1H), 1.31 (dt, *J*= 13.5, 3.6 Hz, 1H), 1.21 - 1.09 (m, 1H).

Example 107: ((1S,4R,6R)-6-((5-bromopyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)(4-fluoro-2-(2H-1,2,3 -triazol-2-yl)phenyl)methanone.

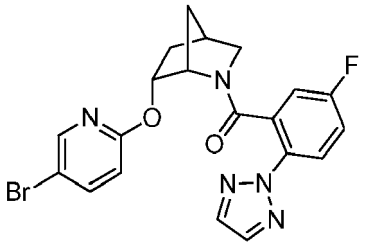
[0516]



[0517] Prepared analogous to Example 47 substituting intermediate A-6 with intermediate A-12. MS (ESI): mass calcd. for $C_{20}H_{17}BrFN_5O_2$, 457.1; m/z found, 458.1 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers, (0.89:0.11), major rotamer reported) δ 7.85 (d, *J*= 2.6 Hz, 1H), 7.82 (s, 2H), 7.71 - 7.61 (m, 2H), 7.05 (dd, *J*= 8.5, 5.9 Hz, 1H), 6.68 - 6.58 (m, 2H), 4.91 (dt, *J*= 10.1, 3.3 Hz, 1H), 4.00 (s, 1H), 3.61 (dt, *J*= 10.9, 3.3 Hz, 1H), 3.38 (dd, *J*= 10.9, 1.4 Hz, 1H), 2.69 - 2.59 (m, 1H), 2.26 - 2.14 (m, 1H), 1.47 - 1.25 (m, 3H).

Example 108: ((1S,4R,6R)-6-((5-bromopyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)(5-fluoro-2-(2H-1,2,3 -triazol-2-yl)phenyl)methanone.

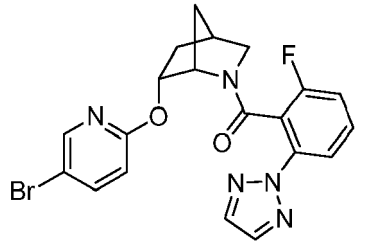
[0518]



[0519] Prepared analogous to Example 47 substituting intermediate A-6 with intermediate A-10. MS (ESI): mass calcd. for $C_{20}H_{17}BrFN_5O_2$, 457.1; m/z found, 458.1 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers, (0.91:0.09), major rotamer reported) δ 7.84 - 7.81 (m, 2H), 7.80 (s, 2H), 7.68 (dd, *J*= 8.8, 2.6 Hz, 1H), 7.07 (ddd, *J*= 9.0, 7.6, 2.9 Hz, 1H), 6.81 (dd, *J*= 8.1, 2.9 Hz, 1H), 6.66 (d, *J*= 8.8 Hz, 1H), 4.90 (dt, *J*= 10.2, 3.4 Hz, 1H), 4.04 - 4.00 (m, 1H), 3.56 (dt, *J*= 11.0, 3.2 Hz, 1H), 3.37 (dd, *J*= 11.0, 1.5 Hz, 1H), 2.65 - 2.57 (m, 1H), 2.25 - 2.13 (m, 1H), 1.50 - 1.32 (m, 2H), 1.32 - 1.23 (m, 1H).

Example 109: ((1S,4R,6R)-6-((5-bromopyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)(2-fluoro-6-(2H-1,2,3 -triazol-2-yl)phenyl)methanone.

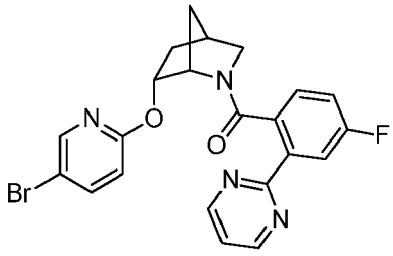
[0520]



[0521] Prepared analogous to Example 47 substituting intermediate A-6 with intermediate A-11. MS (ESI): mass calcd. for $C_{20}H_{17}BrFN_5O_2$, 457.1; m/z found, 458.1 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers, (0.88:0.12), major rotamer reported) δ 7.83 (s, 2H), 7.79 - 7.76 (m, 1H), 7.75 (dt, *J*= 8.2, 1.0 Hz, 1H), 7.63 (dd, *J*= 8.8, 2.5 Hz, 1H), 7.39 - 7.31 (m, 1H), 6.76 - 6.66 (m, 2H), 4.85 (dt, *J*= 10.1, 3.4 Hz, 1H), 4.01 - 3.92 (m, 1H), 3.62 (dt, *J*= 10.9, 3.2 Hz, 1H), 3.42 (dd, *J*= 10.9, 1.5 Hz, 1H), 2.64 - 2.58 (m, 1H), 2.24 - 2.14 (m, 1H), 1.42 - 1.31 (m, 2H), 1.30 - 1.17 (m, 1H).

Example 110: ((1S,4R,6R)-6-((5-bromopyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)(4-fluoro-2-(pyrimidin-2-yl)phenyl)methanone.

[0522]

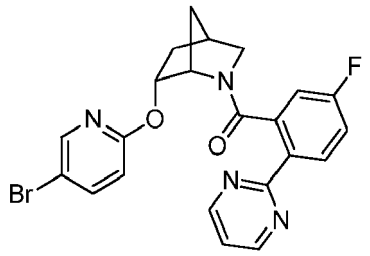


[0523] Prepared analogous to Example 47 substituting intermediate A-6 with intermediate A-23. MS (ESI): mass calcd.

for $C_{22}H_{18}BrFN_4O_2$, 468.1; m/z found, 469.1 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Chloroform-d, Compound present as a mixture of rotamers, (0.88:0.12), major rotamer reported) δ 8.79 (d, *J*= 4.9 Hz, 2H), 7.93 (dd, *J*= 10.0, 2.7 Hz, 1H), 7.86 (dd, *J*= 2.6, 0.6 Hz, 1H), 7.67 (dd, *J*= 8.8, 2.6 Hz, 1H), 7.22 (t, *J*= 4.9 Hz, 1H), 7.04 (dd, *J*= 8.4, 5.6 Hz, 1H), 6.70 - 6.64 (m, 2H), 4.93 (dt, *J*= 10.1, 3.3 Hz, 1H), 4.09 - 4.04 (m, 1H), 3.63 (dt, *J*= 10.9, 3.1 Hz, 1H), 3.43 - 3.34 (m, 1H), 2.66 - 2.59 (m, 1H), 2.26 - 2.15 (m, 1H), 1.46 - 1.33 (m, 2H), 1.31 - 1.23 (m, 1H).

Example 111: ((1S,4R,6R)-6-((5-bromopyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)(5-fluoro-2-(pyrimidin-2-yl)phenyl)methanone.

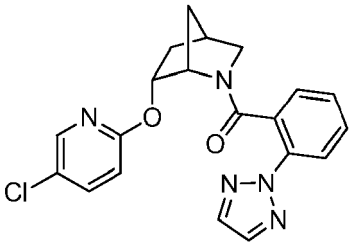
[0524]



[0525] Prepared analogous to Example 47 substituting intermediate A-6 with intermediate A-7. MS (ESI): mass calcd. for $C_{22}H_{18}BrFN_4O_2$, 468.1; m/z found, 469.1 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers, (0.90:0.10), major rotamer reported) δ 8.76 (d, *J*= 4.9 Hz, 2H), 8.23 (dd, *J*= 8.8, 5.6 Hz, 1H), 7.83 (dd, *J*= 2.6, 0.7 Hz, 1H), 7.68 (dd, *J*= 8.8, 2.6 Hz, 1H), 7.18 (t, *J*= 4.9 Hz, 1H), 7.08 - 7.02 (m, 1H), 6.81 (dd, *J*= 8.6, 2.7 Hz, 1H), 6.68 (d, *J*= 8.8 Hz, 1H), 4.93 (dt, *J*= 10.0, 3.3 Hz, 1H), 4.14 - 4.06 (m, 1H), 3.64 (dt, *J*= 10.9, 3.2 Hz, 1H), 3.40 (dd, *J*= 10.7, 1.5 Hz, 1H), 2.69 - 2.61 (m, 1H), 2.30 - 2.15 (m, 1H), 1.47 - 1.35 (m, 2H), 1.34 - 1.24 (m, 1H).

Example 112: (2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((5-chloropyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[0526]



[0527] Step A: (1S,4R,6R)-tert-butyl 6-((5-chloropyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptane-2-carboxylate. To intermediate B-5 (150 mg, 0.70 mmol) dissolved in DMF (5 mL) was added NaH (37 mg, 0.91 mmol, 60% dispersion in mineral oil). After 5 minutes the sides of the flask were rinsed with additional DMF (1 mL) and 5-chloro-2-fluoropyridine (0.11 mL, 1.13 mmol) was then added and the mixture heated to 70 °C. After heating at 70 °C for 7 h, the mixture was cooled to room temperature, quenched with saturated NH_4Cl solution, diluted with EtOAc and H_2O. The aqueous layer was extracted with EtOAc (3X). The combined organics were washed with H_2O, 5% aqueous LiCl, brine, dried with Na_2SO_4, filtered, and concentrated. Purification via silica gel chromatography (0-25% EtOAc in hexanes) gave the title compound (149 mg, 0.46 mmol, 65%) as a colorless solid. MS (ESI) mass calcd. for $C_{16}H_{21}ClN_2O_3$, 324.1; m/z found 325.1 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers, only major rotamer reported) δ 8.06 (d, *J* = 2.6 Hz, 1H), 7.51 (dd, *J* = 8.8, 2.7 Hz, 1H), 6.66 (d, *J* = 8.7 Hz, 1H), 5.22 (dt, *J* = 10.1, 3.2 Hz, 1H), 4.52 - 4.49 (m, 1H), 3.38 (dt, *J*= 9.6, 3.1 Hz, 1H), 3.18 (dd, *J*= 9.5, 1.3 Hz, 1H), 2.58 - 2.54 (m, 1H), 2.23 - 2.12 (m, 1H), 1.75 - 1.68 (m, 1H), 1.64 - 1.59 (m, 1H), 1.36 (dt, *J*= 13.4, 3.6 Hz, 1H), 1.15 (s, 9H).

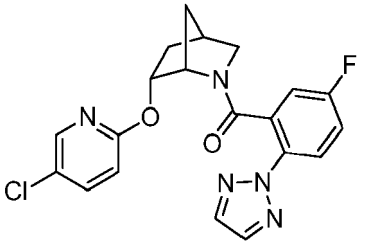
[0528] Step B: (1S,4R,6R)-6-((5-chloropyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptane · xHCl. To the title compound of step A (149 mg, 0.46 mmol) in EtOAc (1 mL) was added 4M HCl in dioxane (4 mL) and the reaction mixture was stirred at room temperature for 3h. Then, the reaction was concentrated to give the title compound of step B (129 mg) as a colorless solid and used without further purification. MS (ESI) mass calcd. for $C_{11}H_{13}ClN_2O$, 224.1; m/z found 225.1

$[M+H]^+$.

[0529] Step C: (2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((5-chloropyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone. To the title compound of step B (32 mg) and intermediate A-1 (25 mg, 0.14 mmol) in DMF (1 mL) was added DIPEA (0.25 mL, 1.5 mmol) and HATU (51 mg, 0.135 mmol), and the reaction mixture was stirred at room temperature for 1 h. The reaction was quenched by the addition of H_2O and the aqueous layer was extracted with EtOAc (3X). The combined organics were concentrated. Purification of the concentrate was performed using Agilent Prep Method X to give the title compound (34 mg). MS (ESI): mass calcd. for $C_{20}H_{18}ClN_5O_2$, 395.1; m/z found, 396.1 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers, (0.89:0.11), major rotamer reported) δ 7.85 (dd, *J*= 8.2, 1.1 Hz, 1H), 7.81 (s, 2H), 7.67 (d, *J*= 2.6 Hz, 1H), 7.53 (dd, *J*= 8.8, 2.7 Hz, 1H), 7.40 - 7.34 (m, 1H), 7.07 (dd, *J*= 7.6, 1.5 Hz, 1H), 6.91 (td, *J*= 7.5, 1.2 Hz, 1H), 6.69 (d, *J*= 8.8 Hz, 1H), 4.90 (dt, *J*= 10.1, 3.3 Hz, 1H), 4.07 - 3.97 (m, 1H), 3.59 (dt, *J* = 10.9, 3.2 Hz, 1H), 3.38 (dd, *J*= 10.8, 1.4 Hz, 1H), 2.65 - 2.56 (m, 1H), 2.26 - 2.12 (m, 1H), 1.42 - 1.34 (m, 2H), 1.31 - 1.23 (m, 1H).

Example 113: ((1S,4R,6R)-6-((5-chloropyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)(5-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone.

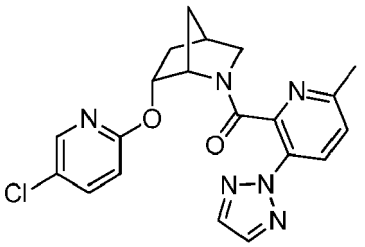
[0530]



[0531] Prepared analogous to Example 112 substituting intermediate A-1 with intermediate A-10. MS (ESI): mass calcd. for $C_{20}H_{17}ClFN_5O_2$, 413.1; m/z found, 414.1 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers, (0.92:0.08), major rotamer reported) δ 7.85 - 7.79 (m, 3H), 7.72 (d, *J* = 2.7 Hz, 1H), 7.56 (dd, *J* = 8.8, 2.7 Hz, 1H), 7.11 - 7.01 (m, 1H), 6.81 (dd, *J* = 8.2, 2.9 Hz, 1H), 6.70 (d, J= 8.7 Hz, 1H), 4.91 (dt, *J*= 10.1, 3.4 Hz, 1H), 4.11 - 3.98 (m, 1H), 3.56 (dt, *J*= 10.9, 3.2 Hz, 1H), 3.37 (dd, *J*= 10.9, 1.5 Hz, 1H), 2.68 - 2.56 (m, 1H), 2.26 - 2.13 (m, 1H), 1.47 - 1.32 (m, 2H), 1.32 - 1.22 (m, 1H).

Example 114: ((1S,4R,6R)-6-((5-chloropyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)methanone.

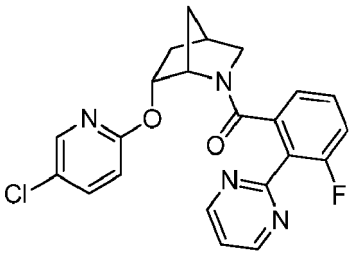
[0532]



[0533] Prepared analogous to Example 112 substituting intermediate A-1 with intermediate A-40. MS (ESI): mass calcd. for $C_{20}H_{19}ClN_6O_2$, 410.1; m/z found, 411.1 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers, (0.88:0.12), major rotamer reported) δ 8.04 (d, *J*= 8.4 Hz, 1H), 7.83 (s, 2H), 7.61 (d, *J*= 2.7 Hz, 1H), 7.44 (dd, *J*= 8.8, 2.7 Hz, 1H), 7.14 (d, *J*= 8.4 Hz, 1H), 6.70 (d, *J*= 8.8 Hz, 1H), 4.83 (dt, *J*= 10.2, 3.3 Hz, 1H), 4.22 - 4.14 (m, 1H), 3.65 (dt, *J*= 10.9, 3.2 Hz, 1H), 3.43 (dd, *J*= 11.0, 1.4 Hz, 1H), 2.63 - 2.58 (m, 1H), 2.29 (s, 3H), 2.23 - 2.13 (m, 1H), 1.48 - 1.32 (m, 3H).

Example 115: ((1S,4R,6R)-6-((5-chloropyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)(3-fluoro-2-(pyrimidin-2-yl)phenyl)methanone.

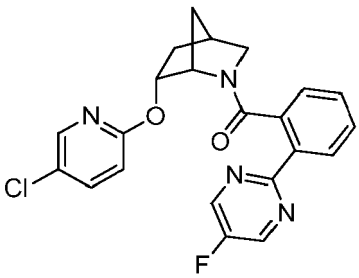
[0534]



[0535] Prepared analogous to Example 112 substituting intermediate A-1 with intermediate A-2. MS (ESI): mass calcd. for $C_{22}H_{18}ClFN_4O_2$, 424.1; m/z found, 425.1 $[M+H]^+$. ^1H NMR (400 MHz, Methanol-d_4, Compound present as a mixture of rotamers, (0.84:0.16), major rotamer reported) δ 8.90 (d, *J*= 4.9 Hz, 2H), 7.80 (d, *J*= 2.8 Hz, 1H), 7.69 (dd, *J*= 8.8, 2.7 Hz, 1H), 7.49 (t, *J*= 5.0 Hz, 1H), 7.26 - 7.18 (m, 1H), 7.14 -7.05 (m, 1H), 6.95 - 6.81 (m, 2H), 5.02 (dt, *J* = 10.1, 3.3 Hz, 1H), 4.29 - 4.20 (m, 1H), 3.28 - 3.17 (m, 2H), 2.59 - 2.50 (m, 1H), 2.29 - 2.17 (m, 1H), 1.52 (d, *J*= 10.6 Hz, 1H), 1.33 (dt, *J*= 13.5, 3.6 Hz, 1H), 1.04 - 0.89 (m, 1H).

Example 116: ((1S,4R,6R)-6-((5-chloropyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)(2-(5-fluoropyrimidin-2-yl)phenyl)methanone.

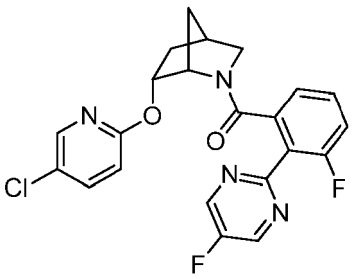
[0536]



[0537] Prepared analogous to Example 112 substituting intermediate A-1 with intermediate A-34. MS (ESI): mass calcd. for $C_{22}H_{18}ClFN_4O_2$, 424.1; m/z found, 425.2 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers, (0.88:0.12), major rotamer reported) δ 8.81 (d, *J*= 0.6 Hz, 2H), 8.21 - 8.15 (m, 1H), 7.73 - 7.67 (m, 2H), 7.44 - 7.39 (m, 1H), 7.02 - 6.99 (m, 2H), 6.85 (d, *J*= 8.7 Hz, 1H), 5.00 (dt, *J*= 10.2, 3.3 Hz, 1H), 4.13 - 4.06 (m, 1H), 3.60 (dt, *J*= 11.0, 3.2 Hz, 1H), 3.34 - 3.32 (m, 1H), 2.71 - 2.64 (m, 1H), 2.31 - 2.22 (m, 1H), 1.58 - 1.50 (m, 1H), 1.41 (dt, *J*= 13.3, 3.6 Hz, 1H), 1.38 - 1.33 (m, 1H).

Example 117: ((1S,4R,6R)-6-((5-chloropyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)(3-fluoro-2-(5-fluoropyrimidin-2-yl)phenyl)methanone.

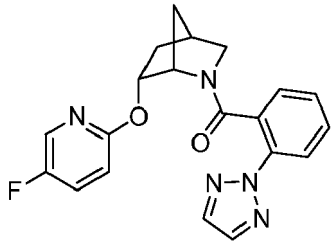
[0538]



[0539] Prepared analogous to Example 112 substituting intermediate A-1 with intermediate A-35. MS (ESI): mass calcd. for $C_{22}H_{17}ClF_2N_4O_2$, 442.1; m/z found, 443.1 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers, (0.82:0.18), major rotamer reported) δ 8.87 (d, *J*= 0.7 Hz, 2H), 7.82 (dd, *J*= 2.7, 0.7 Hz, 1H), 7.70 (dd, *J*= 8.8, 2.7 Hz, 1H), 7.24 - 7.18 (m, 1H), 7.13 - 7.06 (m, 1H), 6.93 (dd, *J*= 7.6, 1.4 Hz, 1H), 6.87 (dd, *J*= 8.8, 0.7 Hz, 1H), 5.06 (dt, *J*= 10.1, 3.3 Hz, 1H), 4.26 - 4.20 (m, 1H), 3.26 - 3.20 (m, 1H), 2.61 - 2.57 (m, 1H), 2.31 - 2.22 (m, 1H), 1.61 - 1.55 (m, 1H), 1.35 (dt, *J*= 13.5, 3.6 Hz, 1H), 1.17 - 1.09 (m, 1H). 1H buried under solvent peak.

Example 118: (2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((5-fluoropyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[0540]



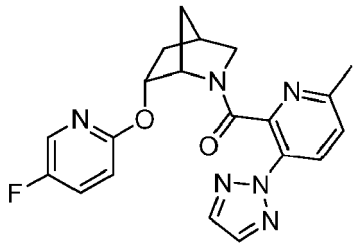
[0541] Step A: (1S,4R,6R)-tert-butyl 6-((5-fluoropyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptane-2-carboxylate. To intermediate B-5 (200 mg, 0.94 mmol) dissolved in DMF (3 mL) was added NaH (41 mg, 1.03 mmol, 60% dispersion in mineral oil). After 5 minutes the sides of the flask were rinsed with additional DMF (1 mL) and 2,5-difluoropyridine (0.11 mL, 1.22 mmol) was then added and the mixture heated to 60 °C. After heating at 60 °C for 3 h, the mixture was cooled to room temperature, quenched with saturated NH_4Cl solution, diluted with EtOAc and H_2O. The aqueous layer was extracted with EtOAc (3X). The combined organics were washed with H_2O, 5% aqueous LiCl, brine, dried with Na_2SO_4, filtered, and concentrated. Purification via silica gel chromatography (0-30% EtOAc in hexanes) gave the title compound (193 mg, 0.63 mmol, 67%) as a colorless solid. MS (ESI) mass calcd. for $C_{16}H_{21}FN_2O_3$, 308.2; m/z found 309.2 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers, only major rotamer reported) δ 7.95 (d, *J*= 3.1 Hz, 1H), 7.37 - 7.30 (m, 1H), 6.67 (dd, *J*= 9.0, 3.6 Hz, 1H), 5.21 (dt, *J*= 10.2, 3.2 Hz, 1H), 4.53 - 4.50 (m, 1H), 3.39 (dt, *J* = 9.6, 3.1 Hz, 1H), 3.19 (dd, *J*= 9.5, 1.4 Hz, 1H), 2.58 - 2.53 (m, 1H), 2.24 - 2.12 (m, 1H), 1.77 - 1.69 (m, 1H), 1.64 - 1.59 (m, 1H), 1.36 (dt, *J*= 13.4, 3.6 Hz, 1H), 1.15 (s, 9H).

[0542] Step B: (1S,4R,6R)-6-((5-fluoropyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptane · xHCl. To the title compound of step A (193 mg, 0.63 mmol) in EtOAc (1 mL) was added 4M HCl in dioxane (4 mL) and the reaction mixture was stirred at room temperature for 2h. The reaction was concentrated to give the title compound of step B (182 mg) as an off-white solid and used without further purification. MS (ESI) mass calcd. for $C_{11}H_{13}FN_2O$, 208.1; m/z found 209.1 $[M+H]^+$.

[0543] Step C: (2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((5-fluoropyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone. To the title compound of step B (32 mg) and intermediate A-1 (27 mg, 0.13 mmol) in DMF (1 mL) was added DIPEA (0.1 mL, 0.58 mmol) and HATU (48 mg, 0.13 mmol), and the reaction mixture was stirred at room temperature for 1 h. The reaction was quenched by the addition of H_2O and the aqueous layer was extracted with EtOAc (3X). The combined organics were concentrated. Purification of the concentrate was performed using Agilent Prep Method X to give the title compound (31 mg). MS (ESI): mass calcd. for $C_{20}H_{18}FN_5O_2$, 379.1; m/z found, 380.2 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers, (0.88:0.12), major rotamer reported) δ 7.85 (dd, *J*= 8.2, 1.1 Hz, 1H), 7.81 (s, 2H), 7.60 (d, *J* = 3.1 Hz, 1H), 7.39 - 7.31 (m, 2H), 7.12 (dd, *J*= 7.7, 1.5 Hz, 1H), 6.92 (td, *J*= 7.6, 1.2 Hz, 1H), 6.70 (dd, *J*= 9.0, 3.6 Hz, 1H), 4.91 (dt, *J*= 10.1, 3.3 Hz, 1H), 4.04 - 3.95 (m, 1H), 3.59 (dt, *J*= 10.9, 3.2 Hz, 1H), 3.38 (dd, *J*= 11.0, 1.4 Hz, 1H), 2.65 - 2.58 (m, 1H), 2.24 - 2.13 (m, 1H), 1.44 - 1.20 (m, 3H).

Example 119: ((1S,4R,6R)-6-((5-fluoropyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)methanone.

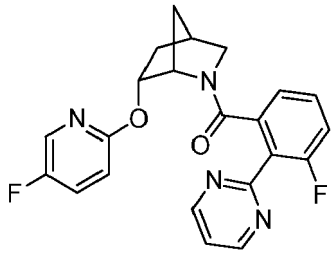
[0544]



[0545] Prepared analogous to Example 118 substituting intermediate A-1 with intermediate A-40. MS (ESI): mass calcd. for $C_{20}H_{19}FN_6O_2$, 394.2; m/z found, 395.2 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers, (0.88:0.12), major rotamer reported) δ 8.03 (d, *J*= 8.4 Hz, 1H), 7.82 (s, 2H), 7.53 (d, *J*= 3.1 Hz, 1H), 7.29 - 7.22 (m, 1H), 7.13 (d, *J*= 8.4 Hz, 1H), 6.71 (dd, *J*= 9.0, 3.7 Hz, 1H), 4.84 (dt, *J*= 10.3, 3.2 Hz, 1H), 4.19 - 4.15 (m, 1H), 3.65 (dt, *J*= 11.0, 3.2 Hz, 1H), 3.44 (dd, *J*= 10.8, 1.4 Hz, 1H), 2.63 - 2.58 (m, 1H), 2.30 (s, 3H), 2.23 - 2.13 (m, 1H), 1.47 - 1.33 (m, 3H).

Example 120: (3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-fluoropyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

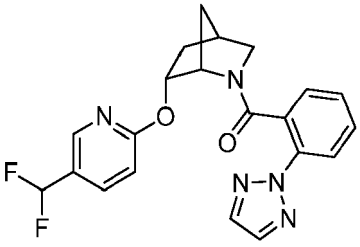
[0546]



[0547] Prepared analogous to Example 118 substituting intermediate A-1 with intermediate A-2. MS (ESI): mass calcd. for $C_{22}H_{18}F_2N_4O_2$, 408.1; m/z found, 409.2 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers, (0.89:0.11), major rotamer reported) δ 8.85 (d, *J*= 4.9 Hz, 2H), 7.70 (d, *J*= 3.1 Hz, 1H), 7.40 - 7.32 (m, 1H), 7.28 - 7.27 (m, 1H), 7.15 - 7.05 (m, 1H), 7.06 - 6.94 (m, 2H), 6.72 (dd, *J*= 9.0, 3.6 Hz, 1H), 4.98 (dt, *J*= 10.0, 3.3 Hz, 1H), 4.26 - 4.15 (m, 1H), 3.35 - 3.26 (m, 2H), 2.60 - 2.48 (m, 1H), 2.25 - 2.14 (m, 1H), 1.42 (d, *J*= 10.3 Hz, 1H), 1.30 (dt, *J*= 13.4, 3.5 Hz, 1H), 1.00 - 0.92 (m, 1H).

Example 121: (2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((5-(difluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[0548]



[0549] Step A: (1S,4R,6R)-tert-butyl 6-((5-(difluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptane-2-carboxylate. To intermediate B-5 (200 mg, 0.94 mmol) dissolved in DMF (3 mL) was added NaH (41 mg, 1.03 mmol, 60% dispersion in mineral oil). After 5 minutes the sides of the flask were rinsed with additional DMF (1 mL) and 2-chloro-5-(difluoromethyl)pyridine (0.15 mL, 1.22 mmol) was then added and the mixture heated to 60 °C. After heating at 60 °C for 3 h, the mixture was cooled to room temperature, quenched with saturated NH_4Cl solution, diluted with EtOAc and H_2O. The aqueous layer was extracted with EtOAc (3X). The combined organics were washed with H_2O, 5% aqueous LiCl, brine,

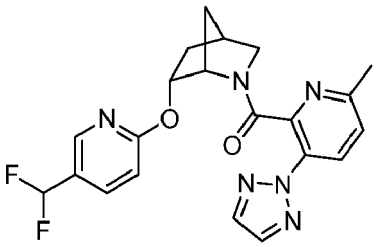
dried with Na_2SO_4, filtered, and concentrated. Purification via silica gel chromatography (0-20% EtOAc in hexanes) gave the title compound (76 mg, 0.22 mmol, 24%) as a colorless solid. MS (ESI) mass calcd. for $C_{17}H_{22}F_2N_2O_3$, 340.2; m/z found 341.2 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers, only major rotamer reported) δ 8.27 - 8.23 (m, 1H), 7.72 (dd, *J*= 8.7, 2.5 Hz, 1H), 6.83 - 6.46 (m, 2H), 5.32 (dt, *J*= 10.1, 3.2 Hz, 1H), 4.57 - 4.52 (m, 1H), 3.40 (dt, *J* = 9.6, 3.1 Hz, 1H), 3.20 (dd, *J* = 9.5, 1.3 Hz, 1H), 2.61 - 2.55 (m, 1H), 2.26 - 2.15 (m, 1H), 1.77 - 1.71 (m, 1H), 1.67 - 1.60 (m, 1H), 1.40 (dt, *J*= 13.5, 3.8 Hz, 1H), 1.12 (s, 9H).

[0550] Step B: (1S,4R,6R)-6-((5-(difluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptane · xHCl. To the title compound of step A (76 mg, 0.22 mmol) in EtOAc (4 mL) was added 4M HCl in dioxane (1 mL) and the reaction mixture was stirred at room temperature for 2h. The reaction was concentrated to give the title compound of step B (74 mg) as an off-white solid and used without further purification. MS (ESI) mass calcd. for $C_{12}H_{14}F_2N_2O$, 240.1; m/z found 241.1 $[M+H]^+$.

[0551] Step C: (2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((5-(difluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone. To the title compound of step B (24 mg) and intermediate A-1 (20 mg, 0.095 mmol) in DMF (1 mL) was added DIPEA (0.1 mL, 0.58 mmol) and HATU (36 mg, 0.095 mmol), and the reaction mixture was stirred at room temperature for 1 h. The reaction was quenched by the addition of H_2O and the aqueous layer was extracted with EtOAc (3X). The combined organics were washed with H_2O, 5% aqueous LiCl, brine, dried with Na_2SO_4, filtered, and concentrated. Purification of the concentrate was performed using Agilent Prep Method X to give the title compound (29 mg). MS (ESI): mass calcd. for $C_{21}H_{19}F_2N_5O_2$, 411.2; m/z found, 412.2 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers, (0.89:0.11), major rotamer reported) δ 7.88 - 7.85 (m, 1H), 7.83 (dd, *J*= 8.3, 1.1 Hz, 1H), 7.81 (s, 2H), 7.77 - 7.70 (m, 1H), 7.34 - 7.28 (m, 1H), 7.05 (dd, *J* = 7.6, 1.5 Hz, 1H), 6.85 - 6.79 (m, 2H), 6.60 (t, *J*= 56.0 Hz, 1H), 5.00 (dt, *J*= 10.2, 3.3 Hz, 1H), 4.09 - 3.99 (m, 1H), 3.60 (dt, *J*= 11.0, 3.2 Hz, 1H), 3.40 (dd, *J* = 10.9, 1.4 Hz, 1H), 2.66 - 2.56 (m, 1H), 2.28 - 2.13 (m, 1H), 1.44 - 1.35 (m, 2H), 1.33 - 1.25 (m, 1H).

Example 122: ((1S,4R,6R)-6-((5-(difluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)methanone.

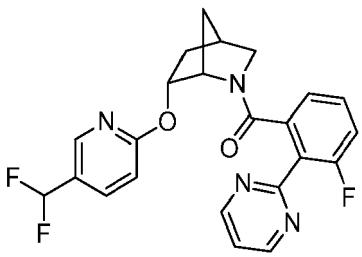
[0552]



[0553] Prepared analogous to Example 121 substituting intermediate A-1 with intermediate A-40. MS (ESI): mass calcd. for $C_{21}H_{20}F_2N_6O_2$, 426.2; m/z found, 427.2 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers, (0.86:0.14), major rotamer reported) δ 8.01 (d, *J*= 8.4 Hz, 1H), 7.87 - 7.81 (m, 3H), 7.64 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.06 (d, *J*= 8.4 Hz, 1H), 6.81 (d, *J*= 8.6 Hz, 1H), 6.57 (t, *J*= 56.0 Hz, 1H), 4.95 (dt, *J*= 10.4, 3.3 Hz, 1H), 4.25 - 4.17 (m, 1H), 3.67 (dt, *J*= 11.0, 3.2 Hz, 1H), 3.46 (dd, *J*= 11.0, 1.4 Hz, 1H), 2.68 - 2.61 (m, 1H), 2.27 - 2.16 (m, 4H), 1.50 - 1.40 (m, 3H).

Example 123: ((1S,4R,6R)-6-((5-(difluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)(3-fluoro-2-(pyrimidin-2-yl)phenyl)methanone.

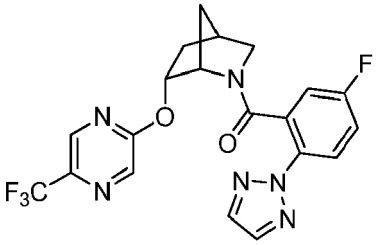
[0554]



[0555] Prepared analogous to Example 121 substituting intermediate A-1 with intermediate A-2. MS (ESI): mass calcd. for $C_{23}H_{19}F_3N_4O_2$, 440.1; m/z found, 441.2 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers, (0.88:0.12), major rotamer reported) δ 8.85 (d, *J*= 4.9 Hz, 2H), 7.98 - 7.92 (m, 1H), 7.75 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.29 - 7.26 (m, 1H), 7.09 - 7.02 (m, 1H), 6.96 - 6.88 (m, 2H), 6.83 (d, *J* = 8.6 Hz, 1H), 6.61 (t, *J* = 55.9 Hz, 1H), 5.07 (dt, *J*= 10.1, 3.3 Hz, 1H), 4.27 - 4.20 (m, 1H), 3.35 - 3.28 (m, 2H), 2.59 - 2.51 (m, 1H), 2.25 - 2.12 (m, 1H), 1.43 (d, *J*= 10.3 Hz, 1H), 1.35 (dt, *J*= 13.5, 3.5 Hz, 1H), 1.01 - 0.89 (m, 1H).

Example 124: (5-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[0556]



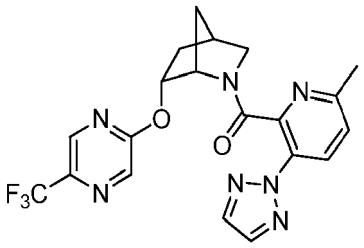
[0557] Step A: (1S,4R,6R)-tert-butyl 6-((5-(trifluoromethyl)pyrazin-2-yl)oxy)-2-azabicyclo[2.2.1]heptane-2-carboxylate. To intermediate B-5 (125 mg, 0.59 mmol) dissolved in DMF (5 mL) was added NaH (47 mg, 1.17 mmol, 60% dispersion in mineral oil). After 5 minutes the sides of the flask were rinsed with additional DMF (1 mL) and 2-chloro-5-(trifluoromethyl)pyrazine (0.12 mL, 0.94 mmol) was then added and the reaction mixture stirred overnight at room temperature. Then, the mixture was quenched with saturated NH_4Cl solution, diluted with EtOAc and H_2O. The aqueous layer was extracted with EtOAc (3X). The combined organics were washed with H_2O, 5% aqueous LiCl, brine, dried with Na_2SO_4, filtered, and concentrated. Purification via silica gel chromatography (0-40% EtOAc in hexanes) gave the title compound (89 mg, 0.25 mmol, 42%) as a colorless solid. MS (ESI) mass calcd. for $C_{16}H_{20}F_3N_3O_3$, 359.2; m/z found 304.0 $[M+2H-t\text{Bu}]^+$. ^1H NMR (500 MHz, Methanol-d_4) δ 8.60 (s, 1H), 8.35 - 8.26 (m, 1H), 5.49 - 5.39 (m, 1H), 4.59 - 4.53 (m, 1H), 3.39 (dt, J = 9.6, 3.2 Hz, 1H), 3.15 (d, J = 9.5 Hz, 1H), 2.67 - 2.62 (m, 1H), 2.37 - 2.22 (m, 1H), 1.80 - 1.73 (m, 3H), 1.08 (s, 9H).

[0558] Step B: (1S,4R,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)oxy)-2-azabicyclo[2.2.1]heptane · xHCl. To the title compound of step A (89 mg, 0.25 mmol) in EtOAc (3 mL) was added 4M HCl in dioxane (0.3 mL) and the reaction mixture was stirred at room temperature overnight. The reaction was concentrated to give the title compound of step B (80 mg) as a yellow oil and used without further purification. MS (ESI) mass calcd. for $C_{11}H_{12}F_3N_3O$, 259.1; m/z found 260.1 $[M+H]^+$.

[0559] Step C: (5-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone. To the title compound of step B (24 mg) and intermediate A-10 (20 mg, 0.097 mmol) in DMF (1 mL) was added DIPEA (84 μL, 0.49 mmol) and HATU (34 mg, 0.089 mmol), and the reaction mixture was stirred at room temperature overnight. The reaction was quenched by the addition of H_2O and the aqueous layer was extracted with EtOAc (3X). The combined organics were washed with H_2O, 5% aqueous LiCl, brine, dried with Na_2SO_4, filtered, and concentrated. Purification of the concentrate was performed using Gilson Prep Method X to give the title compound (17 mg). MS (ESI): mass calcd. for $C_{20}H_{16}F_4N_6O_2$, 448.1; m/z found, 449.1 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers, (0.83:0.17), major rotamer reported) δ 8.40 (s, 1H), 8.23 (s, 1H), 7.96 (s, 2H), 7.90 (dd, J = 9.0, 4.7 Hz, 1H), 7.22 - 7.14 (m, 1H), 6.87 (d, J = 8.1 Hz, 1H), 5.10 (dt, J = 10.2, 3.3 Hz, 1H), 4.02 (s, 1H), 3.52 (dt, J = 10.9, 3.3 Hz, 1H), 3.35 (dd, J = 11.1, 1.6 Hz, 1H), 2.71 - 2.63 (m, 1H), 2.35 - 2.24 (m, 1H), 1.59 - 1.51 (m, 1H), 1.49 (dt, J = 13.5, 3.7 Hz, 1H), 1.46 - 1.21 (m, 1H).

Example 125: (6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

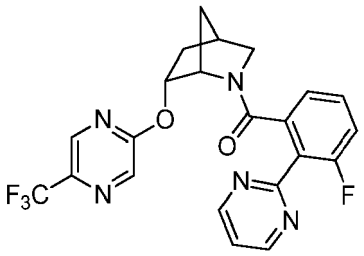
[0560]



[0561] Prepared analogous to Example 124 substituting intermediate A-10 with intermediate A-40. MS (ESI): mass calcd. for $C_{20}H_{18}F_3N_7O_2$, 445.1; m/z found, 446.1 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers, (0.90:0.10), major rotamer reported) δ 8.28 (d, J = 1.3 Hz, 1H), 8.19 - 8.14 (m, 2H), 8.00 (s, 2H), 7.29 (d, J = 8.5 Hz, 1H), 5.08 (dt, J = 10.4, 3.2 Hz, 1H), 4.25 - 4.20 (m, 1H), 3.61 (dt, J = 11.0, 3.2 Hz, 1H), 3.41 (dd, J = 11.0, 1.6 Hz, 1H), 2.75 - 2.67 (m, 1H), 2.36 - 2.27 (m, 1H), 2.22 (s, 3H), 1.66 - 1.59 (m, 1H), 1.60 - 1.49 (m, 2H).

Example 126: (3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

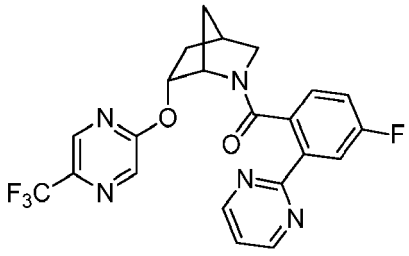
[0562]



[0563] Prepared analogous to Example 124 substituting intermediate A-10 with intermediate A-2. MS (ESI): mass calcd. for $C_{22}H_{17}F_4N_5O_2$, 459.1; m/z found, 460.1 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers, (0.76:0.24), major rotamer reported) δ 8.91 (d, J = 5.0 Hz, 2H), 8.42 (d, J = 1.3 Hz, 1H), 8.26 - 8.23 (m, 1H), 7.50 (t, J = 5.0 Hz, 1H), 7.21 - 7.15 (m, 1H), 7.07 - 7.00 (m, 1H), 6.95 (dd, J = 7.6, 1.2 Hz, 1H), 5.14 (dt, J = 10.2, 3.3 Hz, 1H), 4.33 - 4.24 (m, 1H), 3.29 - 3.27 (m, 2H), 2.63 - 2.56 (m, 1H), 2.34 - 2.25 (m, 1H), 1.56 (d, J = 11.1 Hz, 1H), 1.44 (dt, J = 13.7, 3.6 Hz, 1H), 1.05 - 0.91 (m, 1H).

Example 127: (4-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

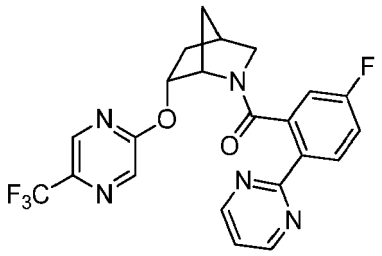
[0564]



[0565] Prepared analogous to Example 124 substituting intermediate A-10 with intermediate A-23. MS (ESI): mass calcd. for $C_{22}H_{17}F_4N_5O_2$, 459.1; m/z found, 460.1 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers, (0.80:0.20), major rotamer reported) δ 8.88 (d, J = 4.9 Hz, 2H), 8.40 (s, 1H), 8.20 (s, 1H), 7.92 (dd, J = 10.1, 2.7 Hz, 1H), 7.46 - 7.41 (m, 1H), 7.08 (dd, J = 8.4, 5.5 Hz, 1H), 6.66 (td, J = 8.2, 2.7 Hz, 1H), 5.09 (dt, J = 10.2, 3.3 Hz, 1H), 4.11 (s, 1H), 3.60 (dt, J = 11.0, 3.2 Hz, 1H), 3.36 (dd, J = 11.0, 1.6 Hz, 1H), 2.74 - 2.65 (m, 1H), 2.35 - 2.27 (m, 1H), 1.56 - 1.47 (m, 2H), 1.35 - 1.27 (m, 1H).

Example 128: (5-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

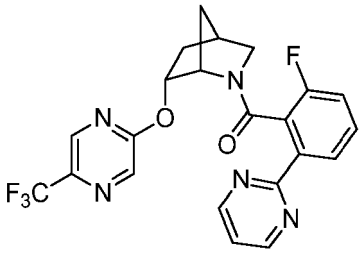
[0566]



[0567] Prepared analogous to Example 124 substituting intermediate A-10 with intermediate A-7. MS (ESI): mass calcd. for $C_{22}H_{17}F_4N_5O_2$, 459.1; m/z found, 460.1 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers, (0.85:0.15), major rotamer reported) δ 8.85 (d, J = 4.9 Hz, 2H), 8.40 (s, 1H), 8.26 (dd, J = 8.8, 5.5 Hz, 1H), 8.22 (s, 1H), 7.39 (t, J = 4.9 Hz, 1H), 7.15 - 7.09 (m, 1H), 6.78 (dd, J = 8.6, 2.7 Hz, 1H), 5.11 (dt, J = 10.2, 3.4 Hz, 1H), 4.14 (s, 1H), 3.61 (dt, J = 11.0, 3.2 Hz, 1H), 3.36 (dd, J = 10.9, 1.6 Hz, 1H), 2.74 - 2.66 (m, 1H), 2.36 - 2.26 (m, 1H), 1.58 - 1.54 (m, 1H), 1.52 (dt, J = 13.6, 3.6 Hz, 1H), 1.40 - 1.33 (m, 1H).

Example 129: (2-fluoro-6-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

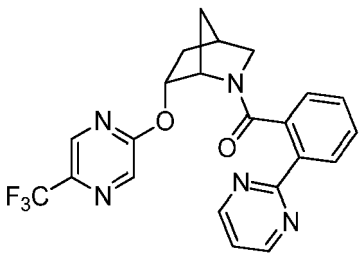
[0568]



[0569] Prepared analogous to Example 124 substituting intermediate A-10 with intermediate A-6. MS (ESI): mass calcd. for $C_{22}H_{17}F_4N_5O_2$, 459.1; m/z found, 460.0 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers, (0.74:0.26), major rotamer reported) δ 8.88 (d, J = 4.9 Hz, 2H), 8.35 - 8.33 (m, 1H), 8.17 - 8.12 (m, 2H), 7.43 (t, J = 4.9 Hz, 1H), 7.41 - 7.35 (m, 1H), 6.70 - 6.64 (m, 1H), 5.07 (dt, J = 10.2, 3.4 Hz, 1H), 4.13 - 4.10 (m, 1H), 3.64 (dt, J = 11.0, 3.2 Hz, 1H), 3.39 (dd, J = 11.0, 1.6 Hz, 1H), 2.72 - 2.68 (m, 1H), 2.36 - 2.27 (m, 1H), 1.87 - 1.83 (m, 1H), 1.55 - 1.53 (m, 1H), 1.32 - 1.25 (m, 1H).

Example 130: (2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

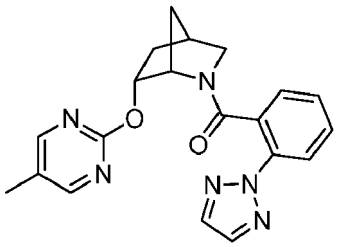
[0570]



[0571] Prepared analogous to Example 124 substituting intermediate A-10 with intermediate A-37. MS (ESI): mass calcd. for $C_{22}H_{18}F_3N_5O_2$, 441.1; m/z found, 442.1 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers, (0.85:0.15), major rotamer reported) δ 8.86 (d, J = 4.9 Hz, 2H), 8.38 (s, 1H), 8.16 (dd, J = 8.0, 1.2 Hz, 1H), 8.11 (s, 1H), 7.44 - 7.33 (m, 2H), 7.01 (dd, J = 7.7, 1.4 Hz, 1H), 6.91 (t, J = 7.5, 1.3 Hz, 1H), 5.08 (dt, J = 10.2, 3.3 Hz, 1H), 4.12 (s, 1H), 3.58 (dt, J = 10.9, 3.2 Hz, 1H), 3.37 (dd, J = 10.9, 1.6 Hz, 1H), 2.73 - 2.66 (m, 1H), 2.35 - 2.22 (m, 1H), 1.56 - 1.48 (m, 2H), 1.28 - 1.21 (m, 1H).

Example 131: (2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((5-methylpyrimidin-2-yl)oxy)-2-azabicyclo [2.2.1]heptan-2-yl)methanone.

[0572]



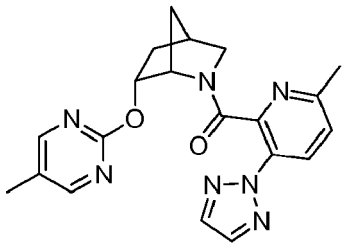
[0573] Step A: (1S,4R,6R)-tert-butyl 6-((5-methylpyrimidin-2-yl)oxy)-2-azabicyclo[2.2.1]heptane-2-carboxylate. To intermediate B-5 (106 mg, 0.497 mmol) and 2-chloro-5-methylpyrimidine (93 mg, 0.72 mmol) dissolved in DMF (2 mL) was added NaH (40 mg, 0.99 mmol, 60% dispersion in mineral oil), and the reaction mixture was stirred at room temperature for 2 h. Then, the mixture was quenched with H_2O, diluted with EtOAc and the aqueous layer extracted with EtOAc (3X). The combined organics were washed with H_2O, 5% aqueous LiCl, brine, dried with Na_2SO_4, filtered, and concentrated. Purification of the concentrate via silica gel chromatography (0-60% EtOAc in hexanes) gave the title compound (129 mg, 0.422 mmol, 85%) as a colorless solid. MS (ESI) mass calcd. for $C_{16}H_{23}N_3O_3$, 305.2; m/z found 306.2 $[M+H]^+$. ^1H NMR (500 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.68:0.32), major rotamer reported) δ 8.29 (s, 2H), 5.22 - 5.14 (m, 1H), 4.59 - 4.51 (m, 1H), 3.37 (dt, *J*= 9.5, 3.1 Hz, 1H), 3.20 (dd, *J* = 9.4, 1.4 Hz, 1H), 2.55 - 2.51 (m, 1H), 2.21 (s, 3H), 2.17 - 2.11 (m, 1H), 1.69 - 1.67 (m, 1H), 1.63 - 1.59 (m, 1H), 1.54 - 1.47 (m, 1H), 1.07 (s, 9H).

[0574] Step B: (1S,4R,6R)-6-((5-methylpyrimidin-2-yl)oxy)-2-azabicyclo[2.2.1]heptane · xHCl. To the title compound of step A (129 mg, 0.422 mmol) in EtOAc (2 mL) was added 4M HCl in dioxane (4 mL) and the reaction mixture was stirred at room temperature for 1 h. The reaction was concentrated to give the title compound of step B (147 mg) as a colorless solid and used without further purification. MS (ESI) mass calcd. for $C_{11}H_{15}N_3O$, 205.1; m/z found 206.1 $[M+H]^+$.

[0575] Step C: (2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((5-methylpyrimidin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone. To the title compound of step B (34 mg) and intermediate A-1 (29 mg, 0.16 mmol) in DMF (0.8 mL) was added DIPEA (0.1 mL, 0.58 mmol) and HATU (59 mg, 0.16 mmol), and the reaction mixture was stirred at room temperature for 6 h. The reaction was quenched by the addition of H_2O and the aqueous layer was extracted with EtOAc (3X). The combined organics were washed with H_2O, 5% aqueous LiCl, brine, dried with Na_2SO_4, filtered, and concentrated. Purification of the concentrate was performed using Agilent Prep Method X to give the title compound (20 mg). MS (ESI): mass calcd. for $C_{20}H_{20}N_6O_2$, 376.2; m/z found, 377.2 $[M+H]^+$. ^1H NMR (500 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.78:0.22), major rotamer reported) δ 8.11 (s, 2H), 7.83 (dd, *J*= 8.2, 1.1 Hz, 1H), 7.80 (s, 2H), 7.30 - 7.26 (m, 1H), 7.20 (dd, *J*= 7.7, 1.5 Hz, 1H), 6.82 (t, *J*= 7.6 Hz, 1H), 4.92 (dt, *J*= 10.2, 3.3 Hz, 1H), 4.15 - 3.99 (m, 1H), 3.62 (dt, *J*= 10.9, 3.2 Hz, 1H), 3.41 (d, *J*= 10.8 Hz, 1H), 2.65 - 2.60 (m, 1H), 2.24 - 2.20 (m, 4H), 1.53 (dt, *J*= 13.5, 3.4 Hz, 1H), 1.41 (d, *J*= 3.2 Hz, 2H).

Example 132: (6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-methylpyrimidin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

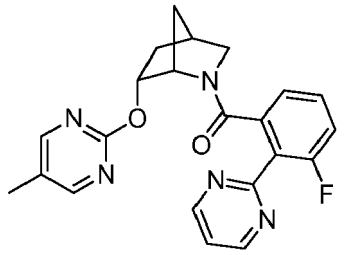
[0576]



[0577] Prepared analogous to Example 131 substituting intermediate A-1 with intermediate A-40. MS (ESI): mass calcd. for $C_{20}H_{21}N_7O_2$, 391.2; m/z found, 392.2 $[M+H]^+$. ^1H NMR (500 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.74:0.26), major rotamer reported) δ 8.04 (d, *J*= 8.4 Hz, 1H), 8.03 (d, *J*= 0.9 Hz, 2H), 7.80 (s, 2H), 7.07 (d, *J*= 8.4 Hz, 1H), 4.81 (dt, *J* = 10.3, 3.4 Hz, 1H), 4.38 - 4.29 (m, 1H), 3.72 (dt, *J*= 10.9, 3.2 Hz, 1H), 3.46 (dd, *J*= 10.9, 1.5 Hz, 1H), 2.67 - 2.65 (m, 1H), 2.25 (s, 3H), 2.24 - 2.19 (m, 1H), 2.16 (s, 3H), 1.66 - 1.61 (m, 1H), 1.57 - 1.52 (m, 1H), 1.51 - 1.47 (m, 1H).

Example 133: (3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-methylpyrimidin-2-yl)oxy)-2-azabicyclo [2.2.1]heptan-2-yl)methanone.

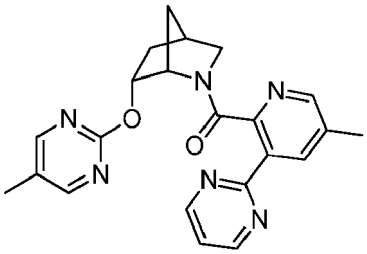
[0578]



[0579] Prepared analogous to Example 131 substituting intermediate A-1 with intermediate A-2. MS (ESI): mass calcd. for $C_{22}H_{20}FN_5O_2$, 405.2; m/z found, 406.1 $[M+H]^+$. ^1H NMR (500 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.75:0.25), major rotamer reported) δ 8.83 (d, *J*= 4.9 Hz, 2H), 8.18 (d, *J*= 0.9 Hz, 2H), 7.26 - 7.24 (m, 1H), 7.08 (dd, *J*= 7.5, 1.2 Hz, 1H), 7.05 - 7.00 (m, 1H), 6.95 - 6.91 (m, 1H), 5.00 (dt, *J*= 10.2, 3.3 Hz, 1H), 4.31 - 4.22 (m, 1H), 3.36 - 3.32 (m, 2H), 2.61 - 2.50 (m, 1H), 2.22 (s, 3H), 1.52 - 1.41 (m, 2H), 1.12 - 1.07 (m, 1H). 1H buried under water peak.

Example 134: (5-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-methylpyrimidin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[0580]

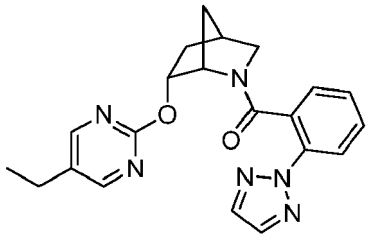


[0581] Prepared analogous to Example 131 substituting intermediate A-1 with intermediate A-47. MS (ESI): mass calcd. for $C_{22}H_{22}N_6O_2$, 402.2; m/z found, 403.2 $[M+H]^+$. ^1H NMR (500 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.60:0.40), major rotamer reported) δ 8.76 (d, *J*= 4.8 Hz, 2H), 8.28 (dd, *J*= 2.2, 0.8 Hz, 1H), 8.03 (d, *J*= 0.9 Hz, 2H), 7.81 (dd, *J*= 2.2, 0.8 Hz, 1H), 7.19 (t, *J*= 4.8 Hz, 1H), 4.88 (dt, *J*= 10.3, 3.4 Hz, 1H), 4.45 - 4.38 (m, 1H), 3.76 (dt, *J* = 10.8, 3.2 Hz, 1H), 3.45 (dd, *J*= 10.7, 1.4 Hz, 1H), 2.72 - 2.64 (m, 1H), 2.31 (s, 3H), 2.20 (s, 3H), 1.74

- 1.53 (m, 3H). 1H buried under solvent.

Example 135: (2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((5-ethylpyrimidin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

[0582]



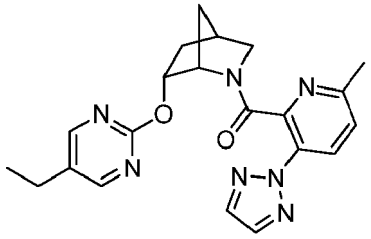
[0583] Step A: (1S,4R,6R)-tert-butyl 6-((5-ethylpyrimidin-2-yl)oxy)-2-azabicyclo[2.2.1]heptane-2-carboxylate. To intermediate B-5 (120 mg, 0.563 mmol) and 2-chloro-5-ethylpyrimidine (128 mg, 0.9 mmol), dissolved in DMF (4 mL), was added NaH (29 mg, 0.73 mmol, 60% dispersion in mineral oil) and the mixture stirred at room temperature for 1 h. The reaction mixture was quenched with H_2O, diluted with EtOAc and the aqueous layer was extracted with EtOAc (3X). The combined organics were washed with H_2O, 5% aqueous LiCl, brine, dried with Na_2SO_4, filtered, and concentrated. Purification of the concentrate via silica gel chromatography (0-50% EtOAc in hexanes) gave the title compound (160 mg, 0.501 mmol, 89%) as a colorless solid. MS (ESI) mass calcd. for $C_{17}H_{25}N_3O_3$, 319.2; m/z found 320.2 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers, only major rotamer reported) δ 8.34 (s, 2H), 5.21 (dt, *J* = 10.3, 3.4 Hz, 1H), 4.60 - 4.55 (m, 1H), 3.40 (dt, *J*= 9.5, 3.1 Hz, 1H), 3.23 (dd, *J*= 9.5, 1.4 Hz, 1H), 2.61 - 2.55 (m, 3H), 2.22 - 2.15 (m, 1H), 1.75 - 1.69 (m, 1H), 1.65 - 1.62 (m, 1H), 1.55 (dt, *J* = 13.5, 3.8 Hz, 1H), 1.25 - 1.22 (m, 3H), 1.09 (s, 9H).

[0584] Step B: (1S,4R,6R)-6-((5-ethylpyrimidin-2-yl)oxy)-2-azabicyclo[2.2.1]heptane · xHCl. To the title compound of step A (160 mg, 0.501 mmol) in EtOAc (1.5 mL) was added 4M HCl in dioxane (4 mL) and the reaction mixture was stirred at room temperature for 1h. Then, the reaction was concentrated to give the title compound of step B (148 mg) as a colorless solid and used without further purification. MS (ESI) mass calcd. for $C_{12}H_{17}N_3O$, 219.1; m/z found 220.1 $[M+H]^+$.

[0585] Step C: (2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((5-ethylpyrimidin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone. To the title compound of step B (37 mg) and intermediate A-1 (30 mg, 0.16 mmol) in DMF (1 mL) was added DIPEA (0.1 mL, 0.6 mmol) and HATU (61 mg, 0.16 mmol), and the reaction mixture was stirred at room temperature for 1 h. The reaction was quenched by the addition of H_2O and the aqueous layer was extracted with EtOAc (3X). The combined organics were concentrated. Purification of the concentrate was performed using Agilent Prep Method X to give the title compound (33 mg). MS (ESI): mass calcd. for $C_{21}H_{22}N_6O_2$, 390.2; m/z found, 391.2 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.81:0.19), only major rotamer reported) δ 8.14 - 7.16 (m, 7H), 6.79 (t, *J*= 7.6 Hz, 1H), 4.92 (dt, *J*= 10.3, 3.3 Hz, 1H), 4.05 (s, 1H), 3.62 (dt, *J*= 10.9, 3.2 Hz, 1H), 3.41 (d, *J*= 10.8 Hz, 1H), 2.65 - 2.59 (m, 1H), 2.54 (q, *J*= 7.6 Hz, 2H), 2.28 - 2.12 (m, 1H), 1.85 - 1.76 (m, 1H), 1.70 - 1.63 (m, 1H), 1.53 (dt, *J* = 13.3, 3.2 Hz, 1H), 1.26 (t, *J* = 7.6 Hz, 3H).

Example 136: ((1S,4R,6R)-6-((5-ethylpyrimidin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)methanone.

[0586]

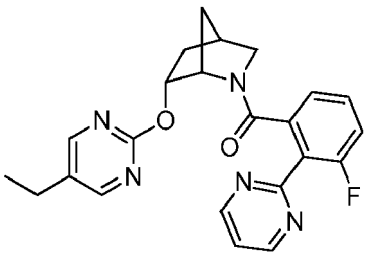


[0587] Prepared analogous to Example 135 substituting intermediate A-1with intermediate A-40. MS (ESI): mass

calcd. for $C_{21}H_{23}N_7O_2$, 405.2; m/z found, 406.2 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.69:0.31), only major rotamer reported) δ 8.08 - 8.01 (m, 3H), 7.80 (s, 2H), 7.05 (d, *J*= 8.5 Hz, 1H), 4.82 (dt, *J*= 10.3, 3.4 Hz, 1H), 4.47 - 4.30 (m, 1H), 3.73 (dt, *J*= 10.8, 3.2 Hz, 1H), 3.47 (dd, *J*= 10.9, 1.5 Hz, 1H), 2.70 - 2.65 (m, 1H), 2.55 - 2.45 (m, 2H), 2.27 - 2.16 (m, 4H), 1.65 (dt, *J*= 13.3, 3.7 Hz, 1H), 1.64 - 1.47 (m, 2H), 1.27 - 1.18 (m, 3H).

Example 137: ((1S,4R,6R)-6-((5-ethylpyrimidin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)(3-fluoro-2-(pyrimidin-2-yl)phenyl)methanone.

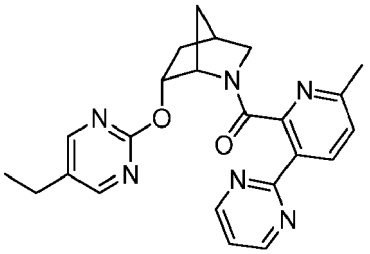
[0588]



[0589] Prepared analogous to Example 135 substituting intermediate A-1with intermediate A-2. MS (ESI): mass calcd. for $C_{23}H_{22}FN_5O_2$, 419.2; m/z found, 420.2 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.78:0.22), only major rotamer reported) δ 8.84 (d, *J*= 4.9 Hz, 2H), 8.20 (s, 2H), 7.07 (dd, *J*= 7.5, 1.2 Hz, 1H), 7.01 - 6.97 (m, 1H), 6.94 - 6.89 (m, 1H), 5.00 (dt, *J*= 10.1, 3.3 Hz, 1H), 4.31 - 4.22 (m, 1H), 3.37 - 3.29 (m, 2H), 2.57 (q, *J*= 7.6 Hz, 3H), 2.25 - 2.16 (m, 1H), 1.53 - 1.44 (m, 2H), 1.27 (t, *J*= 7.6 Hz, 3H), 1.15 - 1.06 (m, 1H). 1H buried under solvent.

Example 138: ((1S,4R,6R)-6-((5-ethylpyrimidin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)(6-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)methanone.

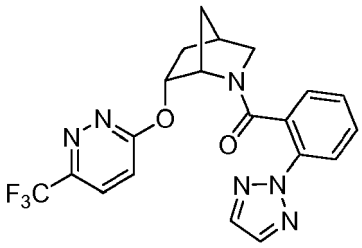
[0590]



[0591] Prepared analogous to Example 135 substituting intermediate A-1with intermediate A-41. MS (ESI): mass calcd. for $C_{23}H_{24}N_6O_2$, 416.2; m/z found, 417.2 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, , Compound present as a mixture of rotamers (0.63:0.37), only major rotamer reported) δ 8.74 (d, *J*= 4.8 Hz, 2H), 8.38 (d, *J*= 8.1 Hz, 1H), 8.00 (s, 2H), 7.17 (t, *J*= 4.8 Hz, 1H), 7.04 (d, *J*= 8.2 Hz, 1H), 4.81 (dt, *J*= 10.4, 3.4 Hz, 1H), 4.51 - 4.46 (m, 1H), 3.80 (dt, *J*= 10.8, 3.2 Hz, 1H), 3.47 (dd, *J*= 10.6, 1.4 Hz, 1H), 2.72 - 2.66 (m, 1H), 2.48 (q, *J*= 7.6 Hz, 2H), 2.28 - 2.17 (m, 4H), 1.67 (dt, *J*= 13.3, 3.7 Hz, 1H), 1.61 - 1.54 (m, 2H), 1.21 (t, *J*= 7.7 Hz, 3H).

Example 139: (2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((6-(trifluoromethyl)pyridazin-3-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[0592]



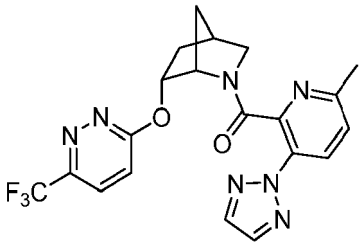
[0593] Step A: (1S,4R,6R)-tert-butyl 6-((6-(triiluoromethyl)pyridazin-3-yl)oxy)-2-azabicyclo[2.2.1]heptane-2-carboxylate. To intermediate B-5 (106 mg, 0.457 mmol) and 3-chloro-6-(trifluoromethyl)pyridazine (120 mg, 0.66 mmol) dissolved in DMF (2 mL) was added NaH (40 mg, 0.99 mmol, 60% dispersion in mineral oil), and the reaction mixture was stirred at room temperature for 2 h. Then, the mixture was quenched with saturated NH_4Cl solution, diluted with EtOAc and H_2O. The aqueous layer was extracted with EtOAc (3X). The combined organics were washed with H_2O, 5% aqueous LiCl, brine, dried with Na_2SO_4, filtered, and concentrated. Purification of the concentrate via silica gel chromatography (0-50% EtOAc in hexanes) gave the title compound (189 mg) as an off-white solid. MS (ESI) mass calcd. for $C_{16}H_{20}F_3N_3O_3$, 359.2; m/z found 304.1 $[M+2H\text{-}tBu]^+$. ^1H NMR (500 MHz, Chloroform-d, Compound present as a mixture of rotamers, (0.74:0.26), major rotamer reported) δ 7.70 (d, *J*= 9.2 Hz, 1H), 7.07 (d, *J*= 9.2 Hz, 1H), 5.59 (dt, *J*= 10.1, 3.1 Hz, 1H), 4.76 - 4.67 (m, 1H), 3.43 (dt, *J* = 9.6, 3.1 Hz, 1H), 3.23 - 3.17 (m, 1H), 2.64 - 2.60 (m, 1H), 2.34 - 2.26 (m, 1H), 1.81 - 1.76 (m, 1H), 1.68 - 1.65 (m, 1H), 1.50 - 1.45 (m, 1H), 1.10 (s, 9H).

[0594] Step B: (1S,4R,6R)-6-((6-(trifluoromethyl)pyridazin-3-yl)oxy)-2-azabicyclo[2.2.1]heptane · xHCl. To the title compound of step A (189 mg, 0.53 mmol) in EtOAc (2 mL) was added 4M HCl in dioxane (4 mL) and the reaction mixture was stirred at room temperature for 6 h. The reaction was concentrated to give the title compound of step B (146 mg) as an off-white solid and used without further purification. MS (ESI) mass calcd. for $C_{11}H_{12}F_3N_3O$, 259.1; m/z found 260.1 $[M+H]^+$.

[0595] Step C: (2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((6-(trifluoromethyl)pyridazin-3-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone. To the title compound of step B (34 mg) and intermediate A-1 (24 mg, 0.126 mmol) in DMF (0.5 mL) was added DIPEA (0.1 mL, 0.58 mmol) and HATU (48 mg, 0.126 mmol), and the reaction mixture was stirred at room temperature for 1 h. Analysis of the reaction mixture showed unreacted starting material and additional intermediate A-1 (10 mg) was added. The reaction mixture was stirred for an additional 15 minutes at room temperature. The reaction was then quenched by the addition of H_2O and the aqueous layer was extracted with EtOAc (3X). The combined organics were concentrated and subjected directly to purification using Agilent Prep Method X to give the title compound (33 mg). MS (ESI): mass calcd. for $C_{20}H_{17}F_3N_6O_2$, 430.1; m/z found, 431.2 $[M+H]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5μm, 100 $\times$ 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 30 °C). R_t = 6.08 min (major rotamer) at 254 nm.

Example 140: (6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((6-(trifluoromethyl)pyridazin-3-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

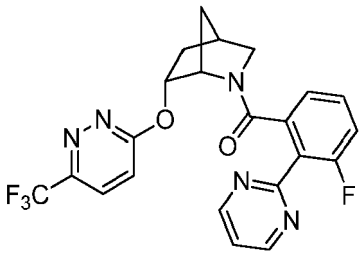
[0596]



[0597] Prepared analogous to Example 139 substituting intermediate A-1 with intermediate A-40. MS (ESI): mass calcd. for $C_{20}H_{18}F_3N_7O_2$, 445.1; m/z found, 446.2 $[M+H]^+$. ^1H NMR (500 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.82:0.18), major rotamer reported) δ 8.04 (d, *J*= 8.4 Hz, 1H), 7.81 (s, 2H), 7.62 (d, *J*= 9.1 Hz, 1H), 7.15 (dd, *J*= 9.2, 0.7 Hz, 1H), 7.11 (d, *J*= 8.5 Hz, 1H), 5.31 (dt, *J* = 10.1, 3.3 Hz, 1H), 4.46 - 4.41 (m, 1H), 3.70 (dt, *J*= 11.0, 3.2 Hz, 1H), 3.47 (dd, *J*= 11.0, 1.5 Hz, 1H), 2.73 - 2.68 (m, 1H), 2.37 - 2.28 (m, 1H), 2.23 (s, 3H), 1.63 - 1.58 (m, 1H), 1.57 - 1.49 (m, 2H).

Example 141: (3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((6-(trifluoromethyl)pyridazin-3-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

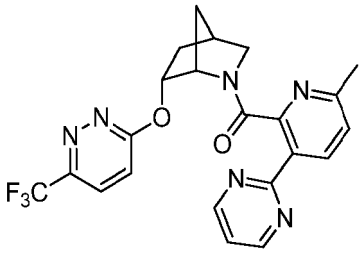
[0598]



[0599] Prepared analogous to Example 139 substituting intermediate A-1 with intermediate A-2. MS (ESI): mass calcd. for $C_{22}H_{17}F_4N_5O_2$, 459.1; m/z found, 460.1 $[M+H]^+$. ^1H NMR (500 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.78:0.22), major rotamer reported) δ 8.85 (d, *J*= 4.9 Hz, 2H), 7.73 (d, *J*= 9.2 Hz, 1H), 7.28 (t, *J*= 4.9 Hz, 1H), 7.15 (dd, *J*= 9.2, 0.7 Hz, 1H), 7.12 - 7.09 (m, 1H), 7.09 - 7.04 (m, 1H), 6.98 (dd, *J*= 7.5, 1.3 Hz, 1H), 5.39 (dt, *J*= 9.9, 3.3 Hz, 1H), 4.40 - 4.31 (m, 1H), 3.41 - 3.33 (m, 1H), 3.32 (dd, *J*= 11.0, 1.3 Hz, 1H), 2.66 - 2.57 (m, 1H), 2.41-2.33 (m, 1H), 1.53 - 1.48 (m, 1H), 1.38 (dt, *J* = 13.7, 3.6 Hz, 1H), 1.20 - 1.10 (m, 1H).

Example 142: (6-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((6-(trifluoromethyl)pyridazin-3-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

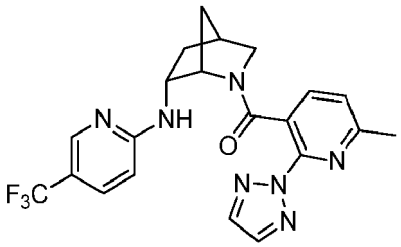
[0600]



[0601] Prepared analogous to Example 139 substituting intermediate A-1 with intermediate A-41. MS (ESI): mass calcd. for $C_{22}H_{19}F_3N_6O_2$, 456.2; m/z found, 457.2 $[M+H]^+$. ^1H NMR (500 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.78:0.22), major rotamer reported) δ 8.77 (d, *J*= 4.8 Hz, 2H), 8.39 (d, *J*= 8.1 Hz, 1H), 7.64 (d, *J*= 9.2 Hz, 1H), 7.23 - 7.19 (m, 2H), 7.09 (d, *J*= 8.1 Hz, 1H), 5.34 (dt, *J*= 10.1, 3.3 Hz, 1H), 4.47 - 4.42 (m, 1H), 3.75 (dt, *J*= 10.9, 3.2 Hz, 1H), 3.49 (dd, *J*= 10.8, 1.3 Hz, 1H), 2.75 - 2.70 (m, 1H), 2.38 - 2.28 (m, 1H), 2.20 (s, 3H), 1.58 - 1.51 (m, 3H).

Example 143: (6-methyl-2-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[0602]

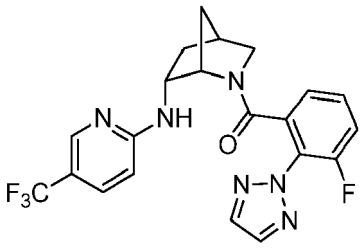


[0603] Prepared analogous to Example 53 substituting intermediate A-1 with intermediate A-3. MS (ESI): mass calcd.

for $C_{21}H_{20}F_3N_7O$, 443.2; m/z found, 444.2 $[M+H]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5μm, 100 × 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 30 °C). R_t = 5.80 min (major rotamer) at 254 nm.

Example 144: (3-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

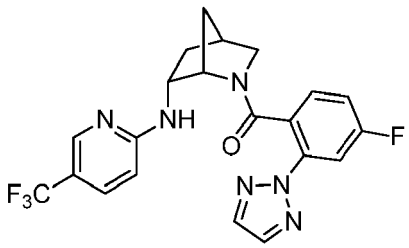
[0604]



[0605] Prepared analogous to Example 53 substituting intermediate A-1 with intermediate A-16. MS (ESI): mass calcd. for $C_{21}H_{18}F_4N_6O$, 446.1; m/z found, 447.1 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers, major rotamer reported) δ 8.00 (s, 2H), 7.91 (s, 1H), 7.58 (dd, J = 8.9, 2.6 Hz, 1H), 7.23 - 7.16 (m, 1H), 6.92 - 6.84 (m, 1H), 6.80 (d, J = 7.6 Hz, 1H), 6.64 - 6.53 (m, 1H), 4.15 - 3.93 (m, 2H), 3.27 - 3.18 (m, 2H), 2.56 - 2.50 (m, 1H), 2.28 - 2.14 (m, 1H), 1.55 (d, J = 10.2 Hz, 1H), 1.29 - 1.09 (m, 2H).

Example 145: (4-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

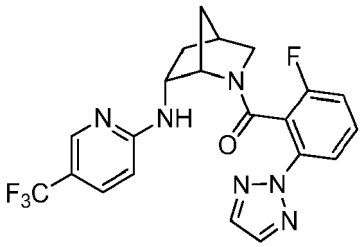
[0606]



[0607] Prepared analogous to Example 53 substituting intermediate A-1 with intermediate A-12. MS (ESI): mass calcd. for $C_{21}H_{18}F_4N_6O$, 446.1; m/z found, 447.1 $[M+H]^+$. Analytical HPLC using a XBridge C18 column (5um, 100 × 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 2 min and then hold at 100% ACN for 2 min, at a flow rate of 2.5 mL/min (Temperature = 45 °C). R_t = 2.05 min at 254 nm.

Example 146: (2-fluoro-6-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

[0608]

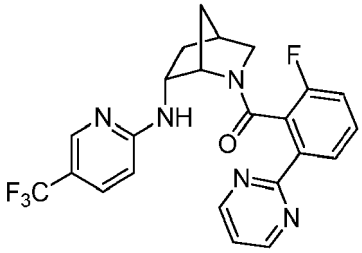


[0609] Prepared analogous to Example 53 substituting intermediate A-1 with intermediate A-11. MS (ESI): mass calcd.

for $C_{21}H_{18}F_4N_6O$, 446.1; m/z found, 447.1 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers, major rotamer reported) δ 7.98 (s, 2H), 7.78 (s, 1H), 7.75 (dt, J = 8.3, 0.9 Hz, 1H), 7.56 (dd, J = 8.8, 2.4 Hz, 1H), 7.35 - 7.27 (m, 1H), 6.66 - 6.56 (m, 1H), 6.49 (t, J = 8.6 Hz, 1H), 3.98 - 3.89 (m, 1H), 3.88 - 3.82 (m, 1H), 3.49 (dt, J = 11.0, 3.2 Hz, 1H), 3.34 - 3.32 (m, 1H), 2.63 - 2.55 (m, 1H), 2.27 - 2.15 (m, 1H), 1.44 (d, J = 10.1 Hz, 1H), 1.32 - 1.19 (m, 2H).

Example 147: (2-fluoro-6-(pyrimidin-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

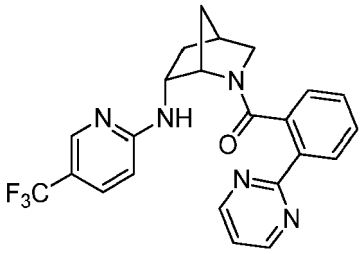
[0610]



[0611] Prepared analogous to Example 53 substituting intermediate A-1 with intermediate A-6. MS (ESI): mass calcd. for $C_{23}H_{19}F_4N_5O$, 457.2; m/z found, 458.1 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers, major rotamer reported) δ 8.86 (d, J = 4.9 Hz, 2H), 8.06 (dd, J = 7.9, 1.0 Hz, 1H), 7.83 - 7.73 (m, 1H), 7.56 (dd, J = 8.9, 2.4 Hz, 1H), 7.41 (t, J = 4.9 Hz, 1H), 7.31 - 7.24 (m, 1H), 6.66 - 6.59 (m, 1H), 6.58 - 6.53 (m, 1H), 3.99 - 3.90 (m, 2H), 3.55 (dt, J = 10.9, 3.2 Hz, 1H), 3.35 - 3.32 (m, 1H), 2.64 - 2.58 (m, 1H), 2.26 - 2.16 (m, 1H), 1.44 (d, J = 10.4 Hz, 1H), 1.33 - 1.26 (m, 1H), 1.19 - 1.13 (m, 1H).

Example 148: (2-(pyrimidin-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo [2.2.1]heptan-2-yl)methanone.

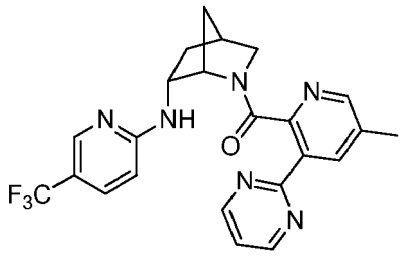
[0612]



[0613] Prepared analogous to Example 53 substituting intermediate A-1 with intermediate A-37. MS (ESI): mass calcd. for $C_{23}H_{20}F_3N_5O$, 439.2; m/z found, 440.1 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers (0.91:0.09), major rotamer reported) δ 8.84 (d, J = 4.9 Hz, 2H), 8.13 (dd, J = 7.9, 1.2 Hz, 1H), 7.87 -7.78 (m, 1H), 7.65 - 7.54 (m, 1H), 7.38 (t, J = 4.9 Hz, 1H), 7.29 (td, J = 7.7, 1.4 Hz, 1H), 6.98 - 6.87 (m, 1H), 6.87 - 6.76 (m, 1H), 6.66 - 6.49 (m, 1H), 4.08 - 3.92 (m, 1H), 3.52 (dt, J = 10.9, 3.3 Hz, 1H), 2.66 - 2.59 (m, 1H), 2.30 - 2.19 (m, 1H), 1.54 - 1.45 (m, 1H), 1.35 - 1.19 (m, 3H). 1H buried under solvent peak.

Example 149: (5-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

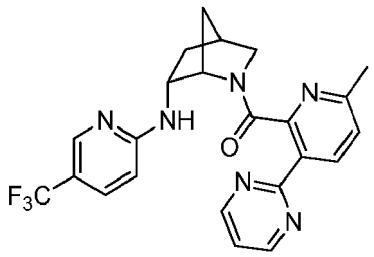
[0614]



[0615] Prepared analogous to Example 53 substituting intermediate A-1 with intermediate A-47. MS (ESI): mass calcd. for $C_{23}H_{21}F_3N_6O$, 454.2; m/z found, 455.2 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.89:0.11), only major rotamer reported) δ 8.82 (d, *J*= 4.9 Hz, 2H), 8.41 - 8.37 (m, 1H), 8.33 (dd, *J*= 2.1, 0.9 Hz, 1H), 8.26 - 8.22 (m, 1H), 7.70 - 7.58 (m, 1H), 7.45 (dd, *J*= 8.9, 2.5 Hz, 1H), 7.28 (t, *J*= 4.9 Hz, 1H), 6.38 (d, *J*= 8.8 Hz, 1H), 4.32 - 4.28 (m, 1H), 4.22 - 4.11 (m, 1H), 3.72 (dt, *J*= 10.9, 3.2 Hz, 1H), 3.32 (dd, *J*= 10.9, 1.5 Hz, 1H), 2.83 - 2.72 (m, 1H), 2.46 - 2.36 (m, 4H), 1.94 - 1.87 (m, 1H), 1.71 (d, *J*= 10.0 Hz, 1H), 1.20 (dt, *J*= 13.0, 3.5 Hz, 1H).

Example 150: (6-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

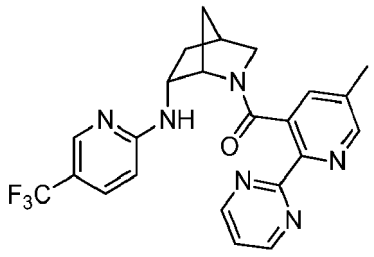
[0616]



[0617] Prepared analogous to Example 53 substituting intermediate A-1 with intermediate A-41. MS (ESI): mass calcd. for $C_{23}H_{21}F_3N_6O$, 454.2; m/z found, 455.2 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.91:0.09), only major rotamer reported) δ 8.79 (d, *J*= 4.9 Hz, 2H), 8.45 (d, *J*= 8.1 Hz, 1H), 8.31 - 8.23 (m, 1H), 7.70 - 7.59 (m, 1H), 7.47 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.29 (d, *J* = 8.1 Hz, 1H), 7.24 (t, *J* = 4.9 Hz, 1H), 6.44 (d, *J* = 8.8 Hz, 1H), 4.26 - 4.21 (m, 1H), 4.13 (s, 1H), 3.73 (dt, *J*= 10.8, 3.2 Hz, 1H), 3.31 (dd, *J*= 10.8, 1.5 Hz, 1H), 2.82 - 2.73 (m, 1H), 2.62 (s, 3H), 2.51 - 2.37 (m, 1H), 1.98 - 1.85 (m, 1H), 1.70 (d, *J*= 10.2 Hz, 1H), 1.20 (dt, *J*= 13.5, 3.5 Hz, 1H).

Example 151: (5-methyl-2-(pyrimidin-2-yl)pyridin-3-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

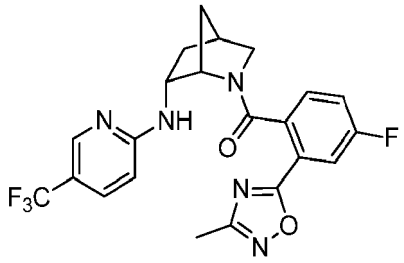
[0618]



[0619] Prepared analogous to Example 53 substituting intermediate A-1 with intermediate A-46. MS (ESI): mass calcd. for $C_{23}H_{21}F_3N_6O$, 454.2; m/z found, 455.2 $[M+H]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5μm, 100 $\times$ 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 30 °C). R_t = 5.33 min (major rotamer) at 254 nm.

Example 152: (4-fluoro-2-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

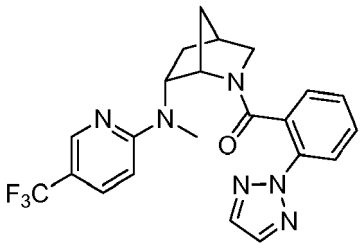
[0620]



[0621] Prepared analogous to Example 53 substituting intermediate A-1 with intermediate A-51. MS (ESI): mass calcd. for $C_{22}H_{19}F_4N_5O_2$, 461.1; m/z found, 462.1 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers, major rotamer reported) δ 7.84 (s, 1H), 7.70 (dd, J = 9.1, 2.6 Hz, 1H), 7.59 - 7.53 (m, 1H), 7.02 (dd, J = 8.5, 5.3 Hz, 1H), 6.72 (td, J = 8.2, 2.6 Hz, 1H), 6.62 - 6.47 (m, 1H), 4.06 - 3.97 (m, 2H), 3.61 (dt, J = 11.1,3.2 Hz, 1H), 3.41 - 3.35 (m, 1H), 2.76 - 2.67 (m, 1H), 2.44 (s, 3H), 2.34 - 2.23 (m, 1H), 1.74 - 1.60 (m, 2H), 1.35 - 1.26 (m, 1H).

Example 153: (2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-(methyl(5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

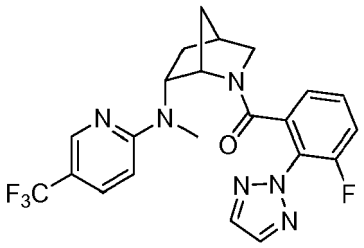
[0622]



[0623] To the title compound of example 53 (10 mg, 0.023 mmol) dissolved in DMF (0.5 mL) was added NaOtBu (2.5 mg, 0.026 mmol) .After 5 minutes, MeI (1.5 μL, 0.025 mmol) was added and the reaction mixture as stirred at room temperature overnight. Then, the mixture was diluted with EtOAc and H_2O. The aqueous layer was extracted with EtOAc (2X). The combined organics were washed with H_2O, dried with Na_2SO_4, filtered, and concentrated. Purification of the concentrate was performed using Agilent Prep Method X to give the title compound (3 mg) as a brown solid. MS (ESI): mass calcd. for $C_{22}H_{21}F_3N_6O$, 442.2; m/z found, 443.1 $[M+H]^+$. ^1H NMR (400 MHz, Methanol-d_4, Compound present as a mixture of rotamers (0.91:0.09), major rotamer reported) δ 8.06 (s, 1H), 7.95 (s, 2H), 7.80 (d, J = 8.3 Hz, 1H), 7.68 - 7.60 (m, 1H), 7.35 - 7.25 (m, 1H), 7.00 - 6.90 (m, 1H), 6.82 - 6.75 (m, 1H), 6.65 (d, J = 8.9 Hz, 1H), 4.58 - 4.46 (m, 1H), 3.88 (s, 1H), 3.49 - 3.42 (m, 2H), 3.11 (s, 3H), 2.69 (s, 1H), 2.09 - 1.98 (m, 1H), 1.99 - 1.88 (m, 1H), 1.49 (d, J = 9.9 Hz, 1H), 1.27 - 1.17 (m, 1H).

Example 154: (3-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-(methyl(5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

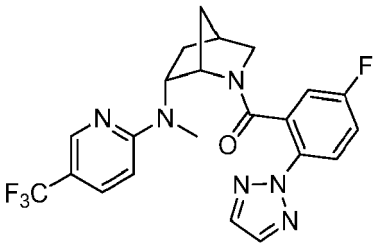
[0624]



[0625] Prepared analogous to Example 53 substituting intermediate A-1 with intermediate A-16 followed by the alkylation step of Example 153. MS (ESI): mass calcd. for $C_{22}H_{20}F_4N_6O$, 460.2; m/z found, 461.1 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers (0.86:0.14), major rotamer reported) δ 7.98 (s, 3H), 7.76 - 7.70 (m, 1H), 7.65 (dd, J = 9.1, 2.5 Hz, 1H), 7.33 - 7.26 (m, 1H), 6.70 (d, J = 9.1 Hz, 1H), 6.59 - 6.50 (m, 1H), 4.49 - 4.40 (m, 1H), 3.99 - 3.93 (m, 1H), 3.51 (dt, J = 11.4, 3.0 Hz, 1H), 3.43 (dd, J = 11.4, 1.6 Hz, 1H), 3.09 (d, J = 1.3 Hz, 3H), 2.69 (s, 1H), 2.08 - 1.93 (m, 2H), 1.46 (d, J = 9.7 Hz, 1H), 1.19 - 1.12 (m, 1H).

Example 155: (5-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-(methyl(5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

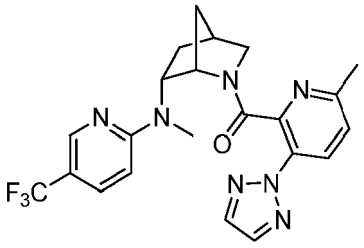
[0626]



[0627] Prepared analogous to Example 53 substituting intermediate A-1 with intermediate A-10 followed by the alkylation step of Example 153. MS (ESI): mass calcd. for $C_{22}H_{20}F_4N_6O$, 460.2; m/z found, 461.1 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers (0.93:0.07), major rotamer reported) δ 8.08 (s, 1H), 7.95 (s, 2H), 7.79 (dd, J = 9.0, 4.7 Hz, 1H), 7.63 (dd, J = 9.1, 2.6 Hz, 1H), 7.07 - 6.99 (m, 1H), 6.69 (dd, J = 8.1, 2.9 Hz, 1H), 6.66 (d, J = 9.1 Hz, 1H), 4.52 - 4.44 (m, 1H), 3.92 - 3.87 (m, 1H), 3.44 - 3.40 (m, 2H), 3.10 (s, 3H), 2.70 - 2.65 (m, 1H), 2.08 - 1.99 (m, 1H), 1.97 - 1.90 (m, 1H), 1.52 - 1.45 (m, 1H), 1.19 - 1.11 (m, 1H).

Example 156: ((1S,4S,6R)-6-(methyl(5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)methanone.

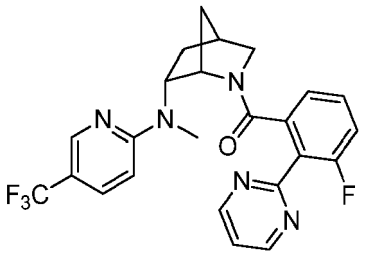
[0628]



[0629] Prepared analogous to Example 53 substituting intermediate A-1 with intermediate A-40 followed by the alkylation step of Example 153. MS (ESI): mass calcd. for $C_{22}H_{22}F_3N_7O$, 457.2; m/z found, 458.1 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers (0.93:0.07), major rotamer reported) δ 8.09 (d, J = 8.4 Hz, 1H), 8.07 (s, 1H), 7.97 (s, 2H), 7.66 (dd, J = 9.1, 2.6 Hz, 1H), 7.17 (d, J = 8.4 Hz, 1H), 6.68 (d, J = 9.1 Hz, 1H), 4.72 - 4.63 (m, 1H), 3.95 - 3.87 (m, 1H), 3.54 (dt, J = 11.4, 3.1 Hz, 1H), 3.51 - 3.42 (m, 1H), 3.12 (s, 3H), 2.77 - 2.69 (m, 1H), 2.15 (s, 3H), 2.11 - 1.99 (m, 1H), 1.92 - 1.80 (m, 1H), 1.57 (d, J = 10.4 Hz, 1H), 1.47 - 1.38 (m, 1H).

Example 157: (3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4S,6R)-6-(methyl(5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

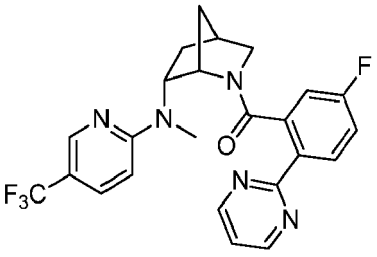
[0630]



[0631] Prepared analogous to Example 53 substituting intermediate A-1 with intermediate A-2 followed by the alkylation step of Example 153. MS (ESI): mass calcd. for $C_{24}H_{21}F_4N_5O$, 471.2; m/z found, 472.1 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers (0.90:0.10), major rotamer reported) δ 8.89 (d, J = 5.0 Hz, 2H), 8.20 - 8.12 (m, 1H), 7.66 (dd, J = 9.1, 2.6 Hz, 1H), 7.49 (t, J = 4.9 Hz, 1H), 7.09 - 7.00 (m, 1H), 6.87 - 6.80 (m, 1H), 6.72 - 6.66 (m, 2H), 4.62 - 4.53 (m, 1H), 4.15 - 4.08 (m, 1H), 3.36 (dd, J = 11.5, 1.6 Hz, 1H), 3.20 (dt, J = 11.5, 3.2 Hz, 1H), 3.10 (s, 3H), 2.66 - 2.57 (m, 1H), 2.08 - 1.98 (m, 1H), 1.90 (dt, J = 13.8, 3.7 Hz, 1H), 1.54 (d, J = 10.1 Hz, 1H), 0.95 - 0.87 (m, 1H).

Example 158: (5-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4S,6R)-6-(methyl(5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

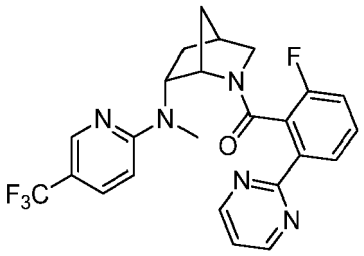
[0632]



[0633] Prepared analogous to Example 53 substituting intermediate A-1 with intermediate A-7 followed by the alkylation step of Example 153. MS (ESI): mass calcd. for $C_{24}H_{21}F_4N_5O$, 471.2; m/z found, 472.2 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers (0.91:0.09), major rotamer reported) δ 8.83 (d, J = 4.9 Hz, 2H), 8.15 (dd, J = 8.8, 5.5 Hz, 1H), 8.08 (s, 1H), 7.63 (dd, J = 9.1, 2.6 Hz, 1H), 7.38 (t, J = 4.9 Hz, 1H), 6.98 (ddd, J = 8.8, 8.1, 2.7 Hz, 1H), 6.66 (d, J = 9.1 Hz, 1H), 6.58 (dd, J = 8.4, 2.7 Hz, 1H), 4.55 - 4.45 (m, 1H), 4.02 - 3.95 (m, 1H), 3.51 (dt, J = 11.3, 3.1 Hz, 1H), 3.48 - 3.41 (m, 1H), 3.14 (s, 3H), 2.75 - 2.67 (m, 1H), 2.10 - 2.00 (m, 1H), 1.99 - 1.92 (m, 1H), 1.49 (d, J = 10.1 Hz, 1H), 1.19 - 1.09 (m, 1H).

Example 159: (2-fluoro-6-(pyrimidin-2-yl)phenyl)((1S,4S,6R)-6-(methyl(5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

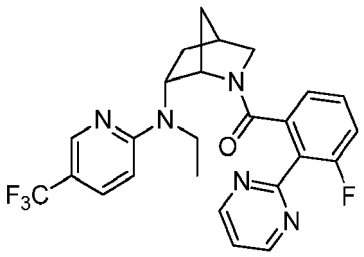
[0634]



[0635] Prepared analogous to Example 53 substituting intermediate A-1 with intermediate A-6 followed by the alkylation step of Example 153. MS (ESI): mass calcd. for $C_{24}H_{21}F_4N_5O$, 471.2; m/z found, 472.2 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers (0.85:0.15), major rotamer reported) δ 8.86 (d, J = 4.9 Hz, 2H), 8.02 (dd, J = 7.8, 1.0 Hz, 1H), 7.98 (s, 1H), 7.63 (dd, J = 9.2, 2.6 Hz, 1H), 7.42 (t, J = 4.9 Hz, 1H), 7.28 - 7.22 (m, 1H), 6.68 (d, J = 9.2 Hz, 1H), 6.63 - 6.58 (m, 1H), 4.48 - 4.40 (m, 1H), 4.08 - 4.00 (m, 1H), 3.55 (dt, J = 11.3, 3.0 Hz, 1H), 3.46 - 3.41 (m, 1H), 3.11 - 3.09 (m, 3H), 2.72 - 2.68 (m, 1H), 2.07 - 1.94 (m, 2H), 1.48 - 1.42 (m, 1H), 1.07 - 1.02 (m, 1H).

Example 160: (2-fluoro-6-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

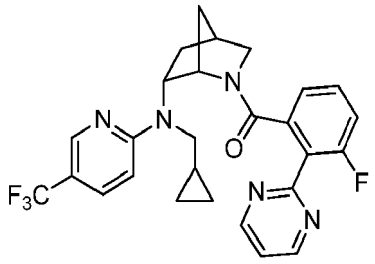
[0636]



[0637] To the title compound of Example 66 (38 mg, 0.066 mmol) dissolved in DMF (1.3 mL) was added NaOtBu (7 mg, 0.072 mmol). After 5 minutes, EtI (5.5 μL, 0.069 mmol) was added and the reaction mixture as stirred at room temperature overnight. Analysis of the reaction mixture showed that starting material (Example 66) still remained. NaH (5 mg, 0.13 mmol, 60% dispersion in mineral oil) and additional EtI (5.5 μL, 0.069 mmol) were added to the reaction flask, and the reaction mixture was stirred at room temperature for 2h. Then, the mixture was diluted with EtOAc and H_2O. The aqueous layer was extracted with EtOAc (2X). The combined organics were washed with H_2O, dried with Na_2SO_4, filtered, and concentrated. Purification of the concentrate was performed using Agilent Prep Method X to give the title compound (16 mg) as a white solid. MS (ESI): mass calcd. for $C_{25}H_{23}F_4N_5O$, 485.2; m/z found, 486.1 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers (0.93:0.07), major rotamer reported) δ 8.89 (d, J = 5.0 Hz, 2H), 8.12 (s, 1H), 7.63 (dd, J = 9.0, 2.6 Hz, 1H), 7.49 (t, J = 5.0 Hz, 1H), 7.03 - 6.96 (m, 1H), 6.83 - 6.76 (m, 1H), 6.71 - 6.64 (m, 2H), 4.48 - 4.39 (m, 1H), 4.13 (s, 1H), 3.88 - 3.75 (m, 1H), 3.36 - 3.32 (m, 2H), 3.16 (dt, J = 11.4, 3.2 Hz, 1H), 2.61 (s, 1H), 2.14 - 2.05 (m, 1H), 1.83 - 1.75 (m, 1H), 1.53 (d, J = 10.1 Hz, 1H), 1.17 (t, J = 7.0 Hz, 3H), 0.86 - 0.79 (m, 1H).

Example 161: ((1S,4S,6R)-6-((cyclopropylmethyl)(5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)(3-fluoro-2-(pyrimidin-2-yl)phenyl)methanone.

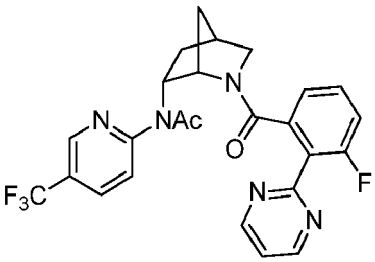
[0638]



[0639] To the title compound of Example 66 (30 mg, 0.053 mmol) dissolved in DMF (1 mL) was added NaH (6 mg, 0.16 mmol, 60% dispersion in mineral oil).After 10 minutes, (bromomethyl)cyclopropane (10 μL, 0.11 mmol) was added and the reaction mixture as stirred at room temperature overnight. Then, the mixture was diluted with EtOAc and H_2O. The aqueous layer was extracted with EtOAc (2X). The combined organics were washed with H_2O, dried with Na_2SO_4, filtered, and concentrated. Purification of the concentrate was performed using Gilson Prep Method X to give the title compound (19 mg) as a white solid. MS (ESI): mass calcd. for $C_{27}H_{25}F_4N_5O$, 511.2; m/z found, 512.3 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers (0.93:0.07), major rotamer reported) δ 8.89 (d, J = 4.9 Hz, 2H), 8.13 (s, 1H), 7.61 (dd, J = 9.1, 2.6 Hz, 1H), 7.48 (t, J = 5.0 Hz, 1H), 7.02 - 6.95 (m, 1H), 6.85 - 6.78 (m, 1H), 6.75 (d, J = 9.1 Hz, 1H), 6.68 (dd, J = 7.6, 1.1 Hz, 1H), 4.51 - 4.41 (m, 1H), 4.20 - 4.10 (m, 1H), 3.85 - 3.73 (m, 1H), 3.28 - 3.23 (m, 1H), 3.20 - 3.11 (m, 1H), 2.63 - 2.58 (m, 1H), 2.19 - 2.08 (m, 1H), 1.90 - 1.82 (m, 1H), 1.57 - 1.51 (m, 1H), 1.29 (s, 1H), 0.99 - 0.90 (m, 1H), 0.86 - 0.77 (m, 1H), 0.62 - 0.49 (m, 2H), 0.49 - 0.42 (m, 1H), 0.37 - 0.28 (m, 1H).

Example 162: N-((1S,4R,6R)-2-(3-fluoro-2-(pyrimidin-2-yl)benzoyl)-2-azabicyclo[2.2.1]heptan-6-yl)-N-(5-(trifluoromethyl)pyridin-2-yl)acetamide.

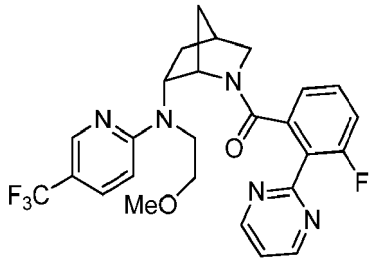
[0640]



[0641] To the title compound of Example 66 (30 mg, 0.053 mmol) was added Ac_2O (0.1 mL, 1.05 mmol), and the reaction mixture as stirred at 100 °C overnight. Then, the mixture was concentrated and the concentrate was purified directly using Gilson Prep Method X to give the title compound. MS (ESI): mass calcd. for $C_{25}H_{21}F_4N_5O_2$, 499.2; m/z found, 500.1 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers (0.79:0.21), major rotamer reported) δ 9.02 - 8.98 (m, 1H), 8.89 (d, J = 4.9 Hz, 2H), 8.31 (dd, J = 8.1, 2.5 Hz, 1H), 7.64 - 7.46 (m, 4H), 7.38 - 7.32 (m, 1H), 4.55 - 4.48 (m, 1H), 4.38 - 4.33 (m, 1H), 3.08 (dt, J = 11.1, 3.2 Hz, 1H), 2.68 (d, J = 11.2 Hz, 1H), 2.39 (s, 1H), 1.91 - 1.81 (m, 1H), 1.75 (s, 3H), 1.52 (d, J = 10.4 Hz, 1H), 0.96 - 0.90 (m, 1H), 0.69 - 0.61 (m, 1H).

Example 163: (3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4S,6R)-6-((2-methoxyethyl)(5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

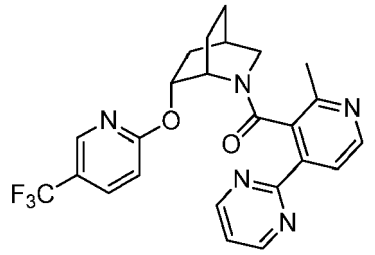
[0642]



[0643] To the title compound of Example 66 (43 mg, 0.094 mmol) dissolved in DMF (2 mL) was added NaH (19 mg, 0.47 mmol, 60% dispersion in mineral oil). After 10 minutes, 2-chloroethyl methyl ether (26 μL, 0.28 mmol) was added and the reaction mixture as stirred at room temperature overnight. Analysis of the reaction mixture showed that starting material (Example 66) still remained. NaH (19 mg, 0.47 mmol, 60% dispersion in mineral oil) and additional 2-chloroethyl methyl ether (26 μL, 0.28 mmol) were added to the reaction flask, and the reaction mixture was stirred at 50 °C for 3h. Then, the mixture was diluted with EtOAc and H_2O. The aqueous layer was extracted with EtOAc (2X). The combined organics were washed with H_2O, dried with Na_2SO_4, filtered, and concentrated. Purification of the concentrate was performed using Gilson Prep Method X to give the title compound (10 mg) as an off-white solid. MS (ESI): mass calcd. for $C_{26}H_{25}F_4N_5O_2$, 515.2; m/z found, 516.2 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers (0.92:0.08), major rotamer reported) δ 8.89 (d, J = 5.0 Hz, 2H), 8.16 (s, 1H), 7.61 (dd, J = 9.1, 2.6 Hz, 1H), 7.49 (t, J = 5.0 Hz, 1H), 7.03 - 6.96 (m, 1H), 6.84 - 6.77 (m, 1H), 6.74 (d, J = 8.9 Hz, 1H), 6.71 (dd, J = 7.6, 1.1 Hz, 1H), 4.46 - 4.36 (m, 1H), 4.16 (s, 1H), 4.04 - 3.90 (m, 1H), 3.61 - 3.43 (m, 3H), 3.38 - 3.32 (m, 3H), 3.16 (dt, J = 12.1, 3.1 Hz, 1H), 2.65 - 2.56 (m, 1H), 2.14 - 2.02 (m, 1H), 1.91 - 1.82 (m, 1H), 1.54 (d, J = 10.3 Hz, 1H), 0.83 (d, J = 10.3 Hz, 1H). 1H buried under solvent peak.

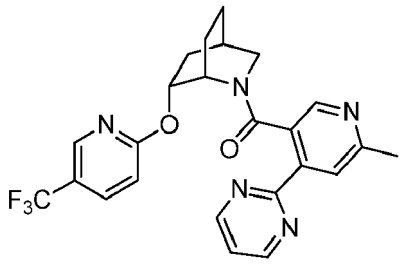
Example 164: (2-methyl-4-(pyrimidin-2-yl)pyridin-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[0644]



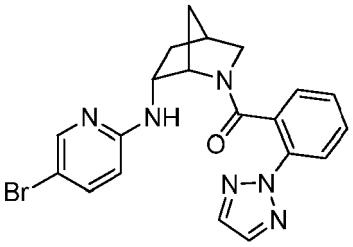
Example 165: (6-methyl-4-(pyrimidin-2-yl)pyridin-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[0645]



Example 166: (2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-bromopyridin-2-yl)amino)-2-azabicyclo [2.2.1]heptan-2-yl)methanone.

[0646]

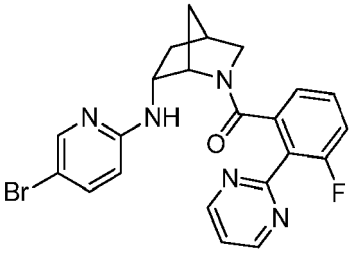


[0647] Step A: (1S,4S,6R)-tert-butyl 6-((5-bromopyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptane-2-carboxylate. To a microwave vial containing 5-bromo-2-iodopyridine (669 mg, 2.36 mmol) and degassed THF (12 mL) was added NaOtBu (453 mg, 4.71 mmol), Xantphos (98 mg, 0.17 mmol) and $Pd_2(dba)_3$ (86 mg, 0.094 mmol). The reaction mixture was purged with N_2 for 10 minutes and then intermediate B-10 (500 mg, 2.36 mmol) was added and the reaction mixture heated to 90 °C overnight. Upon completion of the reaction, the mixture was cooled to room temperature, filtered through Celite and washed with EtOAc. The filtrate was concentrated in vacuo and the crude residue subjected directly to silica gel chromatography (0-60% EtOAc in hexanes) to give the title compound of step A (91 mg). Further flushing of the column with 0-10% MeOH (with 10% 2 M NH_3) in DCM gave (1S,4R,6R)-N-(5-bromopyridin-2-yl)-2-azabicyclo[2.2.1]heptan-6-amine (483 mg). (1S,4S,6R)-tert-butyl 6-((5-bromopyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptane-2-carboxylate: MS (ESI) mass calcd. for $C_{16}H_{22}BrN_3O_2$, 367.1; m/z found 370.0 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4) δ 7.98 (d, J = 2.5 Hz, 1H), 7.49 (dd, J = 9.0, 2.5 Hz, 1H), 6.51 (d, J = 8.9 Hz, 1H), 4.46 - 4.41 (m, 1H), 4.12 - 4.05 (m, 1H), 3.29 - 3.27 (m, 1H), 3.07 (d, J = 9.6 Hz, 1H), 2.57 - 2.51 (m, 1H), 2.27 - 2.18 (m, 1H), 1.70 - 1.67 (m, 2H), 1.18 - 1.09 (m, 10H). (1S,4R,6R)-N-(5-bromopyridin-2-yl)-2-azabicyclo[2.2.1]heptan-6-amine: ^1H NMR (500 MHz, Methanol-d_4) δ 8.11 (dd, J = 2.5, 0.7 Hz, 1H), 7.58 (dd, J = 8.9, 2.5 Hz, 1H), 6.65 (dd, J = 8.9, 0.7 Hz, 1H), 4.44 (dd, J = 3.1, 2.0 Hz, 1H), 4.14 - 4.10 (m, 1H), 3.21 (dt, J = 10.9, 3.4 Hz, 1H), 3.11 (dd, J = 10.9, 1.8 Hz, 1H), 2.74 - 2.70 (m, 1H), 2.39 - 2.29 (m, 1H), 2.05 - 2.02 (m, 1H), 1.90 - 1.83 (m, 1H), 1.38 (dt, J = 13.4, 3.5 Hz, 1H).

[0648] Step B: (2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-bromopyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone. To (1S,4R,6R)-N-(5-bromopyridin-2-yl)-2-azabicyclo[2.2.1]heptan-6-amine from Step A (70 mg, 0.26 mmol) and intermediate A-1 (63 mg, 0.33 mmol) in DMF (2 mL) was added DIPEA (0.27 mL, 1.57 mmol) and HATU (109 mg, 0.29 mmol), and the reaction mixture was stirred at room temperature for 1 h. The reaction was quenched by the addition of H_2O and the aqueous layer was extracted with EtOAc (2X). The combined organics were concentrated and subjected to purification via Gilson Prep Method X to give the title compound (42 mg) as an off-white powder.MS (ESI): mass calcd. for $C_{20}H_{19}BrN_6O$, 438.1; m/z found, 439.0 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers, major rotamer reported) δ 7.94 (s, 2H), 7.83 (d, J = 7.8 Hz, 1H), 7.60 - 7.55 (m, 1H), 7.50 - 7.43 (m, 1H), 7.40 (td, J = 7.9, 1.5 Hz, 1H), 6.96 (s, 1H), 6.82 (s, 1H), 6.46 (s, 1H), 3.85 (s, 2H), 3.50 - 3.41 (m, 1H), 3.28 (dd, J = 11.1, 1.6 Hz, 1H), 2.58 (s, 1H), 2.26 - 2.15 (m, 1H), 1.53 - 1.38 (m, 1H), 1.35 - 1.24 (m, 1H), 1.23 - 1.14 (m, 1H).

Example 167: ((1S,4S,6R)-6-((5-bromopyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)(3-fluoro-2-(pyrimidin-2-yl)phenyl)methanone.

[0649]

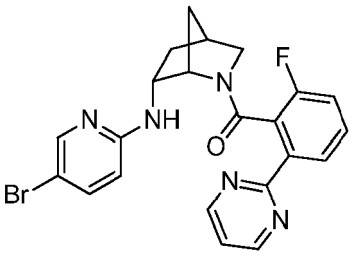


[0650] Prepared analogous to Example 166 substituting intermediate A-1 with intermediate A-2. MS (ESI): mass calcd.

for $C_{22}H_{19}BrFN_5O$, 467.1; m/z found, 470.0 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers (0.81:0.19), major rotamer reported) δ 8.86 (d, J = 4.9 Hz, 2H), 8.07 (dd, J = 8.0, 1.0 Hz, 1H), 7.52 (d, J = 2.4 Hz, 1H), 7.46 - 7.32 (m, 3H), 6.70 - 6.62 (m, 1H), 6.47 (d, J = 9.4 Hz, 1H), 3.96 - 3.89 (m, 1H), 3.87 - 3.78 (m, 1H), 3.53 (dt, J = 10.9, 3.2 Hz, 1H), 2.62 - 2.55 (m, 1H), 2.24 - 2.14 (m, 1H), 1.44 - 1.39 (m, 1H), 1.29 - 1.18 (m, 1H), 1.16 - 1.11 (m, 1H). 1H buried under solvent peak

Example 168: ((1S,4S,6R)-6-((5-bromopyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)(2-fluoro-6-(pyrimidin-2-yl)phenyl)methanone.

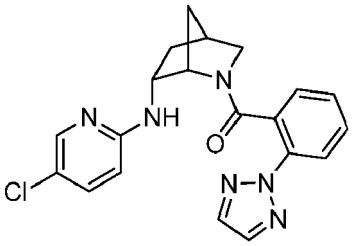
[0651]



[0652] Prepared analogous to Example 166 substituting intermediate A-1 with intermediate A-6. MS (ESI): mass calcd. for $C_{22}H_{19}BrFN_5O$, 467.1; m/z found, 468.0 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers (0.92:0.08), major rotamer reported) δ 8.89 (d, J = 4.9 Hz, 2H), 7.69 (d, J = 2.5 Hz, 1H), 7.48 (t, J = 5.0 Hz, 1H), 7.45 (dd, J = 8.9, 2.5 Hz, 1H), 7.17 - 7.10 (m, 1H), 6.99 - 6.92 (m, 1H), 6.81 (d, J = 7.5 Hz, 1H), 6.43 (d, J = 8.9 Hz, 1H), 4.15 (s, 1H), 4.01 - 3.91 (m, 1H), 3.25 - 3.18 (m, 2H), 2.52 (s, 1H), 2.27 - 2.15 (m, 1H), 1.52 (d, J = 11.7 Hz, 1H), 1.22 - 1.13 (m, 1H), 1.06 (d, J = 10.2 Hz, 1H).

Example 169: (2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-chloropyridin-2-yl)amino)-2-azabicyclo [2.2.1]heptan-2-yl)methanone.

[0653]



[0654] Step A: (1S,4S,6R)-tert-butyl 6-((5-chloropyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptane-2-carboxylate. To a microwave vial containing degassed toluene (3 mL) was added $Pd(OAc)_2$ (6 mg, 0.028 mmol) and racemic BINAP (17 mg, 0.028 mmol) at room temperature and the reaction mixture was purged with N_2 for 5 min. Then, 2-bromo-5-chloro-pyridine (90 mg, 0.47 mmol), intermediate B-10 (109 mg), and sodium tert-butoxide (63 mg, 0.66 mmol) were added and the reaction mixture heated to 90 °C overnight. Upon completion of the reaction, the mixture was cooled to room temperature, filtered through Celite and washed with EtOAc. The filtrate was concentrated in vacuo and the crude residue subjected directly to silica gel chromatography (0-10% MeOH (with 10% 2N NH_3) in DCM) to give the title compound of step A. MS (ESI) mass calcd. for $C_{16}H_{22}ClN_3O_2$, 323.1; m/z found 324.1 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4) δ 7.90 (d, *J* = 2.6 Hz, 1H), 7.39 (dd, *J*= 8.9, 2.7 Hz, 1H), 6.54 (d, *J*= 9.0 Hz, 1H), 4.43 (s, 1H), 4.12 - 4.06 (m, 1H), 3.30 - 3.27 (m, 1H), 3.09 - 3.05 (m, 1H), 2.57 - 2.50 (m, 1H), 2.28 - 2.17 (m, 1H), 1.70 - 1.67 (m, 2H), 1.48 - 1.38 (m, 2H), 1.12 (s, 9H).

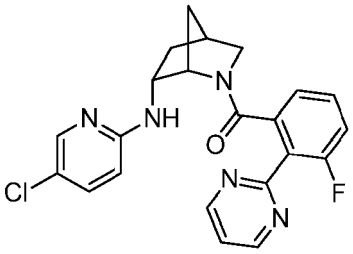
[0655] Step B: (1S,4R,6R)-N-(5-chloropyridin-2-yl)-2-azabicyclo[2.2.1]heptan-6-amine · xHCl. To the title compound of step A (252 mg, 0.701 mmol) in EtOAc (9 mL) was added 4M HCl in dioxane (0.9 mL). After 1h, the reaction was concentrated to give the title compound of step B (231 mg, 90% purity), which was used without further purification. MS (ESI) mass calcd. for $C_{11}H_{14}ClN_3$, 223.1; m/z found 224.1 $[M+H]^+$.

[0656] Step C: (2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-chloropyridin-2-yl)amino)-2-azabicyclo[2.2.1]hep-

tan-2-yl)methanone. To the title compound of step B (40 mg) and intermediate A-1 (28 mg, 0.15 mmol) in DMF (1 mL) was added DIPEA (0.2 mL, 1.2 mmol) and HATU (56 mg, 0.15 mmol), and the reaction mixture was stirred at room temperature for 1 h. The reaction was quenched by the addition of H_2O and the aqueous layer was extracted with EtOAc (4X). The combined organics were concentrated and the concentrate subjected directly to purification via Agilent Prep Method X to give the title compound (30 mg). MS (ESI): mass calcd. for $C_{20}H_{19}ClN_6O$, 394.1; m/z found, 395.2 $[M+H]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5μm, 100 × 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 30 °C). R_t = 6.25 min (major rotamer) at 254 nm.

Example 170: ((1S,4S,6R)-6-((5-chloropyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)(3-fluoro-2-(pyrimidin-2-yl)phenyl)methanone.

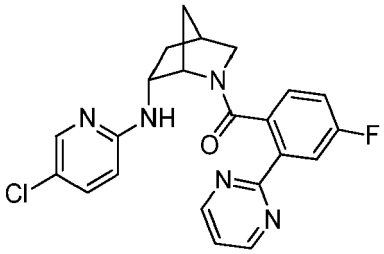
[0657]



[0658] Prepared analogous to Example 169 substituting intermediate A-1 with intermediate A-2. MS (ESI): mass calcd. for $C_{22}H_{19}ClFN_5O$, 423.1; m/z found, 424.2 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.84:0.16), major rotamer reported) δ 8.89 (d, *J*= 4.9 Hz, 2H), 7.83 (d, *J*= 2.0 Hz, 1H), 7.33 (t, *J*= 4.9 Hz, 1H), 7.21 - 7.13 (m, 2H), 7.12 - 7.06 (m, 1H), 6.99 (d, *J*= 7.2 Hz, 1H), 6.14 (d, *J*= 8.9 Hz, 1H), 4.42 (s, 1H), 4.24 - 4.13 (m, 1H), 3.46 (dt, *J* = 11.1, 3.2 Hz, 1H), 3.22 (dd, *J* = 11.2, 1.6 Hz, 1H), 2.68-2.61 (m, 1H), 2.42 - 2.27 (m, 1H), 1.71 - 1.66 (m, 1H), 1.58 - 1.52 (m, 1H), 1.09 - 0.99 (m, 1H).

Example 171: ((1S,4S,6R)-6-((5-chloropyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)(4-fluoro-2-(pyrimidin-2-yl)phenyl)methanone.

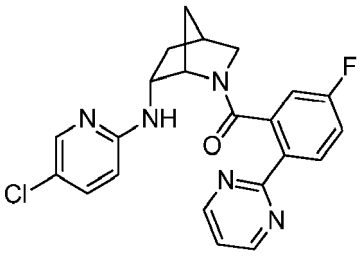
[0659]



[0660] Prepared analogous to Example 169 substituting intermediate A-1 with intermediate A-23. MS (ESI): mass calcd. for $C_{22}H_{19}ClFN_5O$, 423.1; m/z found, 424.0 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers, major rotamer reported) δ 8.86 (d, J = 4.9 Hz, 2H), 7.88 (dd, J = 10.1, 2.7 Hz, 1H), 7.58 (d, J = 2.6 Hz, 1H), 7.44 - 7.35 (m, 2H), 6.98 - 6.92 (m, 1H), 6.64 - 6.56 (m, 1H), 6.51 - 6.43 (m, 1H), 3.93 (s, 1H), 3.91 - 3.86 (m, 1H), 3.52 (dt, J = 10.9, 3.3 Hz, 1H), 3.30 - 3.28 (m, 1H), 2.63 - 2.58 (m, 1H), 2.27 - 2.17 (m, 1H), 1.47 (d, J = 10.0 Hz, 1H), 1.33 - 1.26 (m, 1H), 1.24 - 1.17 (m, 1H).

Example 172: ((1S,4S,6R)-6-((5-chloropyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)(5-fluoro-2-(pyrimidin-2-yl)phenyl)methanone.

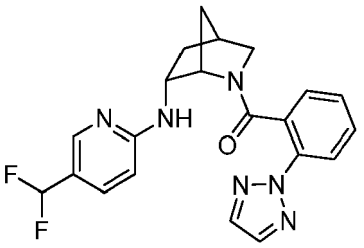
[0661]



[0662] Prepared analogous to Example 169 substituting intermediate A-1 with intermediate A-7. MS (ESI): mass calcd. for $C_{22}H_{19}ClFN_5O$, 423.1; m/z found, 424.0 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers (0.91:0.09), major rotamer reported) δ 8.83 (d, J = 4.8 Hz, 2H), 8.19 (dd, J = 8.8, 5.5 Hz, 1H), 7.55 (d, J = 2.6 Hz, 1H), 7.39 - 7.32 (m, 2H), 7.08 (td, J = 8.5, 2.7 Hz, 1H), 6.72 - 6.64 (m, 1H), 6.50 - 6.42 (m, 1H), 3.95 (s, 1H), 3.92 - 3.86 (m, 1H), 3.50 (dt, J = 11.0, 3.2 Hz, 1H), 3.30 - 3.28 (m, 1H), 2.62 - 2.58 (m, 1H), 2.26 - 2.18 (m, 1H), 1.46 (d, J = 10.1 Hz, 1H), 1.28 - 1.17 (m, 2H).

Example 173: (2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-(difluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[0663]



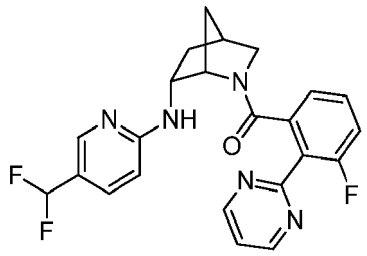
[0664] Step A: (1S,4S,6R)-tert-butyl 6-((5-(difluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptane-2-carboxylate. To a microwave vial containing degassed toluene (6 mL) was added $Pd(OAc)_2$ (25 mg, 0.038 mmol) and racemic BINAP (27 mg, 0.043 mmol) at room temperature and the reaction mixture was purged with N_2 for 5 min. Then, 2-chloro-5-(difluoromethyl)pyridine (70 μL, 0.59 mmol), intermediate B-10 (137 mg), and sodium tert-butoxide (81 mg, 0.82 mmol) were added and the reaction mixture heated to 90 °C overnight. Upon completion of the reaction, the mixture was cooled to room temperature, filtered through Celite and washed with EtOAc. The filtrate was concentrated in vacuo and the crude residue subjected directly to silica gel chromatography (0-60% EtOAc in hexanes) to give the title compound of step A (71 mg, 0.21 mmol, 36%). MS (ESI) mass calcd. for $C_{17}H_{23}F_2N_3O_2$, 339.2; m/z found 340.2 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4) δ 8.12 - 8.07 (m, 1H), 7.56 (dd, J = 8.6, 2.3 Hz, 1H), 6.80 - 6.49 (m, 2H), 4.49 - 4.44 (m, 1H), 4.23 - 4.14 (m, 1H), 3.09 (d, J = 9.5 Hz, 1H), 2.59 - 2.54 (m, 1H), 2.31 - 2.18 (m, 1H), 1.74 - 1.68 (m, 2H), 1.22 - 1.16 (m, 1H), 1.09 (s, 9H). 1 H buried under solvent peak.

[0665] Step B: (1S,4R,6R)-N-(5-(difluoromethyl)pyridin-2-yl)-2-azabicyclo[2.2.1]heptan-6-amine-xHCl. To the title compound of step A (71 mg, 0.21 mmol) in EtOAc (3 mL) was added 4M HCl in dioxane (0.3 mL). After 1h, the reaction was concentrated to give the title compound of step B (65 mg), which was used without further purification. MS (ESI) mass calcd. for $C_{12}H_{15}F_2N_3$, 239.1; m/z found 240.1 $[M+H]^+$.

[0666] Step C: (2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-(difluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone. To the title compound of step B (33 mg) and intermediate A-1 (24 mg, 0.13 mmol) in DMF (1.5 mL) was added DIPEA (0.11 mL, 0.63 mmol) and HATU (44 mg, 0.12 mmol), and the reaction mixture was stirred at room temperature for 1 h. The reaction was quenched by the addition of H_2O and the aqueous layer was extracted with EtOAc (2X). The combined organics were concentrated and the concentrate subjected directly to purification via Agilent Prep Method X to give the title compound (27 mg). MS (ESI): mass calcd. for $C_{21}H_{20}F_2N_6O$, 410.2; m/z found, 411.1 $[M+H]^+$. Analytical HPLC using a XBridge C18 column (5um, 100 $\times$ 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 2min and then hold at 100% ACN for 2 min, at a flow rate of 2.5 mL/min (Temperature = 45 °C). R_t = 1.83 and 2.03 min (major rotamers) at 254 nm.

Example 174: ((1S,4S,6R)-6-((5-(difluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)(3-fluoro-2-(pyrimidin-2-yl)phenyl)methanone.

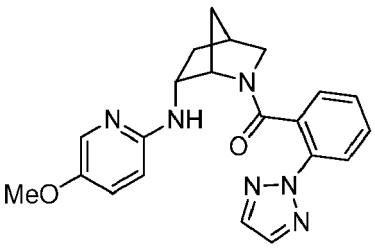
[0667]



[0668] Prepared analogous to Example 173 substituting intermediate A-1 with intermediate A-2. MS (ESI): mass calcd. for $C_{23}H_{20}F_3N_5O$, 439.2; m/z found, 440.1 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers (0.92:0.08), major rotamer reported) δ 8.89 (d, J = 5.0 Hz, 2H), 7.81 (s, 1H), 7.53 (dd, J = 8.8, 2.4 Hz, 1H), 7.48 (t, J = 4.9 Hz, 1H), 7.10 - 7.02 (m, 1H), 6.91 - 6.82 (m, 1H), 6.82 - 6.51 (m, 3H), 4.20 - 4.13 (m, 1H), 4.11 - 4.01 (m, 1H), 3.27 - 3.22 (m, 2H), 2.58 - 2.51 (m, 1H), 2.29 - 2.18 (m, 1H), 1.55 (d, J = 9.6 Hz, 1H), 1.25 - 1.17 (m, 1H), 1.11 (d, J = 9.5 Hz, 1H).

Example 175: (2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-methoxypyridin-2-yl)amino)-2-azabicyclo [2.2.1]heptan-2-yl)methanone.

[0669]



[0670] Step A: (1S,4S,6R)-tert-butyl 6-((5-methoxypyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptane-2-carboxylate. To a microwave vial containing degassed toluene (4 mL) was added $Pd(OAc)_2$ (9 mg, 0.038 mmol) and racemic BINAP (24 mg, 0.038 mmol) at room temperature and the reaction mixture was purged with N_2 for 5 min. Then, 2-chloro-5-methoxypyridine (75 μL, 0.63 mmol), intermediate B-10 (148 mg, 0.695 mmol), and sodium tert-butoxide (85 mg, 0.89 mmol) were added and the reaction mixture heated to 90 °C overnight. Upon completion of the reaction, the mixture was cooled to room temperature, filtered through Celite and washed with EtOAc. The filtrate was concentrated in vacuo and the crude residue subjected directly to silica gel chromatography (0-10% MeOH (with 10% 2 N NH_3) in DCM) to give the title compound of step A (158 mg, 0.49 mmol, 90% purity, 70%) MS (ESI) mass calcd. for $C_{17}H_{25}N_3O_3$, 319.2; m/z found 320.3 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4) δ 7.65 (d, *J*= 3.0 Hz, 1H), 7.18 (dd, *J*= 9.1, 3.0 Hz, 1H), 6.55 (d, *J*= 9.1 Hz, 1H), 4.44 - 4.40 (m, 1H), 4.09 - 4.01 (m, 1H), 3.75 (s, 3H), 3.30 - 3.26 (m, 1H), 3.07 (d, *J* = 9.4 Hz, 1H), 2.57 - 2.49 (m, 1H), 2.30 - 2.19 (m, 1H), 1.71 - 1.67 (m, 2H), 1.48 - 1.45 (m, 1H), 1.11 (s, 9H).

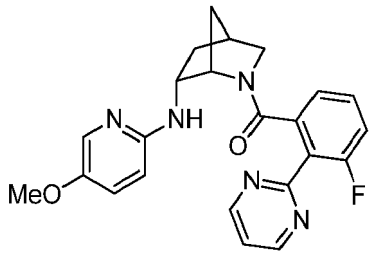
[0671] Step B: (1S,4R,6R)-N-(5-methoxypyridin-2-yl)-2-azabicyclo[2.2.1]heptan-6-amine · xHCl. To the title compound of step A (176 mg, 0.49 mmol, 90 % purity) in EtOAc (6 mL) was added 4M HCl in dioxane (0.6 mL). After 3h, the reaction was concentrated to give the title compound of step B (150 mg), which was used without further purification. MS (ESI) mass calcd. for $C_{12}H_{17}N_3O$, 219.1; m/z found 220.2 $[M+H]^+$.

[0672] Step C: (2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-methoxypyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone. To the title compound of step B (30 mg) and intermediate A-1 (21 mg, 0.11 mmol) in DMF (1 mL) was added DIPEA (0.10 mL, 0.55 mmol) and HATU (39 mg, 0.10 mmol), and the reaction mixture was stirred at room temperature for 1 h. The reaction was quenched by the addition of H_2O and the aqueous layer was extracted with EtOAc (2X). The combined organics were concentrated and the concentrate subjected directly to purification via Gilson Prep Method X to give the title compound (17 mg). MS (ESI): mass calcd. for $C_{21}H_{22}N_6O_2$, 390.2; m/z found, 391.1 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers (0.87:0.13), major

rotamer reported) δ 7.93 (s, 2H), 7.82 (d, J = 8.1 Hz, 1H), 7.39 - 7.33 (m, 1H), 7.29 (d, J = 2.4 Hz, 1H), 7.17 - 7.10 (m, 1H), 7.02 - 6.92 (m, 1H), 6.85 - 6.69 (m, 1H), 6.57 - 6.38 (m, 1H), 3.93 - 3.80 (m, 2H), 3.76 (s, 3H), 3.49 - 3.41 (m, 1H), 3.30 - 3.26 (m, 1H), 2.57 (s, 1H), 2.27 - 2.16 (m, 1H), 1.53 - 1.43 (m, 1H), 1.41 - 1.26 (m, 1H), 1.20 - 1.12 (m, 1H).

Example 176: (3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4S,6R)-6-((5-methoxypyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

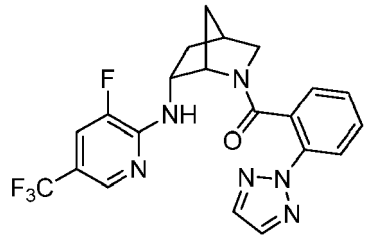
[0673]



[0674] Prepared analogous to Example 175 substituting intermediate A-1 with intermediate A-2. MS (ESI): mass calcd. for $C_{23}H_{22}FN_5O_2$, 419.2; m/z found, 420.1 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers (0.88:0.12), major rotamer reported) δ 8.89 (d, J = 5.0 Hz, 2H), 7.47 (t, J = 4.9 Hz, 1H), 7.41 (d, J = 3.0 Hz, 1H), 7.15 - 7.10 (m, 1H), 7.11 - 7.07 (m, 1H), 6.94 - 6.88 (m, 1H), 6.82 (d, J = 7.6 Hz, 1H), 6.44 (d, J = 9.1 Hz, 1H), 4.18 - 4.11 (m, 1H), 3.98 - 3.92 (m, 1H), 3.76 (s, 3H), 3.23 (t, J = 3.0 Hz, 1H), 3.22 - 3.20 (m, 1H), 2.55 - 2.50 (m, 1H), 2.29 - 2.19 (m, 1H), 1.57 (d, J = 11.2 Hz, 1H), 1.22- 1.16 (m, 1H), 1.16 - 1.11 (m, 1H).

Example 177: (2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((3-fluoro-5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[0675]



[0676] Step A: (1S,4S,6R)-tert-butyl 6-((3-fluoro-5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptane-2-carboxylate. To a microwave vial containing intermediate B-10 (170 mg, 0.801 mmol) in DMF (2.5 mL) was added 2,3-difluoro-5-(trifluoromethyl)pyridine (176 mg, 0.961 mmol) and Et_3N (0.17 mL, 1.20 mmol), and the reaction mixture was sealed and heated to 90 °C bench top overnight. Upon completion of the reaction, the mixture was cooled to room temperature and directly subjected to silica gel chromatography (0-30% EtOAc in hexanes) to give the title compound of step A (322 mg). MS (ESI) mass calcd. for $C_{17}H_{21}F_4N_3O_2$; 375.16, m/z found 376.0 $[M+H]^+$. ^1H NMR (500 MHz, Chloroform-d, Compound present as a mixture of rotamers, major rotamer reported) δ 8.15 (s, 1H), 7.33 - 7.28 (m, 1H), 5.37 - 5.23 (m, 1H), 4.42 - 4.34 (m, 2H), 3.44 - 3.39 (m, 1H), 3.11 (d, *J* = 9.3 Hz, 1H), 2.64 - 2.60 (m, 1H), 2.42 - 2.31 (m, 1H), 1.69 - 1.63 (m, 1H), 1.26 (s, 9H), 1.10 - 1.04 (m, 1H).

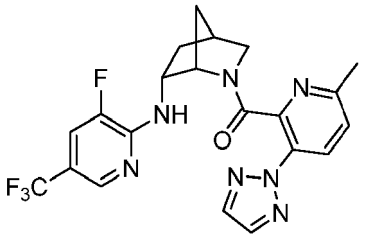
[0677] Step B: (1S,4R,6R)-N-(3-fluoro-5-(trifluoromethyl)pyridin-2-yl)-2-azabicyclo[2.2.1]heptan-6-amine · xHCl. To the title compound of step A (322 mg) in EtOAc (1 mL) was added 4M HCl in dioxane (3 mL), and the reaction mixture was stirred at room temperature for 2 h. The reaction was concentrated to give the title compound of step B (327 mg), which was used without further purification. MS (ESI) mass calcd. for $C_{12}H_{13}F_4N_3$, 275.1; m/z found 276.0 $[M+H]^+$.

[0678] Step C: (2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((3-fluoro-5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone. To the title compound of step B (40 mg) and intermediate A-1 (24 mg, 0.126 mmol) in DMF (0.5 mL) was added DIPEA (0.1 mL, 0.58 mmol) and HATU (48 mg, 0.13 mmol), and the reaction mixture was stirred at room temperature for 1 h. The reaction was quenched by the addition of H_2O and the aqueous layer was extracted with EtOAc (2X). The combined organics were concentrated and the concentrate subjected directly to purifi-

cation via Agilent Prep Method X to give the title compound (26 mg). MS (ESI): mass calcd. for $C_{21}H_{18}F_4N_6O$, 446.1; m/z found, 447.1 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers (0.87:0.13), major rotamer reported) δ 7.95 (s, 2H), 7.81 (d, *J*= 8.2 Hz, 1H), 7.66 (s, 1H), 7.58 - 7.44 (m, 1H), 7.30 (t, *J*= 7.8 Hz, 1H), 7.04-6.95 (m, 1H), 6.83-6.72 (m, 1H), 4.11 - 4.03 (m, 1H), 3.88-3.79 (m, 1H), 3.50 - 3.33 (m, 2H), 2.63-2.57 (m, 1H), 2.22-2.12 (m, 1H), 1.51-1.41 (m, 2H), 1.29-1.18 (m, 1H). Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5μm, 100 $\times$ 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 30 °C). R_t = 6.81 min (major rotamer) at 254 nm.

Example 178: ((1S,4S,6R)-6-((3-fluoro-5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)methanone.

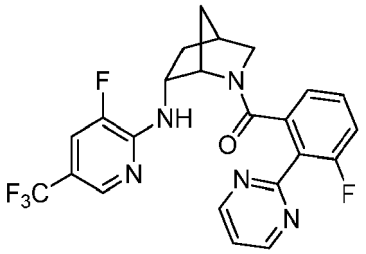
[0679]



[0680] Prepared analogous to Example 177 substituting intermediate A-1 with intermediate A-40. MS (ESI): mass calcd. for $C_{21}H_{19}F_4N_7O$, 461.2; m/z found, 462.1 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers (0.88:0.12), major rotamer reported) δ 8.14 (d, *J*= 8.4 Hz, 1H), 7.98 (s, 2H), 7.84 - 7.78 (m, 1H), 7.43 (dd, *J*= 11.1, 2.0 Hz, 1H), 7.31 (d, *J* = 8.6 Hz, 1H), 4.25 - 4.19 (m, 1H), 4.12 - 4.04 (m, 1H), 3.56 (dt, *J*= 11.0, 3.2 Hz, 1H), 3.35 (dd, *J*= 10.9, 1.4 Hz, 1H), 2.72 - 2.67 (m, 1H), 2.37 (s, 3H), 2.35 - 2.27 (m, 1H), 1.65 - 1.61 (m, 2H), 1.44 - 1.38 (m, 1H).

Example 179: (3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4S,6R)-6-((3-fluoro-5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

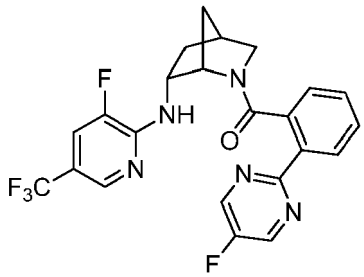
[0681]



[0682] Prepared analogous to Example 177 substituting intermediate A-1 with intermediate A-2. MS (ESI): mass calcd. for $C_{23}H_{18}F_5N_5O$, 475.1; m/z found, 476.1 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers (0.88:0.12), major rotamer reported) δ 8.90 (d, *J*= 4.9 Hz, 2H), 7.80 - 7.73 (m, 1H), 7.52 - 7.46 (m, 2H), 7.08 - 7.01 (m, 1H), 6.95 - 6.87 (m, 1H), 6.80 (d, *J*= 7.7 Hz, 1H), 4.20 (s, 1H), 4.17 - 4.10 (m, 1H), 3.33 - 3.32 (m, 1H), 3.19 (dt, *J* = 11.1, 3.2 Hz, 1H), 2.57 - 2.49 (m, 1H), 2.23 - 2.13 (m, 1H), 1.52 (d, *J* = 9.8 Hz, 1H), 1.45 - 1.36 (m, 1H), 0.93 (d, *J* = 10.1 Hz, 1H).

Example 180: ((1S,4S,6R)-6-((3-fluoro-5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)(2-(5-fluoropyrimidin-2-yl)phenyl)methanone.

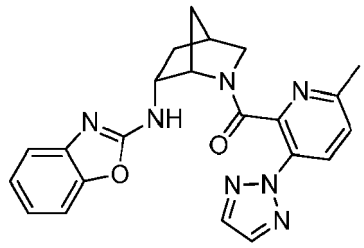
[0683]



[0684] Prepared analogous to Example 177 substituting intermediate A-1 with intermediate A-34. MS (ESI): mass calcd. for $C_{23}H_{18}F_5N_5O$, 475.1; m/z found, 476.1 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers (0.88:0.12), major rotamer reported) δ 8.81 (d, *J*= 0.6 Hz, 2H), 8.11 (d, *J*= 7.3 Hz, 1H), 7.70 - 7.63 (m, 1H), 7.62 - 7.42 (m, 1H), 7.32 - 7.22 (m, 1H), 7.01 - 6.90 (m, 1H), 6.90 - 6.79 (m, 1H), 4.16 - 4.08 (m, 1H), 4.07 - 3.95 (m, 1H), 3.53 (dt, *J*= 10.8, 3.2 Hz, 1H), 3.40 (dd, *J*= 10.8, 1.6 Hz, 1H), 2.68 - 2.63 (m, 1H), 2.26 - 2.16 (m, 1H), 1.58 - 1.51 (m, 1H), 1.51 - 1.45 (m, 1H), 1.38 - 1.28 (m, 1H).

Example 181: ((1S,4S,6R)-6-(benzo[d]oxazol-2-ylamino)-2-azabicyclo[2.2.1]heptan-2-yl)(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)methanone.

[0685]



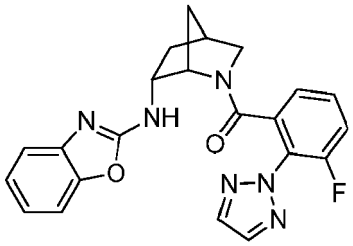
[0686] Step A: (1S,4S)-tert-butyl 6-(benzo[d]oxazol-2-ylamino)-2-azabicyclo[2.2.1]heptane-2-carboxylate. To a microwave vial containing intermediate B-10 (183 mg, 0.862 mmol) in MeCN (2 mL) was added 2-chlorobenzoxazole (0.12 mL, 1.03 mmol) and Et_3N (0.18 mL, 1.29 mmol), and the reaction mixture was sealed and heated to 100 °C bench top overnight. Upon completion of the reaction, the mixture was cooled to room temperature and diluted with H_2O. The reaction mixture was extracted with EtOAc (3X). The combined organics were concentrated and the concentrate subjected directly to silica gel chromatography (0-50% EtOAc in hexanes) to give the title compound of step A (199 mg, 0.604 mmol, 70%) MS (ESI) mass calcd. for $C_{18}H_{23}N_3O_3$; 329.2 m/z found 330.2 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers) δ 7.40-7.34 (m, 1H), 7.26-7.20 (m, 1H), 7.20-7.12 (m, 1H), 7.07-6.99 (m, 1H), 5.88-5.78 and 5.29-5.19 (two m, 1H), 4.51-4.43 (m, 1H), 4.33-4.19 (m, 1H), 3.45-3.33 (m, 1H), 3.15-3.04 (m, 1H), 2.64-2.57 (m, 1H), 2.46-2.31 (m, 1H), 1.80 - 0.99 (series of m, 12H).

[0687] Step B: N-((1S,4R)-2-azabicyclo[2.2.1]heptan-6-yl)benzo[d]oxazol-2-amine · xHCl. To the title compound of step A (199 mg, 0.604 mmol) in EtOAc (1.5 mL) was added 4M HCl in dioxane (4 mL). After 1h, the reaction was concentrated to give the title compound of step B (194 mg), which was used without further purification. MS (ESI) mass calcd. for $C_{13}H_{15}N_3O$, 229.1; m/z found 230.1 $[M+H]^+$.

[0688] Step C: ((1S,4S,6R)-6-(benzo[d]oxazol-2-ylamino)-2-azabicyclo[2.2.1]heptan-2-yl)(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)methanone. To the title compound of step B (40 mg) and intermediate A-40 (30 mg, 0.15 mmol) in DMF (1 mL) was added DIPEA (0.13 mL, 0.75 mmol) and HATU (55 mg, 0.15 mmol), and the reaction mixture was stirred at room temperature for 1 h. The reaction was quenched by the addition of H_2O and the aqueous layer was extracted with EtOAc (2X). The combined organics were concentrated and the concentrate subjected directly to purification via Agilent Prep Method X to give the title compound (24 mg). MS (ESI): mass calcd. for $C_{22}H_{21}N_7O_2$, 415.2; m/z found, 416.2 $[M+H]^+$. ^1H NMR (400 MHz, Methanol-d_4, Compound present as a mixture of rotamers (0.81:0.19), major rotamer reported) δ 8.12 - 8.05 (m, 1H), 7.99 (s, 2H), 7.26 - 7.21 (m, 1H), 7.16 - 7.08 (m, 3H), 7.08 - 7.01 (m, 1H), 4.26 - 4.21 (m, 1H), 3.98 - 3.88 (m, 1H), 3.59 (dt, *J*= 11.0, 3.2 Hz, 1H), 3.35 (d, *J* = 11.0 Hz, 1H), 2.76 - 2.68 (m, 1H), 2.40 - 2.28 (m, 1H), 2.09 (s, 3H), 1.68 - 1.60 (m, 2H), 1.40 - 1.33 (m, 1H).

Example 182: ((1S,4S,6R)-6-(benzo[d]oxazol-2-ylamino)-2-azabicyclo[2.2.1]heptan-2-yl)(3-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone.

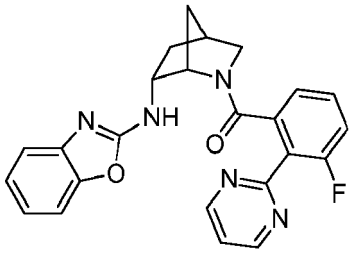
[0689]



[0690] Prepared analogous to Example 181 substituting intermediate A-40 with intermediate A-16. MS (ESI): mass calcd. for $C_{22}H_{19}FN_6O_2$, 418.2; m/z found, 419.2 $[M+H]^+$. ^1H NMR (400 MHz, Methanol-d_4, Compound present as a mixture of rotamers (0.93:0.07), major rotamer reported) δ 8.00 (s, 2H), 7.37 - 7.31 (m, 1H), 7.20 - 7.16 (m, 1H), 7.12 (d, *J* = 7.1 Hz, 2H), 6.91 (d, *J* = 8.2 Hz, 2H), 6.49 - 6.37 (m, 1H), 4.12 (s, 1H), 4.01 - 3.88 (m, 1H), 3.63 (s, 1H), 3.27 - 3.22 (m, 1H), 2.60 - 2.54 (m, 1H), 2.31 - 2.21 (m, 1H), 1.59 (d, *J*= 10.3 Hz, 1H), 1.32 - 1.19 (m, 2H).

Example 183: ((1S,4S,6R)-6-(benzo[d]oxazol-2-ylamino)-2-azabicyclo[2.2.1]heptan-2-yl)(3-fluoro-2-(pyrimidin-2-yl)phenyl)methanone.

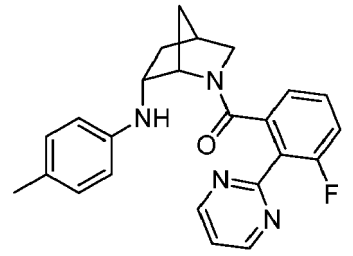
[0691]



[0692] Prepared analogous to Example 181 substituting intermediate A-40 with intermediate A-2. MS (ESI): mass calcd. for $C_{24}H_{20}FN_5O_2$, 429.2; m/z found, 430.2 $[M+H]^+$. ^1H NMR (400 MHz, Methanol-d_4, Compound present as a mixture of rotamers (0.93:0.07), major rotamer reported) δ 8.91 (d, *J* = 5.0 Hz, 2H), 7.49 (t, *J*= 5.0 Hz, 1H), 7.30 (d, *J*= 7.9 Hz, 1H), 7.21 - 7.06 (m, 3H), 6.93 (d, *J*= 7.5 Hz, 1H), 6.86 - 6.79 (m, 1H), 6.62 - 6.49 (m, 1H), 4.27 (s, 1H), 4.05 - 3.97 (m, 1H), 3.29 - 3.28 (m, 1H), 3.27 (s, 1H), 2.67 - 2.56 (m, 1H), 2.37 - 2.25 (m, 1H), 1.63 (d, *J*= 10.2 Hz, 1H), 1.35 - 1.23 (m, 2H).

Example 184: (3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4S,6R)-6-(p-tolylamino)-2-azabicyclo [2.2.1]heptan-2-yl)methanone.

[0693]



[0694] Step A: (1S,4S)-tert-butyl 6-(p-tolylamino)-2-azabicyclo[2.2.1]heptane-2-carboxylate. To a microwave vial con-

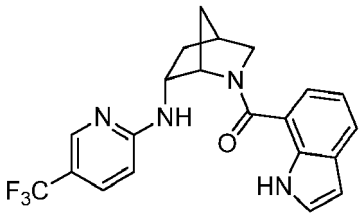
taining degassed dioxane (2 mL), intermediate B-10 (60 mg, 0.28 mmol) and 4-bromotoluene (73 mg, 0.42 mmol) was added BrettPhos Palladacycle (11 mg, 0.014 mmol), BrettPhos (8 mg, 0.014 mmol) and sodium tert-butoxide (33 mg, 0.34 mmol). The reaction mixture was heated to 90 °C bench top for 3 h. Upon completion of the reaction, the mixture was cooled to room temperature and diluted with H_2O and EtOAc. The reaction mixture was extracted with EtOAc (3X) and the combined organics washed with brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated in vacuo and the crude residue subjected directly to silica gel chromatography (0-40% EtOAc in hexanes) to give the title compound of step A (68 mg, 0.22 mmol, 80%) MS (ESI) mass calcd. for $C_{18}H_{26}N_2O_2$, 302.2; m/z found 303.1 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers, major rotamer reported) δ 6.91 (d, J = 8.1 Hz, 2H), 6.55 (d, J = 8.3 Hz, 2H), 4.39 (s, 1H), 3.86 - 3.73 (m, 1H), 3.27 (dt, J = 9.4, 3.2 Hz, 1H), 3.05 (d, J = 9.3 Hz, 1H), 2.52 - 2.48 (m, 1H), 2.28 - 2.21 (m, 1H), 2.18 (s, 3H), 1.74 - 1.40 (m, 3H), 1.08 (s, 9H).

[0695] Step B: (1S,4R)-N-(p-tolyl)-2-azabicyclo[2.2.1]heptan-6-amine · xHCl. To the title compound of step A (68 mg, 0.22 mmol) in EtOAc (3 mL) was added 4M HCl in dioxane (0.3 mL), and the reaction mixture was stirred at room temperature overnight. The reaction was concentrated to give the title compound of step B (70 mg), which was used without further purification. MS (ESI) mass calcd. for $C_{13}H_{18}N_2$, 202.2; m/z found 203.3 $[M+H]^+$.

[0696] Step C: (3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4S,6R)-6-(p-tolylamino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone. To the title compound of step B (61 mg) and intermediate A-2 (71 mg, 0.27 mmol, 82% purity) in DMF (2 mL) was added DIPEA (0.23 mL, 1.33 mmol) and HATU (93 mg, 0.24 mmol), and the reaction mixture was stirred at room temperature for 1 h. The reaction was quenched by the addition of H_2O and the aqueous layer was extracted with EtOAc (2X). The combined organics were concentrated and the concentrate subjected directly to purification via Gilson Prep Method X to give the title compound (31 mg). MS (ESI): mass calcd. for $C_{24}H_{23}FN_4O$, 402.2; m/z found, 403.2 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers (0.88:0.12), major rotamer reported) δ 8.88 (d, J = 5.0 Hz, 2H), 7.48 (t, J = 5.0 Hz, 1H), 7.09 - 7.02 (m, 1H), 6.85 - 6.77 (m, 4H), 6.34 - 6.27 (m, 2H), 4.10 (s, 1H), 3.73 - 3.64 (m, 1H), 3.29 - 3.11 (m, 2H), 2.57 - 2.48 (m, 1H), 2.32 - 2.23 (m, 1H), 2.21 (s, 3H), 1.60 (d, J = 10.1 Hz, 1H), 1.26 - 1.19 (m, 1H), 1.15 - 1.09 (m, 1H).

Example 185: (1H-indol-7-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo [2.2.1]heptan-2-yl)methanone.

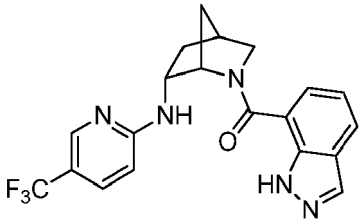
[0697]



[0698] Prepared analogous to Example 53 substituting intermediate A-1 with intermediate A-29. MS (ESI): mass calcd. for $C_{21}H_{19}F_3N_4O$, 400.2; m/z found, 401.1 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers, major rotamer reported) δ 7.53 (s, 1H), 7.32 - 7.25 (m, 1H), 7.23 (d, J = 3.1 Hz, 1H), 7.17 (dt, J = 8.0, 1.0 Hz, 1H), 6.70 - 6.60 (m, 2H), 6.37 (dd, J = 3.1, 0.9 Hz, 1H), 6.33 (s, 1H), 4.59 (s, 1H), 3.98 - 3.89 (m, 1H), 3.63 (dt, J = 11.1, 3.3 Hz, 1H), 3.51 (dd, J = 11.2, 1.6 Hz, 1H), 2.76 - 2.66 (m, 1H), 2.33 - 2.20 (m, 1H), 2.05 - 1.95 (m, 1H), 1.81 - 1.74 (m, 1H), 1.36 - 1.25 (m, 1H).

Example 186: (1H-indazol-7-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo [2.2.1]heptan-2-yl)methanone.

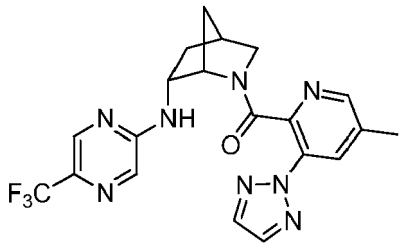
[0699]



[0700] Prepared analogous to Example 53 substituting intermediate A-1 with intermediate A-44. MS (ESI): mass calcd. for $C_{20}H_{18}F_3N_5O$, 401.1; m/z found, 402.1 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4) δ 7.88 (s, 1H), 7.55 (d, J = 8.1 Hz, 1H), 7.52 (s, 1H), 7.22 (d, J = 7.1 Hz, 1H), 7.09 (dd, J = 8.9, 2.5 Hz, 1H), 6.89 - 6.80 (m, 1H), 6.11 (d, J = 8.9 Hz, 1H), 4.76 (s, 1H), 4.00 - 3.92 (m, 1H), 3.67 - 3.56 (m, 2H), 2.76 - 2.68 (m, 1H), 2.36 - 2.25 (m, 1H), 2.17 - 2.08 (m, 1H), 1.83 (d, J = 10.4 Hz, 1H), 1.33 - 1.22 (m, 1H).

Example 187: (5-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

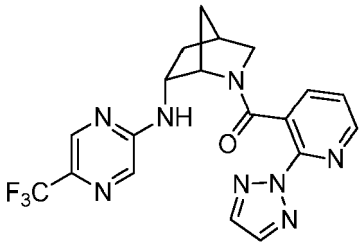
[0701]



[0702] Prepared analogous to Example 59 substituting intermediate A-1 with intermediate A-19. MS (ESI): mass calcd. for $C_{20}H_{19}F_3N_8O$, 444.2; m/z found, 445.2 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.85:0.15), major rotamer reported) δ 8.32 - 8.26 (m, 1H), 8.18 (s, 1H), 8.11 - 8.06 (m, 1H), 7.88 (s, 3H), 7.56 (s, 1H), 4.31 (s, 1H), 4.26 - 4.12 (m, 1H), 3.72 (dt, *J*= 11.0, 3.2 Hz, 1H), 3.35 (dd, *J* = 11.0, 1.7 Hz, 1H), 2.85 - 2.72 (m, 1H), 2.47 - 2.36 (m, 4H), 1.98 - 1.89 (m, 1H), 1.72 (d, *J*= 10.5 Hz, 1H), 1.21 (dt, *J*= 13.4, 4.0 Hz, 1H).

Example 188: (2-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

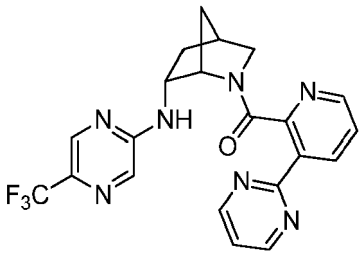
[0703]



[0704] Prepared analogous to Example 59 substituting intermediate A-1 with intermediate A-39. MS (ESI): mass calcd. for $C_{19}H_{17}F_3N_8O$, 430.1; m/z found, 431.1 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers (0.91:0.09), major rotamer reported) δ 8.36 (dd, *J* = 4.8, 1.8 Hz, 1H), 8.07 (s, 2H), 7.98 - 7.83 (m, 2H), 7.61 - 7.48 (m, 1H), 6.89 - 6.75 (m, 1H), 4.01 - 3.89 (m, 1H), 3.85 - 3.70 (m, 1H), 3.51 (dt, *J* = 11.2, 3.2 Hz, 1H), 3.35 (dd, *J* = 11.1, 1.7 Hz, 1H), 2.64 (s, 1H), 2.30 - 2.19 (m, 1H), 1.57 - 1.47 (m, 1H), 1.43 - 1.32 (m, 1H), 1.32 - 1.21 (m, 1H).

Example 189: (3-(pyrimidin-2-yl)pyridin-2-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

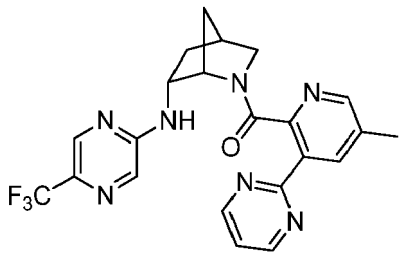
[0705]



[0706] Prepared analogous to Example 59 substituting intermediate A-1 with intermediate A-42. MS (ESI): mass calcd. for $C_{21}H_{18}F_3N_7O$, 441.2; m/z found, 442.2 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers (0.85:0.15), major rotamer reported) δ 8.89 (d, *J* = 4.9 Hz, 2H), 8.53 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.02 (d, *J* = 4.8 Hz, 1H), 7.94 - 7.86 (m, 2H), 7.44 (t, *J* = 4.9 Hz, 1H), 7.37 (dd, *J* = 8.0, 4.8 Hz, 1H), 4.20 - 4.14 (m, 1H), 4.11 - 4.01 (m, 1H), 3.63 (dt, *J* = 10.9, 3.2 Hz, 1H), 3.35 (d, *J* = 10.9 Hz, 1H), 2.77 - 2.68 (m, 1H), 2.36 - 2.30 (m, 1H), 1.70 - 1.54 (m, 2H), 1.40 - 1.30 (m, 1H).

Example 190: (5-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

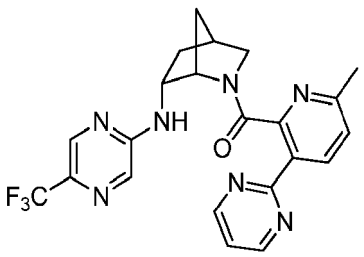
[0707]



[0708] Prepared analogous to Example 59 substituting intermediate A-1 with intermediate A-47. MS (ESI): mass calcd. for $C_{22}H_{20}F_3N_7O$, 455.2; m/z found, 456.2 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers (0.88:0.12), major rotamer reported) δ 8.88 (d, *J* = 4.9 Hz, 2H), 8.33 (dd, *J* = 2.1, 0.9 Hz, 1H), 7.90 (s, 1H), 7.89 - 7.88 (m, 1H), 7.82 (s, 1H), 7.43 (t, *J* = 4.9 Hz, 1H), 4.20 - 4.15 (m, 1H), 4.10 - 3.99 (m, 1H), 3.60 (dt, *J* = 10.9, 3.2 Hz, 1H), 3.35 (dd, *J* = 11.0, 1.5 Hz, 1H), 2.73 - 2.67 (m, 1H), 2.33 (s, 3H), 2.32 - 2.26 (m, 1H), 1.66 - 1.51 (m,2H), 1.38 - 1.31 (m, 1H).

Example 191: (6-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[0709]

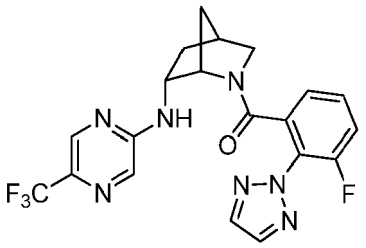


[0710] Prepared analogous to Example 59 substituting intermediate A-1 with intermediate A-41. MS (ESI): mass calcd. for $C_{22}H_{20}F_3N_7O$, 455.2; m/z found, 456.2 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers (0.86:0.14), major rotamer reported) δ 7.37 (d, *J* = 4.9 Hz, 2H), 6.88 (d, *J* = 8.1 Hz, 1H), 6.45 (s, 1H), 6.33 (d, *J* = 1.4 Hz, 1H), 5.91 (t, *J* = 4.9 Hz, 1H), 5.74 (d, *J* = 8.1 Hz, 1H), 2.76 - 2.67 (m, 1H), 2.59 - 2.48 (m, 1H), 2.11 (dt,

J = 11.0, 3.2 Hz, 1H), 1.83 (dd, *J* = 10.9, 1.6 Hz, 1H), 1.20 - 1.18 (m, 1H), 0.87 - 0.75 (m, 4H), 0.17 - -0.00 (m, 2H), -0.13 - -0.27 (m, 1H).

Example 192: (3-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

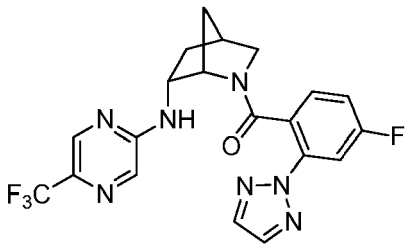
[0711]



[0712] Prepared analogous to Example 59 substituting intermediate A-1 with intermediate A-16. MS (ESI): mass calcd. for $C_{20}H_{17}F_4N_7O$, 447.1; m/z found, 448.2 $[M+H]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5μm, 100 × 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 30 °C). R_t = 6.35 min (major rotamer) at 254 nm.

Example 193: (4-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

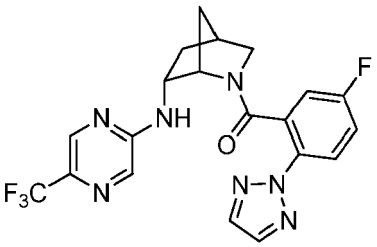
[0713]



[0714] Prepared analogous to Example 59 substituting intermediate A-1 with intermediate A-12. MS (ESI): mass calcd. for $C_{20}H_{17}F_4N_7O$, 447.1; m/z found, 448.2 $[M+H]^+$. $]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5μm, 100 × 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 30 °C). R_t = 6.56 min (major rotamer) at 254 nm.

Example 194: ((5-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[0715]

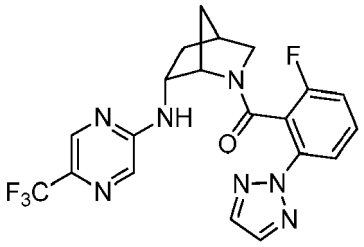


[0716] Prepared analogous to Example 59 substituting intermediate A-1 with intermediate A-10. MS (ESI): mass calcd. for $C_{20}H_{17}F_4N_7O$, 447.1; m/z found, 448.2 $[M+H]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5μm, 100 × 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold

at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 30 °C). R_t = 6.36 min (major rotamer) at 254 nm.

Example 195: (2-fluoro-6-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

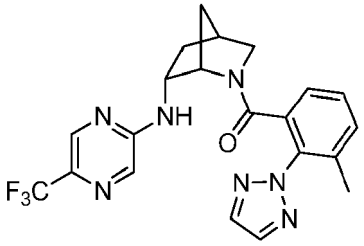
[0717]



[0718] Prepared analogous to Example 59 substituting intermediate A-1 with intermediate A-11. MS (ESI): mass calcd. for $C_{20}H_{17}F_4N_7O$, 447.1; m/z found, 448.2 $[M+H]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5μm, 100 × 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 30 °C). R_t = 6.41 min (major rotamer) at 254 nm.

Example 196: (3-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

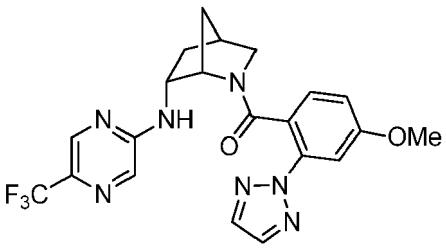
[0719]



[0720] Prepared analogous to Example 59 substituting intermediate A-1 with intermediate A-22. MS (ESI): mass calcd. for $C_{21}H_{20}F_3N_7O$, 443.2; m/z found, 444.2 $[M+H]^+$. $]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5μm, 100 × 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 30 °C). R_t = 6.61 min (major rotamer) at 254 nm.

Example 197: (4-methoxy-2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

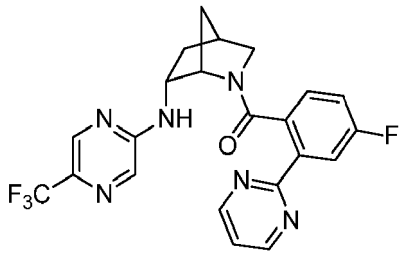
[0721]



[0722] Prepared analogous to Example 59 substituting intermediate A-1 with intermediate A-5. MS (ESI): mass calcd. for $C_{21}H_{20}F_3N_7O_2$, 459.2; m/z found, 460.1 $[M+H]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5μm, 100 × 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 30 °C). R_t = 6.30 min (major rotamer) at 254 nm.

Example 198: (4-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

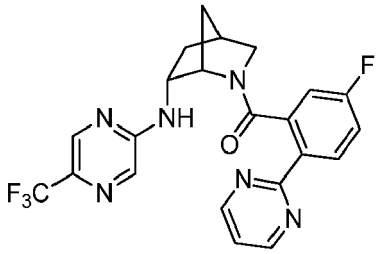
[0723]



[0724] Prepared analogous to Example 59 substituting intermediate A-1 with intermediate A-23. MS (ESI): mass calcd. for $C_{22}H_{18}F_4N_6O$, 458.1; m/z found, 459.2 $[M+H]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5μm, 100 × 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 30 °C). R_t = 6.24 min (major rotamer) at 254 nm.

Example 199: (5-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

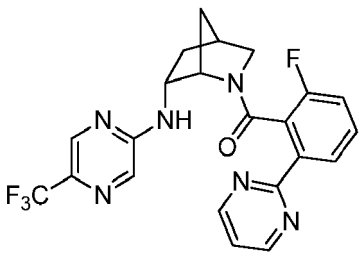
[0725]



[0726] Prepared analogous to Example 59 substituting intermediate A-1 with intermediate A-7. MS (ESI): mass calcd. for $C_{22}H_{18}F_4N_6O$, 458.1; m/z found, 459.9 $[M+H]^+$. ^1H NMR (600 MHz, Methanol-d_4, Compound present as a mixture of rotamers (0.93:0.07), major rotamer reported) δ 8.84 (d, *J* = 4.8 Hz, 2H), 8.19 (dd, *J* = 8.8, 5.5 Hz, 1H), 7.95 - 7.87 (m, 2H), 7.38 (t, *J* = 4.9 Hz, 1H), 7.04 (td, *J* = 8.4, 2.7 Hz, 1H), 6.74 - 6.64 (m, 1H), 4.04 - 3.93 (m, 2H), 3.54 (dt, *J* = 11.0, 3.2 Hz, 1H), 3.36 - 3.33 (m, 1H), 2.66 - 2.62 (m, 1H), 2.30 - 2.22 (m, 1H), 1.50 (d, *J* = 10.0 Hz, 1H), 1.34 - 1.24 (m, 2H).

Example 200: (2-fluoro-6-(pyrimidin-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[0727]

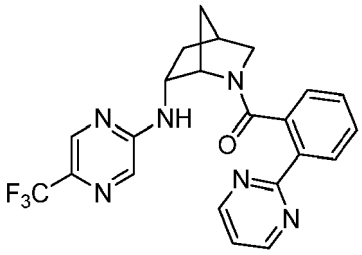


[0728] Prepared analogous to Example 59 substituting intermediate A-1 with intermediate A-6. MS (ESI): mass calcd. for $C_{22}H_{18}F_4N_6O$, 458.1; m/z found, 459.2 $[M+H]^+$. $]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a

XBridge C18 column (5μm, 100 × 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 30 °C). R_t = 6.16 min (major rotamer) at 254 nm.

Example 201: (2-(pyrimidin-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

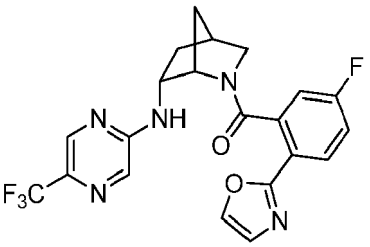
[0729]



[0730] Prepared analogous to Example 59 substituting intermediate A-1 with intermediate A-37. MS (ESI): mass calcd. for $C_{22}H_{19}F_3N_6O$, 440.2; m/z found, 441.9 $[M+H]^+$. ^1H NMR (500 MHz, Methanol- d_4, Compound present as a mixture of rotamers (0.93:0.07), major rotamer reported) δ 8.86 (d, *J* = 4.9 Hz, 2H), 8.12 (d, *J* = 7.6 Hz, 1H), 7.94 - 7.87 (m, 1H), 7.86 - 7.78 (m, 1H), 7.40 (t, *J* = 4.9 Hz, 1H), 7.30 (td, *J* = 7.7, 1.4 Hz, 1H), 7.02 - 6.92 (m, 1H), 6.87 - 6.75 (m, 1H), 4.06 - 3.90 (m, 2H), 3.52 (dt, *J* = 11.0, 3.1 Hz, 1H), 3.36 - 3.33 (m, 1H), 2.67 - 2.60 (m, 1H), 2.31 - 2.20 (m, 1H), 1.47 (d, *J* = 10.0 Hz, 1H), 1.32 - 1.26 (m, 1H), 1.25 - 1.15 (m, 1H).

Example 202: (5-fluoro-2-(oxazol-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

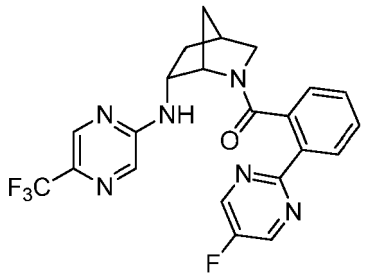
[0731]



[0732] Prepared analogous to Example 59 substituting intermediate A-1 with intermediate A-49. MS (ESI): mass calcd. for $C_{21}H_{17}F_4N_5O_2$, 447.1; m/z found, 448.2 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers, major rotamer reported) δ 8.30 (s, 1H), 8.11 (dd, *J* = 8.8, 5.3 Hz, 1H), 7.99 - 7.89 (m, 1H), 7.85 (d, *J* = 1.4 Hz, 1H), 7.80 (d, *J* = 0.9 Hz, 1H), 7.29 - 7.26 (m, 1H), 7.21 (ddd, *J* = 8.9, 7.9, 2.7 Hz, 1H), 7.05 (dd, *J* = 8.3, 2.6 Hz, 1H), 4.88 (s, 1H), 4.85 - 4.70 (m, 1H), 3.22 (dt, *J* = 8.9, 2.9 Hz, 1H), 2.95 (dd, *J* = 8.9, 1.5 Hz, 1H), 2.63 - 2.55 (m, 1H), 2.49 - 2.31 (m, 1H), 1.90 - 1.75 (m, 2H), 1.18 - 1.11 (m, 1H).

Example 203: (2-(5-fluoropyrimidin-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

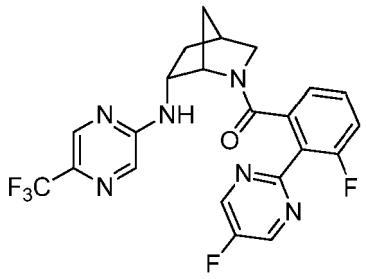
[0733]



[0734] Prepared analogous to Example 59 substituting intermediate A-1 with intermediate A-34. MS (ESI): mass calcd. for $C_{22}H_{18}F_4N_6O$, 458.1; m/z found, 459.2 $[M+H]^+$. ^1H NMR (400 MHz, Methanol-d_4, Compound present as a mixture of rotamers (0.93:0.07), major rotamer reported) δ 8.81 (s, 2H), 8.12 (d, *J* = 7.9 Hz, 1H), 7.97 - 7.87 (m, 1H), 7.86 - 7.76 (m, 1H), 7.29 (td, *J* = 7.7, 1.4 Hz, 1H), 6.95 (d, *J* = 7.5 Hz, 1H), 6.85 - 6.70 (m, 1H), 4.08 - 3.90 (m, 2H), 3.55 (dt, *J* = 10.9, 3.2 Hz, 1H), 3.38 - 3.32 (m, 1H), 2.66 (s, 1H), 2.31 - 2.18 (m, 1H), 1.51 (d, *J* = 10.0 Hz, 1H), 1.41 - 1.24 (m, 2H).

Example 204: (3-fluoro-2-(5-fluoropyrimidin-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

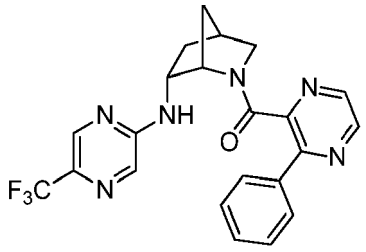
[0735]



[0736] Prepared analogous to Example 59 substituting intermediate A-1 with intermediate A-35. MS (ESI): mass calcd. for $C_{22}H_{17}F_5N_6O$, 476.1; m/z found, 477.9 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers (0.91:0.09), major rotamer reported) δ 8.88 (d, *J* = 0.7 Hz, 2H), 7.96 - 7.89 (m, 2H), 7.11 - 7.03 (m, 1H), 6.93 - 6.81 (m, 2H), 4.20 (s, 1H), 4.10 - 4.02 (m, 1H), 3.28 - 3.25 (m, 2H), 2.58 (s, 1H), 2.32 - 2.19 (m, 1H), 1.57 (d, *J* = 10.1 Hz, 1H), 1.32 - 1.21 (m, 1H), 1.15 - 1.02 (m, 1H).

Example 205: (3-phenylpyrazin-2-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo [2.2.1]heptan-2-yl)methanone.

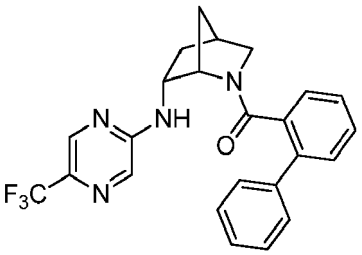
[0737]



[0738] Prepared analogous to Example 59 substituting intermediate A-1 with intermediate A-43. MS (ESI): mass calcd. for $C_{22}H_{19}F_3N_6O$, 440.2; m/z found, 441.2 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers, major rotamer reported) δ 8.48 (d, *J* = 2.4 Hz, 1H), 7.93 (s, 1H), 7.84 (s, 1H), 7.78 (d, *J* = 2.4 Hz, 1H), 7.73 - 7.66 (m, 2H), 7.56 - 7.50 (m, 3H), 3.90 - 3.82 (m, 1H), 3.81 - 3.73 (m, 1H), 3.34 (dd, *J* = 11.3, 1.6 Hz, 1H), 3.27 (dt, *J* = 11.3, 3.2 Hz, 1H), 2.53 - 2.48 (m, 1H), 2.20 - 2.08 (m, 1H), 1.38 - 1.28 (m, 1H), 1.29 - 1.19 (m, 1H), 0.66 - 0.55 (m, 1H).

Example 206: [1,1'-biphenyl]-2-yl((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo [2.2.1]heptan-2-yl)methanone.

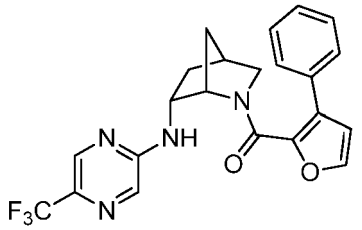
[0739]



[0740] Prepared analogous to Example 59 substituting intermediate A-1 with [1,1'-biphenyl]-2-carboxylic acid. MS (ESI): mass calcd. for $C_{24}H_{21}F_3N_4O$, 438.2; m/z found, 439.2 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4) δ 7.91 (br. s, 1H), 7.76 (br. s, 1H), 7.49 - 7.33 (m, 6H), 7.25 (td, *J* = 7.6, 1.4 Hz, 1H), 6.87 (dd, *J* = 7.6, 1.3 Hz, 1H), 6.68 (td, *J* = 7.5, 1.3 Hz, 1H), 3.93 - 3.72 (m, 2H), 3.25 (dd, *J* = 11.2, 1.6 Hz, 1H), 3.09 (dt, *J* = 11.2, 3.2 Hz, 1H), 2.43 - 2.33 (m, 1H), 2.16 - 2.05 (m, 1H), 1.26 - 1.11 (m, 3H).

Example 207: (3-phenylfuran-2-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo [2.2.1]heptan-2-yl)methanone.

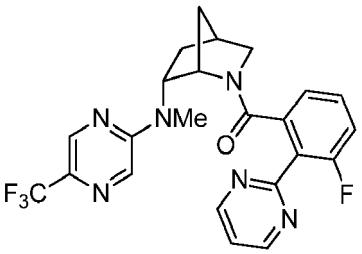
[0741]



[0742] Prepared analogous to Example 59 substituting intermediate A-1 with intermediate A-45. MS (ESI): mass calcd. for $C_{22}H_{19}F_3N_4O_2$, 428.1; m/z found, 429.1 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers (0.93:0.07), major rotamer reported) δ 8.09 - 8.05 (m, 1H), 7.74 (d, *J* = 1.4 Hz, 1H), 7.43 - 7.36 (m, 4H), 7.36 - 7.31 (m, 1H), 7.06 (d, *J* = 1.8 Hz, 1H), 6.41 (d, *J* = 1.8 Hz, 1H), 4.50 - 4.46 (m, 1H), 4.04 - 3.96 (m, 1H), 3.49 - 3.45 (m, 2H), 2.64 - 2.58 (m, 1H), 2.28 - 2.20 (m, 1H), 1.61 - 1.49 (m, 2H), 1.32 - 1.24 (m, 1H).

Example 208: (3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4S,6R)-6-(methyl(5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[0743]

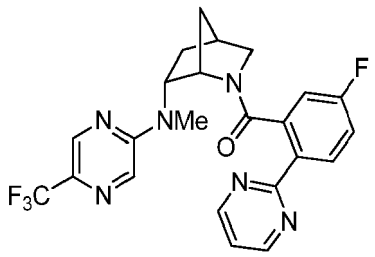


[0744] Prepared analogous to Example 59 substituting intermediate A-1 with intermediate A-2, followed by alkylation step of Example 153. MS (ESI): mass calcd. for $C_{23}H_{20}F_4N_6O$, 472.2; m/z found, 473.2 $[M+H]^+$. ^1H NMR (500 MHz,

Methanol-d_4, Compound present as a mixture of rotamers (0.88:0.12), major rotamer reported) δ 8.90 (d, *J* = 5.0 Hz, 2H), 8.18 - 8.16 (m, 1H), 8.14 - 8.12 (m, 1H), 7.50 (t, *J* = 5.0 Hz, 1H), 7.10 - 7.01 (m, 1H), 6.91 - 6.83 (m, 1H), 6.78 (dd, *J* = 7.6, 1.2 Hz, 1H), 4.56 - 4.47 (m, 1H), 4.15 - 4.09 (m, 1H), 3.37 (dd, *J* = 11.5, 1.6 Hz, 1H), 3.22 - 3.16 (m, 4H), 2.63 - 2.59 (m, 1H), 2.08 - 1.98 (m, 1H), 1.97 - 1.88 (m, 1H), 1.55 - 1.48 (m, 1H), 0.84 - 0.77 (m, 1H).

Example 209: (5-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4S,6R)-6-(methyl(5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

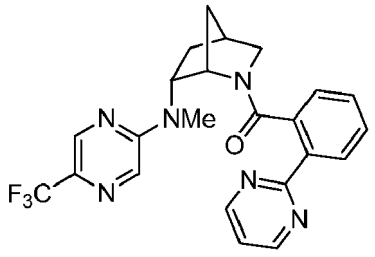
[0745]



[0746] Prepared analogous to Example 208 substituting intermediate A-2 with intermediate A-7. MS (ESI): mass calcd. for $C_{23}H_{20}F_4N_6O$, 472.2; m/z found, 473.2 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers (0.89:0.11), major rotamer reported) δ 8.84 (d, *J* = 4.9 Hz, 2H), 8.18 (dd, *J* = 8.8, 5.5 Hz, 1H), 8.15 (s, 1H), 8.09 - 8.04 (m, 1H), 7.39 (t, *J* = 4.9 Hz, 1H), 7.05 - 6.96 (m, 1H), 6.64 (dd, *J* = 8.5, 2.7 Hz, 1H), 4.51 - 4.41 (m, 1H), 4.03 - 3.95 (m, 1H), 3.54 (dt, *J* = 11.3, 3.1 Hz, 1H), 3.45 (dd, *J* = 11.3, 1.6 Hz, 1H), 3.24 (s, 3H), 2.78 - 2.69 (m, 1H), 2.13 - 1.97 (m, 2H), 1.57 - 1.46 (m, 1H), 1.23 - 1.11 (m, 1H).

Example 210: ((1S,4S,6R)-6-(methyl(5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)(2-(pyrimidin-2-yl)phenyl)methanone.

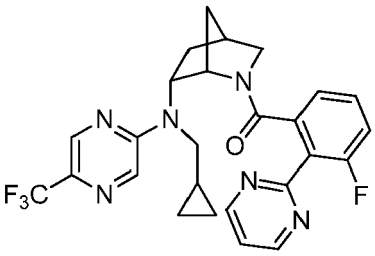
[0747]



[0748] Prepared analogous to Example 208 substituting intermediate A-2 with intermediate A-37. MS (ESI): mass calcd. for $C_{23}H_{21}F_3N_6O$, 454.2; m/z found, 455.2 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers (0.88:0.12), major rotamer reported) δ 8.85 (d, *J* = 4.9 Hz, 2H), 8.10 (dd, *J* = 7.9, 1.2 Hz, 1H), 8.08 (s, 2H), 7.39 (t, *J* = 4.9 Hz, 1H), 7.26 (td, *J* = 7.7, 1.4 Hz, 1H), 6.92 (dd, *J* = 7.6, 1.3 Hz, 1H), 6.82 (td, *J* = 7.5, 1.3 Hz, 1H), 4.50 - 4.43 (m, 1H), 3.99 - 3.92 (m, 1H), 3.52 (dt, *J* = 11.3, 3.1 Hz, 1H), 3.44 (dd, *J* = 11.3, 1.5 Hz, 1H), 3.23 (s, 3H), 2.76 - 2.67 (m, 1H), 2.12 - 1.91 (m, 2H), 1.52 - 1.42 (m, 1H), 1.19 - 1.07 (m, 1H).

Example 211: ((1S,4S,6R)-6-((cyclopropylmethyl)(5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)(3-fluoro-2-(pyrimidin-2-yl)phenyl)methanone.

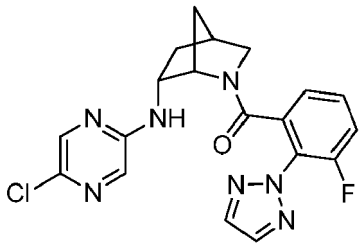
[0749]



[0750] Prepared analogous to Example 59 substituting intermediate A-1 with intermediate A-2, followed by alkylation step of Example 161. MS (ESI): mass calcd. for $C_{26}H_{24}F_4N_6O$, 512.2; m/z found, 513.2 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers (0.93:0.07), major rotamer reported) δ 8.89 (d, *J* = 4.9 Hz, 2H), 8.18 (br. s, 1H), 8.15 (br. s, 1H), 7.49 (t, *J* = 5.0 Hz, 1H), 7.04 - 6.98 (m, 1H), 6.89 - 6.81 (m, 1H), 6.78 (dd, *J* = 7.6, 1.2 Hz, 1H), 4.48 - 4.40 (m, 1H), 4.18 - 4.14 (m, 1H), 3.84 (dd, *J* = 16.1, 5.9 Hz, 1H), 3.39 - 3.33 (m, 2H), 3.14 (dt, *J* = 11.4, 3.2 Hz, 1H), 2.63 - 2.58 (m, 1H), 2.19 - 2.08 (m, 1H), 1.91 - 1.84 (m, 1H), 1.53 (d, *J* = 10.3 Hz, 1H), 1.01 - 0.92 (m, 1H), 0.77 - 0.70 (m, 1H), 0.65 - 0.52 (m, 2H), 0.51 - 0.43 (m, 1H), 0.38 - 0.30 (m, 1H).

Example 212: ((1S,4S,6R)-6-((5-chloropyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)(3-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone.

[0751]



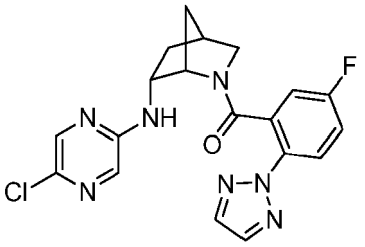
[0752] Step A: (1S,4S,6R)-tert-butyl 6-((5-chloropyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptane-2-carboxylate. To a microwave vial containing intermediate B-10 (300 mg, 1.41 mmol) in MeCN (3 mL) was added 2,5-dichloropyrazine (0.17 mL, 1.70 mmol) and Et_3N (0.30 mL, 2.12 mmol), and the reaction mixture was sealed and heated to 90 °C bench top overnight. Upon completion of the reaction, the mixture was cooled to room temperature and diluted with H_2O. The reaction mixture was extracted with EtOAc (3X). The combined organics were concentrated and the concentrate subjected directly to silica gel chromatography (0-60% EtOAc in hexanes) to give the title compound of step A (153 mg, 0.471 mmol, 33%) MS (ESI) mass calcd. for $C_{15}H_{21}ClN_4O_2$; 324.1, m/z found 269.1 $[M+2H\text{-}tBu]^+$. ^1H NMR (500 MHz, Methanol-d_4) δ 7.99 (d, J = 1.4 Hz, 1H), 7.71 (d, J = 1.4 Hz, 1H), 4.45 - 4.39 (m, 1H), 4.16 - 4.12 (m, 1H), 3.08 (d, J = 10.1 Hz, 1H), 2.62 - 2.50 (m, 1H), 2.29 - 2.19 (m, 1H), 1.74 - 1.64 (m, 2H), 1.22 - 1.16 (m, 1H), 1.11 (s, 9H). 1 H buried under solvent.

[0753] Step B: (1S,4R,6R)-N-(5-chloropyrazin-2-yl)-2-azabicyclo[2.2.1]heptan-6-amine · xHCl. To the title compound of step A (150 mg, 0.46 mmol) in EtOAc (5 mL) was added 4M HCl in dioxane (0.6 mL), and the reaction mixture was stirred overnight. The reaction was concentrated to give the title compound of step B (137 mg), which was used without further purification. MS (ESI) mass calcd. for $C_{10}H_{13}ClN_4$, 224.1; m/z found 225.1 $[M+H]^+$.

[0754] Step C: ((1S,4S,6R)-6-((5-chloropyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)(3-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone. To the title compound of step B (34 mg) and intermediate A-16 (28 mg, 0.14 mmol) in DMF (1 mL) was added DIPEA (0.12 mL, 0.69 mmol) and HATU (48 mg, 0.13 mmol), and the reaction mixture was stirred at room temperature for 1 h. The reaction was quenched by the addition of H_2O and the aqueous layer was extracted with EtOAc (2X). The combined organics were concentrated and the concentrate subjected directly to purification via Gilson Prep Method X to give the title compound (35 mg). MS (ESI): mass calcd. for $C_{19}H_{17}ClFN_7O$, 413.1; m/z found, 414.0 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers (0.92:0.08), major rotamer reported) δ 8.01 (s, 2H), 7.70 - 7.66 (m, 1H), 7.62 (d, J = 1.4 Hz, 1H), 7.33 - 7.27 (m, 1H), 7.02 - 6.93 (m, 1H), 6.87 (d, J = 7.7 Hz, 1H), 4.02 (s, 1H), 3.95 - 3.86 (m, 1H), 3.24 - 3.20 (m, 2H), 2.53 (s, 1H), 2.27 - 2.15 (m, 1H), 1.52 (d, J = 10.3 Hz, 1H), 1.22 - 1.05 (m, 2H).

Example 213: 1S,4S,6R)-6-((5-chloropyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)(5-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone.

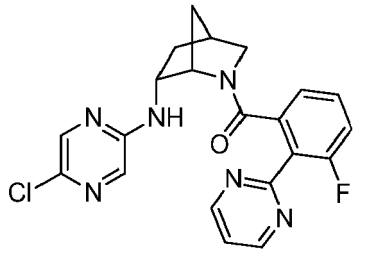
[0755]



[0756] Prepared analogous to Example 212 substituting intermediate A-16 with intermediate A-10. MS (ESI): mass calcd. for $C_{19}H_{17}ClFN_7O$, 413.1; m/z found, 414.0 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers, major rotamer reported) δ 7.95 (s, 2H), 7.84 (dd, J = 9.0, 4.7 Hz, 1H), 7.69 - 7.62 (m, 1H), 7.60 (d, J = 1.4 Hz, 1H), 7.22 - 7.15 (m, 1H), 6.81 - 6.70 (m, 1H), 3.92 - 3.74 (m, 1H), 3.48 - 3.39 (m, 1H), 3.29 - 3.27 (m, 1H), 2.59 (s, 1H), 2.27 - 2.16 (m, 1H), 1.51 - 1.41 (m, 1H), 1.29 - 1.16 (m, 2H). 1H buried under solvent peak.

Example 214: ((1S,4S,6R)-6-((5-chloropyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)(3-fluoro-2-(pyrimidin-2-yl)phenyl)methanone.

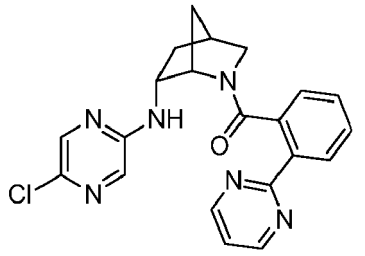
[0757]



[0758] Prepared analogous to Example 212 substituting intermediate A-16 with intermediate A-2. MS (ESI): mass calcd. for $C_{21}H_{18}ClFN_6O$, 424.1; m/z found, 425.1 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers (0.91:0.09), major rotamer reported) δ 8.91 (d, J = 5.0 Hz, 2H), 7.63 (dd, J = 9.3, 1.5 Hz, 2H), 7.50 (t, J = 5.0 Hz, 1H), 7.19 - 7.12 (m, 1H), 7.01 - 6.93 (m, 1H), 6.85 (d, J = 6.9 Hz, 1H), 4.15 (s, 1H), 3.97 - 3.91 (m, 1H), 3.24 - 3.20 (m, 2H), 2.56 - 2.48 (m, 1H), 2.27 - 2.17 (m, 1H), 1.50 (d, J = 10.3 Hz, 1H), 1.22 - 1.15 (m, 1H), 0.94 (d, J = 10.2 Hz, 1H).

Example 215: ((1S,4S,6R)-6-((5-chloropyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)(2-(pyrimidin-2-yl)phenyl)methanone.

[0759]

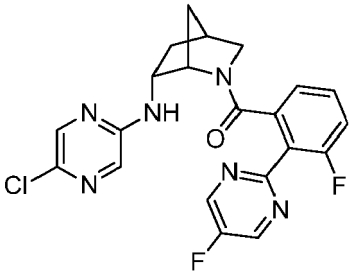


[0760] Prepared analogous to Example 212 substituting intermediate A-16 with intermediate A-37. MS (ESI): mass

calcd. for $C_{21}H_{19}ClN_6O$, 406.1; m/z found, 407.1 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers (0.92:0.08), major rotamer reported) δ 8.85 (d, J = 4.9 Hz, 2H), 8.12 (d, J = 8.0 Hz, 1H), 7.68 - 7.61 (m, 1H), 7.54 - 7.50 (m, 1H), 7.43 - 7.34 (m, 2H), 6.97 (d, J = 7.6 Hz, 1H), 6.95 - 6.85 (m, 1H), 3.94 (s, 1H), 3.91 - 3.84 (m, 1H), 3.50 (dt, J = 11.0, 3.2 Hz, 1H), 3.30 - 3.29 (m, 1H), 2.66 - 2.58 (m, 1H), 2.28 - 2.17 (m, 1H), 1.51 - 1.42 (m, J = 10.1 Hz, 1H), 1.27 - 1.14 (m, 2H).

Example 216: ((1S,4S,6R)-6-((5-chloropyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)(3-fluoro-2-(5-fluoropyrimidin-2-yl)phenyl)methanone.

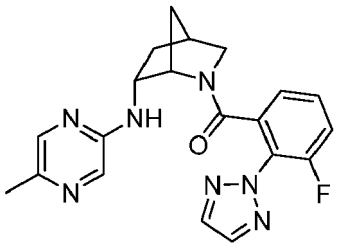
[0761]



[0762] Prepared analogous to Example 212 substituting intermediate A-16 with intermediate A-35. MS (ESI): mass calcd. for $C_{23}H_{18}F_5N_5O$, 475.1; m/z found, 476.1 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers (0.92:0.08), major rotamer reported) δ 8.87 (s, 2H), 7.93 (s, 1H), 7.58 (dd, J = 8.9, 2.5 Hz, 1H), 7.13 - 7.00 (m, 1H), 6.90 - 6.82 (m, 1H), 6.82 - 6.75 (m, 1H), 6.65 - 6.54 (m, 1H), 4.17 (s, 1H), 4.13 - 4.04 (m, 1H), 3.28 - 3.21 (m, 2H), 2.61 - 2.50 (m, 1H), 2.31 - 2.16 (m, 1H), 1.59 (d, J = 10.2 Hz, 1H), 1.27 - 1.08 (m, 2H).

Example 217: (3-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-methylpyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[0763]



[0764] Step A: (1S,4S,6R)-tert-butyl 6-((5-methylpyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptane-2-carboxylate. To a microwave vial containing degassed toluene (9 mL) was added $Pd(OAc)_2$ (24 mg, 0.035 mmol) and racemic BINAP (22 mg, 0.035 mmol) at room temperature and the reaction mixture was purged with N_2 for 5 min. Then, 2-chloro-5-methylpyrazine (112 mg, 0.87 mmol), intermediate B-10 (204 mg), and sodium tert-butoxide (121 mg, 1.22 mmol) were added and the reaction mixture heated to 70 °C overnight. Upon completion of the reaction, the mixture was cooled to room temperature, filtered through Celite and washed with EtOAc. The filtrate was concentrated in vacuo and the crude residue subjected directly to silica gel chromatography (10-80% EtOAc in hexanes) to give the title compound of step A (139 mg, 0.457 mmol, 52%). MS (ESI) mass calcd. for $C_{16}H_{24}N_4O_2$, 304.2; m/z found 305.2 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4) δ 7.93 - 7.79 (m, 2H), 4.45 - 4.40 (m, 1H), 4.16 - 4.12 (m, 1H), 3.09 (dd, *J* = 9.5, 1.2 Hz, 1H), 2.60 - 2.53 (m, 1H), 2.33 (s, 3H), 2.29 - 2.20 (m, 1H), 1.74 - 1.64 (m, 2H), 1.20 - 1.15 (m, 1H), 1.08 (s, 9H). 1 H buried under solvent.

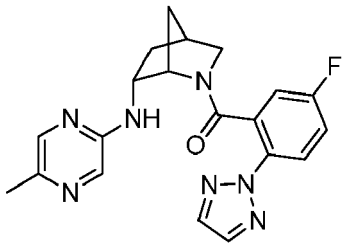
[0765] Step B: (1S,4R,6R)-N-(5-methylpyrazin-2-yl)-2-azabicyclo[2.2.1]heptan-6-amine · xHCl. To the title compound of step A (139 mg, 0.46 mmol) in EtOAc (5 mL) was added 4M HCl in dioxane (0.6 mL), and the reaction mixture was stirred at room temperature overnight. The reaction was concentrated to give the title compound of step B (140 mg), which was used without further purification. MS (ESI) mass calcd. for $C_{11}H_{16}N_4$, 204.1; m/z found 205.2 $[M+H]^+$.

[0766] Step C: (3-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-methylpyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone. To the title compound of step B (31 mg) and intermediate A-16 (28 mg, 0.13 mmol) in DMF (1 mL) was added DIPEA (0.12 mL, 0.67 mmol) and HATU (47 mg, 0.12 mmol), and the reaction mixture was

stirred at room temperature overnight. The reaction was quenched by the addition of H_2O and the aqueous layer was extracted with EtOAc (2X). The combined organics were concentrated and the concentrate subjected directly to purification via Gilson Prep Method X to give the title compound (18 mg). MS (ESI): mass calcd. for $C_{20}H_{20}FN_7O$, 393.2; m/z found, 394.2 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers, major rotamer reported) δ 8.00 (s, 2H), 7.80 - 7.75 (m, 1H), 7.55 - 7.49 (m, 1H), 7.29 - 7.22 (m, 1H), 6.93 - 6.78 (m, 2H), 4.10 - 3.97 (m, 1H), 3.97 - 3.89 (m, 1H), 3.25 - 3.20 (m, 2H), 2.53 (s, 1H), 2.33 (s, 3H), 2.27 - 2.17 (m, 1H), 1.54 (d, J = 10.1 Hz, 1H), 1.23 - 1.11 (m, 2H).

Example 218: (5-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-methylpyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

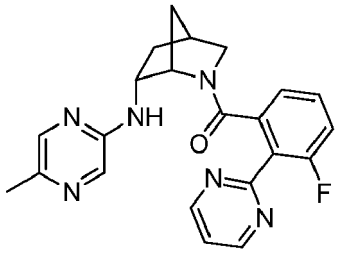
[0767]



[0768] Prepared analogous to Example 217 substituting intermediate A-16 with intermediate A-10. MS (ESI): mass calcd. for $C_{20}H_{20}FN_7O$, 393.2; m/z found, 394.5 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers, major rotamer reported) δ 7.95 (s, 2H), 7.82 (dd, J = 9.0, 4.7 Hz, 1H), 7.78 (s, 1H), 7.50 - 7.45 (m, 1H), 7.19 - 7.11 (m, 1H), 6.69 (s, 1H), 3.91 - 3.77 (m, 2H), 3.48 - 3.38 (m, 1H), 2.58 (s, 1H), 2.32 (s, 3H), 2.27 - 2.18 (m, 1H), 1.50 - 1.38 (m, 1H), 1.29 - 1.14 (m, 2H). 1H buried under solvent.

Example 219: (3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4S,6R)-6-((5-methylpyrazin-2-yl)amino)-2-azabicyclo [2.2.1]heptan-2-yl)methanone.

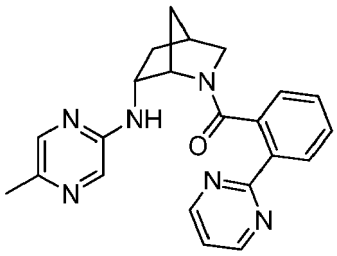
[0769]



[0770] Prepared analogous to Example 217 substituting intermediate A-16 with intermediate A-2. MS (ESI): mass calcd. for $C_{22}H_{21}FN_6O$, 404.2; m/z found, 405.5 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers (0.91:0.09), major rotamer reported) δ 8.90 (d, J = 5.0 Hz, 2H), 7.75 (d, J = 1.5 Hz, 1H), 7.55 - 7.52 (m, 1H), 7.49 (t, J = 5.0 Hz, 1H), 7.15 - 7.09 (m, 1H), 6.92 - 6.86 (m, 1H), 6.85 - 6.82 (m, 1H), 4.18 - 4.13 (m, 1H), 4.01 - 3.93 (m, 1H), 3.27 - 3.20 (m, 2H), 2.53 (s, 1H), 2.33 (s, 3H), 2.27 - 2.19 (m, 1H), 1.53 (d, J = 10.3 Hz, 1H), 1.21 - 1.14 (m, 1H), 1.06 - 1.00 (m, 1H).

Example 220: ((1S,4S,6R)-6-((5-methylpyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)(2-(pyrimidin-2-yl)phenyl)methanone

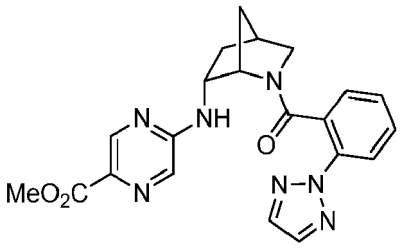
[0771]



[0772] Prepared analogous to Example 217 substituting intermediate A-16 with intermediate A-37. MS (ESI): mass calcd. for $C_{22}H_{22}N_6O$, 386.2; m/z found, 387.1 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers (0.88:0.12), major rotamer reported) δ 8.85 (d, J = 4.9 Hz, 2H), 8.11 (d, J = 7.9 Hz, 1H), 7.75 (s, 1H), 7.43 (s, 1H), 7.39 (t, J = 4.9 Hz, 1H), 7.33 (t, J = 7.7 Hz, 1H), 6.96 (d, J = 7.5 Hz, 1H), 6.87 - 6.76 (m, 1H), 4.03 - 3.84 (m, 2H), 3.51 (dt, J = 11.1, 3.2 Hz, 1H), 2.67 - 2.57 (m, 1H), 2.33 (s, 3H), 2.28 - 2.14 (m, 1H), 1.48 (d, J = 9.8 Hz, 1H), 1.34 - 1.18 (m, 2H). 1H buried under solvent peak.

Example 221: methyl 5-(((1S,4S,6R)-2-(2-(2H-1,2,3-triazol-2-yl)benzoyl)-2-azabicyclo[2.2.1]heptan-6-yl)amino)pyrazine-2-carboxylate

[0773]



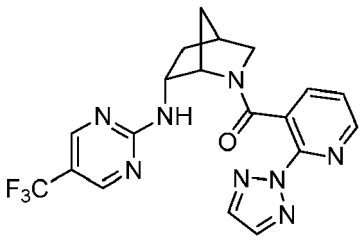
[0774] Step A: (1S,4S,6R)-tert-butyl 6-((5-(methoxycarbonyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptane-2-carboxylate. To a microwave vial containing intermediate B-10 (100 mg, 0.471 mmol) in DMF (2 mL) was added methyl 5-chloropyrazine-2-carboxylate (98 mg, 0.57 mmol) and Et_3N (0.1 mL, 0.72 mmol), and the reaction mixture was sealed and heated to 70 °C bench top overnight. After 14 hours, LCMS analysis of the reaction mixture showed incomplete conversion of the starting material. The temperature was raised to 100 °C and the reaction mixture heated overnight. Upon completion of the reaction, the mixture was cooled to room temperature and directly subjected to silica gel chromatography (0-50% EtOAc in hexanes) to give the title compound of step A (112 mg). MS (ESI) mass calcd. for $C_{17}H_{24}N_4O_4$; 348.2, m/z found 349.2 $[M+H]^+$. ^1H NMR (500 MHz, Chloroform-d, Compound present as a mixture of rotamers) δ 8.78 - 8.68 (m, 1H), 7.93-7.74 (m, 1H), 6.30-6.18 and 5.90 - 5.77 (two m, 1H), 4.46 - 4.36 (m, 1H), 4.33-4.12 (m, 1H), 3.91 (s, 3H), 3.41-3.30 (m, 1H), 3.11-2.99 (m, 1H), 2.63 - 2.51 (m, 1H), 2.39-2.25 (m,1H), 1.78 - 1.59 (m, 2H), 1.51 - 1.01 (m, 10H).

[0775] Step B: methyl 5-((1S,4R,6R)-2-azabicyclo[2.2.1]heptan-6-ylamino)pyrazine-2-carboxylate· xHCl. To the title compound of step A (112 mg, 0.321 mmol) in EtOAc (1 mL) was added 4M HCl in dioxane (3 mL), and the reaction mixture was stirred at room temperature for 2 h. The reaction was concentrated to give the title compound of step B (99 mg), which was used without further purification. MS (ESI) mass calcd. for $C_{12}H_{16}N_4O_2$, 248.1; m/z found 249.1 $[M+H]^+$.

[0776] Step C: methyl 5-(((1S,4S,6R)-2-(2-(2H-1,2,3-triazol-2-yl)benzoyl)-2-azabicyclo[2.2.1]heptan-6-yl)amino)pyrazine-2-carboxylate. To the title compound of step B (99 mg) and intermediate A-1 (70 mg, 0.37 mmol) in DMF (2 mL) was added DIPEA (0.3 mL, 1.7 mmol) and HATU (129 mg, 0.339 mmol), and the reaction mixture was stirred at room temperature for 1 h. The reaction was quenched by the addition of H_2O and the aqueous layer was extracted with EtOAc (2X). The combined organics were concentrated and the concentrate subjected directly to purification via Gilson Prep Method X to give the title compound. MS (ESI): mass calcd. for $C_{21}H_{21}N_7O_3$, 419.2; m/z found, 420.2 $[M+H]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5μm, 100 $\times$ 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 30 °C). R_t = 4.75 min (major rotamer) at 254 nm.

Example 222: (2-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrimidin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

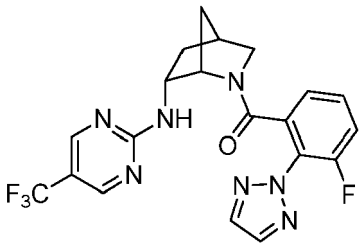
[0777]



[0778] Prepared analogous to Example 60 substituting intermediate A-1 with intermediate A-39. MS (ESI): mass calcd. for $C_{19}H_{17}F_3N_8O$, 430.1; m/z found, 430.9 $[M+H]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5μm, 100 × 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 30 °C). R_t = 5.15 min (major rotamer) at 254 nm.

Example 223: (3-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrimidin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

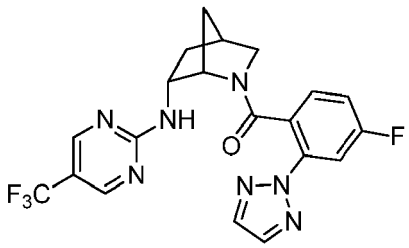
[0779]



[0780] Prepared analogous to Example 60 substituting intermediate A-1 with intermediate A-16. MS (ESI): mass calcd. for $C_{20}H_{17}F_4N_7O$, 447.1; m/z found, 448.9 $[M+H]^+$. ^1H NMR (400 MHz, Methanol-d_4, Compound present as a mixture of rotamers (0.88:0.12), major rotamer reported) δ 8.56 (d, *J* = 3.2 Hz, 1H), 8.20 (d, *J* = 3.1 Hz, 1H), 8.01 (s, 2H), 7.28 - 7.19 (m, 1H), 7.06 - 6.95 (m, 1H), 6.93 - 6.85 (m, 1H), 4.10 - 3.99 (m, 2H), 3.29 - 3.26 (m, 1H), 3.20 (dt, *J*= 11.2, 3.2 Hz, 1H), 2.57 - 2.51 (m, 1H), 2.25 - 2.12 (m, 1H), 1.54 (d, *J* = 10.3 Hz, 1H), 1.39 - 1.28 (m, 1H), 1.23 - 1.08 (m, 1H).

Example 224: (4-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrimidin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

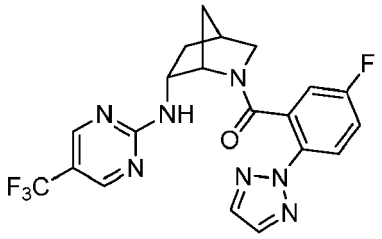
[0781]



[0782] Prepared analogous to Example 60 substituting intermediate A-1 with intermediate A-12. MS (ESI): mass calcd. for $C_{20}H_{17}F_4N_7O$, 447.1; m/z found, 448.1 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers, major rotamer reported) δ 8.56 (s, 1H), 8.22 - 8.13 (m, 1H), 7.98 (s, 2H), 7.64 (dd, *J* = 9.6, 2.6 Hz, 1H), 7.12 - 6.99 (m, 1H), 6.68 - 6.50 (m, 1H), 4.07 - 3.95 (m, 1H), 3.80 (s, 1H), 3.54 - 3.43 (m, 1H), 3.36 (dd, *J* = 10.9, 1.6 Hz, 1H), 2.62 (s, 1H), 2.26 - 2.14 (m, 1H), 1.52 - 1.42 (m, 1H), 1.38 - 1.29 (m, 2H).

Example 225: (5-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrimidin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

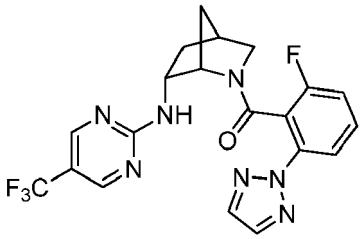
[0783]



[0784] Prepared analogous to Example 60 substituting intermediate A-1 with intermediate A-10. MS (ESI): mass calcd. for $C_{20}H_{17}F_4N_7O$, 447.1; m/z found, 447.9 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers, major rotamer reported)) δ 8.52 (s, 1H), 8.17 (d, *J* = 3.1 Hz, 1H), 7.95 (s, 2H), 7.85 (dd, *J* = 9.0, 4.8 Hz, 1H), 7.16 - 7.06 (m, 1H), 6.86 - 6.74 (m, 1H), 4.07 - 3.97 (m, 1H), 3.80 (s, 1H), 3.47 - 3.33 (m, 2H), 2.65 - 2.54 (m, 1H), 2.25 - 2.15 (m, 1H), 1.47 (d, *J* = 10.2 Hz, 1H), 1.38 - 1.31 (m, 1H), 1.31 - 1.21 (m, 1H).

Example 226: (2-fluoro-6-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrimidin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

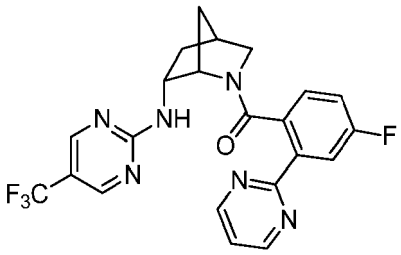
[0785]



[0786] Prepared analogous to Example 60 substituting intermediate A-1 with intermediate A-11. MS (ESI): mass calcd. for $C_{20}H_{17}F_4N_7O$, 447.1; m/z found, 447.9 $[M+H]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5μm, 100 $\times$ 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 30 °C). R_t = 6.18 min (major rotamer) at 254 nm.

Example 227: (4-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrimidin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[0787]

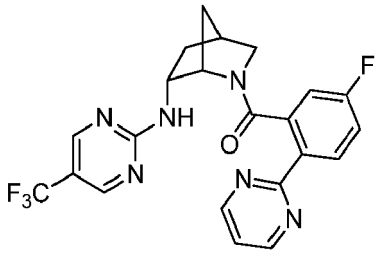


[0788] Prepared analogous to Example 60 substituting intermediate A-1 with intermediate A-23. MS (ESI): mass calcd. for $C_{22}H_{18}F_4N_6O$, 458.1; m/z found, 459.9 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers (0.88:0.12), major rotamer reported) δ 8.88 (d, *J* = 4.9 Hz, 2H), 8.64 - 8.47 (m, 1H), 8.16 (d, *J* = 3.1 Hz, 1H), 7.89 (dd, *J* = 10.0, 2.7 Hz, 1H), 7.42 (t, *J* = 4.9 Hz, 1H), 7.12 - 6.93 (m, 1H), 6.68 (s, 1H), 4.09 - 3.85 (m, 2H), 3.53 (dt,

J = 10.9, 3.2 Hz, 1H), 3.36 (dd, *J* = 10.9, 1.6 Hz, 1H), 2.69 - 2.61 (m, 1H), 2.30 - 2.16 (m, 1H), 1.54 - 1.43 (m, 1H), 1.41 - 1.34 (m, 1H), 1.33 - 1.23 (m, 1H).

Example 228: (5-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrimidin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

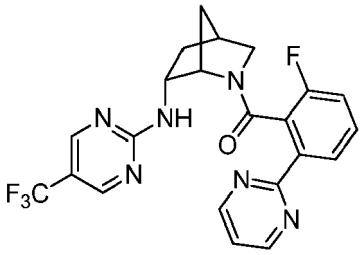
[0789]



[0790] Prepared analogous Example 60 substituting intermediate A-1 with intermediate A-7. MS (ESI): mass calcd. for $C_{22}H_{18}F_4N_6O$, 458.1; m/z found, 459.9 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers (0.91:0.09), major rotamer reported) δ 8.84 (d, *J* = 4.8 Hz, 2H), 8.51 (s, 1H), 8.21 (dd, *J* = 8.8, 5.5 Hz, 1H), 8.16 (d, *J* = 3.1 Hz, 1H), 7.38 (t, *J* = 4.9 Hz, 1H), 7.05 (td, *J* = 8.3, 2.7 Hz, 1H), 6.80 - 6.71 (m, 1H), 4.10 - 4.00 (m, 1H), 3.94 (s, 1H), 3.52 (dt, *J* = 10.7, 3.1 Hz, 1H), 3.36 (dd, *J* = 10.9, 1.6 Hz, 1H), 2.68 - 2.60 (m, 1H), 2.27 - 2.15 (m, 1H), 1.49 (d, *J* = 10.1 Hz, 1H), 1.41 - 1.33 (m, 1H), 1.33 - 1.23 (m, 1H).

Example 229: (2-fluoro-6-(pyrimidin-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrimidin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

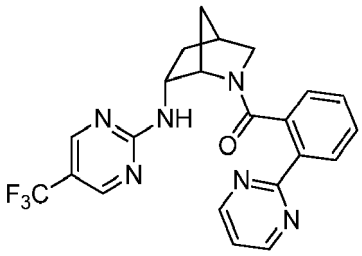
[0791]



[0792] Prepared analogous to Example 60 substituting intermediate A-1 with intermediate A-6. MS (ESI): mass calcd. for $C_{22}H_{18}F_4N_6O$, 458.1; m/z found, 459.9 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers , major rotamer reported) δ 8.87 (d, *J* = 4.9 Hz, 2H), 8.56 - 8.51 (m, 1H), 8.12 - 8.04 (m, 2H), 7.42 (t, *J* = 4.9 Hz, 1H), 7.36 - 7.30 (m, 1H), 6.73 - 6.67 (m, 1H), 4.03 - 3.97 (m, 1H), 3.97 - 3.90 (m, 1H), 3.56 (dt, *J* = 10.9, 3.2 Hz, 1H), 3.36 (dd, *J* = 10.9, 1.7 Hz, 1H), 2.65 - 2.60 (m, 1H), 2.25 - 2.14 (m, 1H), 1.49 - 1.39 (m, 2H), 1.20 - 1.14 (m, 1H).

Example 230: (2-(pyrimidin-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrimidin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

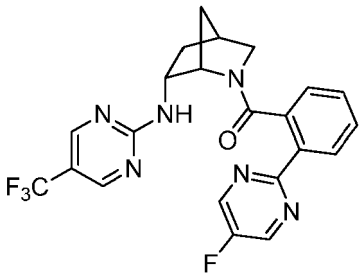
[0793]



[0794] Prepared analogous to Example 60 substituting intermediate A-1 with intermediate A-37. MS (ESI): mass calcd. for $C_{22}H_{19}F_3N_6O$, 440.2; m/z found, 441.9 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers (0.88:0.12), major rotamer reported) δ 8.86 (d, *J* = 4.9 Hz, 2H), 8.56 - 8.48 (m, 1H), 8.15 (d, *J* = 8.0 Hz, 1H), 8.10 (s, 1H), 7.39 (t, *J* = 4.9 Hz, 1H), 7.36 - 7.28 (m, 1H), 7.01 (s, 1H), 6.95 (s, 1H), 4.11 - 3.91 (m, 2H), 3.52 (dt, *J* = 11.0, 3.3 Hz, 1H), 3.35 (dd, *J* = 10.9, 1.6 Hz, 1H), 2.64 (s, 1H), 2.28 - 2.16 (m, 1H), 1.56 - 1.44 (m, 1H), 1.41 - 1.16 (m, 2H).

Example 231: (2-(5-fluoropyrimidin-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrimidin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

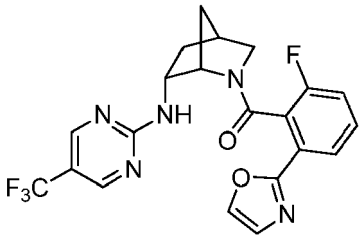
[0795]



[0796] Prepared analogous to Example 60 substituting intermediate A-1 with intermediate A-34. MS (ESI): mass calcd. for $C_{22}H_{18}F_4N_6O$, 458.1; m/z found, 459.9 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers (0.88:0.12), major rotamer reported) δ 8.82 (s, 2H), 8.58 - 8.47 (m, 1H), 8.15 (d, *J* = 7.8 Hz, 1H), 8.13 - 8.04 (m, 1H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.10 - 6.83 (m, 2H), 4.12 - 4.03 (m, 1H), 4.04 - 3.89 (m, 1H), 3.56 (dt, *J* = 10.9, 3.3 Hz, 1H), 3.36 (dd, *J* = 10.9, 1.6 Hz, 1H), 2.70 - 2.62 (m, 1H), 2.29 - 2.17 (m, 1H), 1.61 - 1.14 (m, 3H).

Example 232: (2-fluoro-6-(oxazol-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrimidin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

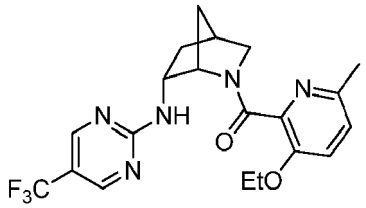
[0797]



[0798] Prepared analogous to Example 60 substituting intermediate A-1 with intermediate A-50. MS (ESI): mass calcd. for $C_{21}H_{17}F_4N_5O_2$, 447.1; m/z found, 447.9 $[M+H]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5μm, 100 $\times$ 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 30 °C). R_t = 6.15 min (major rotamer) at 254 nm.

Example 233: (3-ethoxy-6-methylpyridin-2-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrimidin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

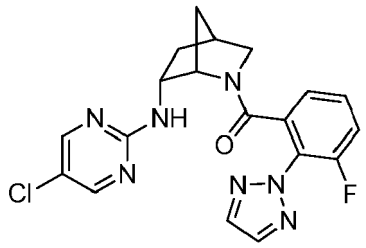
[0799]



[0800] Prepared analogous to Example 60 substituting intermediate A-1 with intermediate A-8. MS (ESI): mass calcd. for $C_{20}H_{22}F_3N_5O_2$, 421.2; m/z found, 422.0 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers (0.85:0.15), major rotamer reported) δ 8.47 (d, *J* = 3.2 Hz, 1H), 8.11 (d, *J* = 3.1 Hz, 1H), 7.23 (d, *J* = 8.6 Hz, 1H), 7.06 (d, *J* = 8.9 Hz, 1H), 4.47 - 4.42 (m, 1H), 4.08 - 3.95 (m, 3H), 3.60 (dt, *J* = 11.1, 3.2 Hz, 1H), 3.38 (dd, *J* = 11.1, 1.6 Hz, 1H), 2.77 - 2.69 (m, 1H), 2.36 - 2.28 (m, 1H), 2.26 (s, 3H), 1.92 - 1.87 (m, 1H), 1.83 - 1.78 (m, 1H), 1.42 - 1.35 (m, 4H).

Example 234: ((1S,4S,6R)-6-((5-chloropyrimidin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)(3-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone.

[0801]



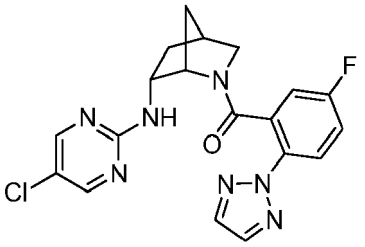
[0802] Step A: (1S,4S,6R)-tert-butyl 6-((5-chloropyrimidin-2-yl)amino)-2-azabicyclo[2.2.1]heptane-2-carboxylate. To a microwave vial containing intermediate B-10 (305 mg, 1.44 mmol) in DMF (6 mL) was added 2,5-dichloropyrimidine (257 mg, 1.72 mmol) and DIPEA (0.99 mL, 5.75 mmol), and the reaction mixture was sealed and heated to 80 °C bench top overnight. Upon completion of the reaction, the mixture was cooled to room temperature and diluted with H_2O. The reaction mixture was extracted with EtOAc (3X). The combined organics were washed with 5% aqueous LiCl, dried (Na_2SO_4), filtered, and concentrated. The concentrate was subjected directly to silica gel chromatography (10-90% EtOAc in hexanes) to give the title compound of step A (433 mg, 1.33 mmol, 93%). MS (ESI) mass calcd. for $C_{15}H_{21}ClN_4O_2$; 324.1, m/z found 269.1 $[M+2H-t\text{Bu}]^+$.

[0803] Step B: (1S,4R,6R)-N-(5-chloropyrimidin-2-yl)-2-azabicyclo[2.2.1]heptan-6-amine · xHCl. To the title compound of step A (433 mg, 1.33 mmol) in EtOAc (7 mL) was added 4M HCl in dioxane (2 mL), and the reaction mixture was stirred at room temperature overnight. The reaction was concentrated to give the title compound of step B (370 mg), which was used without further purification. MS (ESI) mass calcd. for $C_{10}H_{13}ClN_4$, 224.1; m/z found 225.1 $[M+H]^+$.

[0804] Step C: ((1S,4S,6R)-6-((5-chloropyrimidin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)(3-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone. To the title compound of step B (30 mg) and intermediate A-16 (25 mg, 0.12 mmol) in DMF (1 mL) was added DIPEA (0.10 mL, 0.61 mmol) and HATU (42 mg, 0.11 mmol), and the reaction mixture was stirred at room temperature for 1 h. The reaction was quenched by the addition of H_2O and the aqueous layer was extracted with EtOAc (2X). The combined organics were concentrated and the concentrate subjected directly to purification via Gilson Prep Method X to give the title compound (32 mg). MS (ESI): mass calcd. for $C_{19}H_{17}ClFN_7O$, 413.1; m/z found, 414.0 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers (0.89:0.11), major rotamer reported) δ 8.35 - 8.20 (m, 1H), 8.00 (s, 2H), 7.94 - 7.82 (m, 1H), 7.33 - 7.24 (m, 1H), 7.08 - 7.00 (m, 1H), 6.88 (d, J = 7.7 Hz, 1H), 4.01 (s, 1H), 3.98 - 3.92 (m, 1H), 3.27 (dd, J = 11.1, 1.6 Hz, 1H), 3.18 (dt, J = 10.8, 3.0 Hz, 1H), 2.55 - 2.48 (m, 1H), 2.22 - 2.12 (m, 1H), 1.52 (d, J = 10.3 Hz, 1H), 1.30 - 1.22 (m, 1H), 1.18 - 1.10 (m, 1H).

Example 235: ((1S,4S,6R)-6-((5-chloropyrimidin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)(5-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone.

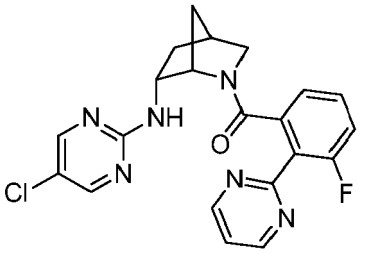
[0805]



[0806] Prepared analogous to Example 234 substituting intermediate A-16 with intermediate A-10. MS (ESI): mass calcd. for $C_{19}H_{17}ClFN_7O$, 413.1; m/z found, 414.0 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d4) δ 8.25 (s, 1H), 8.14 - 8.01 (m, 1H), 7.95 (s, 2H), 7.85 (dd, J = 9.0, 4.8 Hz, 1H), 7.17 (ddd, J = 9.0, 7.8, 2.9 Hz, 1H), 6.84 - 6.75 (m, 1H), 3.98 - 3.86 (m, 1H), 3.85 - 3.75 (m, 1H), 3.44 - 3.38 (m, 1H), 3.36 - 3.32 (m, 1H), 2.63 - 2.54 (m, 1H), 2.23 - 2.12 (m, 1H), 1.49 - 1.41 (m, 1H), 1.34 - 1.20 (m, 2H).

Example 236: ((1S,4S,6R)-6-((5-chloropyrimidin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)(3-fluoro-2-(pyrimidin-2-yl)phenyl)methanone.

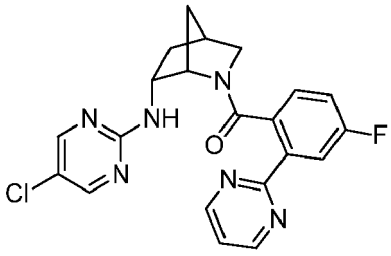
[0807]



[0808] Prepared analogous to Example 234 substituting intermediate A-16 with intermediate A-2. MS (ESI): mass calcd. for $C_{21}H_{18}ClFN_6O$, 424.1; m/z found, 425.1 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers (0.89:0.11), major rotamer reported) δ 8.91 (d, J = 5.0 Hz, 2H), 8.35 - 8.15 (m, 1H), 8.02 - 7.85 (m, 1H), 7.49 (t, J = 5.0 Hz, 1H), 7.20 - 7.12 (m, 1H), 7.10 - 7.01 (m, 1H), 6.88 (d, J = 7.9 Hz, 1H), 4.14 (s, 1H), 4.05 - 3.95 (m, 1H), 3.26 - 3.21 (m, 1H), 2.56 - 2.48 (m, 1H), 2.24 - 2.12 (m, 1H), 1.52 (d, J = 9.5 Hz, 1H), 1.31 - 1.18 (m, 1H), 1.03 (d, J = 10.1 Hz, 1H). 1H buried under solvent.

Example 237: ((1S,4S,6R)-6-((5-chloropyrimidin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)(4-fluoro-2-(pyrimidin-2-yl)phenyl)methanone.

[0809]

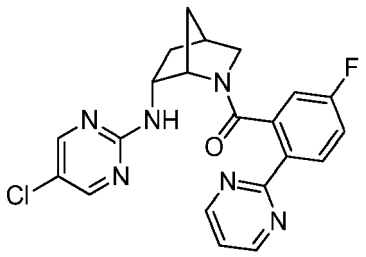


[0810] Prepared analogous to Example 234 substituting intermediate A-16 with intermediate A-23. MS (ESI): mass

calcd. for $C_{21}H_{18}ClFN_6O$, 424.1; m/z found, 425.1 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers, major rotamer reported) δ 8.87 (d, J = 4.9 Hz, 2H), 8.34 - 8.19 (m, 1H), 8.03 - 7.76 (m, 2H), 7.41 (t, J = 4.9 Hz, 1H), 7.10 - 6.98 (m, 1H), 6.80 - 6.67 (m, 1H), 4.01 - 3.85 (m, 2H), 3.51 (dt, J = 11.0, 3.2 Hz, 1H), 3.37 - 3.31 (m, 1H), 2.62 (s, 1H), 2.25 - 2.14 (m, 1H), 1.47 (d, J = 9.9 Hz, 1H), 1.37 - 1.20 (m, 2H).

Example 238: ((1S,4S,6R)-6-((5-chloropyrimidin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)(5-fluoro-2-(pyrimidin-2-yl)phenyl)methanone.

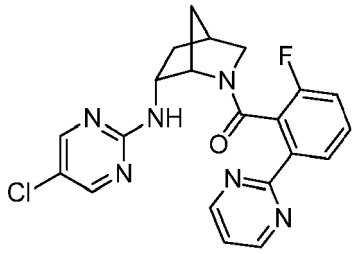
[0811]



[0812] Prepared analogous to Example 234 substituting intermediate A-16 with intermediate A-7. MS (ESI): mass calcd. for $C_{21}H_{18}ClFN_6O$, 424.1; m/z found, 425.1 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers (0.87:0.13), major rotamer reported) δ 8.84 (d, *J* = 4.8 Hz, 2H), 8.29-8.19 (m, 2H), 7.86 (br. s, 1H), 7.38 (t, *J* = 4.9 Hz, 1H), 7.11 (td, *J* = 8.5, 2.7 Hz, 1H), 6.79-6.70 (m, 1H), 3.98-3.88 (m, 2H), 3.50 (dt, *J* = 10.9, 3.2 Hz, 1H), 3.34 (dd, *J* = 11.0, 1.7 Hz, 1H), 2.64-2.59 (m, 1H), 2.24-2.15 (m, 1H), 1.47 (d, *J* = 10.0 Hz, 1H), 1.35 - 1.19 (m, 2H).

Example 239: ((1S,4S,6R)-6-((5-chloropyrimidin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)(2-fluoro-6-(pyrimidin-2-yl)phenyl)methanone.

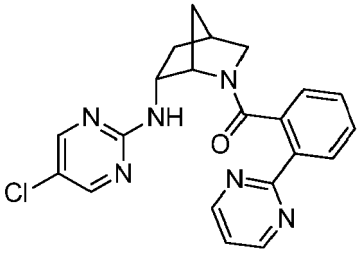
[0813]



[0814] Prepared analogous to Example 234 substituting intermediate A-16 with intermediate A-6. MS (ESI): mass calcd. for $C_{21}H_{18}ClFN_6O$, 424.1; m/z found, 425.1 $[M+H]^+$. Analytical HPLC using a XBridge C18 column (5μm, 100 $\times$ 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 2min and then hold at 100% ACN for 2 min, at a flow rate of 2.5 mL/min (Temperature = 45 °C). R_t = 1.85 and 2.12 min (major rotamers) at 254 nm.

Example 240: ((1S,4S,6R)-6-((5-chloropyrimidin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)(2-(pyrimidin-2-yl)phenyl)methanone.

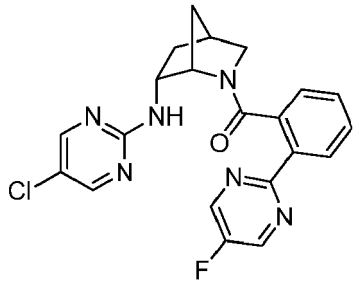
[0815]



[0816] Prepared analogous to Example 234 substituting intermediate A-16 with intermediate A-37. MS (ESI): mass calcd. for $C_{21}H_{19}ClN_6O$, 406.1; m/z found, 407.1 $[M+H]^+$. ^1H NMR (500 MHz, Methanol- d_4, Compound present as a mixture of rotamers (0.88:0.12), major rotamer reported) δ 8.85 (d, J = 4.9 Hz, 2H), 8.29 - 8.18 (m, 1H), 8.14 (dt, J = 8.0, 0.9 Hz, 1H), 7.92 - 7.70 (m, 1H), 7.42 - 7.35 (m, 2H), 7.07 - 6.92 (m, 2H), 4.10 - 3.86 (m, 2H), 3.50 (dt, J = 10.8, 3.3 Hz, 1H), 3.35 - 3.32 (m, 1H), 2.65 - 2.59 (m, 1H), 2.27 - 2.13 (m, 1H), 1.54 - 1.43 (m, 1H), 1.36 - 1.19 (m, 2H).

Example 241: ((1S,4S,6R)-6-((5-chloropyrimidin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)(2-(5-fluoropyrimidin-2-yl)phenyl)methanone.

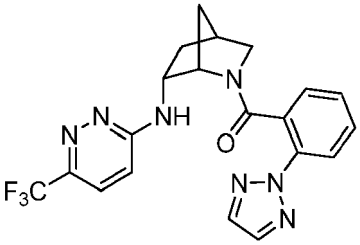
[0817]



[0818] Prepared analogous to Example 234 substituting intermediate A-16 with intermediate A-34. MS (ESI): mass calcd. for $C_{21}H_{18}ClFN_6O$, 424.1; m/z found, 425.1 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers (0.87:0.13), major rotamer reported) δ 8.81 (s, 2H), 8.38 - 8.17 (m, 1H), 8.17 - 8.13 (m, 1H), 7.93 - 7.75 (m, 1H), 7.44 - 7.32 (m, 1H), 7.11 - 6.91 (m, 2H), 4.06 - 3.86 (m, 2H), 3.54 (dt, *J* = 10.8, 3.3 Hz, 1H), 3.34 (dd, *J* = 11.0, 1.7 Hz, 1H), 2.71 - 2.61 (m, 1H), 2.29 - 2.15 (m, 1H), 1.59 - 1.46 (m, 1H), 1.45 - 1.27 (m, 2H).

Example 242: (2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((6-(trifluoromethyl)pyridazin-3-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[0819]



[0820] Step A: (1S,4S,6R)-tert-butyl 6-((6-(trifluoromethyl)pyridazin-3-yl)amino)-2-azabicyclo[2.2.1]heptane-2-carboxylate. To a vial containing intermediate B-10 (100 mg, 0.471 mmol) in MeCN (2 mL) was added 3-chloro-6-(trifluoromethyl)pyridazine (103 mg, 0.565 mmol) and Et_3N (0.15 mL, 1.1 mmol), and the reaction mixture was sealed and heated to 90 °C bench top overnight. Upon completion of the reaction, the mixture was cooled to room temperature and subjected directly to silica gel chromatography (0-50% EtOAc in hexanes) to give the title compound of step A (143 mg), which contained a small amount of impurity. The title compound was carried forward as is to the next step. MS (ESI)

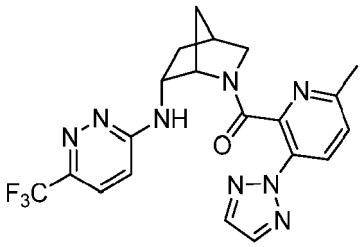
mass calcd. for $C_{16}H_{21}F_3N_4O_2$; 358.2, m/z found 359.2 $[M+H]^+$. ^1H NMR (500 MHz, Chloroform-d, Compound present as a mixture of rotamers) δ 7.45 - 7.33 (m, 1H), 6.71-6.56 (m, 1H), 6.12 and 5.60 (2 br. s, 1H), 4.53 - 4.21 (m, 2H), 3.44 - 3.29 (m, 1H), 3.13-3.01 (m, 1H), 2.63-2.56 (m, 1H), 2.50-2.28 (m, 1H), 1.77 - 1.06 (m, 12H).

[0821] Step B: (1S,4R,6R)-N-(6-(trifluoromethyl)pyridazin-3-yl)-2-azabicyclo[2.2.1]heptan-6-amine · xHCl. To the title compound of step A (143 mg, 0.399 mmol) in EtOAc (1 mL) was added 4M HCl in dioxane (4 mL), and the reaction mixture was stirred at room temperature for 1.5 h. The reaction was concentrated to give the title compound of step B (130 mg), which was used without further purification. MS (ESI) mass calcd. for $C_{11}H_{13}F_3N_4$, 258.1; m/z found 259.2 $[M+H]^+$.

[0822] Step C: (2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((6-(trifluoromethyl)pyridazin-3-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone. To the title compound of step B (33 mg) and intermediate A-1 (21 mg, 0.11 mmol) in DMF (0.5 mL) was added DIPEA (0.1 mL, 0.58 mmol) and HATU (42 mg, 0.11 mmol), and the reaction mixture was stirred at room temperature for 1 h. The reaction was quenched by the addition of H_2O and the aqueous layer was extracted with EtOAc (2X). The combined organics were concentrated and the concentrate subjected directly to purification via Agilent Prep Method X to give the title compound (26 mg). MS (ESI): mass calcd. for $C_{20}H_{18}F_3N_7O$, 429.2; m/z found, 430.2 $[M+H]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5μm, 100 $\times$ 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 30 °C). R_t = 5.48 min (major rotamer) at 254 nm.

Example 243: (6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)((1S,4S,6R)-6-((6-(trifluoromethyl)pyridazin-3-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

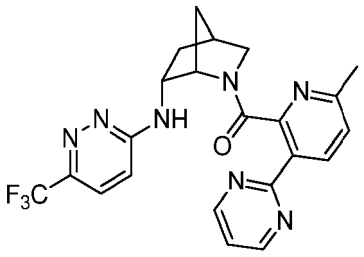
[0823]



[0824] Prepared analogous to Example 242 substituting intermediate A-1 with intermediate A-40. MS (ESI): mass calcd. for $C_{20}H_{19}F_3N_8O$, 444.2; m/z found, 445.2 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.86:0.14), major rotamer reported) δ 8.18 (d, *J* = 8.4 Hz, 1H), 7.86 (s, 2H), 7.36 (d, *J* = 9.3 Hz, 1H), 7.33 (d, *J* = 8.3 Hz, 1H), 6.73 (d, *J* = 9.3 Hz, 1H), 4.34 - 4.29 (m, 1H), 3.72 (dt, *J* = 11.0, 3.2 Hz, 1H), 3.32 (dd, *J* = 11.0, 1.6 Hz, 1H), 2.84 - 2.76 (m, 1H), 2.62 - 2.44 (m, 5H), 2.01 - 1.92 (m, 1H), 1.78 - 1.69 (m, 1H), 1.26 (dt, *J* = 13.4, 3.4 Hz, 1H).

Example 244: (6-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)((1S,4S,6R)-6-((6-(trifluoromethyl)pyridazin-3-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[0825]

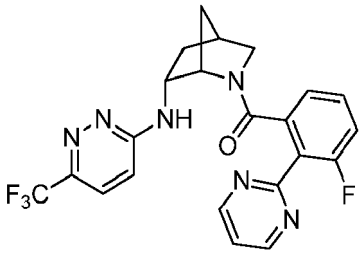


[0826] Prepared analogous to Example 242 substituting intermediate A-1 with intermediate A-41. MS (ESI): mass calcd. for $C_{22}H_{20}F_3N_7O$, 455.2; m/z found, 456.2 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.93:0.07), major rotamer reported) δ 8.79 (d, *J* = 4.8 Hz, 2H), 8.48 (d, *J* = 8.1 Hz, 1H), 8.16 - 7.96 (m, 1H), 7.37 (d, *J* = 9.3 Hz, 1H), 7.32 (d, *J* = 8.1 Hz, 1H), 7.26 - 7.23 (m, 1H), 6.77 (d, *J* = 9.2 Hz, 1H), 4.27 (s, 1H),

3.74 (dt, *J* = 10.9, 3.2 Hz, 1H), 3.33 (dd, *J* = 10.8, 1.6 Hz, 1H), 2.86 - 2.77 (m, 1H), 2.64 - 2.49 (m, 5H), 2.03 - 1.90 (m, 1H), 1.73 (d, *J* = 10.1 Hz, 1H), 1.27 (dt, *J* = 13.2, 3.5 Hz, 1H).

Example 245: (3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4S,6R)-6-((6-(trifluoromethyl)pyridazin-3-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

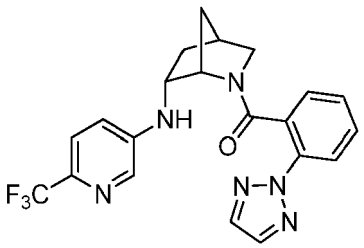
[0827]



[0828] Prepared analogous to Example 242 substituting intermediate A-1 with intermediate A-2. MS (ESI): mass calcd. for $C_{22}H_{18}F_4N_6O$, 458.1; m/z found, 459.2 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.85:0.15), major rotamer reported) δ 8.90 (d, *J* = 4.9 Hz, 2H), 7.39 (t, *J* = 5.0 Hz, 1H), 7.32 - 7.22 (m, 2H), 7.22 - 7.16 (m, 1H), 7.11 - 7.06 (m, 1H), 6.47 (d, *J* = 9.3 Hz, 1H), 4.67 (s, 1H), 3.55 (dt, *J* = 11.1, 3.2 Hz, 1H), 3.26 (dd, *J* = 11.0, 1.5 Hz, 1H), 2.79 - 2.69 (m, 1H), 2.54 - 2.42 (m, 1H), 1.95 - 1.72 (m, 2H), 1.69 - 1.61 (m, 1H), 1.20 - 1.07 (m, 1H).

Example 246: (2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((6-(trifluoromethyl)pyridin-3-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

[0829]



[0830] Step A: (1S,4S,6R)-tert-butyl 6-((6-(trifluoromethyl)pyridin-3-yl)amino)-2-azabicyclo[2.2.1]heptane-2-carboxylate. To a microwave vial containing degassed toluene (2 mL) was added 5-bromo-2-(trifluoromethyl)pyridine (116 mg, 0.514 mmol), intermediate B-10 (120 mg) and racemic BINAP (13 mg, 0.021 mmol) at room temperature and the reaction mixture was purged with N_2 for 5 min. Then, $Pd(OAc)_2$ (14 mg, 0.021 mmol) and sodium tert-butoxide (71 mg, 0.72 mmol) were added and the reaction mixture heated to 70 °C overnight. Upon completion of the reaction, the mixture was cooled to room temperature and the crude material subjected directly to silica gel chromatography (0-50% EtOAc in hexanes) to give the title compound of step A (184 mg). MS (ESI) mass calcd. for $C_{17}H_{22}F_3N_3O_2$, 357.2; m/z found 358.2 $[M+H]^+$. ^1H NMR (500 MHz, Chloroform-d, Compound present as a mixture of rotamers) δ 8.02 and 7.90 (two s, 1H), 7.46-7.35 (m, 1H), 6.88-6.81 and 6.77 - 6.68 (two m, 1H), 5.39-5.29 and 4.72-4.62 (two m, 1H), 4.47-4.33 (m, 1H), 3.87 - 3.72 (m, 1H), 3.41-3.31 (m, 1H), 3.11-2.99 (m, 1H), 2.64 - 2.56 (m, 1H), 2.37 - 2.17 (m, 1H), 1.81-1.67 (m, 1H), 1.66-1.60 (m, 1H), 1.53 - 1.01 (m, 11H).

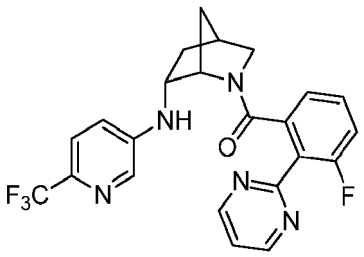
[0831] Step B: (1S,4R,6R)-N-(6-(trifluoromethyl)pyridin-3-yl)-2-azabicyclo[2.2.1]heptan-6-amine · xHCl. To the title compound of step A (77 mg, 0.22 mmol) in EtOAc (0.6 mL) was added 4M HCl in dioxane (3 mL), and the reaction mixture was stirred at room temperature for 2.5 h. The reaction was concentrated to give the title compound of step B (72 mg), which was used without further purification. MS (ESI) mass calcd. for $C_{12}H_{14}F_3N_3$, 257.1; m/z found 258.1 $[M+H]^+$.

[0832] Step C: (2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((6-(trifluoromethyl)pyridin-3-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone. To the title compound of step B (36 mg) and intermediate A-1 (25 mg, 0.13 mmol) in DMF (1 mL) was added DIPEA (0.2 mL, 1.2 mmol) and HATU (46 mg, 0.12 mmol), and the reaction mixture was stirred at room temperature for 1.5 h. The reaction was quenched by the addition of H_2O and the aqueous layer was extracted with EtOAc (2X). The combined organics were concentrated and the concentrate subjected directly to purification via

Gilson Prep Method X to give the title compound (29 mg). MS (ESI): mass calcd. for $C_{21}H_{19}F_3N_6O$, 428.2; m/z found, 429.2 $[M+H]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5μm, 100 × 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 30 °C). R_t = 6.07 min (major rotamer) at 254 nm.

Example 247: (3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4S,6R)-6-((6-(trifluoromethyl)pyridin-3-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

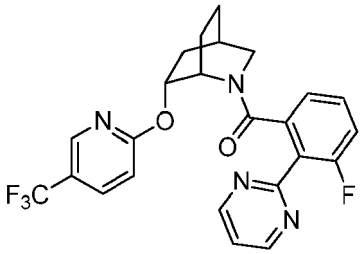
[0833]



[0834] Prepared analogous to Example 246 substituting intermediate A-1 with intermediate A-2. MS (ESI): mass calcd. for $C_{23}H_{19}F_4N_5O$, 457.2; m/z found, 458.1 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers (0.89:0.11), major rotamer reported) δ 8.91 (d, *J* = 5.0 Hz, 2H), 7.87 (d, *J* = 2.7 Hz, 1H), 7.50 (t, *J* = 5.0 Hz, 1H), 7.31 (d, *J* = 8.7 Hz, 1H), 7.06 - 6.99 (m, 1H), 6.87 - 6.80 (m, 2H), 6.73 (dd, *J* = 8.7, 2.8 Hz, 1H), 4.11 (s, 1H), 3.80 - 3.71 (m, 1H), 3.28 - 3.22 (m, 2H), 2.60 - 2.52 (m, 1H), 2.34 - 2.25 (m, 1H), 1.59 (d, *J* = 10.8 Hz, 1H), 1.24 - 1.18 (m, 1H), 1.11 (d, *J* = 10.3 Hz, 1H).

Example 248: (R/S)-(3-fluoro-2-(pyrimidin-2-yl)phenyl)(6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[0835]



[0836] Step A: (R/S)-tert-butyl 6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octane-2-carboxylate. To intermediate C-5A (50 mg, 0.22 mmol) dissolved in DMF (2 mL) was added NaH (18 mg, 0.44 mmol, 60% dispersion in mineral oil). After 5 minutes 2-chloro-5-(trifluoromethyl)pyridine (64 mg, 0.35 mmol) was then added and the mixture stirred at room temperature for 3 h. The reaction mixture was quenched with saturated NH_4Cl solution, and diluted with EtOAc and H_2O. The aqueous layer was extracted with EtOAc (3X). The combined organics were washed with H_2O, brine, dried with $MgSO_4$, filtered and concentrated. Purification via silica gel chromatography (0-40% EtOAc in hexanes) gave the title compound (67 mg, 0.18 mmol, 82%). MS (ESI) mass calcd. for $C_{18}H_{23}F_3N_2O_3$, 372.2; m/z found 373.2 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound present as a mixture of rotamers, (0.68:0.32), major rotamer reported) δ 8.49 - 8.45 (m, 1H), 7.94 (dd, J = 8.8, 2.6 Hz, 1H), 6.90 (d, J = 8.7, 0.8 Hz, 1H), 5.22 (dt, J = 9.7, 2.9 Hz, 1H), 4.48 - 4.41 (m, 1H), 3.42 (dt, J = 10.9, 2.5 Hz, 1H), 3.25 (dt, J = 11.0, 2.6 Hz, 1H), 2.27 - 2.18 (m, 1H), 2.09 - 2.04 (m, 1H), 1.97 - 1.87 (m, 1H), 1.77 - 1.71 (m, 1H), 1.68 - 1.59 (m, 3H), 1.13 (s, 9H).

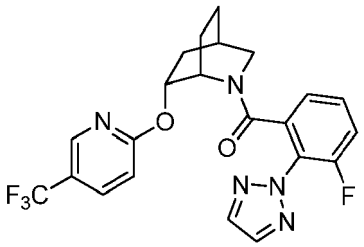
[0837] Step B: (R/S)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octane · xHCl. To the title compound of step A (67 mg, 0.18 mmol) in EtOAc (2 mL) was added 4 M HCl in dioxane (0.23 mL). After 3 h, the reaction was concentrated to give the title compound of step B which was used without further purification. MS (ESI) mass calcd. for $C_{13}H_{15}F_3N_2O$, 272.1; m/z found 273.1 $[M+H]^+$.

[0838] Step C: (R/S)-(3-fluoro-2-(pyrimidin-2-yl)phenyl)(6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]oc-

tan-2-yl)methanone. To the title compound of step B (46 mg) and intermediate A-2 (54 mg, 0.20 mmol, 82% purity) in DMF (1.7 mL) was added DIPEA (0.18 mL, 1.01 mmol) and HATU (71 mg, 0.19 mmol), and the reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with H_2O and EtOAc. The aqueous layer was extracted with EtOAc (3X) and the combined organics were concentrated and subjected directly to purification using Gilson Prep Method X to give the title compound (20 mg). MS (ESI): mass calcd. for $C_{24}H_{20}F_4N_4O_2$, 472.2; m/z found, 473.1 $[M+H]^+$. Analytical HPLC using a XBridge C18 column (5um, 100 × 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 2 min and then hold at 100% ACN for 2 min, at a flow rate of 2.5 mL/min (Temperature = 45 °C). R_t = 2.18 and 2.29 min (major rotamers) at 254 nm. Enantiomers of Example 248 can be separated by Chiral SFC purification using a Chiralpak AZ-H column (5μm 250 × 21 mm), mobile phase of 35% EtOH+(0.2%TEA): 65% CO_2, and a flow rate of 40 mL/min (Temperature = 40 °C).

Example 249: (R/S)- (3-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)(6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

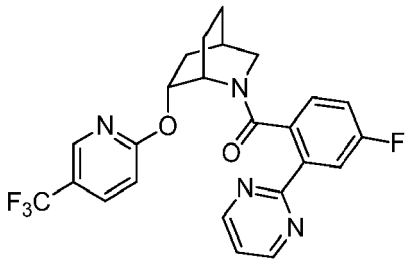
[0839]



[0840] Prepared analogous to Example 248 substituting intermediate A-2 with intermediate A-16. MS (ESI): mass calcd. for $C_{22}H_{19}F_4N_5O_2$, 461.2; m/z found, 461.9 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d4, Compound present as a mixture of rotamers, major rotamer reported) δ 8.25 (s, 1H), 8.11 - 7.95 (m, 3H), 7.27 (t, *J* = 9.3 Hz, 1H), 7.14 -7.00 (m, 2H), 6.91 (d, *J* = 7.8 Hz, 1H), 5.14 - 5.06 (m, 1H), 3.82 (s, 1H), 3.60 (d, *J* = 12.8 Hz, 1H), 3.24 (d, *J* = 12.7 Hz, 1H), 2.34 - 2.24 (m, 1H), 2.11 (s, 1H), 1.81 - 1.41 (series of m, 5H).

Example 250: (R/S)- (4-fluoro-2-(pyrimidin-2-yl)phenyl)(6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone

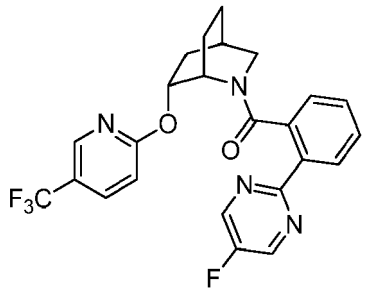
[0841]



[0842] Prepared analogous to Example 248 substituting intermediate A-2 with intermediate A-23. MS (ESI): mass calcd. for $C_{24}H_{20}F_4N_4O_2$, 472.2; m/z found, 472.9 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound is present as a mixture of rotamers) δ 8.96 - 8.78 (m, 2H), 8.22 - 8.14 (m, 1H), 8.04 - 7.97 (m, 1H), 7.92 (dd, *J* = 10.1, 2.6 Hz, 1H), 7.49 - 7.42 (m, 1H), 7.10 - 6.88 (m, 2H), 6.76 - 6.58 (m, 1H), 5.05 - 4.98 (m, 1H), 3.85 - 3.73 (m, 1H), 3.69 (d, *J* = 12.3 Hz, 1H), 3.55 - 3.48 (m, 1H), 2.33 - 2.24 (m, 1H), 2.21 - 2.07 (m, 1H), 1.86 - 1.77 (m, 1H), 1.74 - 1.37 (m, 3H), 1.27 - 1.14 (m, 1H).

Example 251: (R/S)- (2-(5-fluoropyrimidin-2-yl)phenyl)(6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

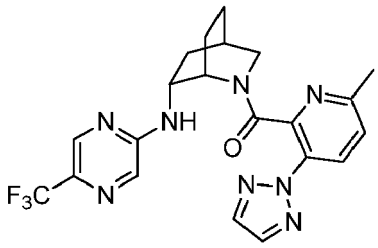
[0843]



[0844] Prepared analogous to Example 248 substituting intermediate A-2 with intermediate A-34. MS (ESI): mass calcd. for $C_{24}H_{20}F_4N_4O_2$, 472.2; m/z found, 472.9 $[M+H]^+$. ^1H NMR (500 MHz, Methanol-d_4, Compound is present as a mixture of rotamers) δ 8.87 - 8.74 (m, 2H), 8.20 - 8.12 (m, 2H), 8.05 - 7.93 (m, 1H), 7.65 - 7.55 (m, 1H), 7.38 - 7.30 (m, 1H), 7.09 - 6.86 (m, 2H), 5.13 - 5.02 (m, 1H), 3.84 - 3.76 (m, 1H), 3.71 - 3.64 (m, 1H), 3.60 - 3.51 (m, 1H), 2.35 - 2.26 (m, 1H), 2.22 - 2.13 (m, 1H), 1.87 - 1.76 (m, 1H), 1.73 - 1.29 (m, 4H).

Example 252: (R/S)-(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)(6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone

[0845]



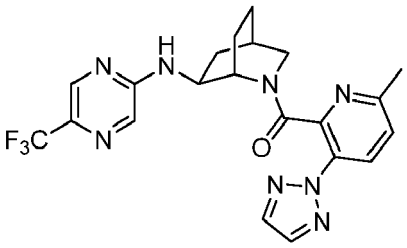
[0846] Step A: (R/S)-tert-butyl 6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.2]octane-2-carboxylate. To a microwave vial containing C-7A (308 mg, 1.36 mmol) in MeCN (5 mL) was added 2-chloro-5-(trifluoromethyl)pyrazine (0.20 mL, 1.63 mmol) and Et_3N (0.28 mL, 2.04 mmol), and the reaction mixture was sealed and heated to 70 °C bench top overnight. Analysis of the reaction mixture still showed unreacted starting material. Additional equivalents of 2-chloro-5-(trifluoromethyl)pyrazine (0.20 mL, 1.63 mmol) and Et_3N (0.28 mL, 2.04 mmol) were added, and the reaction mixture was heated again to 70 °C bench top overnight. Upon completion of the reaction, the mixture was cooled to room temperature and diluted with H_2O. The reaction mixture was extracted with EtOAc (3X). The combined organics were concentrated and the concentrate subjected directly to silica gel chromatography (0-30% EtOAc in hexanes) to give the title compound of step A (245 mg, 0.658 mmol, 48%) MS (ESI) mass calcd. for $C_{17}H_{23}F_3N_4O_2$; 372.2, m/z found 371.1 $[M+2H-t\text{Bu}]^+$.

[0847] Step B: (R/S)-N-(5-(trifluoromethyl)pyrazin-2-yl)-2-azabicyclo[2.2.2]octan-6-amine · xHCl. To the title compound of step A (245 mg, 0.658 mmol) in EtOAc (1 mL) was added 4M HCl in dioxane (4 mL), and the reaction mixture was stirred at room temperature for 3 h. The reaction was concentrated to give the title compound of step B (249 mg), which was used without further purification. MS (ESI) mass calcd. for $C_{12}H_{15}F_3N_4$, 272.1; m/z found 273.0 $[M+H]^+$.

[0848] Step C: (R/S)-(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)(6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone. To the title compound of step B (50 mg) and intermediate A-40 (36 mg, 0.18 mmol) in DMF (0.5 mL) was added DIPEA (0.15 mL, 0.87 mmol) and HATU (68 mg, 0.18 mmol), and the reaction mixture was stirred at room temperature for 3 h. The reaction was diluted with MeOH and the crude reaction mixture subjected directly to purification via Agilent Prep Method X to give the title compound (25 mg). MS (ESI): mass calcd. for $C_{21}H_{21}F_3N_8O$, 458.2; m/z found, 458.9 $[M+H]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5μm, 100 $\times$ 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 30 °C). R_t = 6.45 min (major rotamer) at 254 nm.

Example 253: (R/S)-(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)(6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

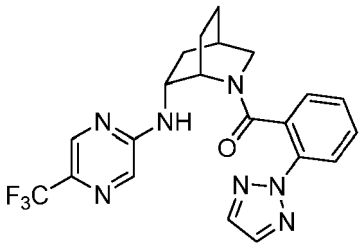
[0849]



[0850] Prepared analogous to Example 252, isolated from Step C during HPLC purification. MS (ESI): mass calcd. for $C_{21}H_{21}F_3N_8O$, 458.2; m/z found, 459.2 $[M+H]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5μm, 100 × 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 30 °C). R_t = 6.26 min (major rotamer) at 254 nm.

Example 254: (R/S)-(2-(2H-1,2,3-triazol-2-yl)phenyl)(6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

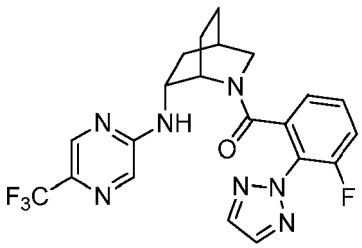
[0851]



[0852] Prepared analogous to Example 252 substituting intermediate A-40 with intermediate A-1. MS (ESI): mass calcd. for $C_{21}H_{20}F_3N_7O$, 443.2; m/z found, 443.9 $[M+H]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5μm, 100 × 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 30 °C). R_t = 6.65 min (major rotamer) at 254 nm.

Example 255: (R/S)- (3-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)(6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo [2.2.2] octan-2-yl)methanone.

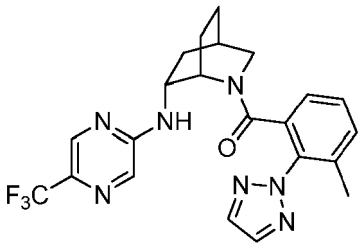
[0853]



[0854] Prepared analogous to Example 252 substituting intermediate A-40 with intermediate A-16. MS (ESI): mass calcd. for $C_{21}H_{19}F_4N_7O$, 461.2; m/z found, 461.9 $[M+H]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5μm, 100 × 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 30 °C). R_t = 6.65 min (major rotamer) at 254 nm.

Example 256: (R/S)- (3-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)(6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo [2.2.2] octan-2-yl)methanone.

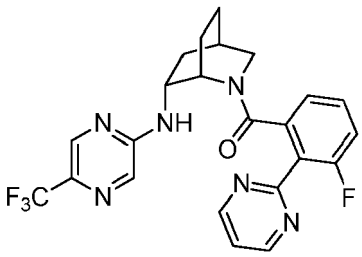
[0855]



[0856] Prepared analogous to Example 252 substituting intermediate A-40 with intermediate A-22. MS (ESI): mass calcd. for $C_{22}H_{22}F_3N_7O$, 457.2; m/z found, 458.0 $[M+H]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5μm, 100 × 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 30 °C). R_t = 6.96 min (major rotamer) at 254 nm.

Example 257: (R/S)- (3-fluoro-2-(pyrimidin-2-yl)phenyl)(6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

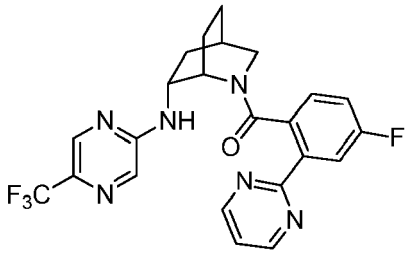
[0857]



[0858] Prepared analogous to Example 252 substituting intermediate A-40 with intermediate A-2. MS (ESI): mass calcd. for $C_{23}H_{20}F_4N_6O$, 472.2; m/z found, 472.9 $[M+H]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5μm, 100 × 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 30 °C). R_t = 6.49 min (major rotamer) at 254 nm.

Example 258: (R/S)- (4-fluoro-2-(pyrimidin-2-yl)phenyl)(6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

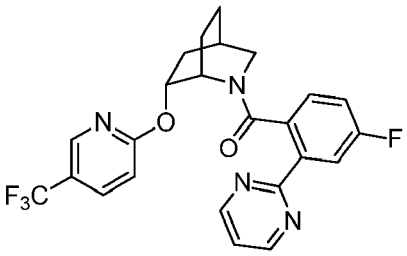
[0859]



[0860] Prepared analogous to Example 252 substituting intermediate A-40 with intermediate A-23. MS (ESI): mass calcd. for $C_{23}H_{20}F_4N_6O$, 472.2; m/z found, 472.9 $[M+H]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5μm, 100 × 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 30 °C). R_t = 6.57 min (major rotamer) at 254 nm.

Example 259: (4-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

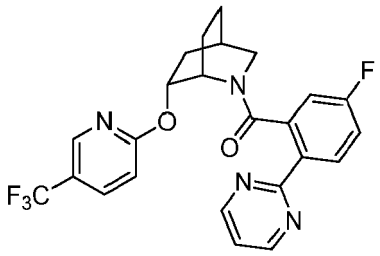
[0861]



[0862] Prepared analogous to Example 76 substituting intermediate A-40 with intermediate A-23. MS (ESI): mass calcd. for $C_{24}H_{20}F_4N_4O_2$, 472.2; m/z found, 473.2 $[M+H]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5μm, 100 × 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 30 °C). R_t = 7.28 min (major rotamer) at 254 nm.

Example 260: (5-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

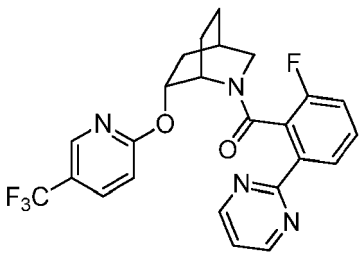
[0863]



[0864] Prepared analogous to Example 76 substituting intermediate A-40 with intermediate A-7. MS (ESI): mass calcd. for $C_{24}H_{20}F_4N_4O_2$, 472.2; m/z found, 473.2 $[M+H]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5μm, 100 × 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 30 °C). R_t = 7.59 min (major rotamer) at 254 nm.

Example 261: (2-fluoro-6-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone

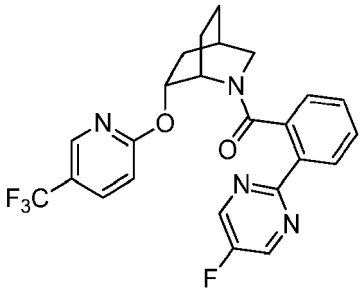
[0865]



[0866] Prepared analogous to Example 76 substituting intermediate A-40 with intermediate A-6. MS (ESI): mass calcd. for $C_{24}H_{20}F_4N_4O_2$, 472.2; m/z found, 473.2 $[M+H]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5μm, 100 × 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 30 °C). R_t = 7.41 min (major rotamer) at 254 nm.

Example 262: (2-(5-fluoropyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

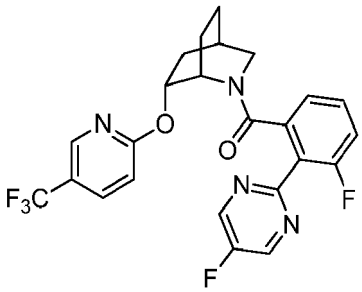
[0867]



[0868] Prepared analogous to Example 76 substituting intermediate A-40 with intermediate A-34. MS (ESI): mass calcd. for $C_{24}H_{20}F_4N_4O_2$, 472.2; m/z found, 473.2 $[M+H]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5μm, 100 × 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 30 °C). R_t = 7.83 min (major rotamer) at 254 nm.

Example 263: (3-fluoro-2-(5-fluoropyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

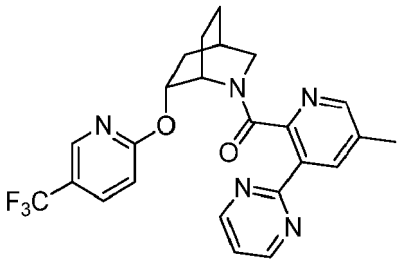
[0869]



[0870] Prepared analogous to Example 76 substituting intermediate A-40 with intermediate A-35. MS (ESI): mass calcd. for $C_{24}H_{19}F_5N_4O_2$, 490.1; m/z found, 491.2 $[M+H]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5μm, 100 × 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 30 °C). R_t = 7.78 min (major rotamer) at 254 nm.

Example 264: (5-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[0871]

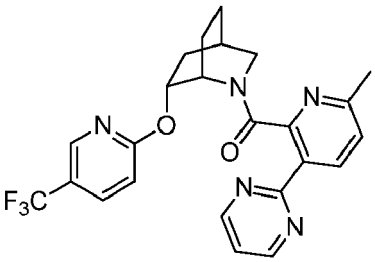


[0872] Prepared analogous to Example 76 substituting intermediate A-40 with intermediate A-47. MS (ESI): mass

calcd. for $C_{24}H_{22}F_3N_5O_2$, 469.2; m/z found, 470.2 $[M+H]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5μm, 100 × 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 30 °C). R_t = 6.999 min (major rotamer) at 254 nm.

Example 265: (6-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

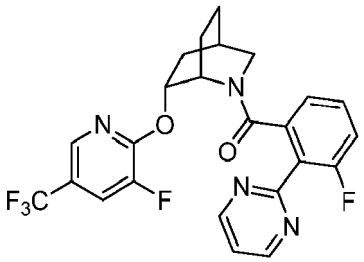
[0873]



[0874] Prepared analogous to Example 76 substituting intermediate A-40 with intermediate A-41. MS (ESI): mass calcd. for $C_{24}H_{22}F_3N_5O_2$, 469.2; m/z found, 470.2 $[M+H]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5μm, 100 × 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 30 °C). R_t = 6.73 min (major rotamer) at 254 nm.

Example 266: (3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((3-fluoro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[0875]



[0876] Step A: (1S,4R,6R)-tert-butyl 6-((3-fluoro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octane-2-carboxylate. To intermediate C-5B (52 mg, 0.23 mmol) dissolved in DMF (2 mL) was added NaH (18 mg, 0.46 mmol, 60% dispersion in mineral oil). After 5 minutes 2,3-difluoro-5-(trifluoromethyl)pyridine (63 mg, 0.34 mmol) was then added and the mixture stirred at room temperature for 1 h. The reaction mixture was quenched with saturated NH_4Cl solution, and diluted with EtOAc and H_2O. The aqueous layer was extracted with EtOAc (3X). The combined organics were washed with H_2O, brine, dried with $MgSO_4$, filtered, and concentrated. Purification via silica gel chromatography (0-100% EtOAc in hexanes) gave the title compound (67 mg, 0.17 mmol, 75%). MS (ESI) mass calcd. for $C_{18}H_{22}F_4N_2O_3$, 390.2; m/z found 336.1 $[M+2H-tBu]^+$.

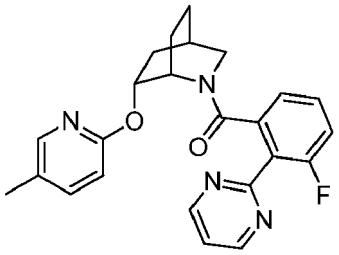
[0877] Step B: (1S,4R,6R)-6-((3-fluoro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octane · xHCl. To the title compound of step A (67 mg, 0.17 mmol) in EtOAc (2 mL) was added 4 M HCl in dioxane (0.22 mL), and the reaction mixture was stirred at room temperature overnight. Analysis of the reaction mixture showed mostly starting material. Additional 4 M HCl in dioxane (0.5 mL) was added and the reaction mixture stirred at room temperature for 5 h. The reaction mixture was then concentrated to give the title compound of step B (30 mg) which was used without further purification. MS (ESI) mass calcd. for $C_{13}H_{14}F_4N_2O$, 290.1; m/z found 291.1 $[M+H]^+$.

[0878] Step C: (3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((3-fluoro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone. To the title compound of step B (30 mg) and intermediate A-2 (27 mg, 0.12 mmol) in DMF (1 mL) was added DIPEA (0.11 mL, 0.62 mmol) and HATU (43 mg, 0.11 mmol). Upon completion of the reaction, purification was performed using Agilent Prep Method X to give the title compound (11 mg). MS (ESI): mass calcd. for $C_{24}H_{19}F_5N_4O_2$, 490.2; m/z found, 491.1 $[M+H]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge

C18 column (5μm, 100 × 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 30 °C). R_t = 7.35 min (major rotamer) at 254 nm.

Example 267: (3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-methylpyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone

[0879]



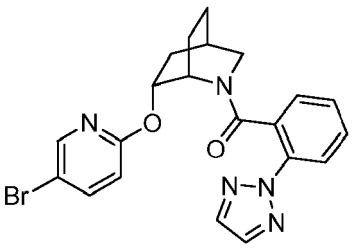
[0880] Step A: (1S,4R,6R)-tert-butyl 6-((5-methylpyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octane-2-carboxylate. To intermediate C-5B (37 mg, 0.16 mmol) dissolved in DMF (1.4 mL) was added NaH (13 mg, 0.33 mmol, 60% dispersion in mineral oil). After 5 minutes 2-chloro-5-methylpyridine (0.03 mL, 0.26 mmol) was then added and the mixture stirred at room temperature for 2 h. Analysis of the reaction mixture showed only starting material was present. The reaction mixture was heated to 70 °C overnight. Analysis of the reaction mixture showed small amount of product formation. Additional NaH was added and the reaction mixture heated to 70 °C over the weekend. The reaction mixture was quenched with saturated NH_4Cl solution, and diluted with EtOAc and H_2O. The aqueous layer was extracted with EtOAc (3X). The combined organics were washed with H_2O, brine, dried with $MgSO_4$, filtered and concentrated. Purification via silica gel chromatography (0-50% EtOAc in hexanes) gave the title compound (8 mg, 0.03 mmol, 15%). MS (ESI) mass calcd. for $C_{18}H_{26}N_2O_3$, 318.2; m/z found 319.2 $[M+H]^+$.

[0881] Step B: (1S,4R,6R)-6-((5-methylpyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octane · xHCl. To the title compound of step A (8 mg, 0.03 mmol) in EtOAc (0.3 mL) was added 4 M HCl in dioxane (0.03 mL) and the reaction mixture was stirred at room temperature overnight. Analysis of the reaction mixture showed that starting material still remained. Additional 4 M HCl in dioxane (0.25 mL) was added and the reaction mixture stirred at room temperature for 5 h. The reaction was concentrated to give the title compound of step B which was used without further purification. MS (ESI) mass calcd. for $C_{13}H_{18}N_2O$, 218.1; m/z found 219.2 $[M+H]^+$.

[0882] Step C: (3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-methylpyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone. To the title compound of step B (5 mg) and intermediate A-2 (6 mg, 0.03 mmol) in DMF (0.3 mL) was added DIPEA (0.02 mL, 0.14 mmol) and HATU (10 mg, 0.03 mmol), and the reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with MeOH and the crude reaction mixture directly subjected to purification using Agilent Prep Method X to give the title compound (1 mg). MS (ESI): mass calcd. for $C_{24}H_{23}FN_4O_2$, 418.2; m/z found, 419.2 $[M+H]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5μm, 100 × 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 30 °C). R_t = 6.35 min (major rotamer) at 254 nm.

Example 268: (2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((5-bromopyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[0883]



[0884] Step A: (1S,4R,6R)-tert-butyl 6-((5-bromopyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octane-2-carboxylate. To inter-

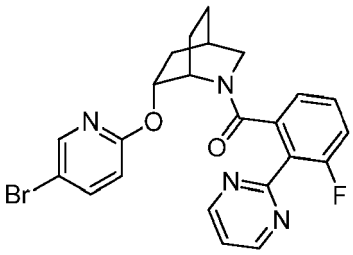
mediate C-5B (37 mg, 0.16 mmol) dissolved in DMF (1.4 mL) was added NaH (13 mg, 0.33 mmol, 60% dispersion in mineral oil). After 5 minutes 5-bromo-2-fluoropyridine (0.03 mL, 0.26 mmol) was then added and the mixture stirred at room temperature for 2 h. The reaction mixture was quenched with saturated NH_4Cl solution, and diluted with EtOAc and H_2O. The aqueous layer was extracted with EtOAc (3X). The combined organics were washed with H_2O, brine, dried with $MgSO_4$, filtered and concentrated. Purification via silica gel chromatography (0-100% EtOAc in hexanes) gave the title compound (63 mg, 0.16 mmol, 100%). MS (ESI) mass calcd. for $C_{17}H_{23}BrN_2O_3$, 382.1; m/z found 383.1 $[M+H]^+$.

[0885] Step B: (1S,4R,6R)-6-((5-bromopyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octane · xHCl. To the title compound of step A (63 mg, 0.16 mmol) in EtOAc (2 mL) was added 4 M HCl in dioxane (0.21 mL) and the reaction mixture was stirred at room temperature overnight. Analysis of the reaction mixture showed that starting material still remained. Additional 4 M HCl in dioxane (0.21 mL) was added and the reaction mixture stirred at room temperature for 5 h. The reaction was concentrated to give the title compound of step B which was used without further purification. MS (ESI) mass calcd. for $C_{12}H_{15}BrN_2O$, 282.0; m/z found 283.0 $[M+H]^+$.

[0886] Step C: (2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((5-bromopyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone. To the title compound of step B (23 mg) and intermediate A-1 (47 mg, 0.25 mmol) in DMF (0.8 mL) was added DIPEA (0.08 mL, 0.49 mmol) and HATU (34 mg, 0.09 mmol), and the reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with MeOH and the crude reaction mixture directly subjected to purification using Agilent Prep Method X to give the title compound (7.7 mg). MS (ESI): mass calcd. for $C_{21}H_{20}BrN_5O_2$, 453.1; m/z found, 454.1 $[M+H]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5μm, 100 × 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 30 °C). R_t = 7.51 min (major rotamer) at 254 nm.

Example 269: ((1S,4R,6R)-6-((5-bromopyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)(3-fluoro-2-(pyrimidin-2-yl)phenyl)methanone.

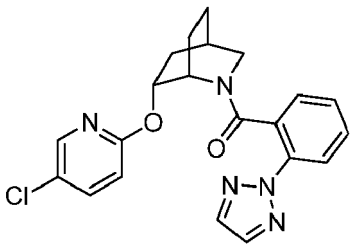
[0887]



[0888] Prepared analogous to Example 268 substituting intermediate A-1 with intermediate A-2. MS (ESI): mass calcd. for $C_{23}H_{20}BrFN_4O_2$, 482.1; m/z found, 483.1 $[M+H]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5μm, 100 × 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 30 °C). R_t = 7.10 min (major rotamer) at 254 nm.

Example 270: (2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((5-chloropyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone

[0889]



[0890] Step A: (1S,4R,6R)-tert-butyl 6-((5-chloropyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octane-2-carboxylate. To intermediate C-5B (37 mg, 0.16 mmol) dissolved in DMF (1.4 mL) was added NaH (13 mg, 0.33 mmol, 60% dispersion in mineral oil). After 5 minutes 5-chloro-2-fluoropyridine (0.03 mL, 0.26 mmol) was then added and the mixture stirred at

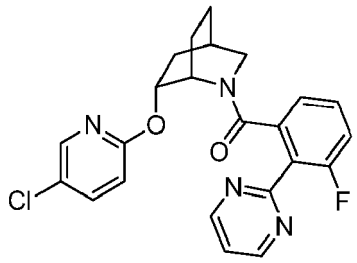
room temperature for 1.5 h. The reaction mixture was quenched with saturated NH_4Cl solution, and diluted with EtOAc and H_2O. The aqueous layer was extracted with EtOAc (3X). The combined organics were washed with H_2O, brine, dried with $MgSO_4$, filtered and concentrated. Purification via silica gel chromatography (0-50% EtOAc in hexanes) gave the title compound (52 mg, 0.15 mmol, 94%). MS (ESI) mass calcd. for $C_{17}H_{23}ClN_2O_3$, 338.1; m/z found 339.2 $[M+H]^+$.

[0891] Step B: (1S,4R,6R)-6-((5-chloropyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octane · xHCl. To the title compound of step A (52 mg, 0.15 mmol) in EtOAc (2 mL) was added 4 M HCl in dioxane (0.19 mL) and the reaction mixture was stirred at room temperature overnight. The reaction was concentrated to give the title compound of step B which was used without further purification. MS (ESI) mass calcd. for $C_{12}H_{15}ClN_2O$, 238.1; m/z found 239.1$[M+H]^+$.

[0892] Step C: (2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((5-chloropyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone. To the title compound of step B (18 mg) and intermediate A-1 (44 mg, 0.23 mmol) in DMF (0.8 mL) was added DIPEA (0.08 mL, 0.45 mmol) and HATU (44 mg, 0.23 mmol), and the reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with MeOH and the crude reaction mixture directly subjected to purification using Agilent Prep Method X to give the title compound (16 mg). MS (ESI): mass calcd. for $C_{21}H_{20}ClN_5O_2$, 409.1; m/z found, 410.1 $[M+H]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5μm, 100 × 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 30 °C). R_t = 7.35 min (major rotamer) at 254 nm.

Example 271: ((1S,4R,6R)-6-((5-chloropyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)(3-fluoro-2-(pyrimidin-2-yl)phenyl)methanone

[0893]

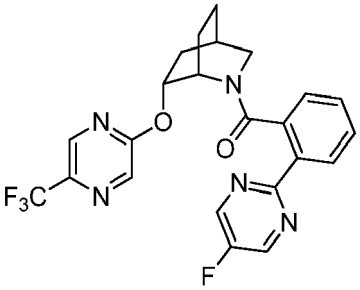


[0894] Prepared analogous to Example 270 substituting intermediate A-1 with intermediate A-2.

[0895] MS (ESI): mass calcd. for $C_{23}H_{20}ClFN_4O_2$, 438.1; m/z found, 439.1 $[M+H]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5μm, 100 × 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 30 °C). R_t = 6.94 min (major rotamer) at 254 nm.

Example 272: (2-(5-fluoropyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

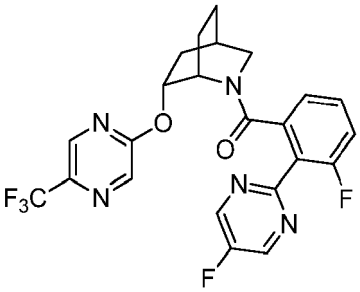
[0896]



[0897] Prepared analogous to Example 77 substituting intermediate A-40 with intermediate A-34. MS (ESI): mass calcd. for $C_{23}H_{19}F_4N_5O_2$, 473.1; m/z found, 474.2 $[M+H]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5μm, 100 × 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 30 °C). R_t = 7.16 min (major rotamer) at 254 nm.

Example 273: (3-fluoro-2-(5-fluoropyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

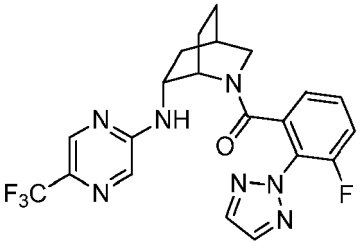
[0898]



[0899] Prepared analogous to Example 77 substituting intermediate A-40 with intermediate A-35. MS (ESI): mass calcd. for $C_{23}H_{18}F_5N_5O_2$, 491.1; m/z found, 492.2 $[M+H]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5μm, 100 × 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 30 °C). R_t = 7.29 min (major rotamer) at 254 nm.

Example 274: (3-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

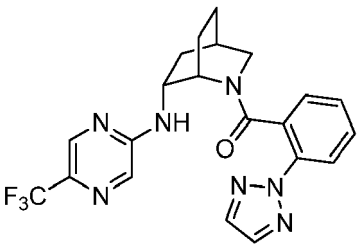
[0900]



[0901] Prepared analogous to Example 83 substituting intermediate A-40 with intermediate A-16. MS (ESI): mass calcd. for $C_{21}H_{19}F_4N_7O$, 461.2; m/z found, 462.2 $[M+H]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5μm, 100 × 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 30 °C). R_t = 6.71 min (major rotamer) at 254 nm.

Example 275: (2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo [2.2.2] octan-2-yl)methanone

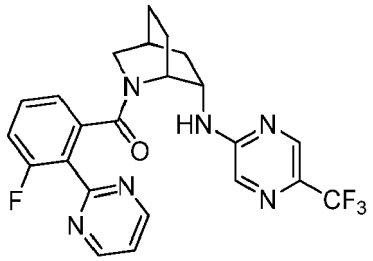
[0902]



[0903] Prepared analogous to Example 83 substituting intermediate A-40 with intermediate A-1. MS (ESI): mass calcd. for $C_{21}H_{20}F_3N_7O$, 443.2; m/z found, 444.2 $[M+H]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5μm, 100 × 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 30 °C). R_t = 6.67 min (major rotamer) at 254 nm.

Example 276: (3-fluoro-2-(pyrimidin-2-yl)phenyl)((1R,4S,6S)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo [2.2.2] octan-2-yl)methanone.

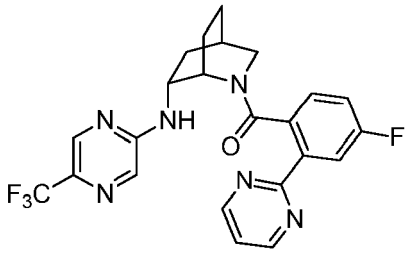
[0904]



[0905] Prepared analogous to Example 83 substituting intermediate A-40 with intermediate A-2 (step C),and substituting intermediate C-7B with its enantiomer (step A), (1R,4S,6S)-tert-butyl 6-amino-2-azabicyclo[2.2.2]octane-2-carboxylate. MS (ESI): mass calcd. for $C_{23}H_{20}F_4N_6O$, 472.2; m/z found, 472.9 $[M+H]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5μm, 100 x 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 30 °C). R_t = 6.39 min (major rotamer) at 254 nm.

Example 277: (4-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo [2.2.2] octan-2-yl)methanone.

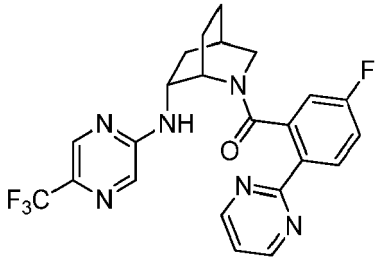
[0906]



[0907] Prepared analogous to Example 83 substituting intermediate A-40 with intermediate A-23. MS (ESI): mass calcd. for $C_{23}H_{20}F_4N_6O$, 472.2; m/z found, 473.2 $[M+H]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5μm, 100 × 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 30 °C). R_t = 6.62 min (major rotamer) at 254 nm.

Example 278: (5-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[0908]

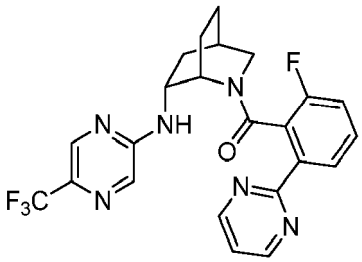


[0909] Prepared analogous to Example 83 substituting intermediate A-40 with intermediate A-7. MS (ESI): mass calcd.

for $C_{23}H_{20}F_4N_6O$, 472.2; m/z found, 473.2 $[M+H]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5μm, 100 × 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 30 °C). R_t = 6.44 min (major rotamer) at 254 nm.

Example 279: (2-fluoro-6-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone

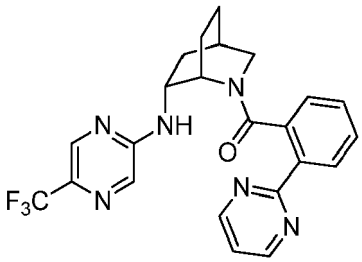
[0910]



[0911] Prepared analogous to Example 83 substituting intermediate A-40 with intermediate A-6. MS (ESI): mass calcd. for $C_{23}H_{20}F_4N_6O$, 472.2; m/z found, 473.2 $[M+H]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5μm, 100 × 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 30 °C). R_t = 6.27 min (major rotamer) and 6.95 at 254 nm.

Example 280: (2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

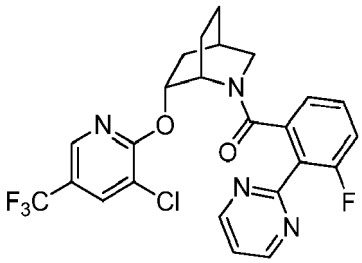
[0912]



[0913] Prepared analogous to Example 83 substituting intermediate A-40 with intermediate A-37. MS (ESI): mass calcd. for $C_{23}H_{21}F_3N_6O$, 454.2; m/z found, 455.4 $[M+H]^+$. Analytical HPLC using a XBridge C18 column (5μm, 100 × 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 2min and then hold at 100% ACN for 2 min, at a flow rate of 2.5 mL/min (Temperature = 45 °C). R_t = 2.01 and 1.98 min (major rotamer) at 254 nm.

Example 281: ((1S,4R,6R)-6-((3-chloro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)(3-fluoro-2-(pyrimidin-2-yl)phenyl)methanone.

[0914]



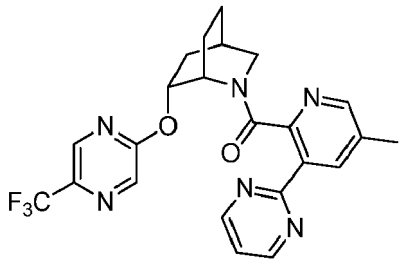
[0915] Step A: (1S,4R,6R)-tert-butyl 6-((3-chloro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octane-2-carboxylate. To intermediate C-5B (100 mg, 0.44 mmol) dissolved in DMF (4 mL) was added NaH (35 mg, 0.88 mmol, 60% dispersion in mineral oil). After 5 minutes 3-chloro-2-fluoro-5-(trifluoromethyl)pyridine (86 μL, 0.66 mmol) was then added and the mixture stirred at room temperature over the weekend. Analysis of the reaction mixture showed mostly starting material. Additional NaH was added. Analysis still showed incomplete conversion, however the reaction mixture was quenched with saturated NH_4Cl solution, and diluted with EtOAc and H_2O. The aqueous layer was extracted with EtOAc (3X). The combined organics were washed with H_2O, brine, dried with $MgSO_4$, filtered, and concentrated. Purification via silica gel chromatography (0-100% EtOAc in hexanes) gave the title compound (38 mg, 0.093 mmol, 21%). MS (ESI) mass calcd. for $C_{18}H_{22}ClF_3N_2O_3$, 406.1; m/z found 351.1 $[M+2H-t\text{Bu}]^+$.

[0916] Step B: (1S,4R,6R)-6-((3-chloro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octane· xHCl. To the title compound of step A (38 mg, 0.093 mmol) in EtOAc (1.2 mL) was added 4 M HCl in dioxane (0.12 mL), and the reaction mixture was stirred at room temperature overnight. Analysis of the reaction mixture showed that starting material was still present. Additional 4 M HCl in dioxane (0.12 mL) was added and the reaction mixture stirred at room temperature overnight. The reaction mixture was then concentrated to give the title compound of step B (29 mg) which was used without further purification. MS (ESI) mass calcd. for $C_{13}H_{14}ClF_3N_2O$, 306.1; m/z found 307.1 $[M+H]^+$.

[0917] Step C: ((1S,4R,6R)-6-((3-chloro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)(3-fluoro-2-(pyrimidin-2-yl)phenyl)methanone. To the title compound of step B (27 mg) and intermediate A-2 (23 mg, 0.11 mmol) in DMF (0.9 mL) was added DIPEA (0.09 mL, 0.53 mmol) and HATU (37 mg, 0.097 mmol), and the reaction mixture was stirred overnight at room temperature. The crude reaction mixture was diluted with MeOH, syringe filtered, and subjected directly to purification using Agilent Prep Method X to give the title compound (11 mg). MS (ESI): mass calcd. for $C_{24}H_9ClF_4N_4O_2$, 506.1; m/z found, 507.1 $[M+H]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5μm, 100 x 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 30 °C). R_t = 7.87 min (major rotamer) at 254 nm.

Example 282: (5-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

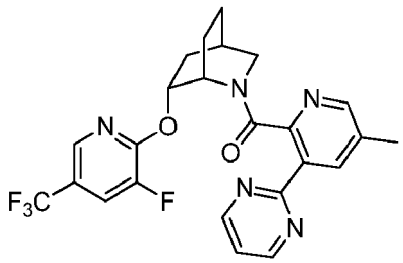
[0918]



[0919] Prepared analogous to Example 77 substituting intermediate A-40 with intermediate A-47. MS (ESI): mass calcd. for $C_{23}H_{21}F_3N_6O_2$, 470.2; m/z found, 471.2 $[M+H]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5μm, 100 × 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 30 °C). R_t = 6.77 min (major rotamer) at 254 nm.

Example 283: ((1S,4R,6R)-6-((3-fluoro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)(5-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)methanone.

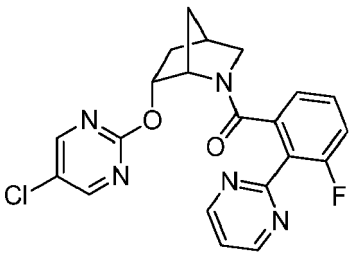
[0920]



[0921] Prepared analogous to Example 266 substituting intermediate A-2 with intermediate A-47. MS (ESI): mass calcd. for $C_{24}H_{21}F_4N_5O_2$, 487.2; m/z found, 488.2 $[M+H]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5μm, 100 × 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 30 °C). R_t = 7.38 min (major rotamer) at 254 nm.

Example 284: ((1S,4R,6R)-6-((5-chloropyrimidin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)(3-fluoro-2-(pyrimidin-2-yl)phenyl)methanone.

[0922]



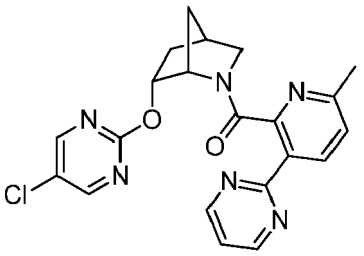
[0923] Step A: (1S,4R,6R)-tert-butyl 6-((5-chloropyrimidin-2-yl)oxy)-2-azabicyclo[2.2.1]heptane-2-carboxylate. To intermediate B-5 (150 mg, 0.70 mmol) and 2,5-dichloropyrimidine (225mg, 1.51 mmol) dissolved in DMF (2 mL) was added NaH (37 mg, 0.91 mmol, 60% dispersion in mineral oil). After 3h LCMS analysis showed that the reaction was incomplete and additional NaH (40 mg, 1.0 mmol, 60% dispersion in mineral oil) was added and the reaction mixture allowed to stir for an additional 45 min and then quenched with H2O. The aqueous layer was extracted with EtOAc (3X). The combined organics were washed with H_2O, 5% aqueous LiCl, dried with $MgSO_4$, filtered, and concentrated. Purification via silica gel chromatography (0-40% EtOAc in hexanes) gave the title compound (211 mg, 0.65 mmol, 92%) as a colorless solid. MS (ESI) mass calcd. for $C_{15}H_{20}ClN_3O_3$, 325.1; m/z found 370.1 $[M+2H\text{-}tBu]^+$. ^1H NMR (500 MHz, Chloroform-d, Compound present as a mixture of rotamers, both rotamers reported) δ 8.44 and 8.39 (two s, 2H), 5.25 - 5.16 (m, 1H), 4.68-4.65 and 4.56-4.52 (two m, 1H), 3.42-3.37 and 3.35-3.31 (two m, 1H), 3.24-3.16 (m, 1H), 2.61 - 2.51 (m, 1H), 2.24 - 2.13 (m, 1H), 1.77 - 1.40 (m, 3H), 1.35 and 1.12 (2s, 9H).

[0924] Step B: (1S,4R,6R)-6-((5-chloropyrimidin-2-yl)oxy)-2-azabicyclo[2.2.1]heptane · xHCl. To the title compound of step A (211 mg, 0.65 mmol) in EtOAc (2 mL) was added 4M HCl in dioxane (4 mL) and the reaction mixture was stirred at room temperature for 1.5h. Then, the reaction was concentrated to give the title compound of step B (155 mg) as an off-white solid and used without further purification. MS (ESI) mass calcd. for $C_{10}H_{12}ClN_3O$, 225.1; m/z found 226.1 $[M+H]^+$.

[0925] Step C: ((1S,4R,6R)-6-((5-chloropyrimidin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)(3-fluoro-2-(pyrimidin-2-yl)phenyl)methanone. To the title compound of step B (30 mg) and intermediate A-2 (27 mg, 0.13 mmol) in DMF (0.4 mL) was added DIPEA (0.1 mL, 0.58 mmol) and HATU (48 mg, 0.13 mmol), and the reaction mixture was stirred at room temperature for 2 h. The reaction was diluted with MeOH, filtered, and purified using Agilent Prep Method X to give the title compound (27 mg). MS (ESI): mass calcd. for $C_{21}H_{17}ClFN_5O_2$, 425.1; m/z found, 426.1 $[M+H]^+$. ^1H NMR (500 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.72:0.28), major rotamer reported) δ 8.85 (d, *J* = 4.9 Hz, 2H), 8.29 (s, 2H), 7.29 - 7.26 (m, 1H), 7.12 - 6.97 (m, 3H), 4.95 (dt, *J* = 10.1, 3.3 Hz, 1H), 4.32 - 4.20 (m, 1H), 3.39 - 3.31 (m, 2H), 2.63 - 2.47 (m, 1H), 2.26 - 2.15 (m, 1H), 1.50 - 1.39 (m, 2H), 1.07 - 0.97 (m, 1H).

Example 285: ((1S,4R,6R)-6-((5-chloropyrimidin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)(6-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)methanone.

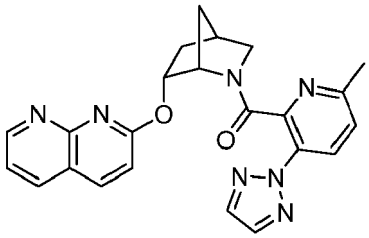
[0926]



[0927] Prepared analogous to Example 284 substituting intermediate A-2 with intermediate A-41. MS (ESI): mass calcd. for $C_{21}H_{19}ClN_6O_2$, 422.1; m/z found, 423.2 $[M+H]^+$. ^1H NMR (500 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.63:0.37), major rotamer reported) δ 8.76 (d, *J* = 4.8 Hz, 2H), 8.43 - 8.41 (m, 1H), 8.11 (s, 2H), 7.19 (t, *J* = 4.9 Hz, 1H), 7.12 (d, *J* = 7.9 Hz, 1H), 4.79 (dt, *J* = 10.3, 3.2 Hz, 1H), 4.48 - 4.39 (m, 1H), 3.78 (dt, *J* = 10.8, 3.0 Hz, 1H), 3.46 (dd, *J* = 10.9, 1.4 Hz, 1H), 2.72 - 2.64 (m, 1H), 2.30 (s, 3H), 2.26 - 2.18 (m, 1H), 1.67 (dt, *J* = 13.5, 3.6 Hz, 1H), 1.56 - 1.45 (m, 2H).

Example 286: ((1S,4R,6R)-6-((1,8-naphthyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)methanone.

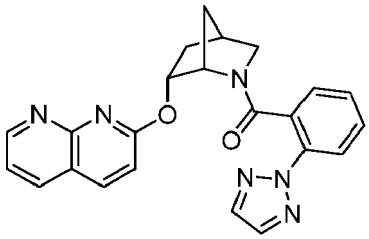
[0928]



[0929] Prepared analogous to Example 287 substituting intermediate A-1 with intermediate A-40. MS (ESI): mass calcd. for $C_{23}H_{21}N_7O_2$, 427.2; m/z found, 428.2 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d) δ 8.86 (dd, *J* = 4.4, 2.0 Hz, 1H), 8.06 (dd, *J* = 7.9, 2.0 Hz, 1H), 7.92 (d, *J* = 8.7 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.81 (s, 2H), 7.33 (dd, *J* = 7.9, 4.4 Hz, 1H), 7.03 (d, *J* = 8.8 Hz, 1H), 6.67 (d, *J* = 8.4 Hz, 1H), 5.39 (dt, *J* = 9.9, 3.1 Hz, 1H), 4.54 - 4.43 (m, 1H), 3.71 (dt, *J* = 11.0, 3.2 Hz, 1H), 3.49 (d, *J* = 11.0 Hz, 1H), 2.69 - 2.66 (m, 1H), 2.39 - 2.23 (m, 1H), 2.03 (s, 3H), 1.58 - 1.50 (m, 3H).

Example 287: ((1S,4R,6R)-6-((1,8-naphthyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)(2-(2H-1,2,3 -triazol-2-yl)phenyl)methanone.

[0930]



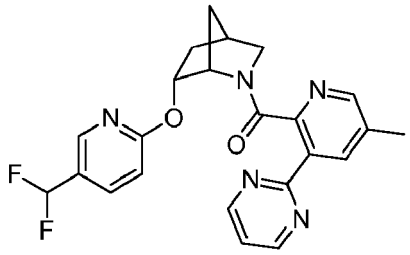
[0931] Step A: (1S,4R,6R)-tert-butyl 6-((1,8-naphthyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptane-2-carboxylate. To intermediate B-5 (150 mg, 0.70 mmol) and 2-chloro-1,8-naphthyridine (225mg, 1.37 mmol) dissolved in DMF (2 mL) was added NaH (37 mg, 0.91 mmol, 60% dispersion in mineral oil). After 50 min the mixture was quenched with H_2O and the aqueous layer was extracted with EtOAc (3X). The combined organics were washed with 5% aqueous LiCl, brine, dried with $MgSO_4$, filtered, and concentrated. Purification via silica gel chromatography (0-100% EtOAc in hexanes) gave the title compound (200 mg) as a colorless solid. MS (ESI) mass calcd. for $C_{19}H_{23}N_3O_3$, 341.2; m/z found 342.2 $[M+H]^+$.

[0932] Step B: 2-((1S,4R,6R)-2-azabicyclo[2.2.1]heptan-6-yloxy)-1,8-naphthyridine · xHCl. To the title compound of step A (200 mg, 0.59 mmol) in EtOAc (2 mL) was added 4M HCl in dioxane (4 mL) and the reaction mixture was stirred at room temperature for 2h. Then, the reaction was concentrated to give the title compound of step B (192 mg) as a colorless solid and used without further purification. MS (ESI) mass calcd. for $C_{14}H_{15}N_3O_3$, 241.1; m/z found 242.1 $[M+H]^+$.

[0933] Step C: ((1S,4R,6R)-6-((1,8-naphthyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)(2-(2H-1,2,3-triazol-2-yl)phenyl)methanone. To the title compound of step B (30 mg) and intermediate A-1 (20 mg, 0.11 mmol) in DMF (0.5 mL) was added DIPEA (0.1 mL, 0.58 mmol) and HATU (40 mg, 0.11 mmol), and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with MeOH, filtered, and purified using Agilent Prep Method X to give the title compound (22 mg). MS (ESI): mass calcd. for $C_{23}H_{20}N_6O_2$, 412.2; m/z found, 413.2 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d) δ 8.87 (dd, *J* = 4.4, 2.0 Hz, 1H), 8.11 (dd, *J* = 7.9, 2.0 Hz, 1H), 8.05 (d, *J* = 8.8 Hz, 1H), 7.82 - 7.74 (m, 3H), 7.35 (dd, *J* = 7.9, 4.4 Hz, 1H), 7.10 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.03 (d, *J* = 8.7 Hz, 1H), 7.00 - 6.92 (m, 1H), 6.54 (t, *J* = 7.6 Hz, 1H), 5.44 (dt, *J* = 10.2, 3.2 Hz, 1H), 4.28 - 4.19 (m, 1H), 3.65 (dt, *J* = 10.9, 3.2 Hz, 1H), 3.43 (d, *J* = 9.5 Hz, 1H), 2.72 - 2.62 (m, 1H), 2.45 - 2.31 (m, 1H), 1.52 - 1.42 (m, 3H).

Example 288: ((1S,4R,6R)-6-((5-(difluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)(5-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)methanone.

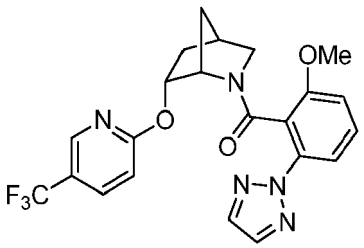
[0934]



[0935] Prepared analogous to Example 121 substituting intermediate A-1 with intermediate A-47. MS (ESI): mass calcd. for $C_{23}H_{21}F_2N_5O_2$, 437.2; m/z found, 438.2 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d) δ 8.77 (d, *J* = 4.9 Hz, 2H), 8.28 - 8.19 (m, 1H), 7.83 - 7.77 (m, 1H), 7.69 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.66 - 7.64 (m, 1H), 7.21 (t, *J* = 4.9 Hz, 1H), 6.91 (d, *J* = 8.6 Hz, 1H), 6.59 (t, *J* = 56.1 Hz, 1H), 5.02 (dt, *J* = 10.3, 3.4 Hz, 1H), 4.33 - 4.21 (m, 1H), 3.70 (dt, *J* = 10.8, 3.2 Hz, 1H), 3.46 (dd, *J* = 10.7, 1.4 Hz, 1H), 2.72 - 2.63 (m, 1H), 2.26 (s, 3H), 2.23 - 2.16 (m, 1H), 1.61 - 1.35 (m, 3H).

Example 289: (2-methoxy-6-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

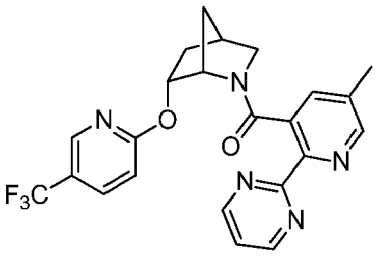
[0936]



[0937] Prepared analogous to Example 25 substituting intermediate A-20 with intermediate A-13. MS (ESI): mass calcd. for $C_{22}H_{20}F_3N_5O_3$, 459.2; m/z found, 460.2 $[M+H]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5μm, 100 × 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 45 °C). R_t = 6.84 min (major rotamer) at 254 nm.

Example 290: (5-methyl-2-(pyrimidin-2-yl)pyridin-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

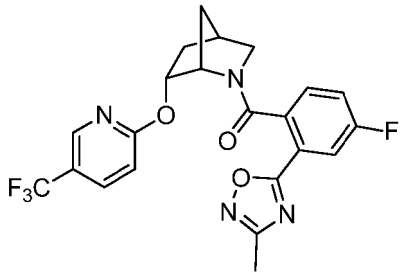
[0938]



[0939] Prepared analogous to Example 25 substituting intermediate A-20 with intermediate A-46. MS (ESI): mass calcd. for $C_{23}H_{20}F_3N_5O_2$, 455.2; m/z found, 456.4 $[M+H]^+$. ^1H NMR (500 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.87:0.13), major rotamer reported) δ 8.87 (d, *J* = 4.8 Hz, 2H), 8.47 (dd, *J* = 2.1, 0.8 Hz, 1H), 8.18 - 8.10 (m, 1H), 7.80 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.31 - 7.28 (m, 2H), 6.83 - 6.78 (m, 1H), 5.02 (dt, *J* = 10.1, 3.3 Hz, 1H), 4.18 - 4.09 (m, 1H), 3.65 (dt, *J* = 10.9, 3.2 Hz, 1H), 3.43 (dd, *J* = 10.9, 1.5 Hz, 1H), 2.70 - 2.60 (m, 1H), 2.28 - 2.18 (m, 1H), 2.04 (s, 3H), 1.47 - 1.38 (m, 2H), 1.32 - 1.24 (m, 1H).

Example 291: (4-fluoro-2-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

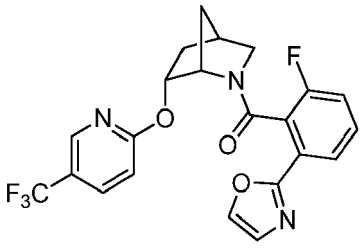
[0940]



[0941] Prepared analogous to Example 25 substituting intermediate A-20 with intermediate A-51. MS (ESI): mass calcd. for $C_{22}H_{18}F_4N_4O_3$, 462.1; m/z found, 463.4 $[M+H]^+$. ^1H NMR (500 MHz, Chloroform-d) δ 8.10 - 8.01 (m, 1H), 7.80 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.72 (dd, *J* = 8.9, 2.6 Hz, 1H), 7.02 (dd, *J* = 8.5, 5.4 Hz, 1H), 6.82 (d, *J* = 8.7 Hz, 1H), 6.76 - 6.68 (m, 1H), 5.06 (dt, *J* = 10.1, 3.3 Hz, 1H), 4.14 - 4.08 (m, 1H), 3.77 (dt, *J* = 11.0, 3.2 Hz, 1H), 3.44 (dd, *J* = 10.9, 1.5 Hz, 1H), 2.76 - 2.71 (m, 1H), 2.45 (s, 3H), 2.35 - 2.22 (m, 1H), 1.73 - 1.66 (m, 1H), 1.59 - 1.55 (m, 1H), 1.46 (dt, *J* = 13.6, 3.6 Hz, 1H).

Example 292: (2-fluoro-6-(oxazol-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

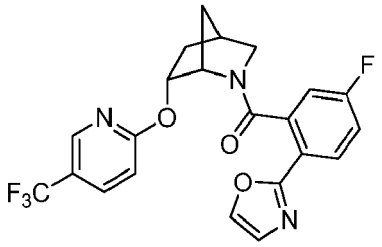
[0942]



[0943] Prepared analogous to Example 25 substituting intermediate A-20 with intermediate A-50. MS (ESI): mass calcd. for $C_{22}H_{17}F_4N_3O_3$, 447.1; m/z found, 448.5 $[M+H]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5μm, 100 $\times$ 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 45 °C). R_t = 7.18 min (major rotamer) at 254 nm.

Example 293: (5-fluoro-2-(oxazol-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

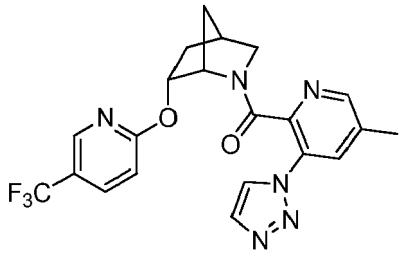
[0944]



[0945] Prepared analogous to Example 25 substituting intermediate A-20 with intermediate A-49. MS (ESI): mass calcd. for $C_{22}H_{17}F_4N_3O_3$, 447.1; m/z found, 448.5 $[M+H]^+$. ^1H NMR (500 MHz, Chloroform-d) δ 8.05 - 8.02 (m, 1H), 7.92 (dd, *J* = 8.7, 5.3 Hz, 1H), 7.80 (dd, *J* = 8.6, 2.5 Hz, 1H), 7.69 (d, *J* = 0.8 Hz, 1H), 7.21 (d, *J* = 0.8 Hz, 1H), 6.99 - 6.92 (m, 1H), 6.81 (d, *J* = 8.7 Hz, 1H), 6.69 (dd, *J* = 8.4, 2.7 Hz, 1H), 5.03 (dt, *J* = 10.2, 3.3 Hz, 1H), 4.16 - 4.08 (m, 1H), 3.74 (dt, *J* = 11.0, 3.2 Hz, 1H), 3.44 (dd, *J* = 10.9, 1.5 Hz, 1H), 2.74 - 2.63 (m, 1H), 2.30 - 2.21 (m, 1H), 1.63 - 1.56 (m, 1H), 1.55 - 1.49 (m, 1H), 1.45 (dt, *J* = 13.5, 3.6 Hz, 1H).

Example 294: (5-methyl-3-(1H-1,2,3-triazol-1-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

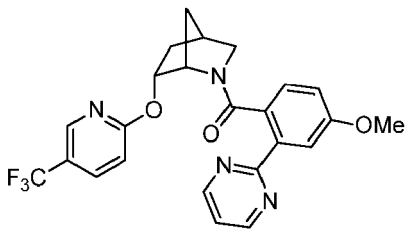
[0946]



[0947] Prepared analogous to Example 25 substituting intermediate A-20 with the N-1 isomer, 5-methyl-3-(1H-1,2,3-triazol-1-yl)picolinonitrile, from intermediate A-19. MS (ESI): mass calcd. for $C_{21}H_{19}F_3N_6O_2$, 444.2; m/z found, 445.6 $[M+H]^+$. ^1H NMR (500 MHz, Chloroform-d) δ 8.12 (d, *J* = 1.1 Hz, 1H), 8.02 - 7.98 (m, 1H), 7.97 - 7.94 (m, 1H), 7.81 (d, *J* = 1.1 Hz, 1H), 7.78 - 7.76 (m, 1H), 7.72 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.74 - 6.69 (m, 1H), 4.99 (dt, *J* = 10.2, 3.3 Hz, 1H), 4.43 - 4.34 (m, 1H), 3.48 (dt, *J* = 11.2, 3.1 Hz, 1H), 3.41 (dd, *J* = 11.2, 1.5 Hz, 1H), 2.66 - 2.60 (m, 1H), 2.34 (s, 3H), 2.25 - 2.17 (m, 1H), 1.60 - 1.53 (m, 1H), 1.40 (dt, *J* = 13.6, 3.6 Hz, 1H), 1.34 - 1.27 (m, 1H).

Example 295: (4-methoxy-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[0948]

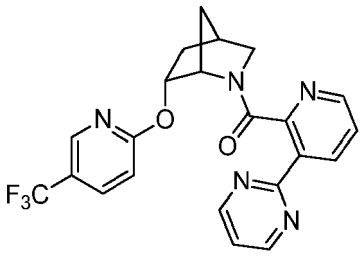


[0949] Prepared analogous to Example 25 substituting intermediate A-20 with intermediate A-15. MS (ESI): mass

calcd. for $C_{24}H_{21}F_3N_4O_3$, 470.2; m/z found, 471.4 $[M+H]^+$. ^1H NMR (500 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.88:0.12), major rotamer reported) δ 8.78 (d, *J* = 4.8 Hz, 2H), 8.14 - 8.06 (m, 1H), 7.79 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.70 (d, *J* = 2.6 Hz, 1H), 7.19 (t, *J* = 4.8 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 1H), 6.85 - 6.83 (m, 1H), 6.45 (dd, *J* = 8.4, 2.6 Hz, 1H), 5.04 (dt, *J* = 10.1, 3.4 Hz, 1H), 4.19 - 4.09 (m, 1H), 3.81 (s, 3H), 3.62 (dt, *J* = 10.9, 3.2 Hz, 1H), 3.40 (dd, *J* = 10.8, 1.5 Hz, 1H), 2.65 - 2.59 (m, 1H), 2.27 - 2.15 (m, 1H), 1.44 - 1.35 (m, 2H), 1.29 - 1.17 (m, 1H).

Example 296: (3-(pyrimidin-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

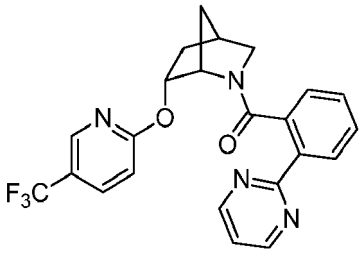
[0950]



[0951] Prepared analogous to Example 25 substituting intermediate A-20 with intermediate A-42. MS (ESI): mass calcd. for $C_{22}H_{18}F_3N_5O_2$, 441.1; m/z found, 442.4 $[M+H]^+$. ^1H NMR (500 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.81:0.19), major rotamer reported) δ 8.78 (d, *J* = 4.8 Hz, 2H), 8.47 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.97 - 7.90 (m, 1H), 7.83 (dd, *J* = 4.7, 1.7 Hz, 1H), 7.73 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.22 (t, *J* = 4.9 Hz, 1H), 7.15 (dd, *J* = 8.0, 4.7 Hz, 1H), 6.91 (d, *J* = 8.7 Hz, 1H), 5.04 (dt, *J* = 10.2, 3.4 Hz, 1H), 4.35 - 4.20 (m, 1H), 3.73 (dt, *J* = 10.8, 3.2 Hz, 1H), 3.47 (d, *J* = 10.9 Hz, 1H), 2.72 - 2.65 (m, 1H), 2.30 - 2.13 (m, 1H), 1.60 - 1.44 (m, 3H).

Example 297: (2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

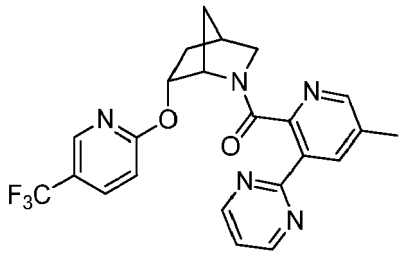
[0952]



[0953] Prepared analogous to Example 25 substituting intermediate A-20 with intermediate A-37. MS (ESI): mass calcd. for $C_{23}H_{19}F_3N_4O_2$, 440.1; m/z found, 441.4 $[M+H]^+$. ^1H NMR (500 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.88:0.12), major rotamer reported) δ 8.78 (d, *J* = 4.8 Hz, 2H), 8.17 (dd, *J* = 8.0, 1.2 Hz, 1H), 8.06 - 8.00 (m, 1H), 7.78 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.30 (td, *J* = 7.7, 1.4 Hz, 1H), 7.19 (t, *J* = 4.8 Hz, 1H), 7.00 (dd, *J* = 7.6, 1.3 Hz, 1H), 6.88 (td, *J* = 7.5, 1.3 Hz, 1H), 6.83 (d, *J* = 8.7 Hz, 1H), 5.01 (dt, *J* = 10.2, 3.4 Hz, 1H), 4.24 - 4.10 (m, 1H), 3.64 (dt, *J* = 10.9, 3.2 Hz, 1H), 3.41 (dd, *J* = 10.8, 1.5 Hz, 1H), 2.66 - 2.61 (m, 1H), 2.27 - 2.12 (m, 1H), 1.47 - 1.37 (m, 2H), 1.34 - 1.19 (m, 1H).

Example 298: (5-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

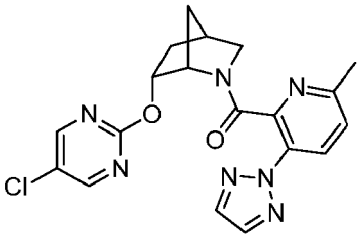
[0954]



[0955] Prepared analogous to Example 25 substituting intermediate A-20 with intermediate A-47. MS (ESI): mass calcd. for $C_{23}H_{20}F_3N_5O_2$, 455.2; m/z found, 456.4 $[M+H]^+$. ^1H NMR (500 MHz, Chloroform-d, Compound present as a mixture of rotamers (0.87:0.13), major rotamer reported) δ 8.78 (d, *J* = 4.8 Hz, 2H), 8.27 - 8.21 (m, 1H), 7.95 - 7.92 (m, 1H), 7.74 (dd, *J* = 8.4, 2.7 Hz, 1H), 7.65 - 7.62 (m, 1H), 7.22 (t, *J* = 4.8 Hz, 1H), 6.95 - 6.90 (m, 1H), 5.03 (dt, *J* = 10.3, 3.3 Hz, 1H), 4.32 - 4.27 (m, 1H), 3.71 (dt, *J* = 10.9, 3.2 Hz, 1H), 3.46 (dd, *J* = 10.8, 1.4 Hz, 1H), 2.72 - 2.64 (m, 1H), 2.26 (s, 3H), 2.25 - 2.18 (m, 1H), 1.59 - 1.45 (m, 3H).

Example 299: ((1S,4R,6R)-6-((5-chloropyrimidin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)methanone.

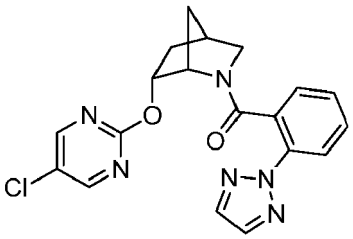
[0956]



[0957] Prepared analogous to Example 284 substituting intermediate A-2 with intermediate A-40. MS (ESI): mass calcd. for $C_{19}H_{18}ClN_7O_2$, 411.1; m/z found, 412.3 $[M+H]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5μm, 100 $\times$ 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 45 °C). R_t = 5.23 min (major rotamer) at 254 nm.

Example 300: (2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((5-chloropyrimidin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

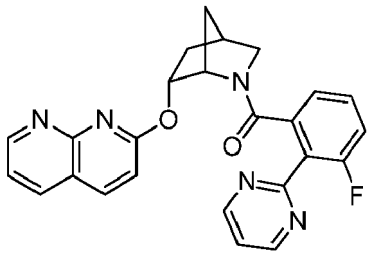
[0958]



[0959] Prepared analogous to Example 284 substituting intermediate A-2 with intermediate A-1. MS (ESI): mass calcd. for $C_{19}H_{17}ClN_6O_2$, 396.1; m/z found, 397.1 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform-d, Compound present as a mixture of rotamers, major reported) δ 8.22 (s, 2H), 7.88 - 7.85 (m, 1H), 7.81 (s, 2H), 7.40 - 7.31 (m, 1H), 7.17 (dd, *J* = 7.7, 1.5 Hz, 1H), 6.90 (t, *J* = 7.5 Hz, 1H), 4.87 (dt, *J* = 10.2, 3.3 Hz, 1H), 4.10 - 3.98 (m, 1H), 3.63 (dt, *J* = 10.9, 3.2 Hz, 1H), 3.42 (dd, *J* = 10.9, 1.4 Hz, 1H), 2.66 - 2.60 (m, 1H), 2.29 - 2.12 (m, 1H), 1.54 (dt, *J* = 13.6, 3.5 Hz, 1H), 1.42 - 1.33 (m, 2H).

Example 301: ((1S,4R,6R)-6-((1,8-naphthyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)(3-fluoro-2-(pyrimidin-2-yl)phenyl)methanone.

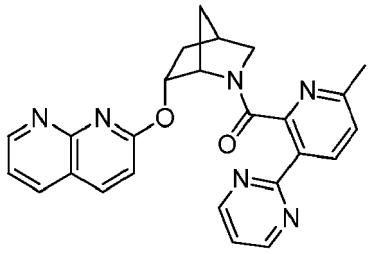
[0960]



[0961] Prepared analogous to Example 287 substituting intermediate A-1 with intermediate A-2. MS (ESI): mass calcd. for $C_{25}H_{20}FN_5O_2$, 441.2; m/z found, 442.2 $[M+H]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5μm, 100 x 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 45 °C). R_t = 4.68 min at 254 nm.

Example 302: ((1S,4R,6R)-6-((1,8-naphthyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)(6-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)methanone.

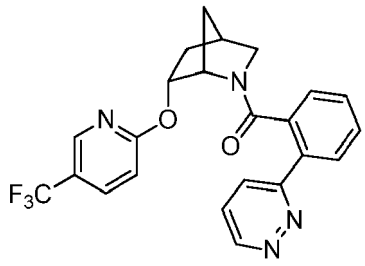
[0962]



[0963] Prepared analogous to Example 287 substituting intermediate A-1 with intermediate A-41. MS (ESI): mass calcd. for $C_{25}H_{22}N_6O_2$, 438.2; m/z found, 439.2 $[M+H]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5μm, 100 x 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 45 °C). R_t = 4.33 min (major rotamer) at 254 nm.

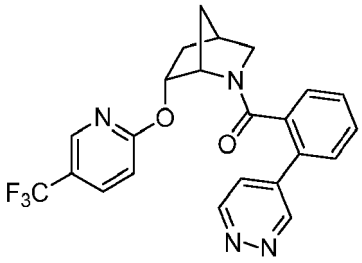
Example 303: (2-(pyridazin-3-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[0964]



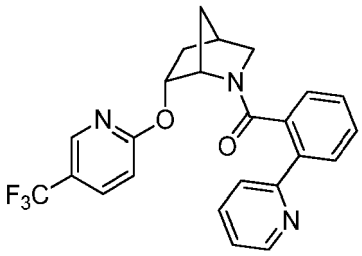
Example 304: (2-(pyridazin-4-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[0965]



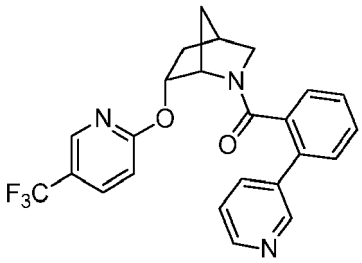
Example 305: (2-(pyridin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[0966]



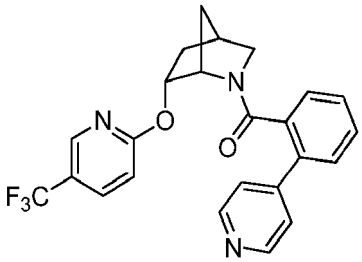
Example 306: (2-(pyridin-3-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

[0967]



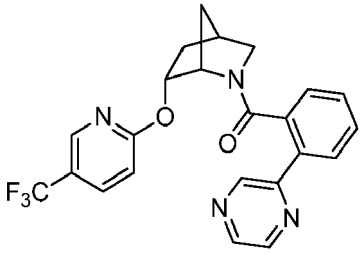
Example 307: (2-(pyridin-4-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[0968]



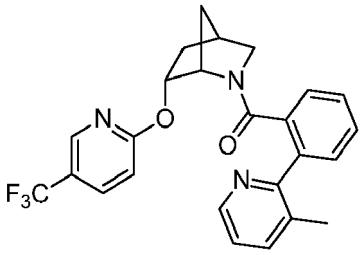
Example 308: (2-(pyrazin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[0969]



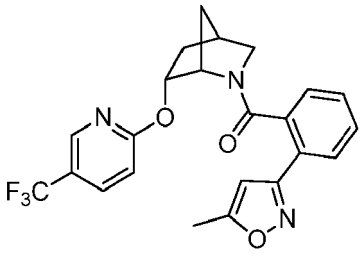
Example 309: (2-(3-methylpyridin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[0970]



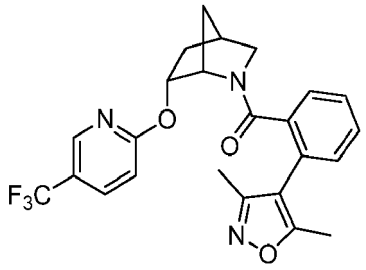
Example 310: (2-(5-methylisoxazol-3-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[0971]



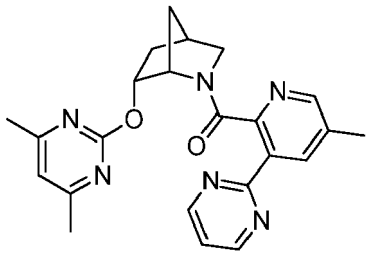
Example 311: (2-(3,5-dimethylisoxazol-4-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[0972]



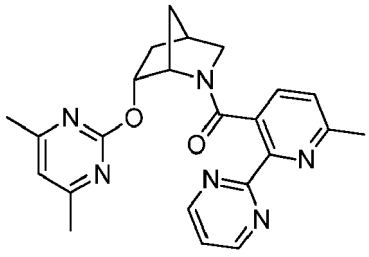
Example 312: ((1S,4R,6R)-6-((4,6-dimethylpyrimidin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)(5-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)methanone.

[0973]



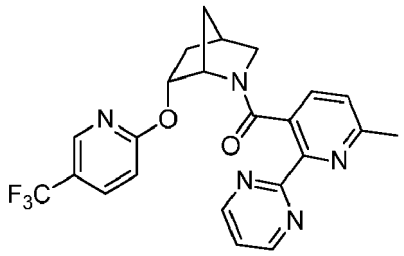
Example 313: ((1S,4R,6R)-6-((4,6-dimethylpyrimidin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)(6-methyl-2-(pyrimidin-2-yl)pyridin-3-yl)methanone.

[0974]



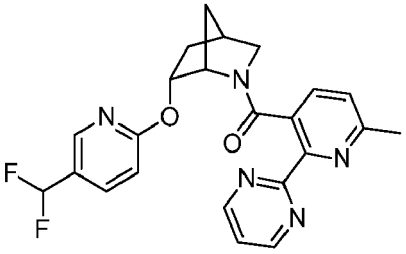
Example 314: (6-methyl-2-(pyrimidin-2-yl)pyridin-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[0975]



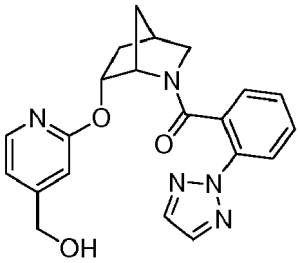
Example 315: ((1S,4R,6R)-6-((5-(difluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)(6-methyl-2-(pyrimidin-2-yl)pyridin-3-yl)methanone.

[0976]



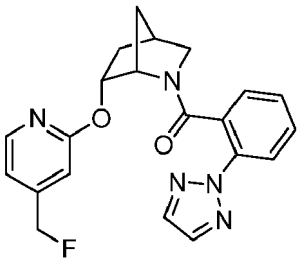
Example 316: (2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((5-(hydroxymethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[0977]



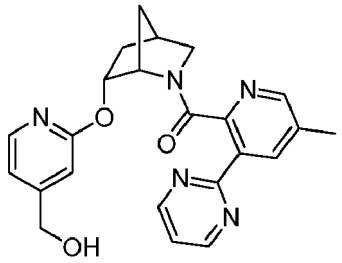
Example 317: (2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((5-(fluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[0978]



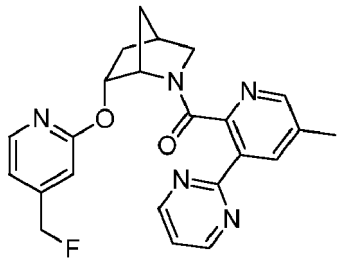
Example 318: ((1S,4R,6R)-6-((5-(hydroxymethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)(5-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)methanone.

[0979]



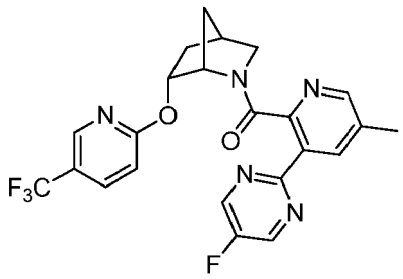
Example 319: ((1S,4R,6R)-6-((5-(fluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)(5-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)methanone.

[0980]



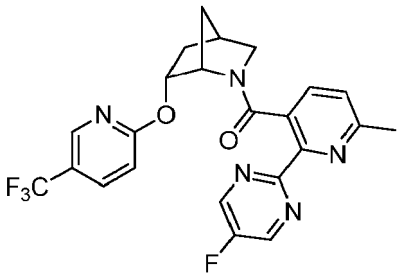
Example 320: (3-(5-fluoropyrimidin-2-yl)-5-methylpyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[0981]



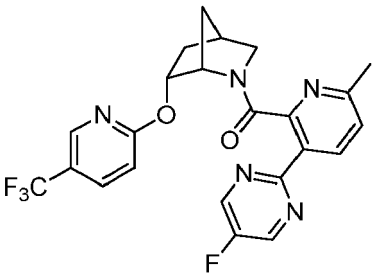
Example 321: (2-(5-fluoropyrimidin-2-yl)-6-methylpyridin-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[0982]



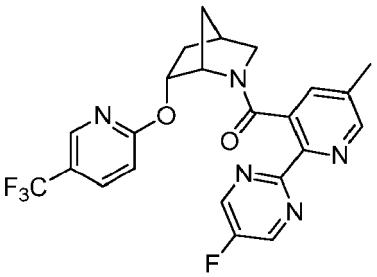
Example 322: (3-(5-fluoropyrimidin-2-yl)-6-methylpyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[0983]



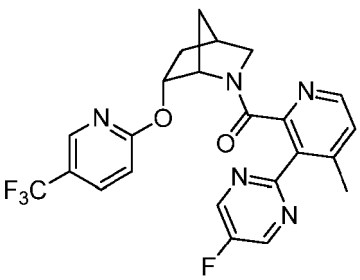
Example 323: (2-(5-fluoropyrimidin-2-yl)-5-methylpyridin-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[0984]



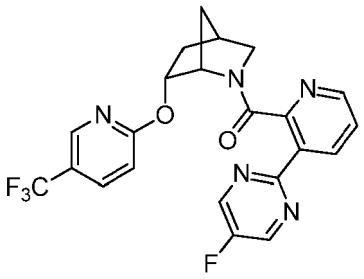
Example 324: (3-(5-fluoropyrimidin-2-yl)-4-methylpyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[0985]



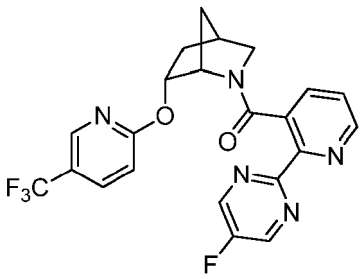
Example 325: (3-(5-fluoropyrimidin-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[0986]



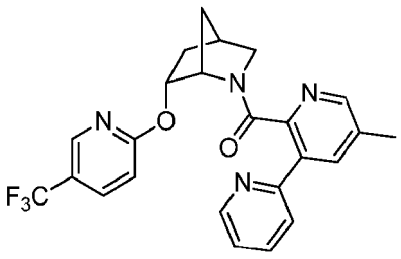
Example 326: (2-(5-fluoropyrimidin-2-yl)pyridin-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[0987]



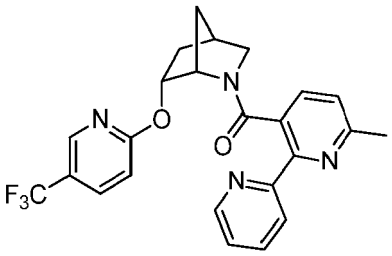
Example 327: (5'-methyl-[2,3'-bipyridin]-2'-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[0988]



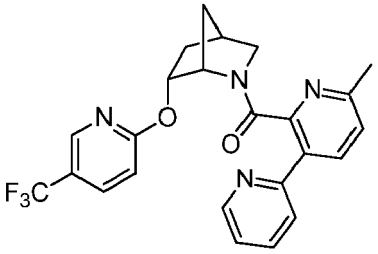
Example 328: (6-methyl-[2,2'-bipyridin]-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[0989]



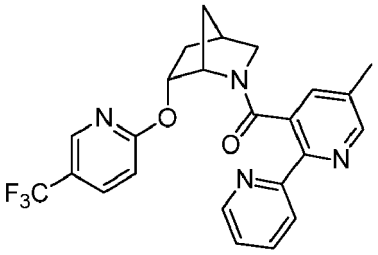
Example 329: (6'-methyl-[2,3'-bipyridin]-2'-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[0990]



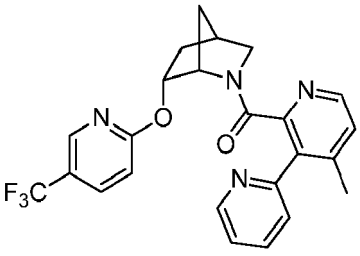
Example 330: (5-methyl-[2,2'-bipyridin]-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[0991]



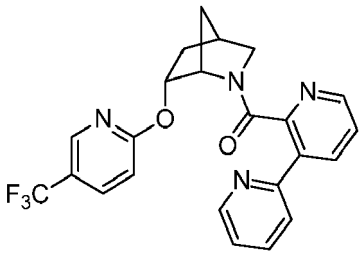
Example 331: (4'-methyl-[2,3'-bipyridin]-2'-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[0992]



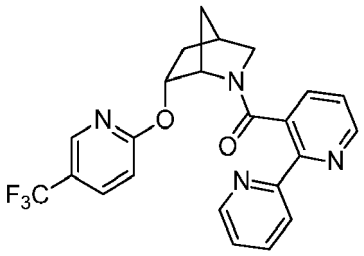
Example 332: [2,3'-bipyridin]-2'-yl((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[0993]



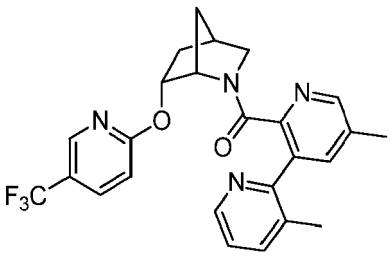
Example 333: [2,2'-bipyridin]-3-yl((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[0994]



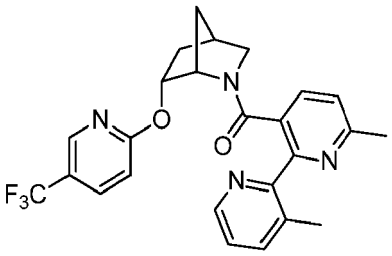
Example 334: (3,5'-dimethyl-[2,3'-bipyridin]-2'-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[0995]



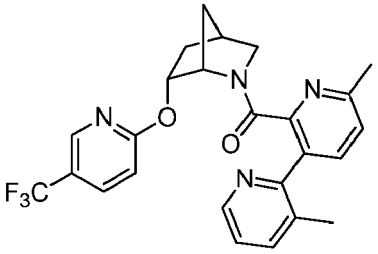
Example 335: (3',6-dimethyl-[2,2'-bipyridin]-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[0996]



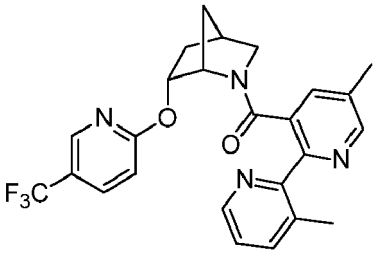
Example 336: (3,6'-dimethyl-[2,3'-bipyridin]-2'-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[0997]



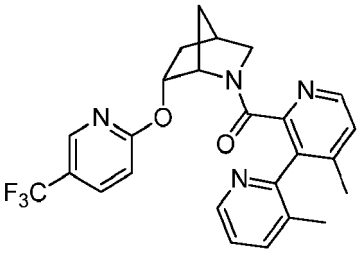
Example 337: (3',5-dimethyl-[2,2'-bipyridin]-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[0998]



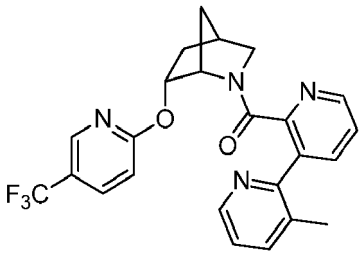
Example 338: (3,4'-dimethyl-[2,3'-bipyridin]-2'-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[0999]



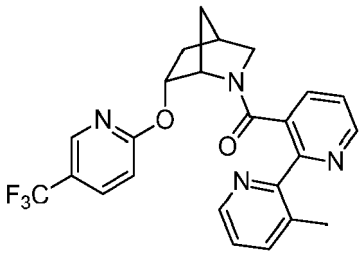
Example 339: (3-methyl-[2,3'-bipyridin]-2'-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1000]



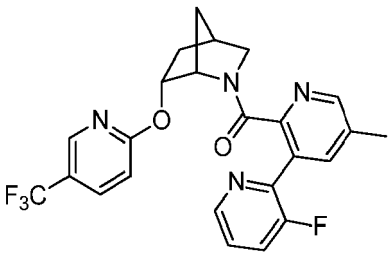
Example 340: (3'-methyl-[2,2'-bipyridin]-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1001]



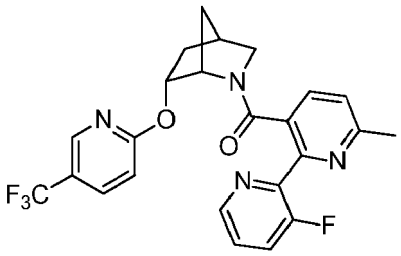
Example 341: (3-fluoro-5'-methyl-[2,3'-bipyridin]-2'-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1002]



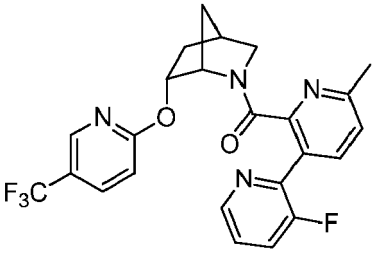
Example 342: (3'-fluoro-6-methyl-[2,2'-bipyridin]-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1003]



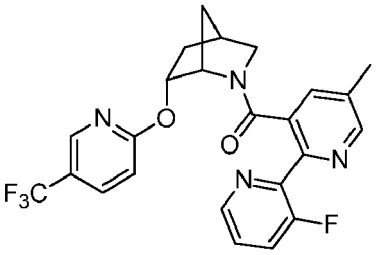
Example 343: (3-fluoro-6'-methyl-[2,3'-bipyridin]-2'-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1004]



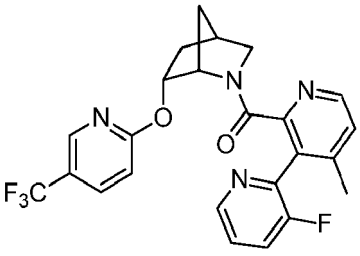
Example 344: (3'-fluoro-5-methyl-[2,2'-bipyridin]-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1005]



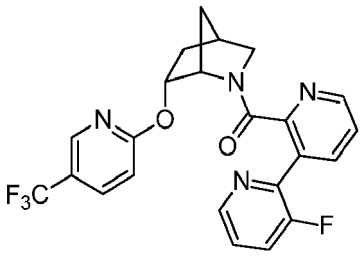
Example 345: (3-fluoro-4'-methyl-[2,3'-bipyridin]-2'-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1006]



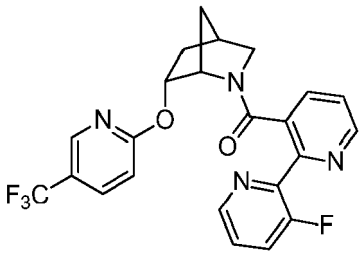
Example 346: (3-fluoro-[2,3'-bipyridin]-2'-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1007]



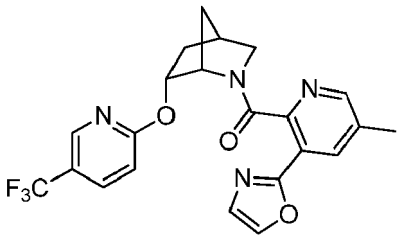
Example 347: (3'-fluoro-[2,2'-bipyridin]-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1008]



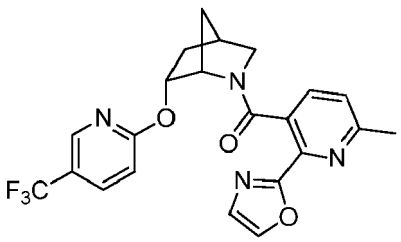
Example 348: (5-methyl-3-(oxazol-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1009]



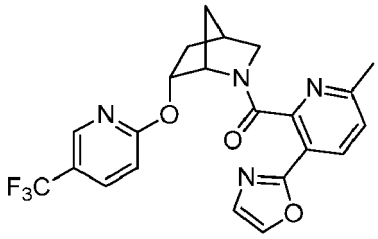
Example 349: (6-methyl-2-(oxazol-2-yl)pyridin-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1010]



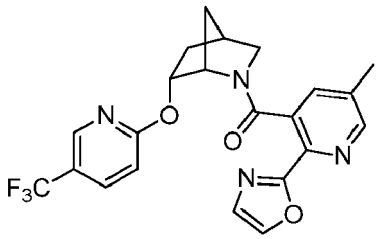
Example 350: (6-methyl-3-(oxazol-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1011]



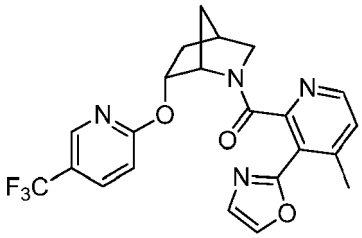
Example 351: (5-methyl-2-(oxazol-2-yl)pyridin-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1012]



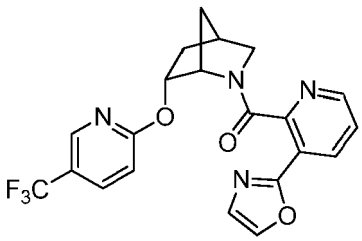
Example 352: (4-methyl-3-(oxazol-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1013]



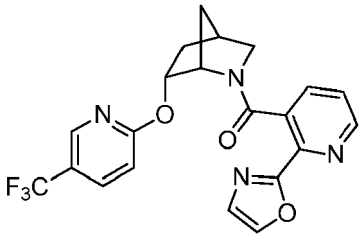
Example 353: (3-(oxazol-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1014]



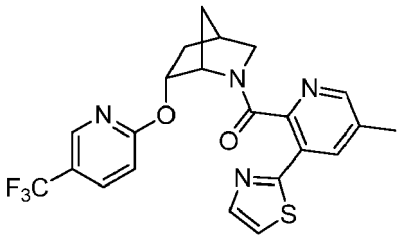
Example 354: (2-(oxazol-2-yl)pyridin-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1015]



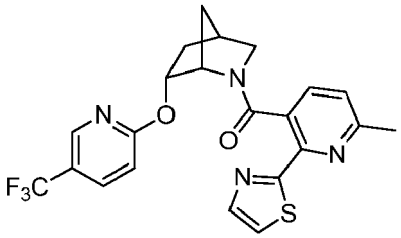
Example 355: (5-methyl-3-(thiazol-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1016]



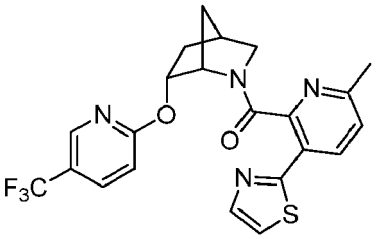
Example 356: (6-methyl-2-(thiazol-2-yl)pyridin-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1017]



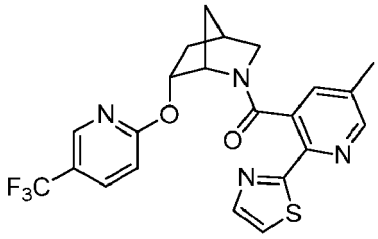
Example 357: (6-methyl-3-(thiazol-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1018]



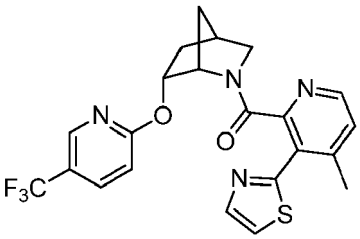
Example 358: (5-methyl-2-(thiazol-2-yl)pyridin-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1019]



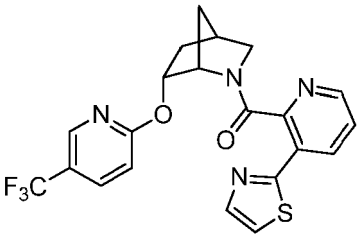
Example 359: (4-methyl-3-(thiazol-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1020]



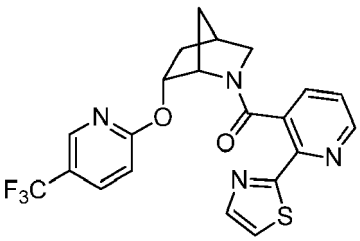
Example 360: (3-(thiazol-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1021]



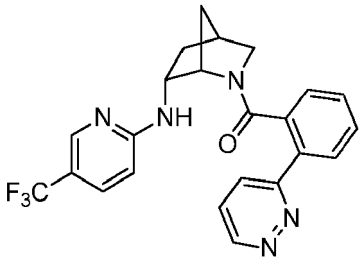
Example 361: (2-(thiazol-2-yl)pyridin-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1022]



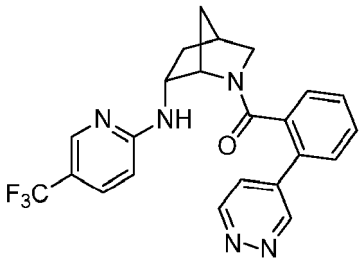
Example 362: (2-(pyridazin-3-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1023]



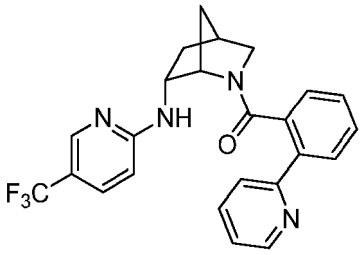
Example 363: (2-(pyridazin-4-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1024]



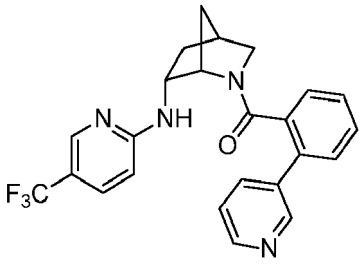
Example 364: (2-(pyridin-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1025]



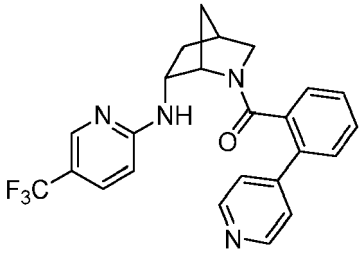
Example 365: (2-(pyridin-3-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1026]



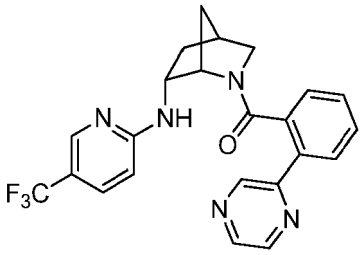
Example 366: (2-(pyridin-4-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1027]



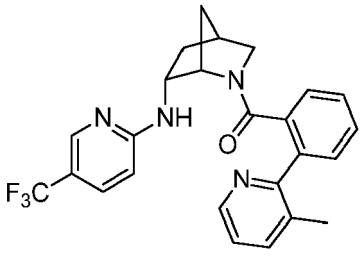
Example 367: (2-(pyrazin-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1028]



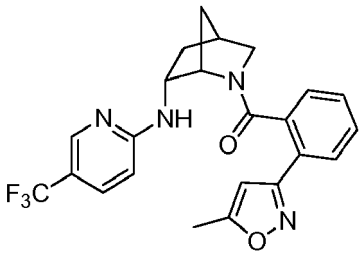
Example 368: (2-(3-methylpyridin-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1029]



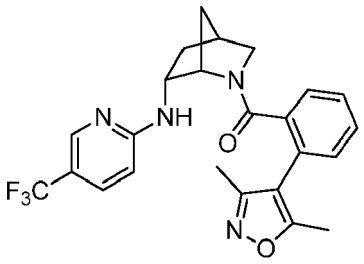
Example 369: (2-(5-methylisoxazol-3-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1030]



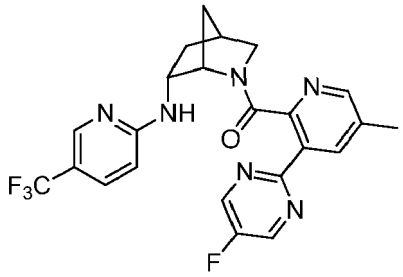
Example 370: (2-(3,5-dimethylisoxazol-4-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1031]



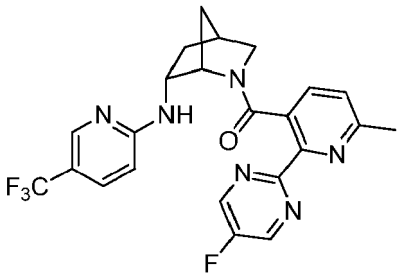
Example 371: (3-(5-fluoropyrimidin-2-yl)-5-methylpyridin-2-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1032]



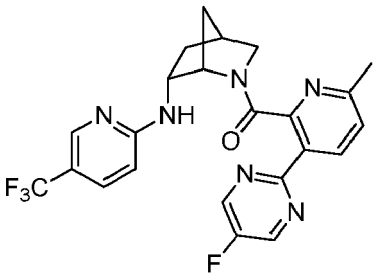
Example 372: (2-(5-fluoropyrimidin-2-yl)-6-methylpyridin-3-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1033]



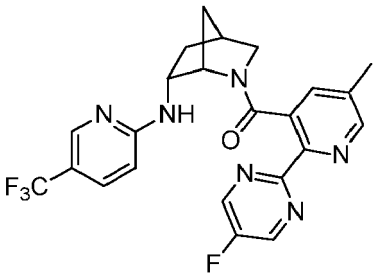
Example 373: (3-(5-fluoropyrimidin-2-yl)-6-methylpyridin-2-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1034]



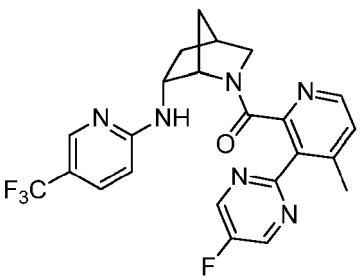
Example 374: (2-(5-fluoropyrimidin-2-yl)-5-methylpyridin-3-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1035]



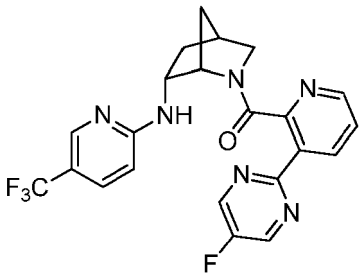
Example 375: (3-(5-fluoropyrimidin-2-yl)-4-methylpyridin-2-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1036]



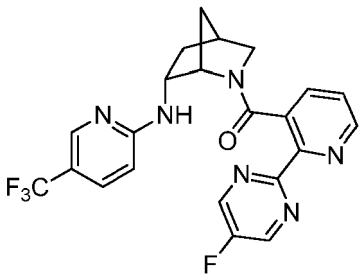
Example 376: (3-(5-fluoropyrimidin-2-yl)pyridin-2-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1037]



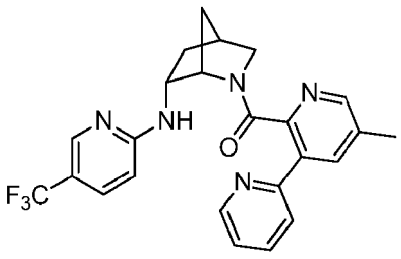
Example 377: (2-(5-fluoropyrimidin-2-yl)pyridin-3-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1038]



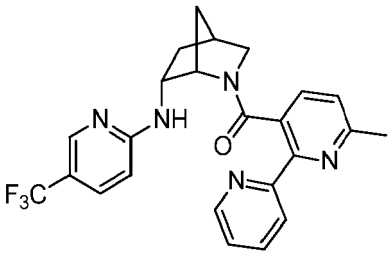
Example 378: (5'-methyl-[2,3'-bipyridin]-2'-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1039]



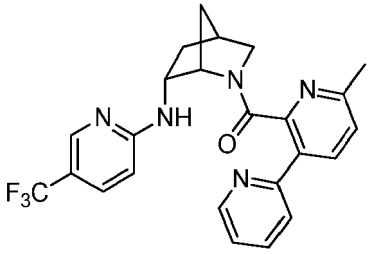
Example 379: (6-methyl-[2,2'-bipyridin]-3-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1040]



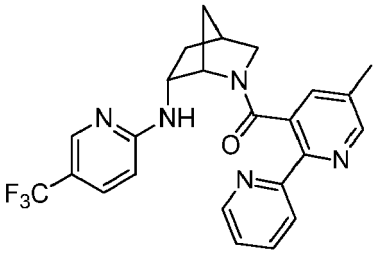
Example 380: (6'-methyl-[2,3'-bipyridin]-2'-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1041]



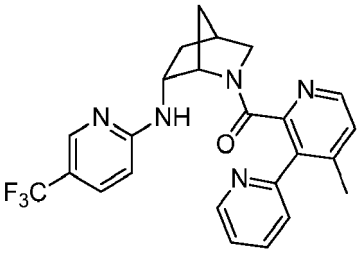
Example 381: (5-methyl-[2,2'-bipyridin]-3-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1042]



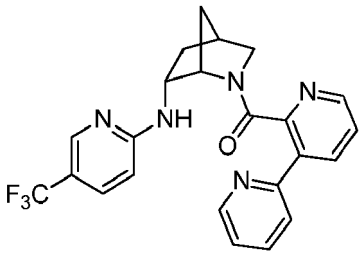
Example 382: (4'-methyl-[2,3'-bipyridin]-2'-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1043]



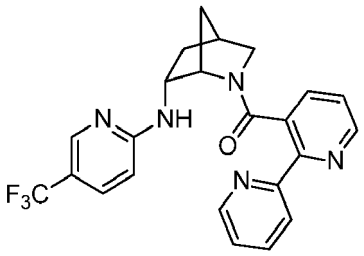
Example 383: [2,3'-bipyridin]-2'-yl((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1044]



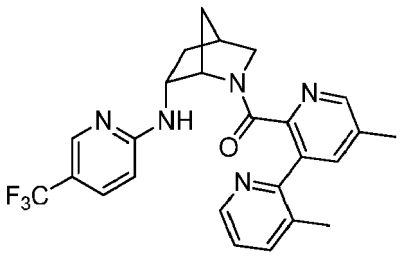
Example 384: [2,2'-bipyridin]-3-yl((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1045]



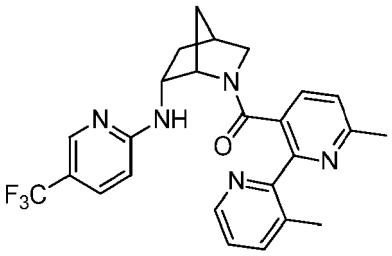
Example 385: (3,5'-dimethyl-[2,3'-bipyridin]-2'-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1046]



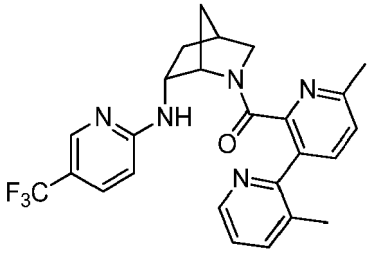
Example 386: (3',6-dimethyl-[2,2'-bipyridin]-3-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1047]



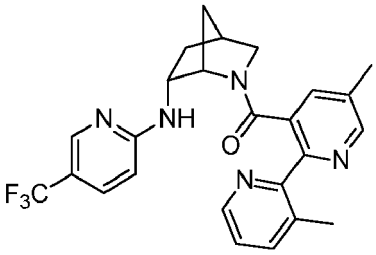
Example 387: (3,6'-dimethyl-[2,3'-bipyridin]-2'-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1048]



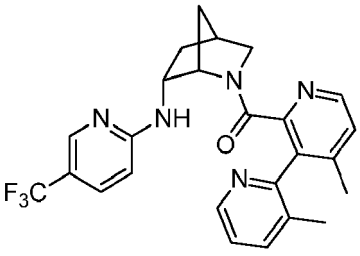
Example 388: (3',5-dimethyl-[2,2'-bipyridin]-3-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1049]



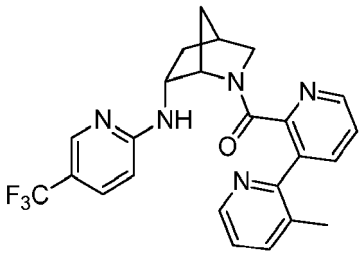
Example 389: (3,4'-dimethyl-[2,3'-bipyridin]-2'-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1050]



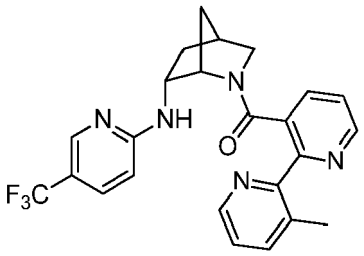
Example 390: (3-methyl-[2,3'-bipyridin]-2'-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1051]



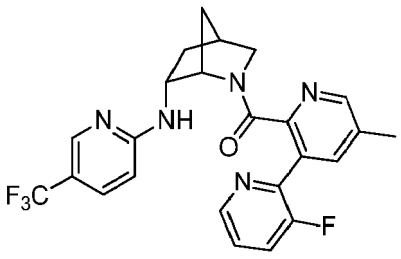
Example 391: (3'-methyl-[2,2'-bipyridin]-3-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1052]



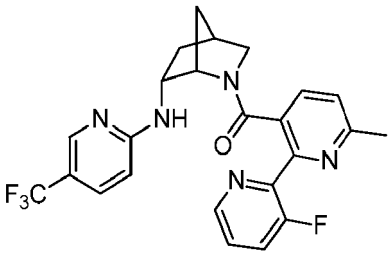
Example 392: (3-fluoro-5'-methyl-[2,3'-bipyridin]-2'-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1053]



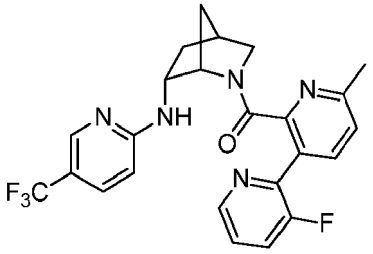
Example 393: (3'-fluoro-6-methyl-[2,2'-bipyridin]-3-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1054]



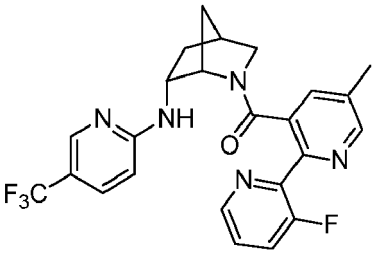
Example 394: (3-fluoro-6'-methyl-[2,3'-bipyridin]-2'-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1055]



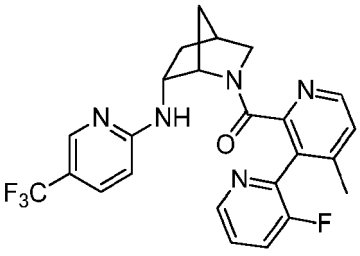
Example 395: (3'-fluoro-5-methyl-[2,2'-bipyridin]-3-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1056]



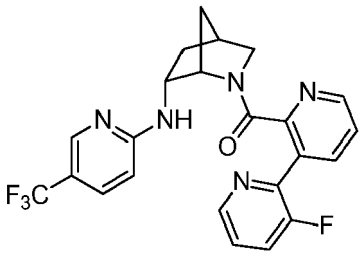
Example 396: (3-fluoro-4'-methyl-[2,3'-bipyridin]-2'-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1057]



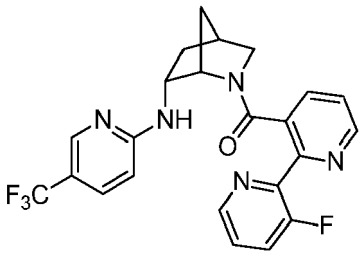
Example 397: (3 -fluoro- [2,3'-bipyridin]-2'-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1058]



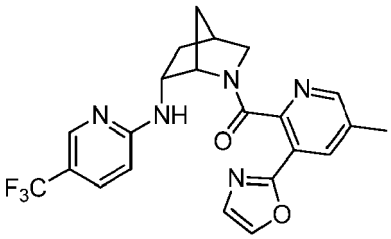
Example 398: (3'-fluoro-[2,2'-bipyridin]-3-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1059]



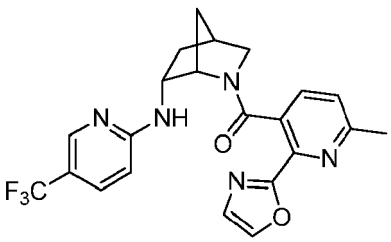
Example 399: (5-methyl-3-(oxazol-2-yl)pyridin-2-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1060]



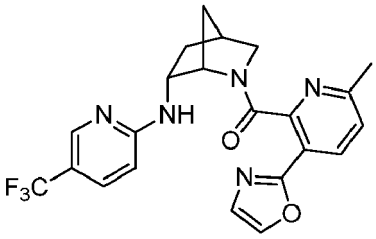
Example 400: (6-methyl-2-(oxazol-2-yl)pyridin-3-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1061]



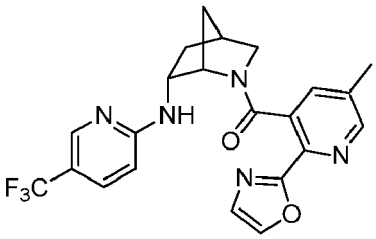
Example 401: (6-methyl-3-(oxazol-2-yl)pyridin-2-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1062]



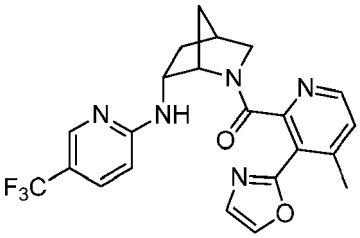
Example 402: (5-methyl-2-(oxazol-2-yl)pyridin-3-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1063]



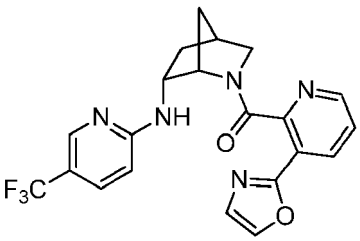
Example 403: (4-methyl-3-(oxazol-2-yl)pyridin-2-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1064]



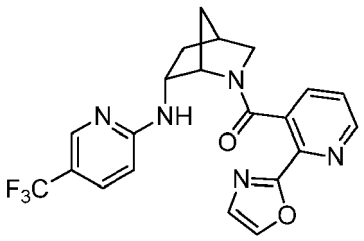
Example 404: (3-(oxazol-2-yl)pyridin-2-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1065]



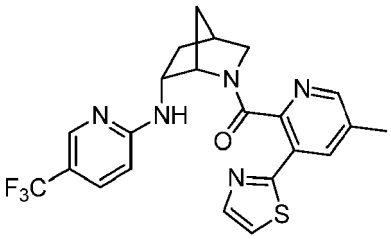
Example 405: (2-(oxazol-2-yl)pyridin-3-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1066]



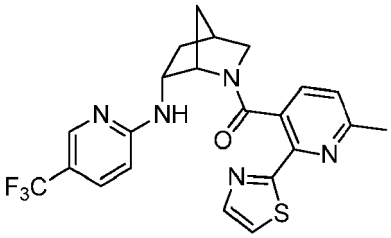
Example 406: (5-methyl-3-(thiazol-2-yl)pyridin-2-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1067]



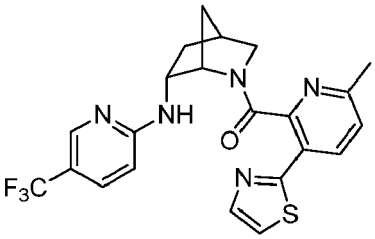
Example 407: (6-methyl-2-(thiazol-2-yl)pyridin-3 -yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1068]



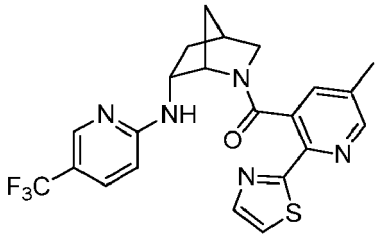
Example 408: (6-methyl-3-(thiazol-2-yl)pyridin-2-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1069]



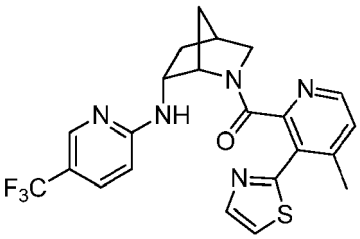
Example 409: (5-methyl-2-(thiazol-2-yl)pyridin-3 -yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1070]



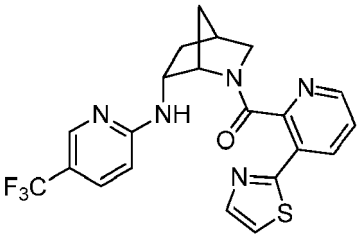
Example 410: (4-methyl-3-(thiazol-2-yl)pyridin-2-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1071]



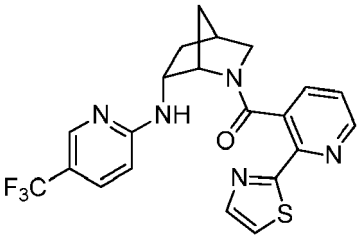
Example 411: (3-(thiazol-2-yl)pyridin-2-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1072]



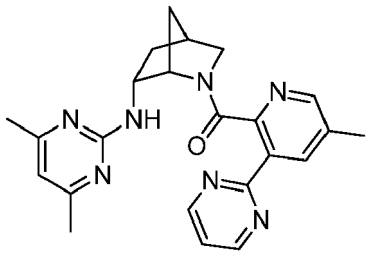
Example 412: (2-(thiazol-2-yl)pyridin-3-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1073]



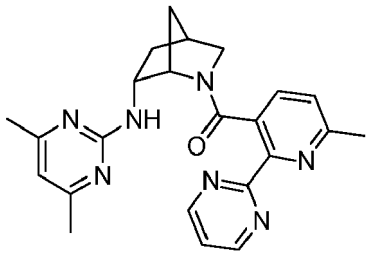
Example 413: ((1S,4S,6R)-6-((4,6-dimethylpyrimidin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)(5-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)methanone.

[1074]



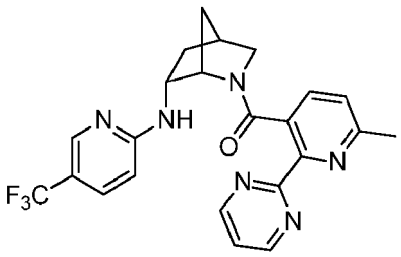
Example 414: ((1S,4S,6R)-6-((4,6-dimethylpyrimidin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)(6-methyl-2-(pyrimidin-2-yl)pyridin-3-yl)methanone.

[1075]



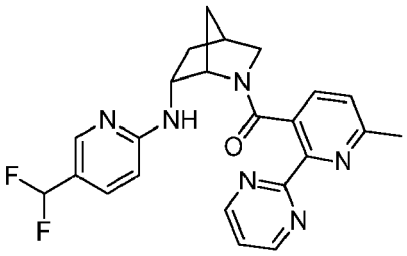
Example 415: (6-methyl-2-(pyrimidin-2-yl)pyridin-3-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1076]



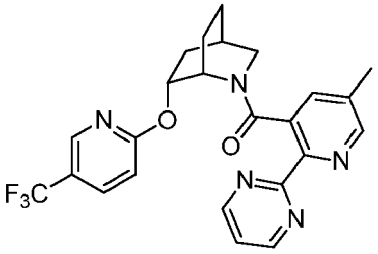
Example 416: ((1S,4S,6R)-6-((5-(difluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)(6-methyl-2-(pyrimidin-2-yl)pyridin-3-yl)methanone.

[1077]



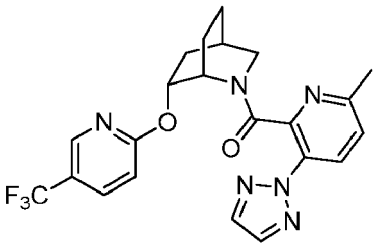
Example 417: (5-methyl-2-(pyrimidin-2-yl)pyridin-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1078]



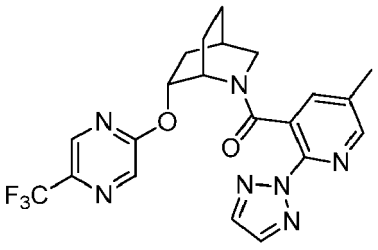
Example 418: (6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1079]



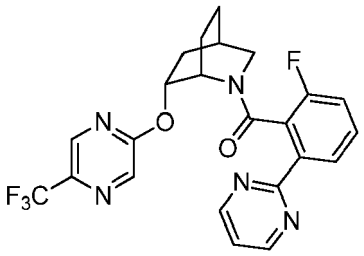
Example 419: (5-methyl-2-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1080]



Example 420: (2-fluoro-6-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

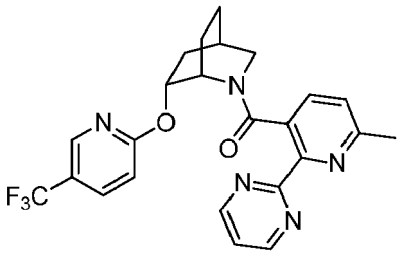
[1081]



[1082] Prepared analogous to Example 77 substituting intermediate A-40 with intermediate A-6. MS (ESI): mass calcd. for $C_{23}H_{19}F_4N_5O_2$, 473.2; m/z found, 474.2 $[M+H]^+$. Analytical HPLC was obtained on a Agilent 1100 Series using a XBridge C18 column (5μm, 100 × 4.6mm), mobile phase of 10-100% ACN in 20 mM NH_4OH over 8 min and then hold at 100% ACN for 3 min, at a flow rate of 1 mL/min (Temperature = 45 °C). R_t = 6.79 min (major rotamer) at 254 nm.

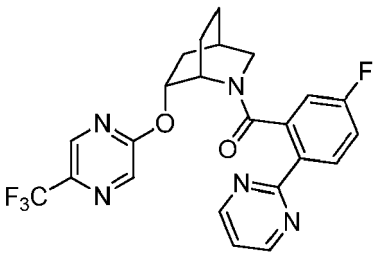
Example 421: (6-methyl-2-(pyrimidin-2-yl)pyridin-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1083]



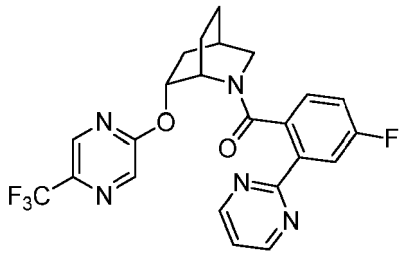
Example 422: (5-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1084]



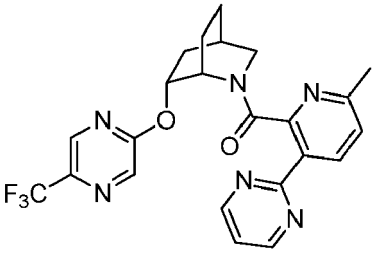
Example 423: (4-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1085]



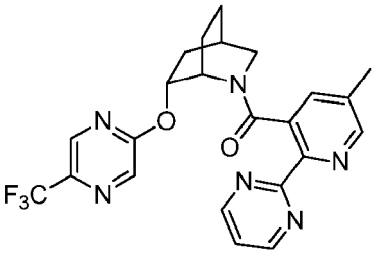
Example 424: (6-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1086]



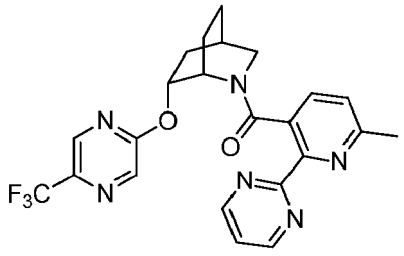
Example 425: (5-methyl-2-(pyrimidin-2-yl)pyridin-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1087]



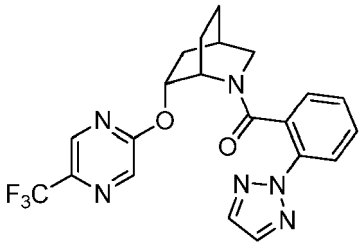
Example 426: (6-methyl-2-(pyrimidin-2-yl)pyridin-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1088]



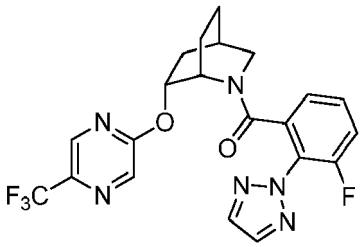
Example 427: (2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1089]



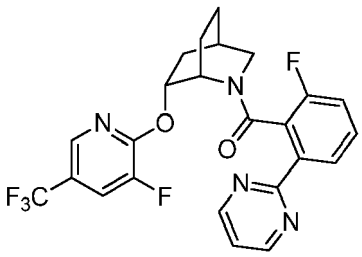
Example 428: (3-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1090]



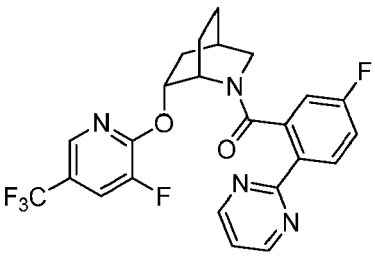
Example 429: ((1S,4R,6R)-6-((3-fluoro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)(2-fluoro-6-(pyrimidin-2-yl)phenyl)methanone.

[1091]



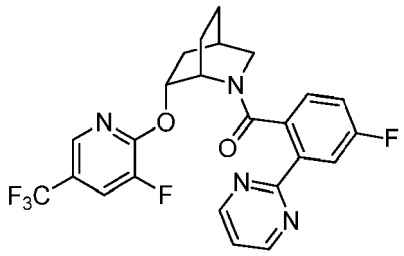
Example 430: (5-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((3-fluoro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1092]



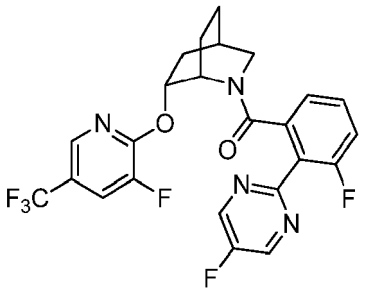
Example 431: (4-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((3-fluoro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1093]



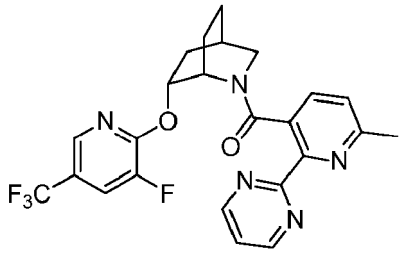
Example 432: (3-fluoro-2-(5-fluoropyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((3-fluoro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1094]



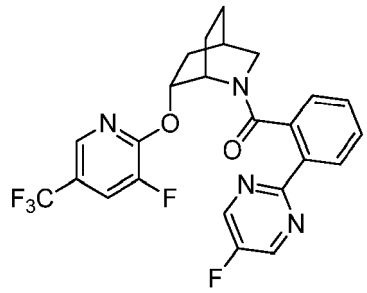
Example 433: ((1S,4R,6R)-6-((3-fluoro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)(6-methyl-2-(pyrimidin-2-yl)pyridin-3-yl)methanone.

[1095]



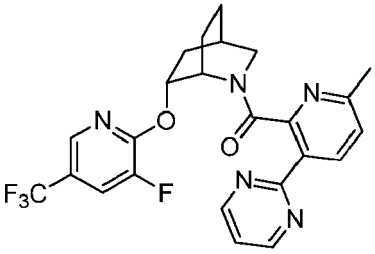
Example 434: ((1S,4R,6R)-6-((3-fluoro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)(2-(5-fluoropyrimidin-2-yl)phenyl)methanone.

[1096]



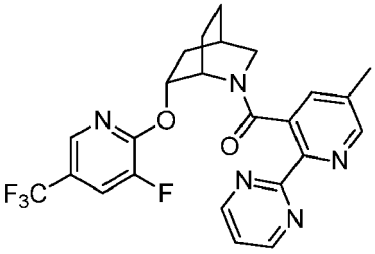
Example 435: ((1S,4R,6R)-6-((3-fluoro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)(6-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)methanone.

[1097]



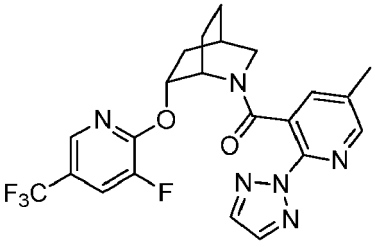
Example 436: ((1S,4R,6R)-6-((3-fluoro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)(5-methyl-2-(pyrimidin-2-yl)pyridin-3-yl)methanone.

[1098]



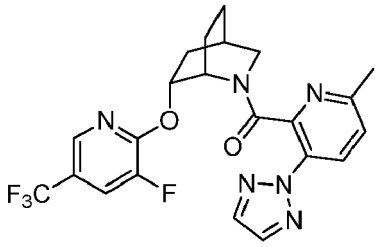
Example 437: ((1S,4R,6R)-6-((3-fluoro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)methanone.

[1099]



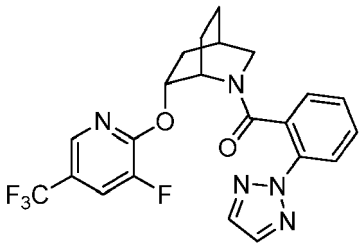
Example 438: ((1S,4R,6R)-6-((3-fluoro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)methanone.

[1100]



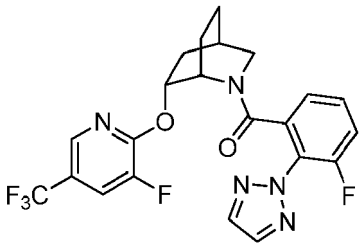
Example 439: (2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((3-fluoro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1101]



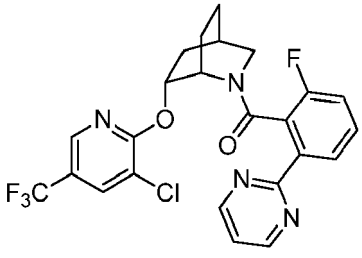
Example 440: (3-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((3-fluoro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1102]



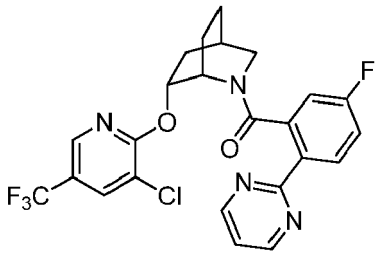
Example 441: ((1S,4R,6R)-6-((3-chloro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)(2-fluoro-6-(pyrimidin-2-yl)phenyl)methanone.

[1103]



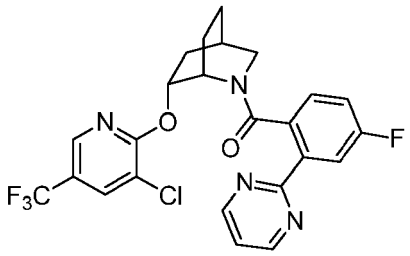
Example 442: ((1S,4R,6R)-6-((3-chloro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)(5-fluoro-2-(pyrimidin-2-yl)phenyl)methanone.

[1104]



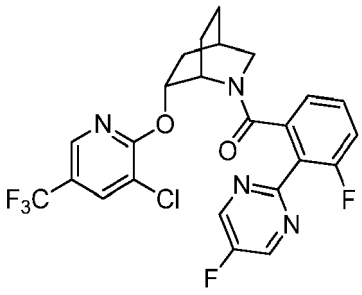
Example 443: ((1S,4R,6R)-6-((3-chloro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)(4-fluoro-2-(pyrimidin-2-yl)phenyl)methanone.

[1105]



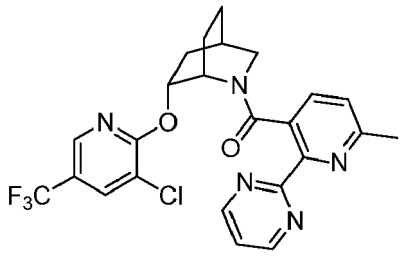
Example 444: ((1S,4R,6R)-6-((3-chloro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)(3-fluoro-2-(5-fluoropyrimidin-2-yl)phenyl)methanone.

[1106]



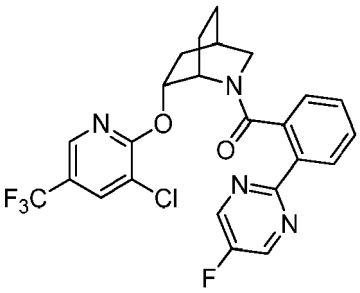
Example 445: ((1S,4R,6R)-6-((3-chloro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)(6-methyl-2-(pyrimidin-2-yl)pyridin-3-yl)methanone.

[1107]



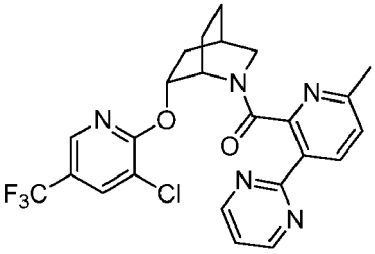
Example 446: ((1S,4R,6R)-6-((3-chloro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)(2-(5-fluoropyrimidin-2-yl)phenyl)methanone.

[1108]



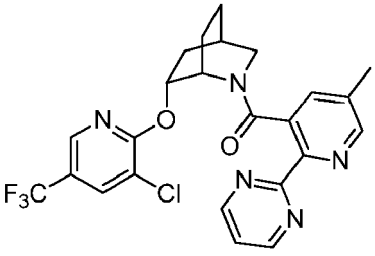
Example 447: ((1S,4R,6R)-6-((3-chloro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)(6-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)methanone.

[1109]



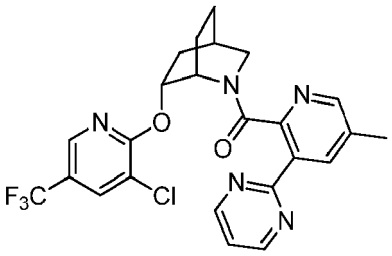
Example 448: ((1S,4R,6R)-6-((3-chloro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)(5-methyl-2-(pyrimidin-2-yl)pyridin-3-yl)methanone.

[1110]



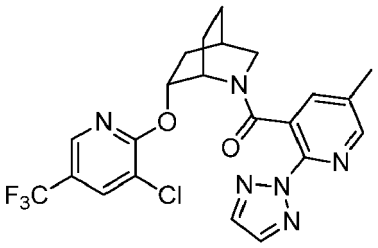
Example 449: ((1S,4R,6R)-6-((3-chloro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)(5-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)methanone.

[1111]



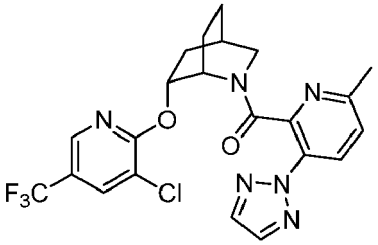
Example 450: ((1S,4R,6R)-6-((3-chloro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)methanone.

[1112]



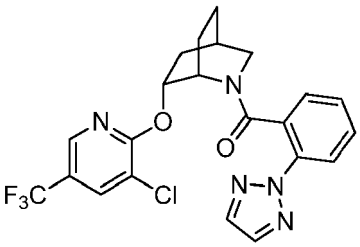
Example 451: ((1S,4R,6R)-6-((3-chloro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)methanone.

[1113]



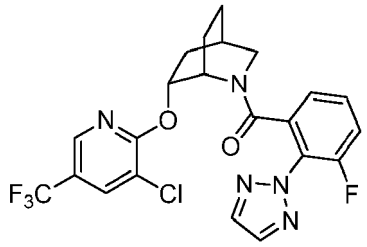
Example 452: (2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((3-chloro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1114]



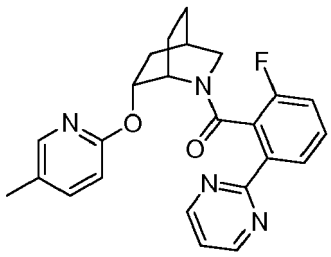
Example 453: ((1S,4R,6R)-6-((3-chloro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)(3-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone.

[1115]



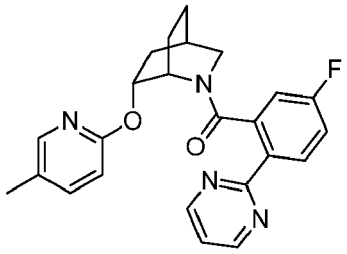
Example 454: (2-fluoro-6-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-methylpyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1116]



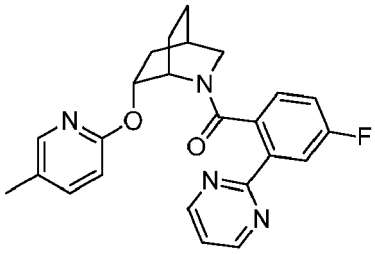
Example 455: (5-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-methylpyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1117]



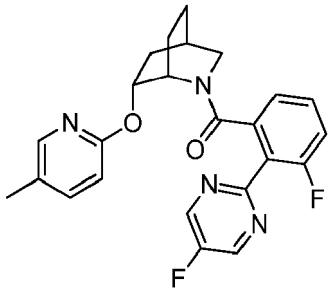
Example 456: (4-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-methylpyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1118]



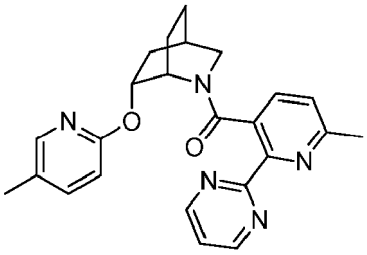
Example 457: (3-fluoro-2-(5-fluoropyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-methylpyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1119]



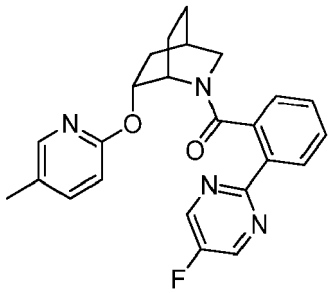
Example 458: (6-methyl-2-(pyrimidin-2-yl)pyridin-3-yl)((1S,4R,6R)-6-((5-methylpyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1120]



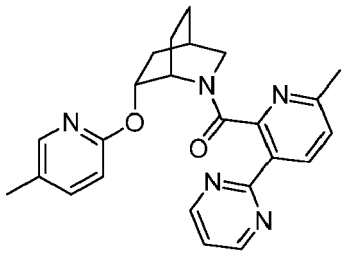
Example 459: (2-(5-fluoropyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-methylpyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1121]



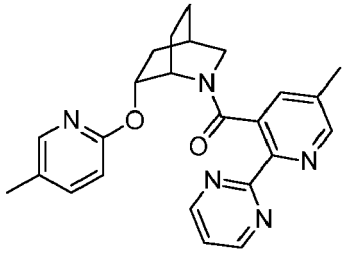
Example 460: (6-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-methylpyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1122]



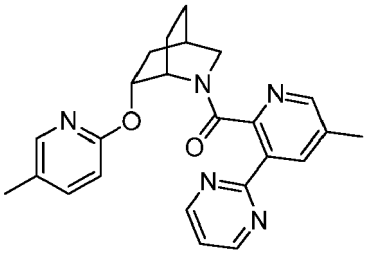
Example 461: (5-methyl-2-(pyrimidin-2-yl)pyridin-3-yl)((1S,4R,6R)-6-((5-methylpyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1123]



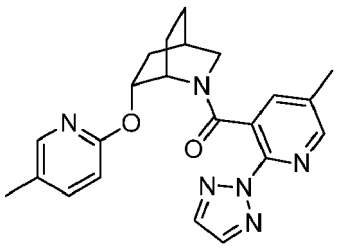
Example 462: (5-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-methylpyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1124]



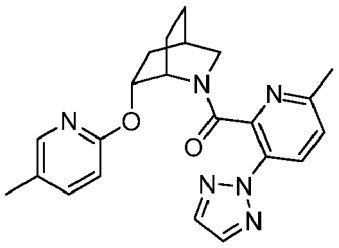
Example 463: (5-methyl-2-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)((1S,4R,6R)-6-((5-methylpyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1125]



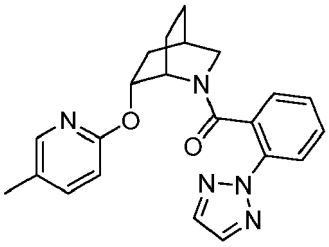
Example 464: (6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-methylpyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1126]



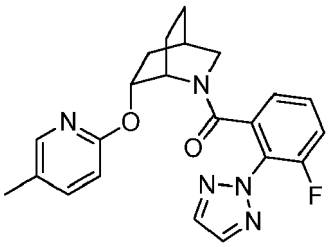
Example 465: (2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((5-methylpyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1127]



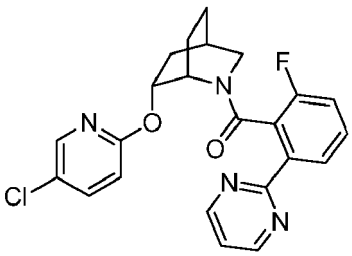
Example 466: (3-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((5-methylpyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1128]



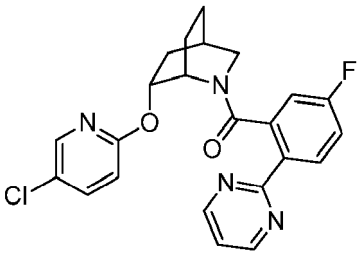
Example 467: ((1S,4R,6R)-6-((5-chloropyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)(2-fluoro-6-(pyrimidin-2-yl)phenyl)methanone.

[1129]



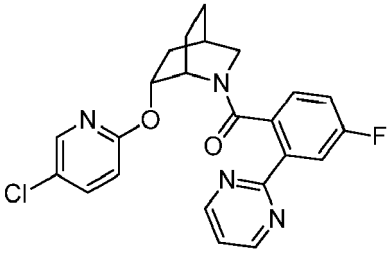
Example 468: ((1S,4R,6R)-6-((5-chloropyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)(5-fluoro-2-(pyrimidin-2-yl)phenyl)methanone.

[1130]



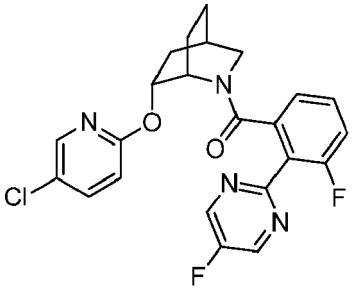
Example 469: ((1S,4R,6R)-6-((5-chloropyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)(4-fluoro-2-(pyrimidin-2-yl)phenyl)methanone.

[1131]



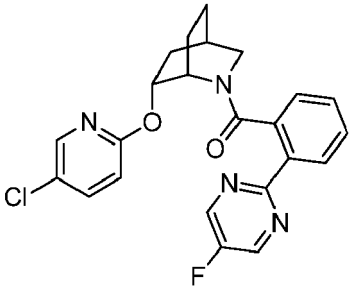
Example 470: ((1S,4R,6R)-6-((5-chloropyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)(3-fluoro-2-(5-fluoropyrimidin-2-yl)phenyl)methanone.

[1132]



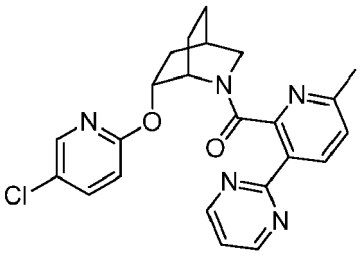
Example 471: ((1S,4R,6R)-6-((5-chloropyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)(2-(5-fluoropyrimidin-2-yl)phenyl)methanone.

[1133]



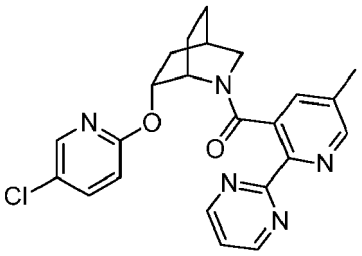
Example 472: ((1S,4R,6R)-6-((5-chloropyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)(6-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)methanone.

[1134]



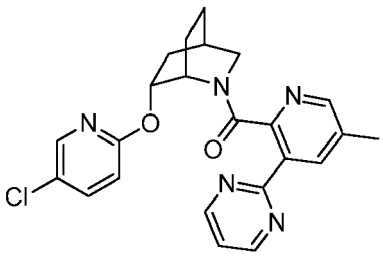
Example 473: ((1S,4R,6R)-6-((5-chloropyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)(5-methyl-2-(pyrimidin-2-yl)pyridin-3-yl)methanone.

[1135]



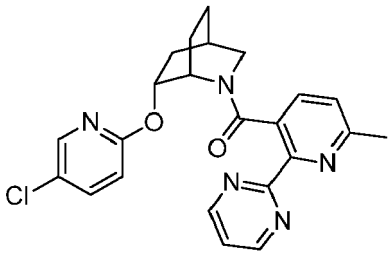
Example 474: ((1S,4R,6R)-6-((5-chloropyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)(5-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)methanone.

[1136]



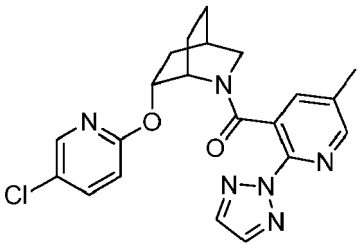
Example 475: ((1S,4R,6R)-6-((5-chloropyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)(6-methyl-2-(pyrimidin-2-yl)pyridin-3-yl)methanone.

[1137]



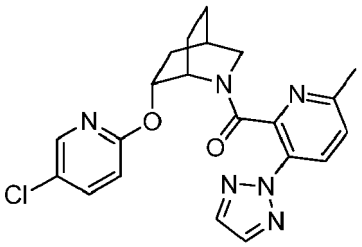
Example 476: ((1S,4R,6R)-6-((5-chloropyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)methanone.

[1138]



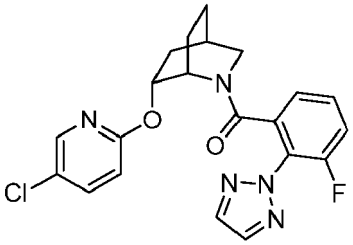
Example 477: ((1S,4R,6R)-6-((5-chloropyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)(6-methyl-3 -(2H-1,2,3-triazol-2-yl)pyridin-2-yl)methanone.

[1139]



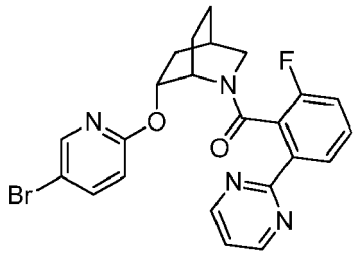
Example 478: ((1S,4R,6R)-6-((5-chloropyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)(3-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone.

[1140]



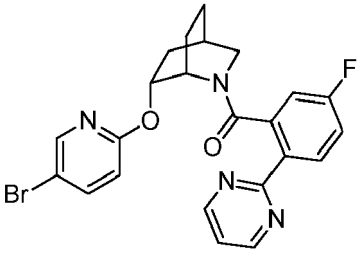
Example 479: ((1S,4R,6R)-6-((5-bromopyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)(2-fluoro-6-(pyrimidin-2-yl)phenyl)methanone.

[1141]



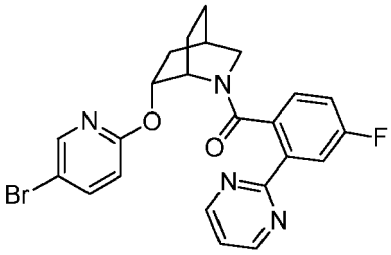
Example 480: ((1S,4R,6R)-6-((5-bromopyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)(5-fluoro-2-(pyrimidin-2-yl)phenyl)methanone.

[1142]



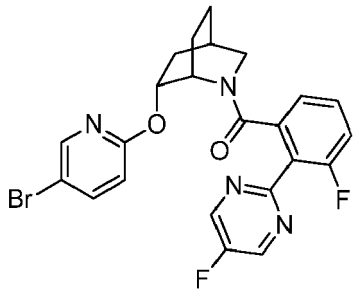
Example 481: ((1S,4R,6R)-6-((5-bromopyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)(4-fluoro-2-(pyrimidin-2-yl)phenyl)methanone.

[1143]



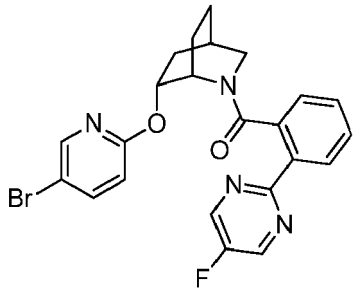
Example 482: ((1S,4R,6R)-6-((5-bromopyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)(3-fluoro-2-(5-fluoropyrimidin-2-yl)phenyl)methanone.

[1144]



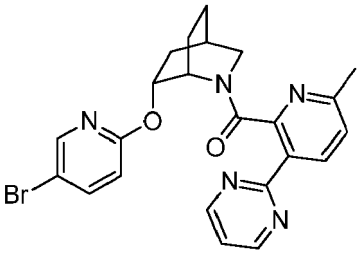
Example 483: ((1S,4R,6R)-6-((5-bromopyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)(2-(5-fluoropyrimidin-2-yl)phenyl)methanone.

[1145]



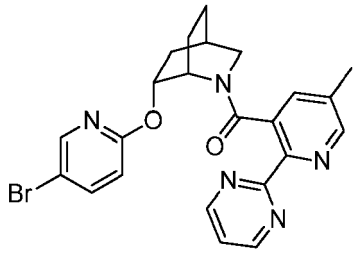
Example 484: ((1S,4R,6R)-6-((5-bromopyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)(6-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)methanone.

[1146]



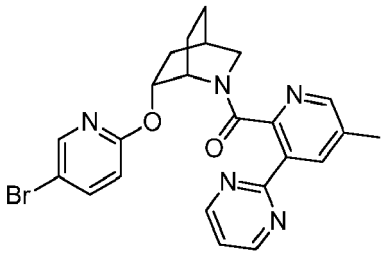
Example 485: ((1S,4R,6R)-6-((5-bromopyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)(5-methyl-2-(pyrimidin-2-yl)pyridin-3-yl)methanone.

[1147]



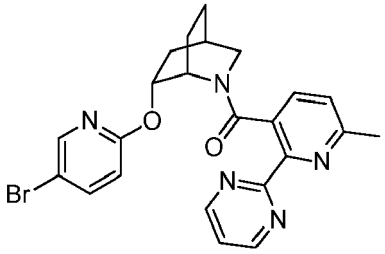
Example 486: ((1S,4R,6R)-6-((5-bromopyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)(5-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)methanone.

[1148]



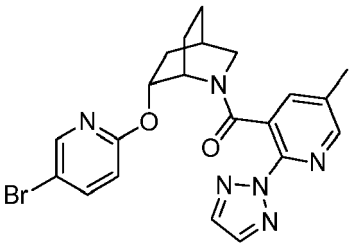
Example 487: ((1S,4R,6R)-6-((5-bromopyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)(6-methyl-2-(pyrimidin-2-yl)pyridin-3-yl)methanone.

[1149]



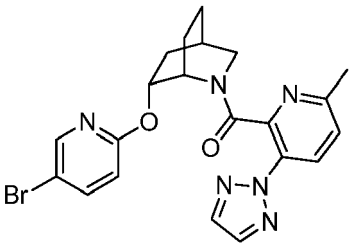
Example 488: ((1S,4R,6R)-6-((5-bromopyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)methanone.

[1150]



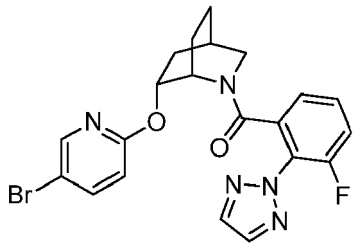
Example 489: ((1S,4R,6R)-6-((5-bromopyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)(6-methyl-3 -(2H-1,2,3-triazol-2-yl)pyridin-2-yl)methanone.

[1151]



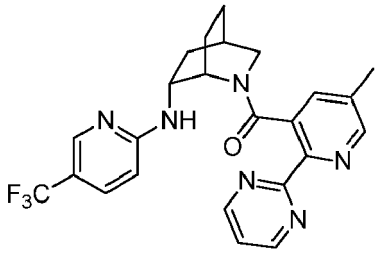
Example 490: ((1S,4R,6R)-6-((5-bromopyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)(3-fluoro-2-(2H-1,2,3 -triazol-2-yl)phenyl)methanone.

[1152]



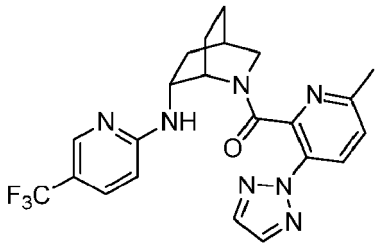
Example 491: (5-methyl-2-(pyrimidin-2-yl)pyridin-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1153]



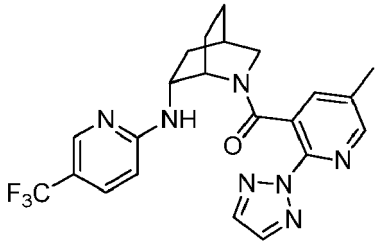
Example 492: (6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1154]



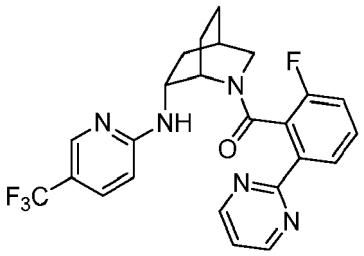
Example 493: (5-methyl-2-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1155]



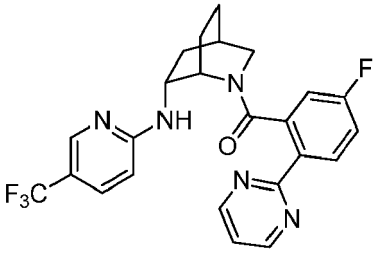
Example 494: (2-fluoro-6-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo [2.2.2] octan-2-yl)methanone.

[1156]



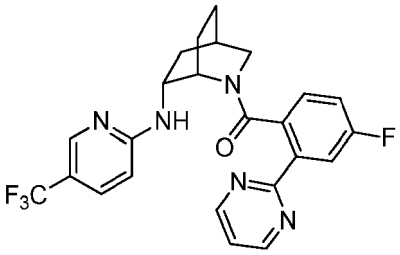
Example 495: (5-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo [2.2.2] octan-2-yl)methanone.

[1157]



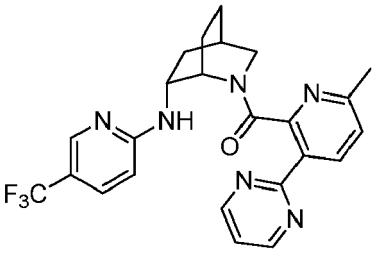
Example 496: (4-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo [2.2.2] octan-2-yl)methanone.

[1158]



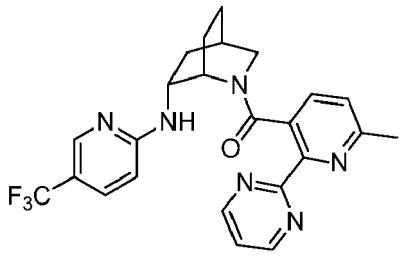
Example 497: (6-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1159]



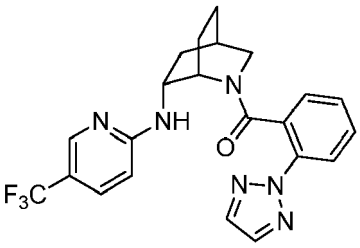
Example 498: (6-methyl-2-(pyrimidin-2-yl)pyridin-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1160]



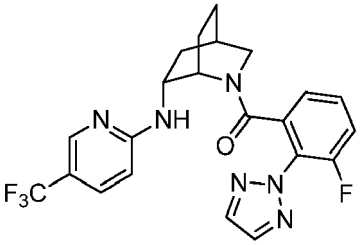
Example 499: (2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo [2.2.2] octan-2-yl)methanone.

[1161]



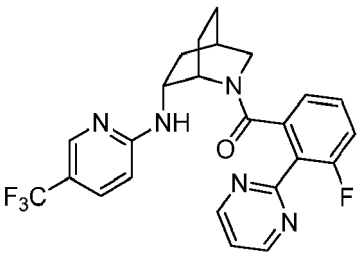
Example 500: (3-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1162]



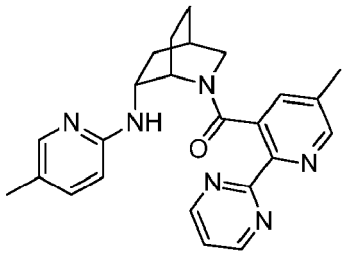
Example 501: (3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo [2.2.2] octan-2-yl)methanone.

[1163]



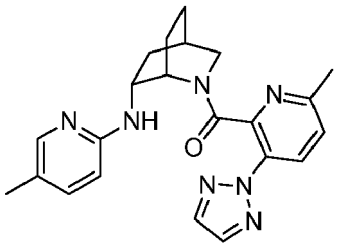
Example 502: (5-methyl-2-(pyrimidin-2-yl)pyridin-3-yl)((1S,4R,6R)-6-((5-methylpyridin-2-yl)amino)-2-azabicyclo [2.2.2] octan-2-yl)methanone.

[1164]



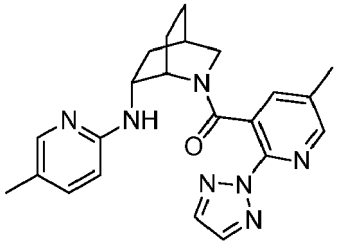
Example 503: (6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-methylpyridin-2-yl)amino)-2-azabicyclo [2.2.2] octan-2-yl)methanone.

[1165]



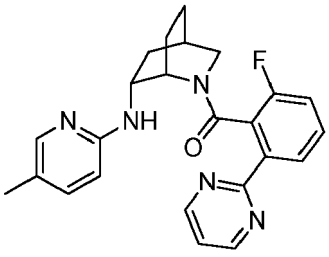
Example 504: (5-methyl-2-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)((1S,4R,6R)-6-((5-methylpyridin-2-yl)amino)-2-azabicyclo [2.2.2] octan-2-yl)methanone.

[1166]



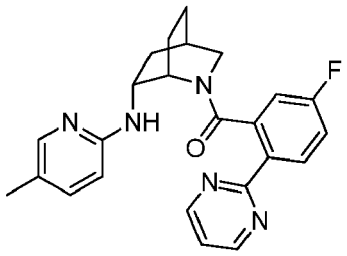
Example 505: (2-fluoro-6-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-methylpyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1167]



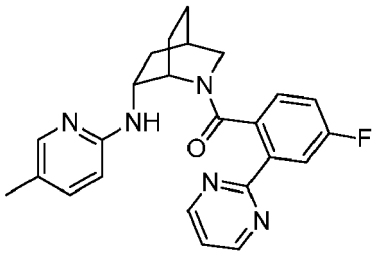
Example 506: (5-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-methylpyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1168]



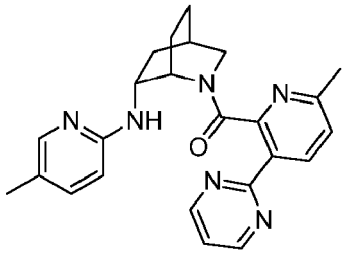
Example 507: (4-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-methylpyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1169]



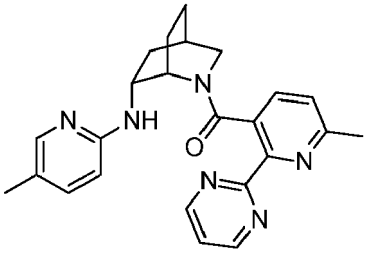
Example 508: (6-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-methylpyridin-2-yl)amino)-2-azabicyclo [2.2.2] octan-2-yl)methanone.

[1170]



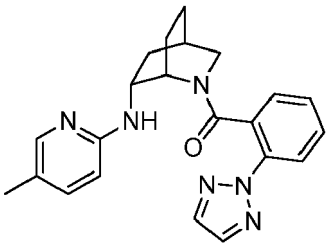
Example 509: (6-methyl-2-(pyrimidin-2-yl)pyridin-3-yl)((1S,4R,6R)-6-((5-methylpyridin-2-yl)amino)-2-azabicyclo [2.2.2] octan-2-yl)methanone.

[1171]



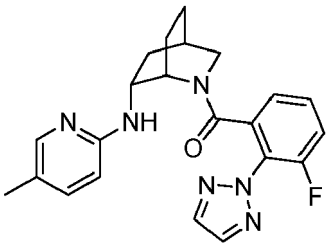
Example 510: (2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((5-methylpyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1172]



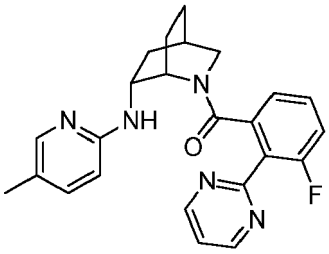
Example 511: (3-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((5-methylpyridin-2-yl)amino)-2-azabicyclo [2.2.2] octan-2-yl)methanone.

[1173]



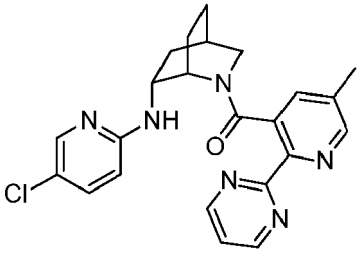
Example 512: (3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-methylpyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1174]



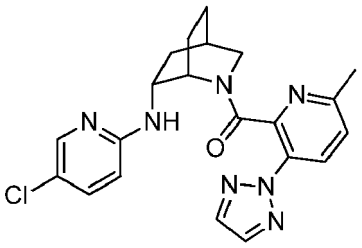
Example 513: ((1S,4R,6R)-6-((5-chloropyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)(5-methyl-2-(pyrimidin-2-yl)pyridin-3-yl)methanone.

[1175]



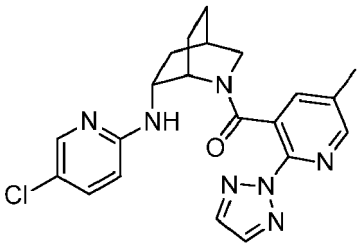
Example 514: ((1S,4R,6R)-6-((5-chloropyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)methanone.

[1176]



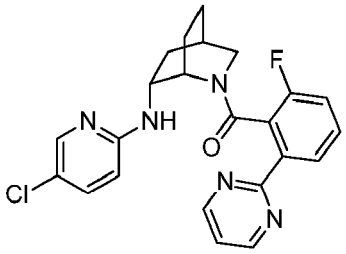
Example 515: ((1S,4R,6R)-6-((5-chloropyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)methanone.

[1177]



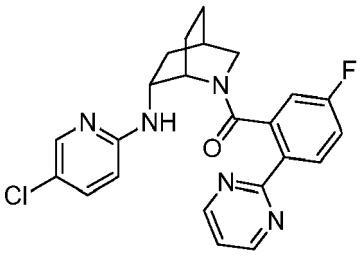
Example 516: ((1S,4R,6R)-6-((5-chloropyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)(2-fluoro-6-(pyrimidin-2-yl)phenyl)methanone.

[1178]



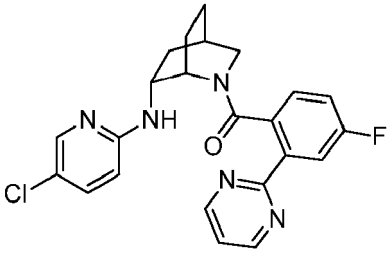
Example 517: ((1S,4R,6R)-6-((5-chloropyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)(5-fluoro-2-(pyrimidin-2-yl)phenyl)methanone.

[1179]



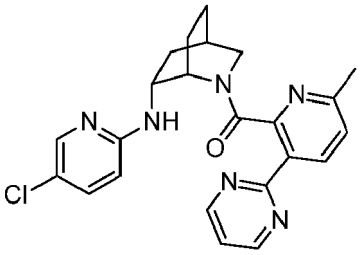
Example 518: ((1S,4R,6R)-6-((5-chloropyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)(4-fluoro-2-(pyrimidin-2-yl)phenyl)methanone.

[1180]



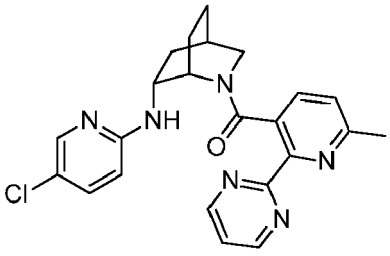
Example 519: ((1S,4R,6R)-6-((5-chloropyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)(6-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)methanone.

[1181]



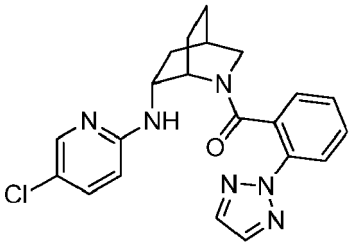
Example 520: ((1S,4R,6R)-6-((5-chloropyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)(6-methyl-2-(pyrimidin-2-yl)pyridin-3-yl)methanone.

[1182]



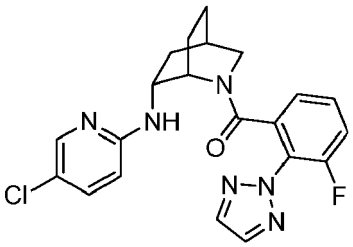
Example 521: (2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((5-chloropyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1183]



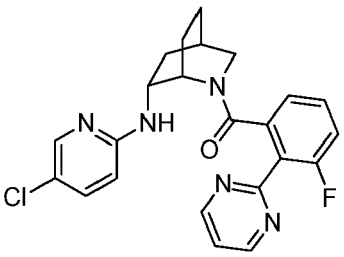
Example 522: ((1S,4R,6R)-6-((5-chloropyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)(3-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone.

[1184]



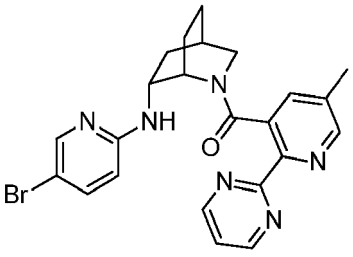
Example 523: ((1S,4R,6R)-6-((5-chloropyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)(3-fluoro-2-(pyrimidin-2-yl)phenyl)methanone.

[1185]



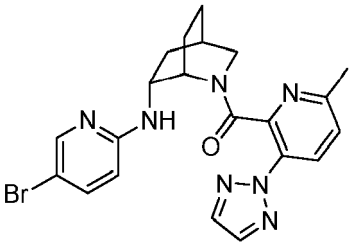
Example 524: ((1S,4R,6R)-6-((5-bromopyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)(5-methyl-2-(pyrimidin-2-yl)pyridin-3-yl)methanone.

[1186]



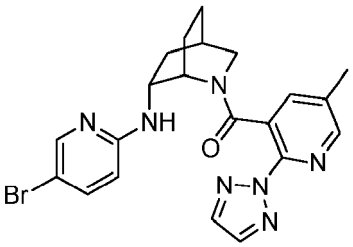
Example 525: ((1S,4R,6R)-6-((5-bromopyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)methanone.

[1187]



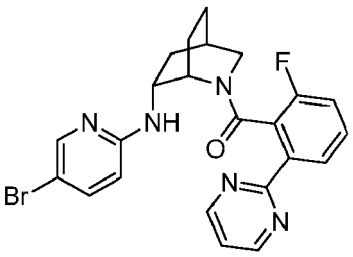
Example 526: ((1S,4R,6R)-6-((5-bromopyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)methanone.

[1188]



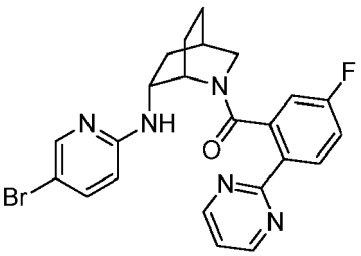
Example 527: ((1S,4R,6R)-6-((5-bromopyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)(2-fluoro-6-(pyrimidin-2-yl)phenyl)methanone.

[1189]



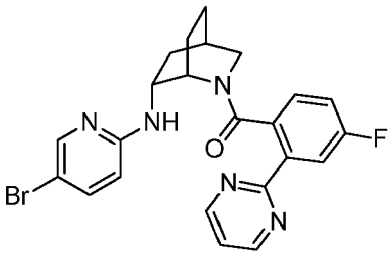
Example 528: ((1S,4R,6R)-6-((5-bromopyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)(5-fluoro-2-(pyrimidin-2-yl)phenyl)methanone.

[1190]



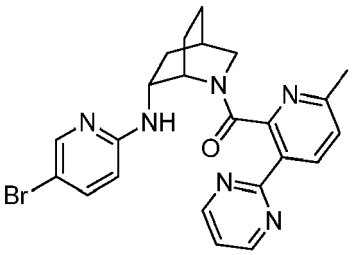
Example 529: ((1S,4R,6R)-6-((5-bromopyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)(4-fluoro-2-(pyrimidin-2-yl)phenyl)methanone.

[1191]



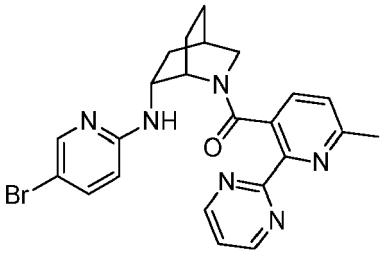
Example 530: ((1S,4R,6R)-6-((5-bromopyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)(6-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)methanone.

[1192]



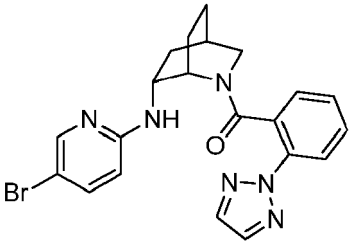
Example 531: ((1S,4R,6R)-6-((5-bromopyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)(6-methyl-2-(pyrimidin-2-yl)pyridin-3-yl)methanone.

[1193]



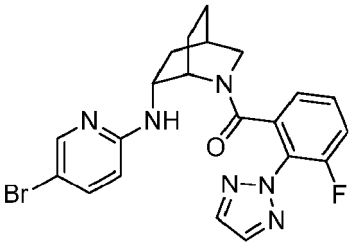
Example 532: (2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((5-bromopyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1194]



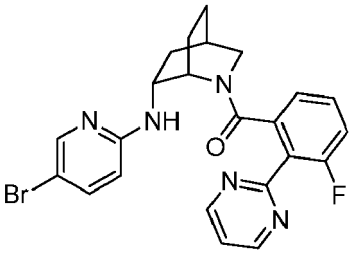
Example 533: ((1S,4R,6R)-6-((5-bromopyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)(3-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone.

[1195]



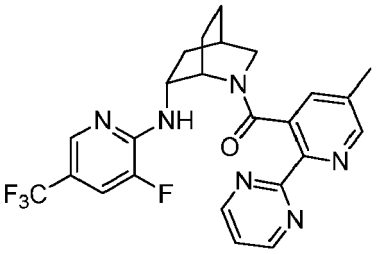
Example 534: ((1S,4R,6R)-6-((5-bromopyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)(3-fluoro-2-(pyrimidin-2-yl)phenyl)methanone.

[1196]



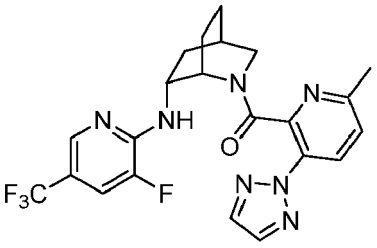
Example 535: ((1S,4R,6R)-6-((3-fluoro-5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)(5-methyl-2-(pyrimidin-2-yl)pyridin-3-yl)methanone.

[1197]



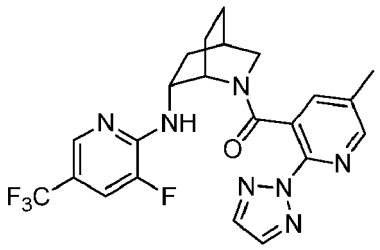
Example 536: ((1S,4R,6R)-6-((3-fluoro-5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)methanone.

[1198]



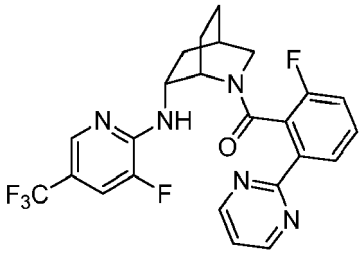
Example 537: ((1S,4R,6R)-6-((3-fluoro-5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)methanone.

[1199]



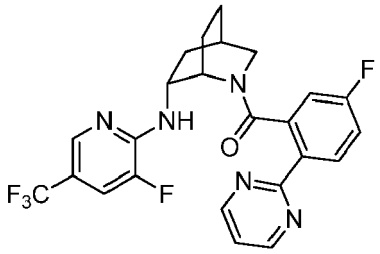
Example 538: ((1S,4R,6R)-6-((3-fluoro-5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)(2-fluoro-6-(pyrimidin-2-yl)phenyl)methanone.

[1200]



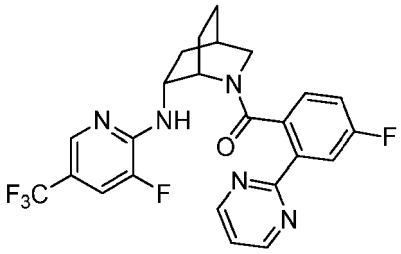
Example 539: (5-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((3-fluoro-5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1201]



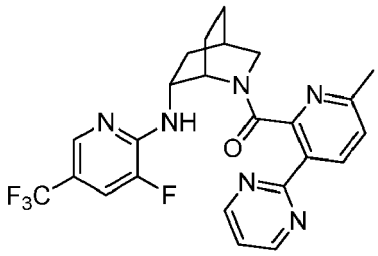
Example 540: (4-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((3-fluoro-5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1202]



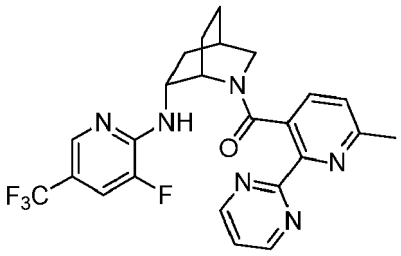
Example 541: ((1S,4R,6R)-6-((3-fluoro-5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)(6-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)methanone.

[1203]



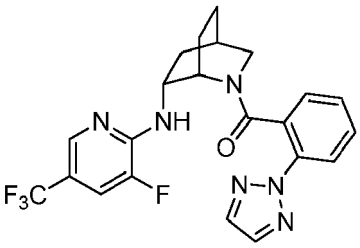
Example 542: ((1S,4R,6R)-6-((3-fluoro-5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)(6-methyl-2-(pyrimidin-2-yl)pyridin-3-yl)methanone.

[1204]



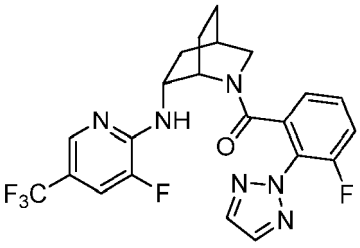
Example 543: (2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((3-fluoro-5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1205]



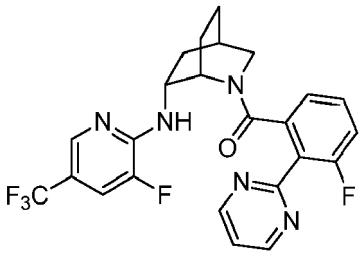
Example 544: (3-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((3-fluoro-5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1206]



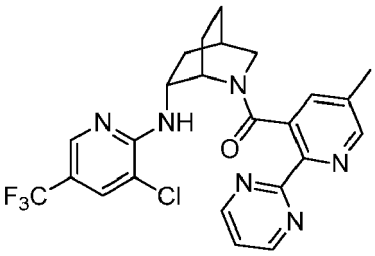
Example 545: (3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((3-fluoro-5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1207]



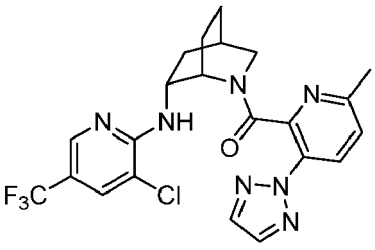
Example 546: ((1S,4R,6R)-6-((3-chloro-5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)(5-methyl-2-(pyrimidin-2-yl)pyridin-3-yl)methanone.

[1208]



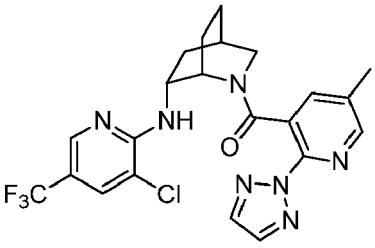
Example 547: ((1S,4R,6R)-6-((3-chloro-5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)methanone.

[1209]



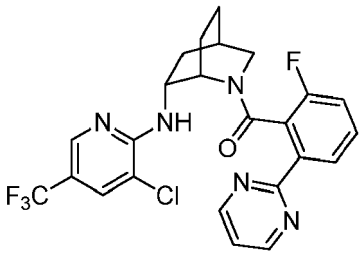
Example 548: ((1S,4R,6R)-6-((3-chloro-5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)methanone.

[1210]



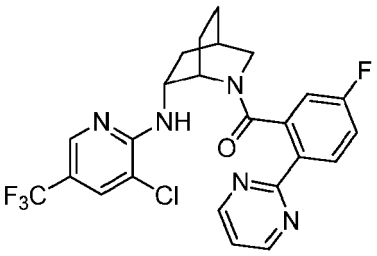
Example 549: ((1S,4R,6R)-6-((3-chloro-5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)(2-fluoro-6-(pyrimidin-2-yl)phenyl)methanone.

[1211]



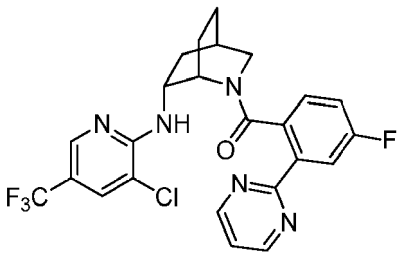
Example 550: ((1S,4R,6R)-6-((3-chloro-5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)(5-fluoro-2-(pyrimidin-2-yl)phenyl)methanone.

[1212]



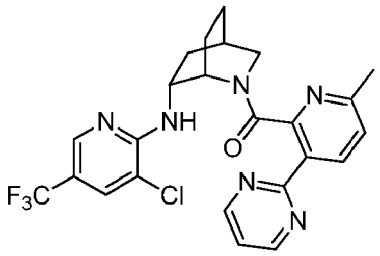
Example 551: ((1S,4R,6R)-6-((3-chloro-5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)(4-fluoro-2-(pyrimidin-2-yl)phenyl)methanone.

[1213]



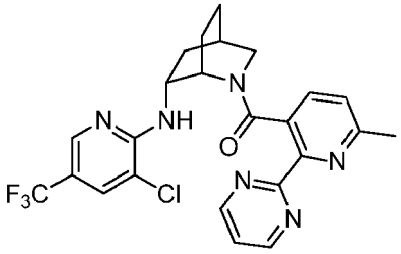
Example 552: ((1S,4R,6R)-6-((3-chloro-5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)(6-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)methanone.

[1214]



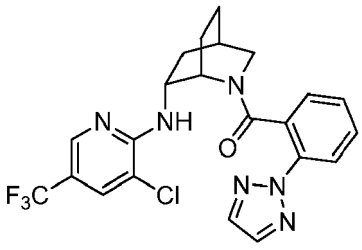
Example 553: ((1S,4R,6R)-6-((3-chloro-5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)(6-methyl-2-(pyrimidin-2-yl)pyridin-3-yl)methanone.

[1215]



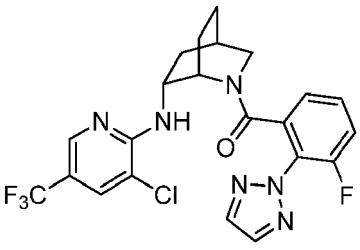
Example 554: (2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((3-chloro-5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1216]



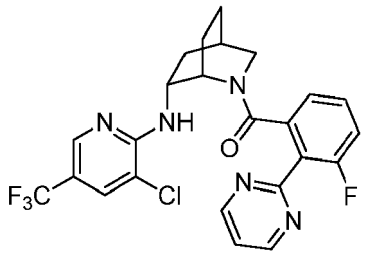
Example 555: ((1S,4R,6R)-6-((3-chloro-5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)(3-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone.

[1217]



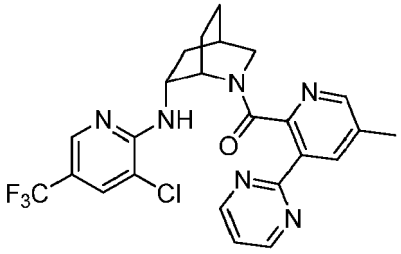
Example 556: ((1S,4R,6R)-6-((3-chloro-5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)(3-fluoro-2-(pyrimidin-2-yl)phenyl)methanone.

[1218]



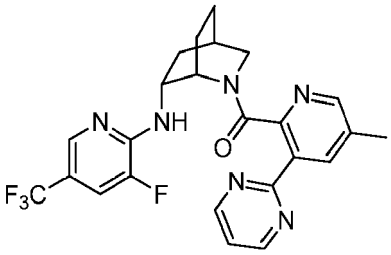
Example 557: ((1S,4R,6R)-6-((3-chloro-5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)(5-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)methanone.

[1219]



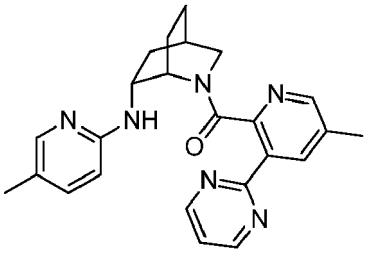
Example 558: ((1S,4R,6R)-6-((3-fluoro-5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)(5-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)methanone.

[1220]



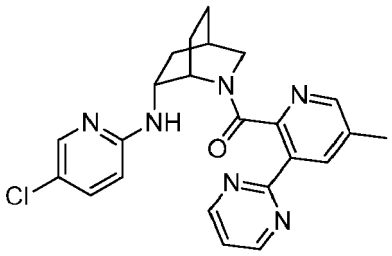
Example 559: (5-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-methylpyridin-2-yl)amino)-2-azabicyclo [2.2.2] octan-2-yl)methanone.

[1221]



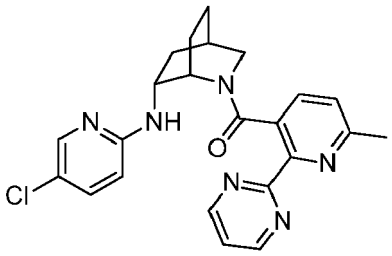
Example 560: ((1S,4R,6R)-6-((5-chloropyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)(5-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)methanone.

[1222]



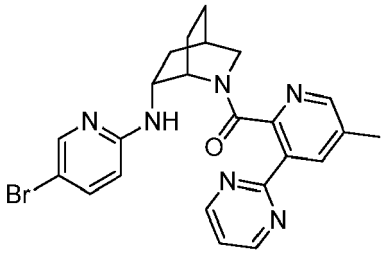
Example 561: ((1S,4R,6R)-6-((5-chloropyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)(6-methyl-2-(pyrimidin-2-yl)pyridin-3-yl)methanone.

[1223]



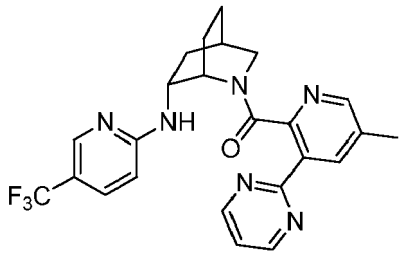
Example 562: ((1S,4R,6R)-6-((5-bromopyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)(5-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)methanone.

[1224]



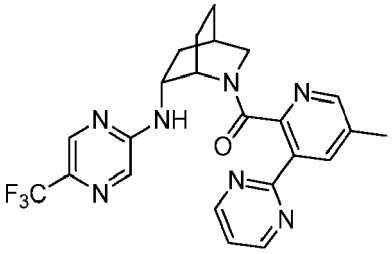
Example 563: (5-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1225]



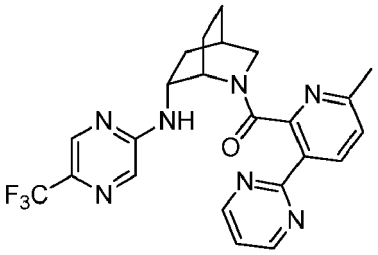
Example 564: (5-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1226]



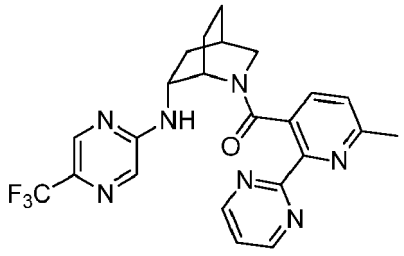
Example 565: (6-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1227]



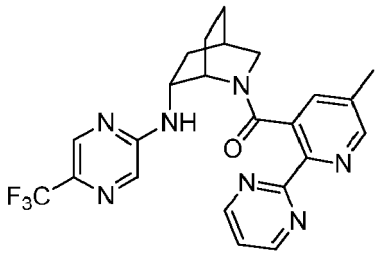
Example 566: (6-methyl-2-(pyrimidin-2-yl)pyridin-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1228]



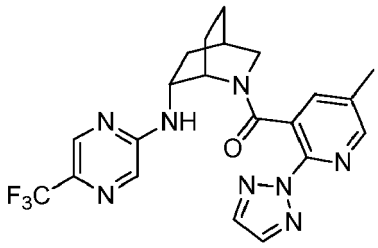
Example 567: (5-methyl-2-(pyrimidin-2-yl)pyridin-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1229]



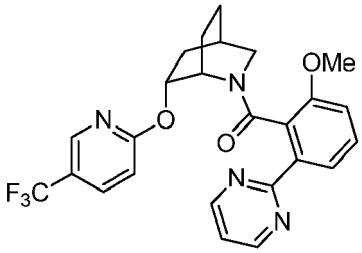
Example 568: (5-methyl-2-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1230]



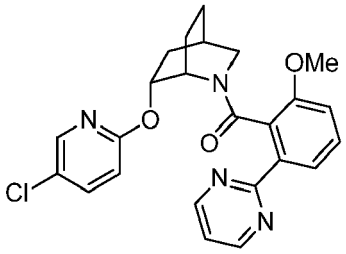
Example 569: (2-methoxy-6-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1231]



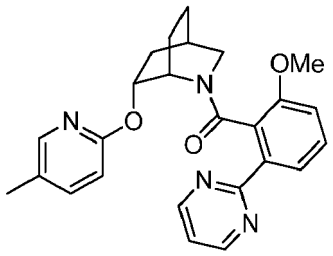
Example 570: ((1S,4R,6R)-6-((5-chloropyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)(2-methoxy-6-(pyrimidin-2-yl)phenyl)methanone.

[1232]



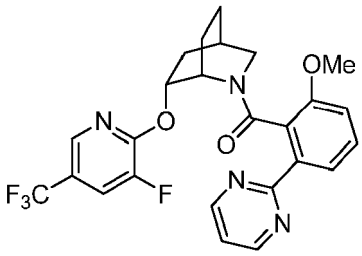
Example 571: (2-methoxy-6-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-methylpyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1233]



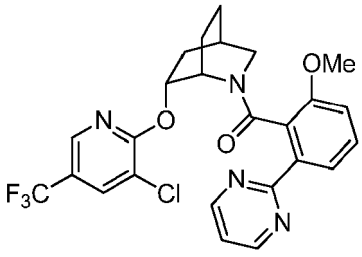
Example 572: ((1S,4R,6R)-6-((3-fluoro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)(2-methoxy-6-(pyrimidin-2-yl)phenyl)methanone.

[1234]



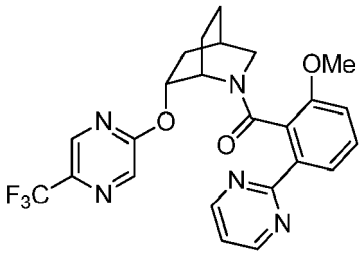
Example 573: ((1S,4R,6R)-6-((3-chloro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)(2-methoxy-6-(pyrimidin-2-yl)phenyl)methanone.

[1235]



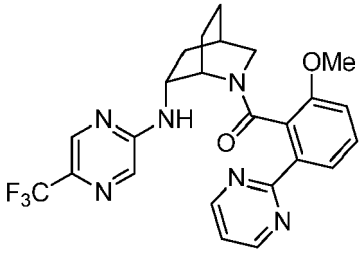
Example 574: (2-methoxy-6-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1236]



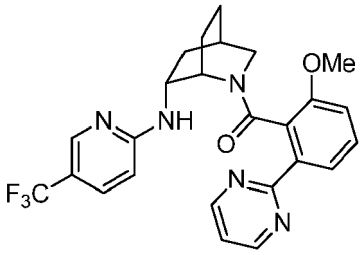
Example 575: (2-methoxy-6-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo [2.2.2] octan-2-yl)methanone.

[1237]



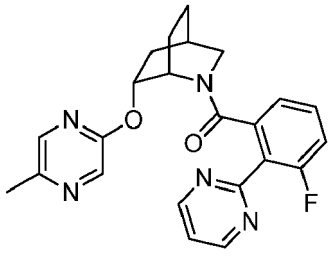
Example 576: (2-methoxy-6-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo [2.2.2] octan-2-yl)methanone.

[1238]



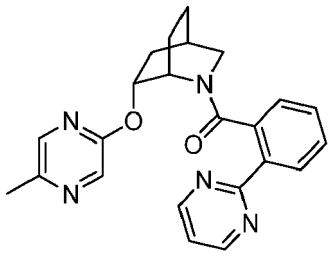
Example 577: (3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-methylpyrazin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1239]



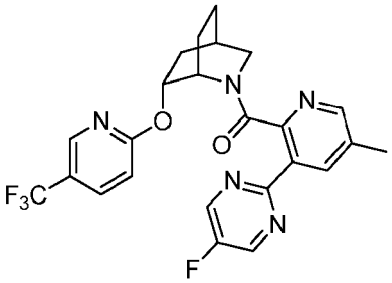
Example 578: ((1S,4R,6R)-6-((5-methylpyrazin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)(2-(pyrimidin-2-yl)phenyl)methanone.

[1240]



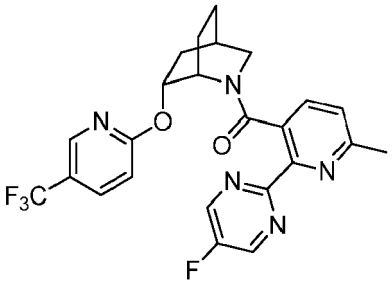
Example 579: (3-(5-fluoropyrimidin-2-yl)-5-methylpyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1241]



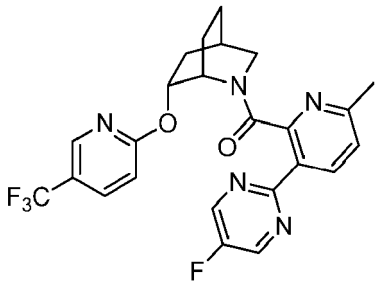
Example 580: (2-(5-fluoropyrimidin-2-yl)-6-methylpyridin-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1242]



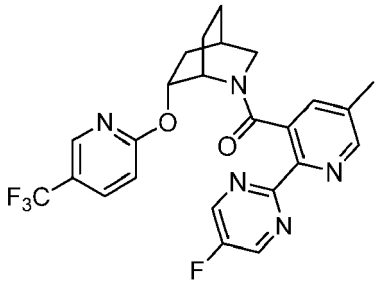
Example 581: (3-(5-fluoropyrimidin-2-yl)-6-methylpyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1243]



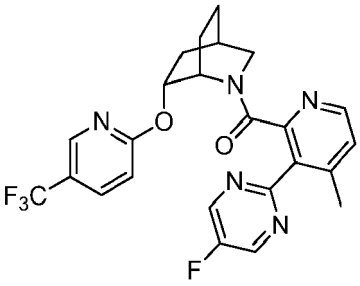
Example 582: (2-(5-fluoropyrimidin-2-yl)-5-methylpyridin-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1244]



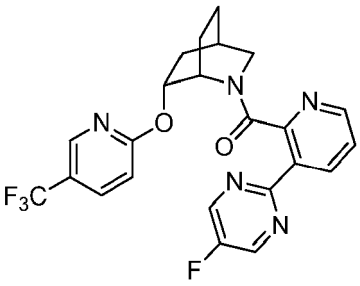
Example 583: (3-(5-fluoropyrimidin-2-yl)-4-methylpyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1245]



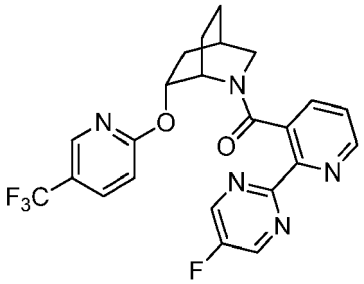
Example 584: (3-(5-fluoropyrimidin-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1246]



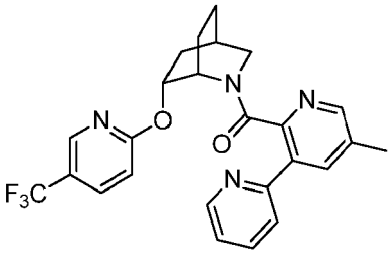
Example 585: (2-(5-fluoropyrimidin-2-yl)pyridin-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1247]



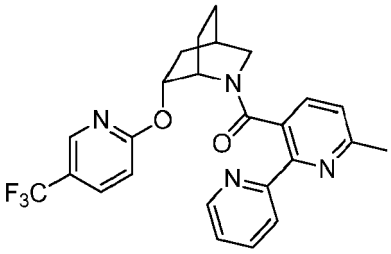
Example 586: (5'-methyl-[2,3'-bipyridin]-2'-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1248]



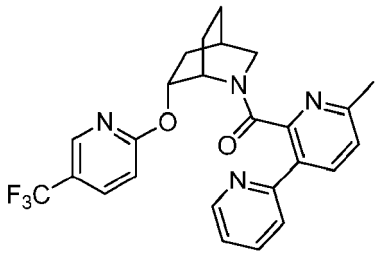
Example 587: (6-methyl-[2,2'-bipyridin]-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1249]



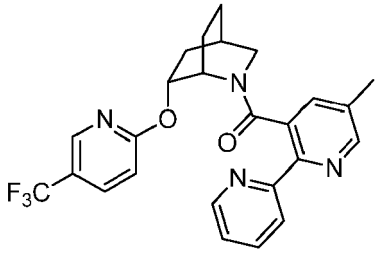
Example 588: (6'-methyl-[2,3'-bipyridin]-2'-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1250]



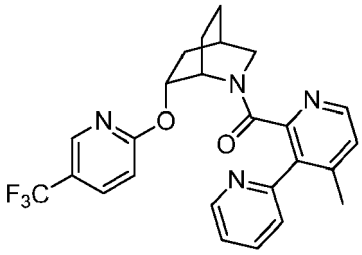
Example 589: (5-methyl-[2,2'-bipyridin]-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1251]



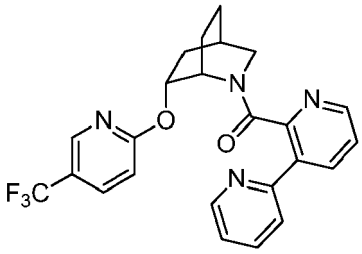
Example 590: (4'-methyl-[2,3'-bipyridin]-2'-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1252]



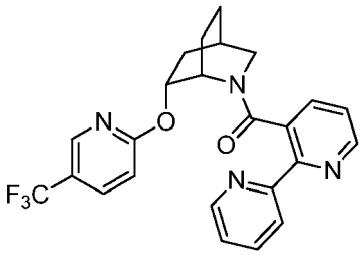
Example 591: [2,3'-bipyridin]-2'-yl((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1253]



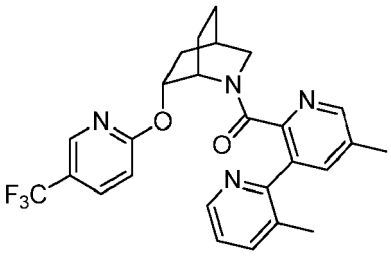
Example 592: [2,2'-bipyridin]-3-yl((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1254]



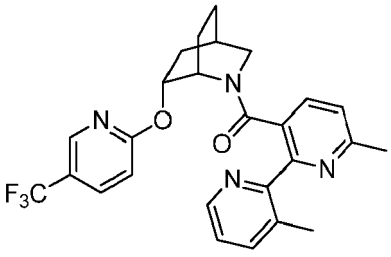
Example 593: (3,5'-dimethyl-[2,3'-bipyridin]-2'-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1255]



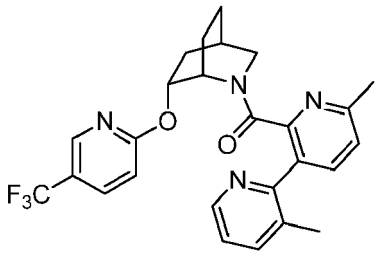
Example 594: (3',6-dimethyl-[2,2'-bipyridin]-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1256]



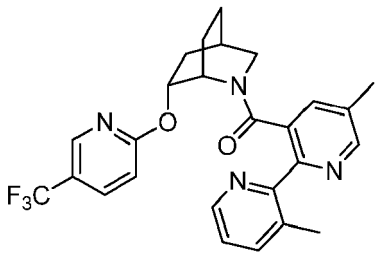
Example 595: (3,6'-dimethyl-[2,3'-bipyridin]-2'-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1257]



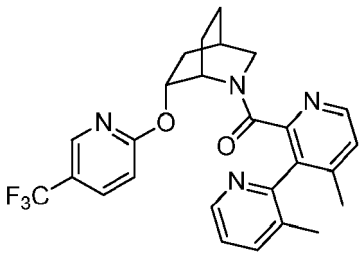
Example 596: (3',5-dimethyl-[2,2'-bipyridin]-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1258]



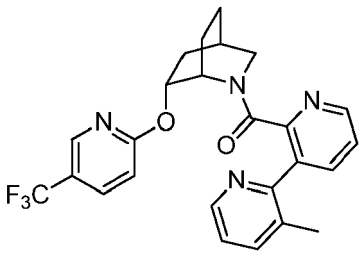
Example 597: (3,4'-dimethyl-[2,3'-bipyridin]-2'-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1259]



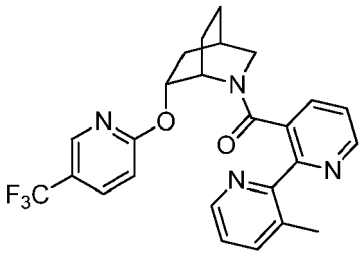
Example 598: (3-methyl-[2,3'-bipyridin]-2'-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1260]



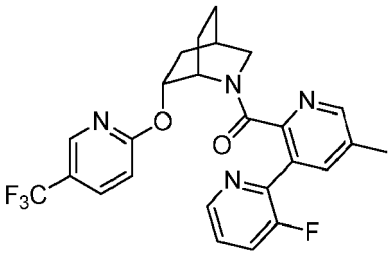
Example 599: (3'-methyl-[2,2'-bipyridin]-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1261]



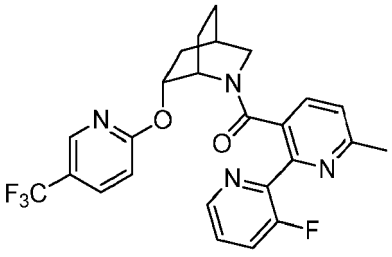
Example 600: (3-fluoro-5'-methyl-[2,3'-bipyridin]-2'-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1262]



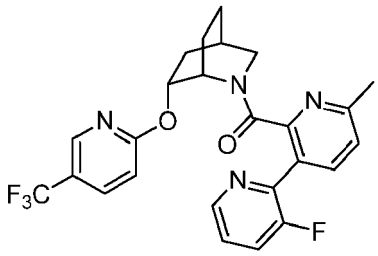
Example 601: (3'-fluoro-6-methyl-[2,2'-bipyridin]-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1263]



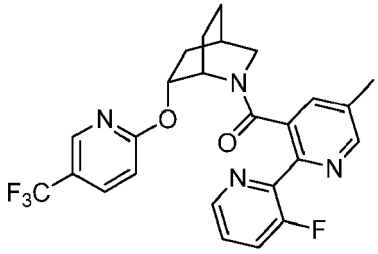
Example 602: (3-fluoro-6'-methyl-[2,3'-bipyridin]-2'-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1264]



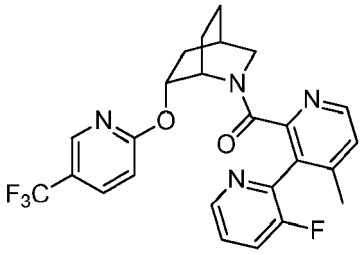
Example 603: (3'-fluoro-5-methyl-[2,2'-bipyridin]-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1265]



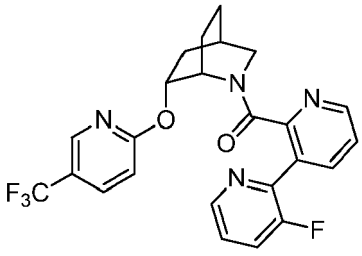
Example 604: (3-fluoro-4'-methyl-[2,3'-bipyridin]-2'-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1266]



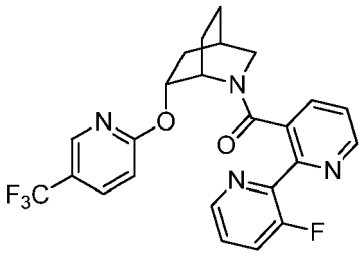
Example 605: (3-fluoro-[2,3'-bipyridin]-2'-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1267]



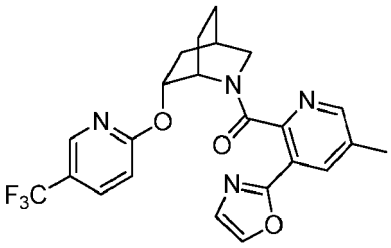
Example 606: (3'-fluoro-[2,2'-bipyridin]-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1268]



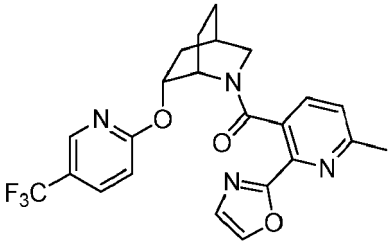
Example 607: (5-methyl-3-(oxazol-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1269]



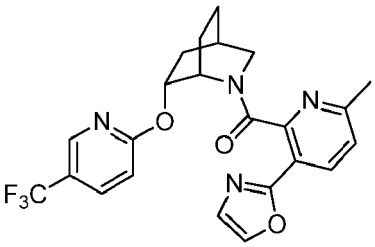
Example 608: (6-methyl-2-(oxazol-2-yl)pyridin-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1270]



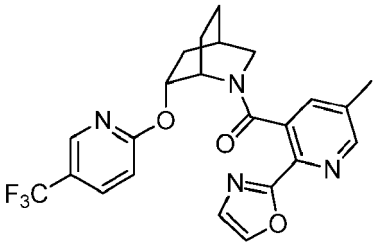
Example 609: (6-methyl-3-(oxazol-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1271]



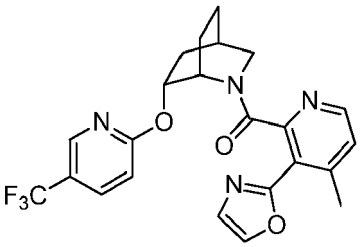
Example 610: (5-methyl-2-(oxazol-2-yl)pyridin-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1272]



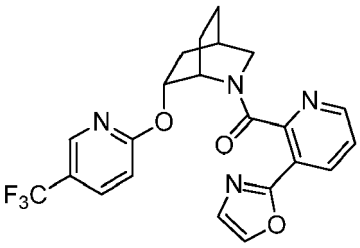
Example 611: (4-methyl-3-(oxazol-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1273]



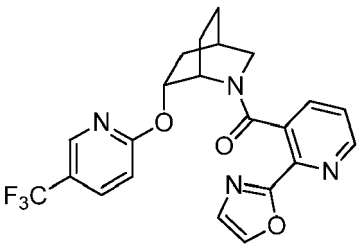
Example 612: 3-(oxazol-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1274]



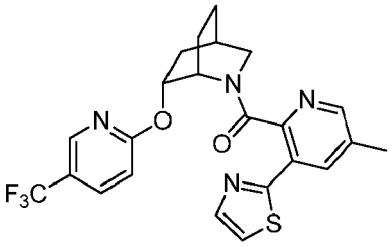
Example 613: (2-(oxazol-2-yl)pyridin-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1275]



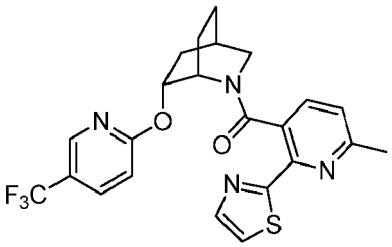
Example 614: 5-methyl-3-(thiazol-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1276]



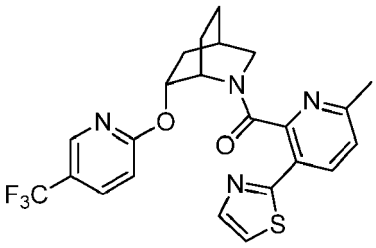
Example 615: (6-methyl-2-(thiazol-2-yl)pyridin-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1277]



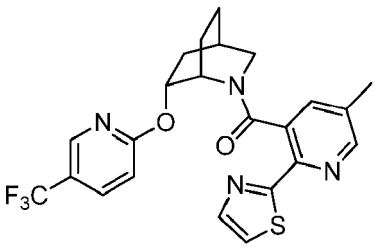
Example 616: (6-methyl-3-(thiazol-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1278]



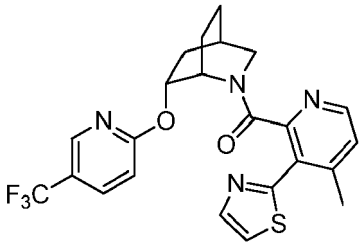
Example 617: (5-methyl-2-(thiazol-2-yl)pyridin-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1279]



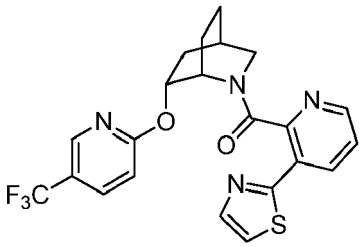
Example 618: (4-methyl-3-(thiazol-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1280]



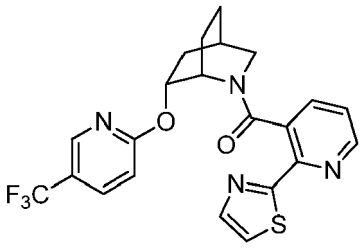
Example 619: (3-(thiazol-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1281]



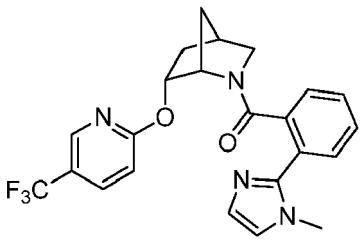
Example 620: (2-(thiazol-2-yl)pyridin-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1282]



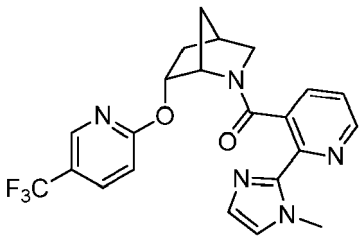
Example 621: (2-(1-methyl-1H-imidazol-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1283]



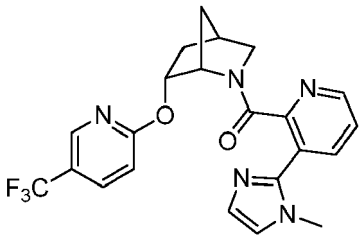
Example 622: (2-(1-methyl-1H-imidazol-2-yl)pyridin-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1284]



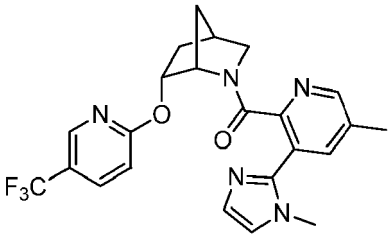
Example 623: (3-(1-methyl-1H-imidazol-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1285]



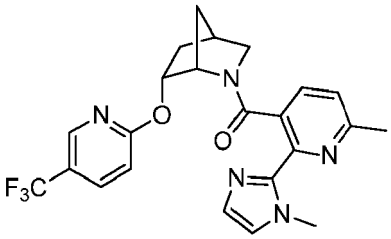
Example 624: (5-methyl-3-(1-methyl-1H-imidazol-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1286]



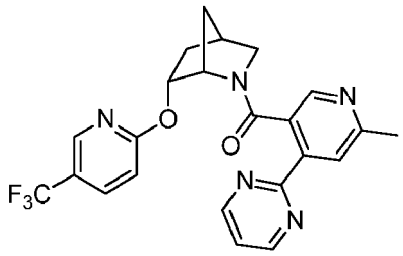
Example 625: (6-methyl-2-(1-methyl-1H-imidazol-2-yl)pyridin-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1287]



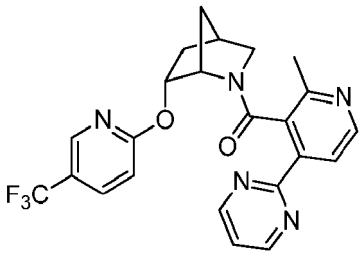
Example 626: (6-methyl-4-(pyrimidin-2-yl)pyridin-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1288]



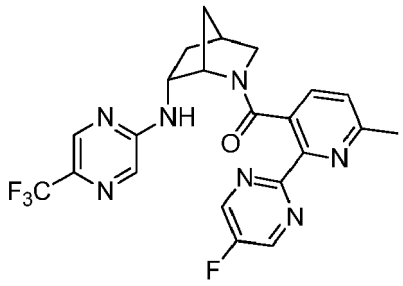
Example 627: (2-methyl-4-(pyrimidin-2-yl)pyridin-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1289]



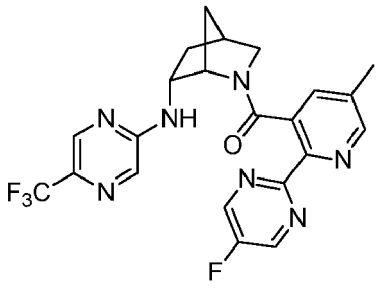
Example 628: (2-(5-fluoropyrimidin-2-yl)-6-methylpyridin-3-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1290]



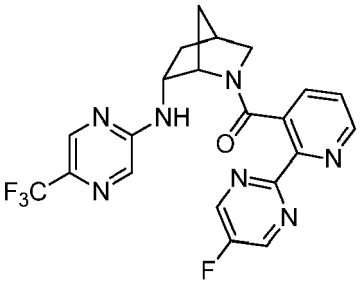
Example 629: (2-(5-fluoropyrimidin-2-yl)-5-methylpyridin-3-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1291]



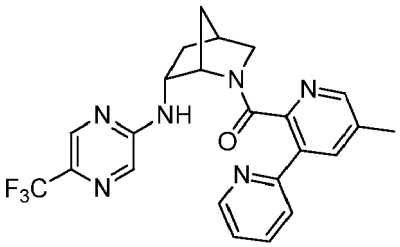
Example 630: (2-(5-fluoropyrimidin-2-yl)pyridin-3-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1292]



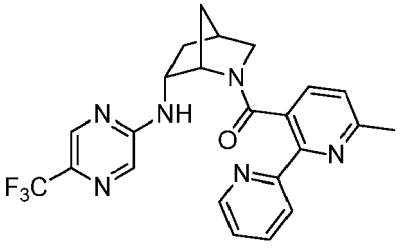
Example 631: (5'-methyl-[2,3'-bipyridin]-2'-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1293]



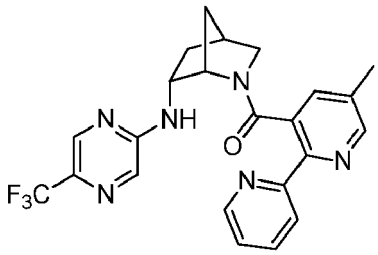
Example 632: (6-methyl-[2,2'-bipyridin]-3-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1294]



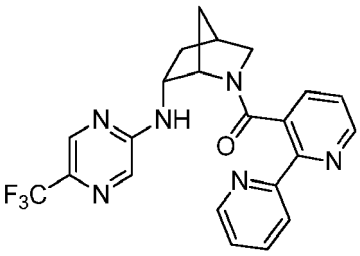
Example 633: (5-methyl-[2,2'-bipyridin]-3-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1295]



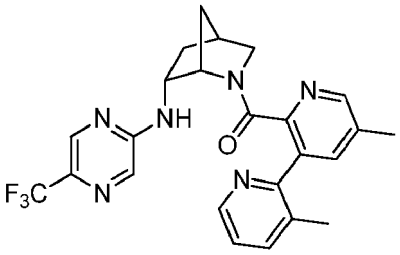
Example 634: [2,2'-bipyridin]-3-yl((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo [2.2.1]heptan-2-yl)methanone.

[1296]



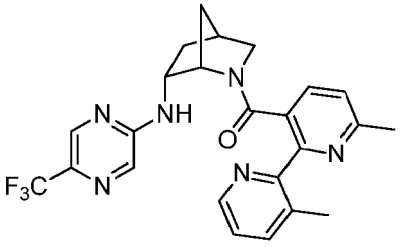
Example 635: (3,5'-dimethyl-[2,3'-bipyridin]-2'-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1297]



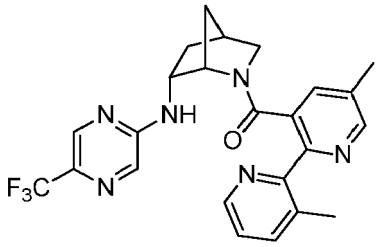
Example 636: (3',6-dimethyl-[2,2'-bipyridin]-3-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1298]



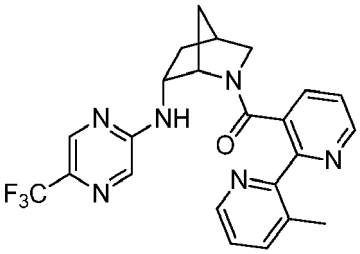
Example 637: (3',5-dimethyl-[2,2'-bipyridin]-3-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1299]



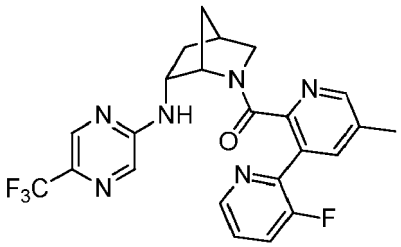
Example 638: (3'-methyl-[2,2'-bipyridin]-3-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1300]



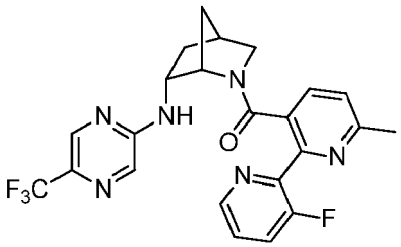
Example 639: (3-fluoro-5'-methyl-[2,3'-bipyridin]-2'-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1301]



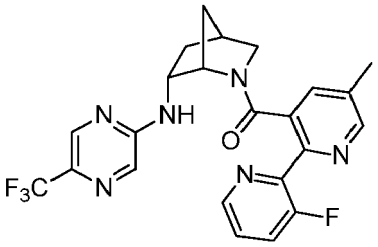
Example 640: (3'-fluoro-6-methyl-[2,2'-bipyridin]-3-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1302]



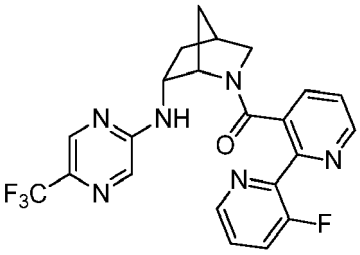
Example 641: (3'-fluoro-5-methyl-[2,2'-bipyridin]-3-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1303]



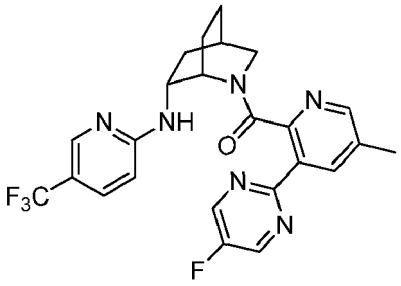
Example 642: (3'-fluoro-[2,2'-bipyridin]-3-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

[1304]



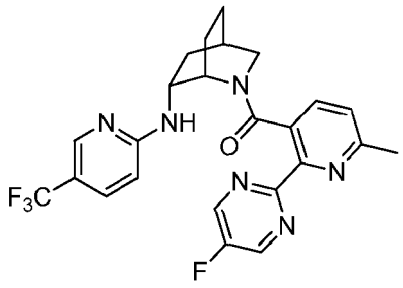
Example 643: (3-(5-fluoropyrimidin-2-yl)-5-methylpyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1305]



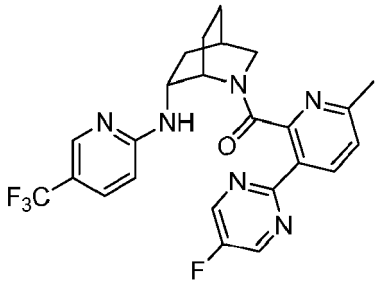
Example 644: (2-(5-fluoropyrimidin-2-yl)-6-methylpyridin-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1306]



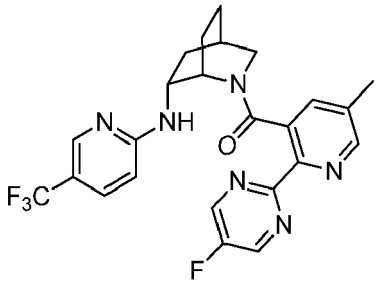
Example 645: (3-(5-fluoropyrimidin-2-yl)-6-methylpyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1307]



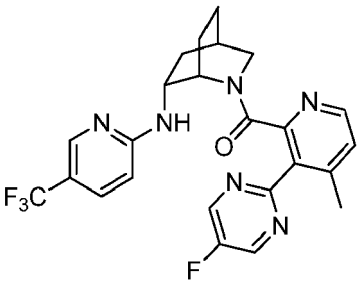
Example 646: (2-(5-fluoropyrimidin-2-yl)-5-methylpyridin-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1308]



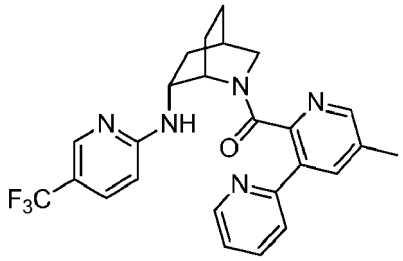
Example 647: (3-(5-fluoropyrimidin-2-yl)-4-methylpyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1309]



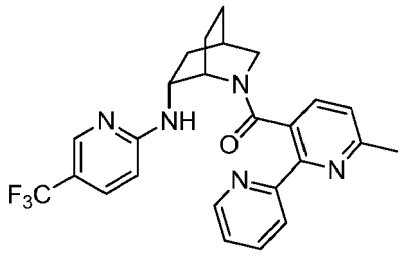
Example 648: (5'-methyl-[2,3'-bipyridin]-2'-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo [2.2.2] octan-2-yl)methanone.

[1310]



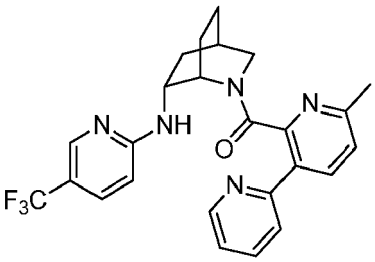
Example 649: (6-methyl-[2,2'-bipyridin]-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo [2.2.2] octan-2-yl)methanone.

[1311]



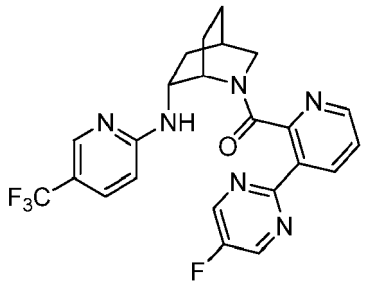
Example 650: (6'-methyl-[2,3'-bipyridin]-2'-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo [2.2.2] octan-2-yl)methanone.

[1312]



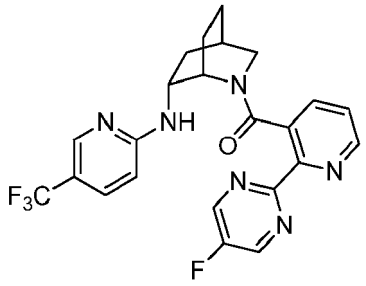
Example 651: (3-(5-fluoropyrimidin-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1313]



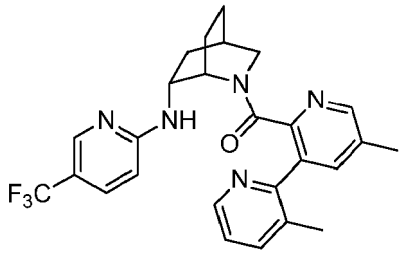
Example 652: (2-(5-fluoropyrimidin-2-yl)pyridin-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1314]



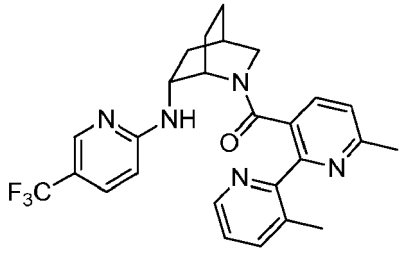
Example 653: (3,5'-dimethyl-[2,3'-bipyridin]-2'-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo [2.2.2] octan-2-yl)methanone.

[1315]



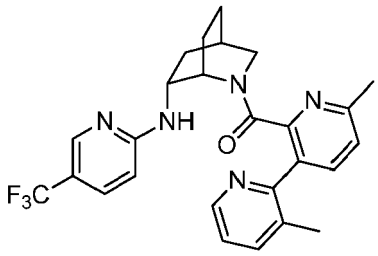
Example 654: (3',6-dimethyl-[2,2'-bipyridin]-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo [2.2.2] octan-2-yl)methanone.

[1316]



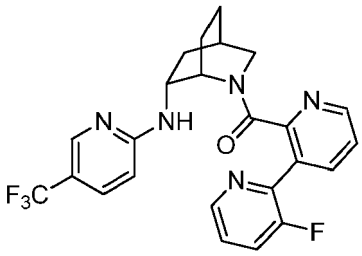
Example 655: (3,6'-dimethyl-[2,3'-bipyridin]-2'-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo [2.2.2] octan-2-yl)methanone.

[1317]



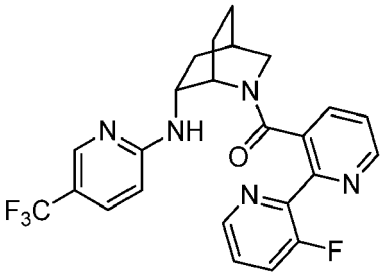
Example 656: (3-fluoro-[2,3'-bipyridin]-2'-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo [2.2.2] octan-2-yl)methanone.

[1318]



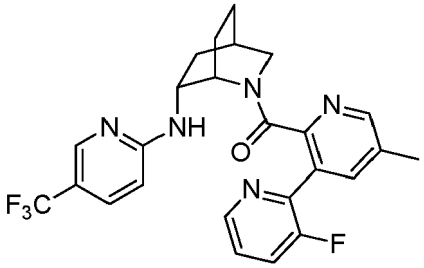
Example 657: (3'-fluoro-[2,2'-bipyridin]-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1319]



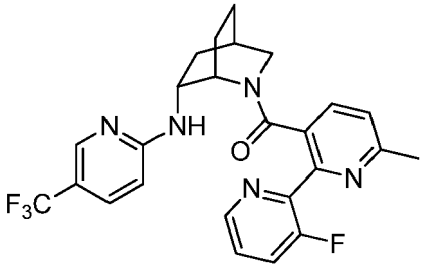
Example 658: (3-fluoro-5'-methyl-[2,3'-bipyridin]-2'-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1320]



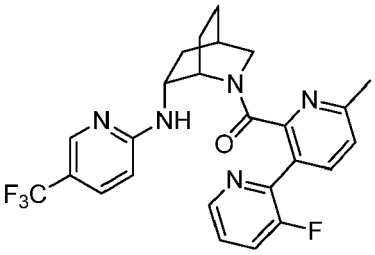
Example 659: (3'-fluoro-6-methyl-[2,2'-bipyridin]-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1321]



Example 660: (3-fluoro-6'-methyl-[2,3'-bipyridin]-2'-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone.

[1322]



Assays:

[1323] The *in vitro* affinity of the compounds of the invention for the rat/human orexin 1 and human orexin 2 receptors was determined by competitive radioligand binding using [^{3}H] (1-(5-(2-fluoro-phenyl)-2-methyl-thiazol-4-yl)-1-((S)-2-(5-phenyl-(1,3,4)oxadiazol-2-ylmethyl)-pyrrolidin-1-yl)-methanone)(Langmead et al., 2004) and [^{3}H]EMPA (n-ethyl-2[96-methoxy-pyridin-3-yl)-(toluene-2-sulfonyl)-amino]-N-pyridin-3-ylmethyl acetamide), respectively (Langmead et al., 2004, British Journal of Pharmacology 141:340-346; Malherbe et al., 2004, British Journal of Pharmacology 156:1326-41).

[1324] The *in vitro* functional antagonism of the compounds on the human orexin 1 and orexin 2 receptors was determined using fluorometric imaging plate reader (FLIPR) based calcium assays.

[1325] Data are analyzed using pc-Sandy macro and graphed on Graphpad Prism 5. For analysis, each concentration point is averaged from triplicate values and the averaged values are plotted on Graphpad Prism. The IC50 was determined by applying the following equation (GraphPad Prism 5.0, SanDiego) for one site competition where X=log (concentration) and Y=specific binding. Top denotes the total [^{3}H]- (1-(5-(2-fluoro-phenyl)-2-methyl-thiazol-4-yl)-1-((S)-2-(5-phenyl-(1,3,4)oxadiazol-2-ylmethyl)-pyrrolidin-1-yl)-methanone) binding, bottom denotes the nonspecific [^{3}H]- (1-(5-(2-fluoro-phenyl)-2-methyl-thiazol-4-yl)-1-((S)-2-(5-phenyl-(1,3,4)oxadiazol-2-ylmethyl)-pyrrolidin-1-yl)-methanone) binding. Graphpad Prism calculates Ki value from IC50 and the pre-determined Kd values for [^{3}H]- (1-(5-(2-fluoro-phenyl)-2-methyl-thiazol-4-yl)-1-((S)-2-(5-phenyl-(1,3,4)oxadiazol-2-ylmethyl)-pyrrolidin-1-yl)-methanone) and [3H]-EMPA. The Ki for each compound is then uploaded into 3DX. Each run comprises individual compounds in triplicate. The data in

Table 1 and Table 2 represent averages from between 2-20 runs

Rat and human orexin 1 receptor radioligand binding studies

[1326] Human Embryonic Kidney 293 cells (HEK293) stably expressing rat orexin 1 receptor (Genebank accession number NM_001525) or Chinese ovary cells (CHO) stably expressing human orexin 1 receptor (Genebank accession number NM _001526) were grown to confluency in DMEM (Hyclone, cat # SH30022), 10% FBS, 1X Pen/Strep, 1X sodium pyruvate, 10 mM HEPES, 600 μg/mL G418 and DMEM/F12 (Gibco, Cat #11039), 10%FBS, 1X Pen/Strep, 600 μg/mL G418 media, respectively on 150 cm^2 tissue culture plates, washed with 5 mM EDTA in PBS (HyClone Dulbecco's Phoshpate Buffered Saline 1X with Calcium and Magnesium, Cat # SH30264.01, hereafter referred to simply as PBS) and scraped into 50 ml tubes. After centrifugation (2K xG, 5 min at 4 °C), the supernatant was aspirated and the pellets frozen and stored at -80°C. Cells were resuspended in PBS in the presence of 1 tablet of protease inhibitor cocktail (Roche, Cat. #11836145001) per 50 mL. Each cell pellet from a 15 cm plate was resuspended in 10 mL, stored on ice, and homogenized for 45 sec prior to addition to the reactions. Competition binding experiments in 96 well polypropylene plates were performed using [^{3}H]- (1-(5-(2-fluoro-phenyl)-2-methyl-thiazol-4-yl)-1-((S)-2-(5-phenyl-(1,3,4)oxadiazol-2-ylmethyl)-pyrrolidin-1-yl)-methanone) (Moraveck Corporation, specific activity = 35.3 Ci/mmol), diluted to a 10 nM concentration in PBS (4 nM final). Compounds were solubilized in 100% DMSO (Acros Organics, Cat. #61042-1000) and tested over a range of 7 concentrations (from 0.1 nM to 10 μM). The final concentration of DMSO in the reactions is equal to or less than 0.1%. Total and nonspecific binding was determined in the absence and presence of 10 μM almorexant. The total volume of each reaction is 200 μL (20 μL of diluted compounds, 80 μL of [^{3}H]- (1-(5-(2-fluoro-phenyl)-2-methyl-thiazol-4-yl)-1-((S)-2-(5-phenyl-(1,3,4)oxadiazol-2-ylmethyl)-pyrrolidin-1-yl)-methanone) diluted in PBS and 100 μL of the cell suspension). Reactions were run for 60 min at room temperature and terminated by filtration through GF/C filter plates (PerkinElmer, Cat. #6005174) presoaked in 0.3% polyethylenimine using the cell harvester (PerkinElmer Filtermate). The plates were washed 3 times by aspirating 30 ml PBS through the plates. Plates were dried in 55 °C oven for 60 min, scintillation fluid was added, and the radioactivity was counted on a Topcount (Packard).

[1327] IC_{50} values (i.e. concentration of unlabelled compound required to compete for 50% of specific binding to the radioligand) was calculated using the GraphPad Prism software (GraphPad Prism Software Inc., San Diego, CA) with a fit to a sigmoidal dose-response curve. Apparent Ki values were calculated as $K_i = IC_{50}/(1+C/K_d)$, where C is concentration of radioligand and K_d = 4 nM for rat orexin 1 receptor and 6 nM for human orexin 1 receptor.

Human orexin 2 receptor radioligand binding studies

[1328] HEK293 stably expressing human orexin 2 receptor (Genebank accession number NM_001526) were grown to confluency in DMEM (Hyclone, cat # SH30022), 10%FBS, 1X Pen/Strep, 1X NaPyruvate, 10 mM HEPES, 600 ug/ml G418 media on 150 cm^2 tissue culture plates, washed with 5 mM EDTA in PBS (HyClone Dulbecco's Phoshpate Buffered Saline 1X with Calcium and Magnesium, Cat # SH30264.01, hereafter referred to simply as PBS) and scraped into 50 ml tubes. After centrifugation (2K xG, 5 min at 4°C), the supernatant was aspirated and the pellets frozen and stored at -80°C. Cells were resuspended in PBS in the presence of 1 tablet of protease inhibitor cocktail (Roche, Cat. #11836145001) per 50 mL. Each cell pellet from a 15 cm plate was resuspended in 10 mL, stored on ice, and homogenized for 45 sec just prior to addition to the reactions. Competition binding experiments in 96 well polypropylene plates were performed using [^{3}H]-EMPA (Moraveck Corporation, specific activity = 29.6 Ci/mmol), diluted to a 5 nM concentration in PBS (2 nM final concentration). Compounds were solubilized in 100% DMSO (Acros Organics, Cat. #61042-1000) and tested over a range of 7 concentration (from 0.1 nM to 10 μM). The final concentration of DMSO in the reactions is equal to or less than 0.1%. Total and nonspecific binding was determined in the absence and presence of 10 μM almorexant. The total volume of each reaction is 200 μL (20 μL of diluted compounds, 80 μL of [^{3}H]-EMPA diluted in PBS and 100 μL of the cell suspension). Reactions were run for 60 min at room temperature and terminated by filtration through GF/C filter plates (PerkinElmer, Cat. #6005174) presoaked in 0.3% polyethylenimine using the cell harvester (PerkinElmer Filtermate). The plates were washed 3 times by aspirating 30 ml PBS through the plates. Plates were dried in 55°C oven for 60 min, scintillation fluid was added, and the radioactivity was counted on a Topcount (Packard).

[1329] IC_{50} values (i.e. concentration of unlabelled compound required to compete for 50% of specific binding to the radioligand) was calculated using the GraphPad Prism software (GraphPad Prism Software Inc., San Diego, CA) with a fit to a sigmoidal dose-response curve. Apparent Ki values were calculated as $K_i = IC_{50}/(1+C/K_d)$, where C is concentration of radioligand and K_d = 2 nM.

Human orexin 1 receptor Ca^{2+} mobilization assay

[1330] CHO cells stably transfected with the human orexin 1 receptor (Genebank accession number NM_001526) were grown to confluency in DMEM/F12, 10% FBS, 1X pen-strep, 400 μg/ml G418. Cells were seeded on to 384-well

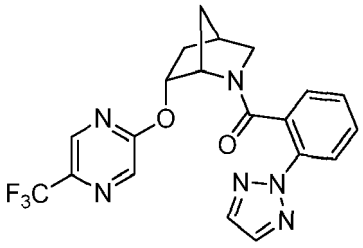
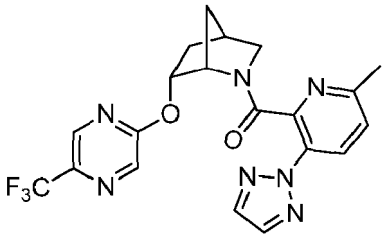
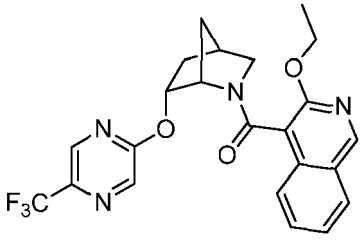
Packard viewplates at a density of 10,000 cells/well and incubated overnight at 37^{0}C, 5% CO2. The cells were dye-loaded with BD Calcium Assay kit (BD, cat # 640178) in HBSS (Gibco, cat# 14025-092) with 2.5 mM probenecid and incubated at 37°C, 5% CO_2 for 45 min. Cells were pre-incubated with compounds (diluted in DMEM/F-12) for 15-30 minutes before agonist (orexin A, 10 nM) stimulation. Ligand-induced Ca^{2+} release was measured using a Fluorometric Imaging Plate Reader (FLIPR, Molecular Devices, Sunnyvale, CA). Functional responses were measured as peak fluorescence intensity minus basal. The concentration of agonist that produced a half-maximal response is represented by the EC_{50} value. Antagonistic potency values were converted to apparent pK_B values using a modified Cheng-Prusoff correction. Apparent pK_B = - log IC_{50}/1+[conc agonist/EC_{50}].

Human orexin 2 receptor Ca^{2+} mobilization assay

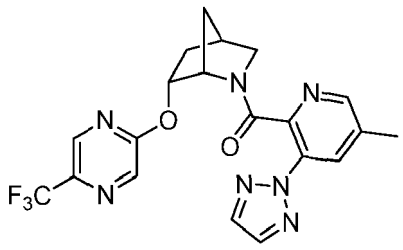
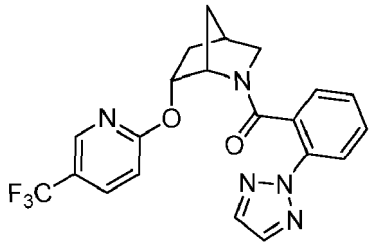
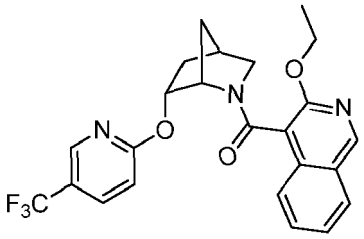
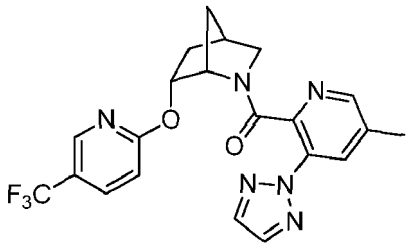
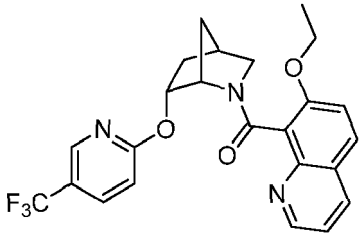
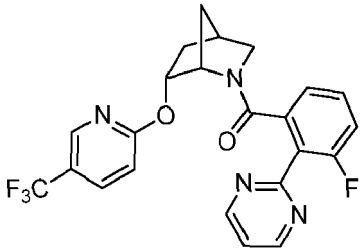
[1331] PFSK-1 cells endogenously expressing the human orexin 2 receptor were grown to confluency in RPMI1640 (Hyclone, cat# 30027.02), 10% FBS, 1X pen-strep. Cells were seeded on to 384-well Packard viewplates at a density of 5,000 cells/well and incubated overnight at 37^{0}C, 5% CO2. The cells were dye-loaded with BD Calcium Assay kit (BD, cat # 640178) in HBSS (Gibco, cat# 14025-092) with 2.5 mM probenecid and incubated at 37°C, 5% CO_2 for 45 min. Cells were pre-incubated with compounds (diluted in DMEM/F-12) for 15-30 minutes before agonist (orexin B, 100 nM) stimulation. Ligand-induced Ca^{2+} release was measured using a Fluorometric Imaging Plate Reader (FLIPR, Molecular Devices, Sunnyvale, CA). Functional responses were measured as peak fluorescence intensity minus basal. The concentration of agonist that produced a half-maximal response is represented by the EC_{50} value. Antagonistic potency values were converted to apparent pK_B values using a modified Cheng-Prusoff correction. Apparent pK_B = - log IC_{50}/1+[conc agonist/EC_{50}].

[1332] Preferred compounds of the invention are set forth in the table below. Orexin receptor activity of certain compounds of the invention is also set forth in Table 1 below.

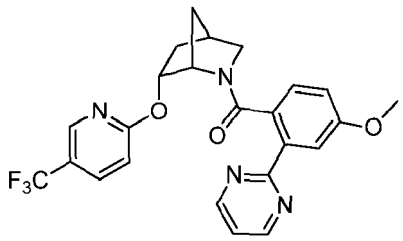
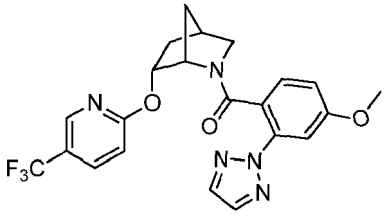
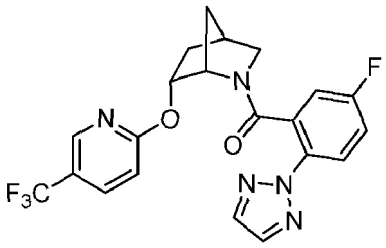
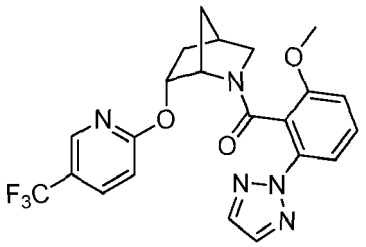
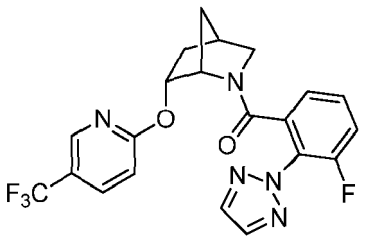
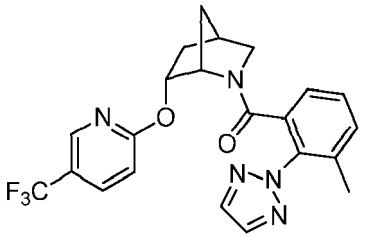
Table 1

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
1		74	120	4700	(R/S)-(2-(2H-1,2,3-triazol-2-yl)phenyl) (6-((5-(trifluoromethyl)pyrazin-2-yl)oxy)-2-azabicyclo[2.2.1] heptan -2-yl)methanone
2		200	342	10000	(R/S)-(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl) (6-((5-(trifluoromethyl)pyrazin-2-yl)oxy)-2-azabicyclo[2.2.1] heptan -2-yl)methanone
3		63	123	8900	(R/S)-(3-ethoxyisoquinolin-4-yl)((5-(trifluoromethyl)pyrazin-2-yl)oxy)-2-azabicyclo[2.2.1] heptan -2-yl)methanone

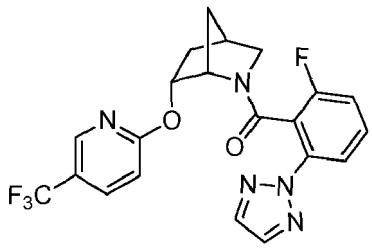
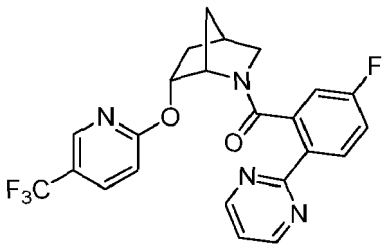
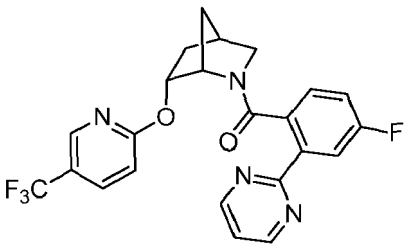
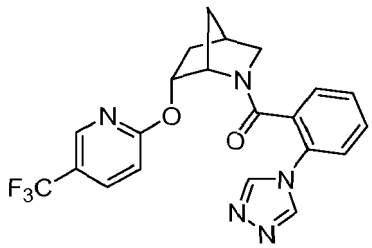
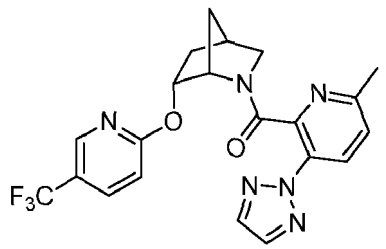
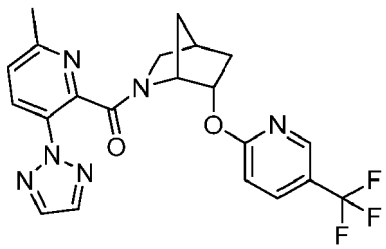
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
4		837		>10000	(R/S)-5-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl) (6-((5-(trifluoromethyl)pyrazin -2-yl)oxy)-2-azabicyclo[2.2.1] heptan -2-yl)methanone
7		21	12	800	(R/S)-(2-(2H-1,2,3-triazol-2-yl)phenyl) (6-((5-(trifluoromethyl)pyridin -2-yl)oxy)-2-azabicyclo[2.2.1] heptan -2-yl)methanone
8		16	15	1450	(R/S)-(3-ethoxyisoquinolin-4-yl)(6-((5-(trifluoromethyl) pyridin -2-yl)oxy)-2-azabicyclo [2.2.1]heptan -2-yl)methanone
9		56	101	2554	(R/S)-(5-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl) (6-((5-(trifluoromethyl)pyridin -2-yl)oxy)-2-azabicyclo[2.2.1] heptan -2-yl)methanone
10		18	27	526	(R/S)-(7-ethoxyquinolin-8-yl) (6-((5-(trifluoromethyl)pyridin -2-yl)oxy)-2-azabicyclo[2.2.1] heptan -2-yl)methanone
11		11	8	1475	(R/S)-(3-fluoro-2-(pyrimidin-2-yl)phenyl) (6-((5-(trifluoromethyl)pyridin -2-yl)oxy)-2-azabicyclo[2.2.1] heptan -2-yl)methanone

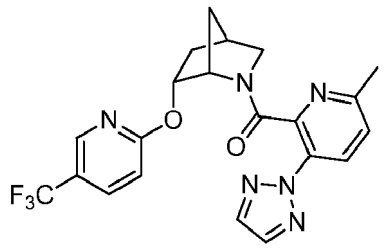
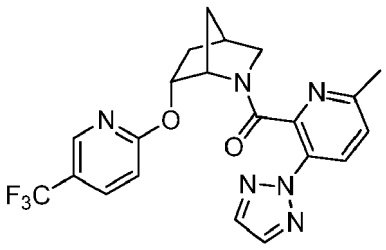
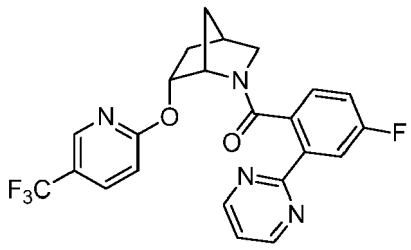
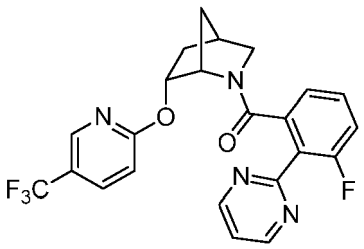
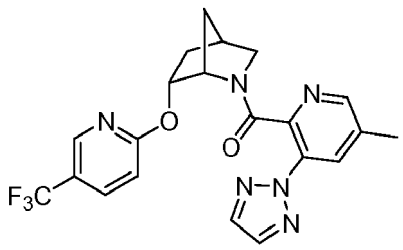
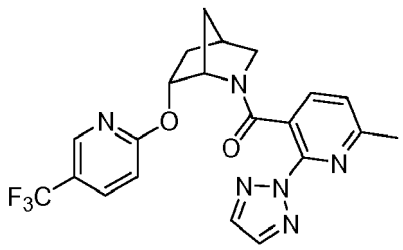
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
12		44	59	>10000	(R/S)-(4-methoxy-2-(pyrimidin-2-yl)phenyl) (6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1] heptan -2-yl)methanone
13		52	109	>10000	(R/S)-4-methoxy-2-(2H-1,2,3-triazol-2-yl)phenyl) (6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1] heptan -2-yl)methanone
14		16	21	855	(R/S)-(5-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl) (6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1] heptan -2-yl)methanone
15		17	40	229	(R/S)-2-methoxy-6-(2H-1,2,3-triazol-2-yl)phenyl) (6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1] heptan -2-yl)methanone
16		8	7	1000	(R/S)-(3-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl) (6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1] heptan -2-yl)methanone
17		8	3	234	(R/S)-(3-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl) (6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1] heptan -2-yl)methanone

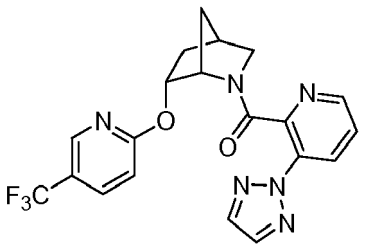
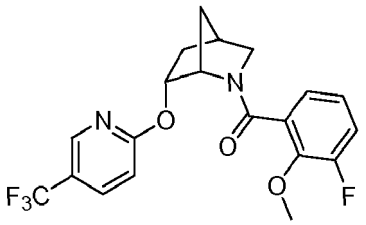
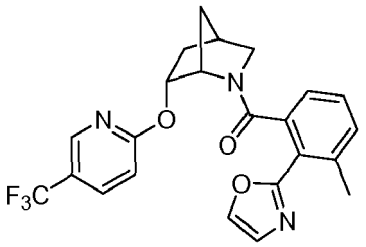
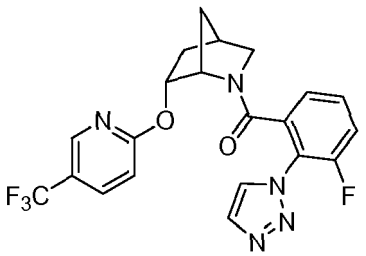
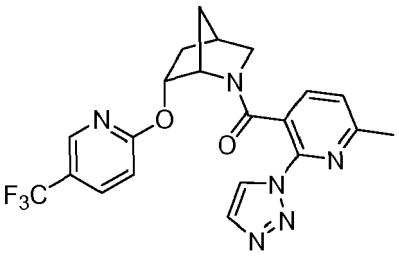
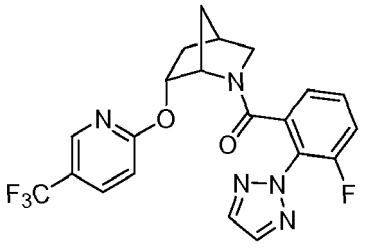
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
18		25	23	1800	(R/S)-(2-fluoro-6-(2H-1,2,3-triazol-2-yl)phenyl) (6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1] heptan -2-yl)methanone
19		18	9	945	(R/S)-(5-fluoro-2-(pyrimidin-2-yl)phenyl) (6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1] heptan -2-yl)methanone
20		15	15	2700	(R/S)-(4-fluoro-2-(pyrimidin-2-yl)phenyl)(-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1] heptan -2-yl)methanone
21		>10000		>10000	(R/S)-(2-(4H-1,2,4-triazol-4-yl)phenyl) (6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1] heptan -2-yl)methanone
22		25	23	1000	(R/S)-(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl) (6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1] heptan -2-yl)methanone
23		>10000		>10000	(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)((1R,4S,6S)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1] heptan -2-yl)methanone

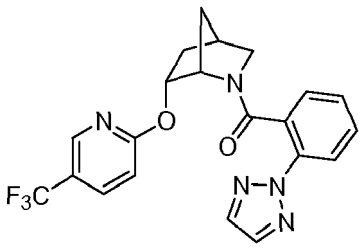
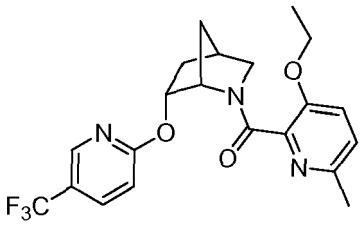
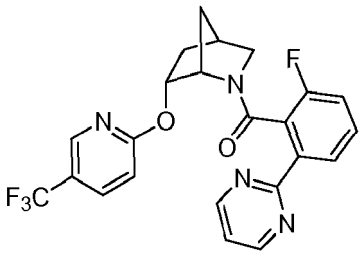
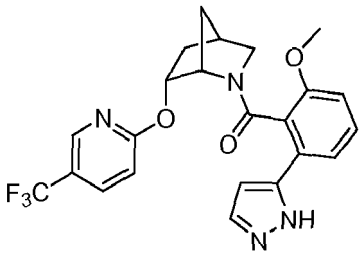
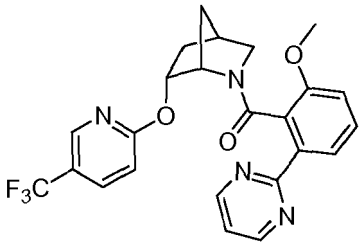
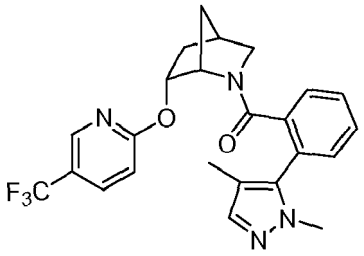
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
24		20	16	692	(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone
25		17	15	466	(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone
26		12	15	2100	(4-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone
27		4	4	767	(3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone
28		32	21	1600	(5-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone
29		55	47	>10000	(6-methyl-2-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

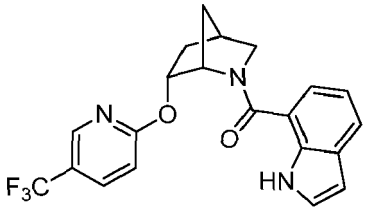
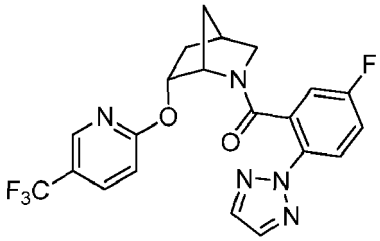
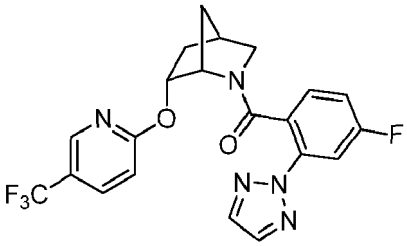
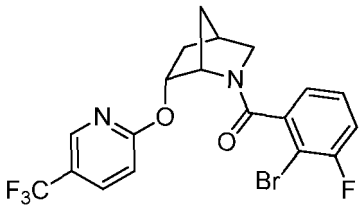
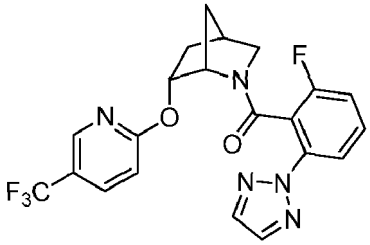
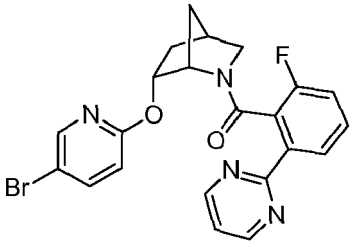
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
30		19	22	1700	(3-(2H-1,2,3-triazol-2-yl) pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1] heptan -2-yl)methanone
31		707		>10000	(3-fluoro-2-methoxyphenyl)((1S,4R ,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1] heptan -2-yl)methanone
32		3	4	143	(3-methyl-2-(oxazol-2-yl) phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1] heptan -2-yl)methanone
33		74	86	3500	(3-fluoro-2-(1H-1,2,3-triazol-1-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1] heptan -2-yl)methanone
34		117	462	1100	(6-methyl-2-(1H-1,2,3-triazol-1-yl)pyridin-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1] heptan -2-yl)methanone
35		8	3	542	(3-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1] heptan -2-yl)methanone

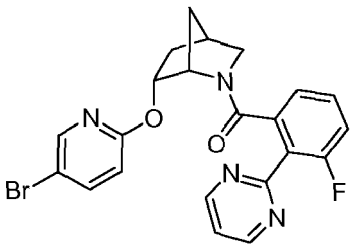
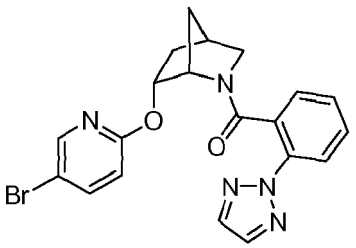
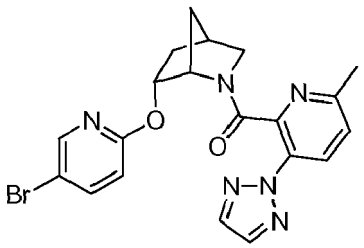
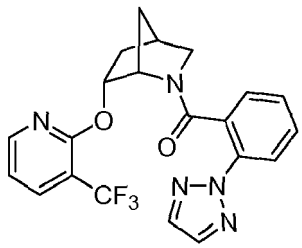
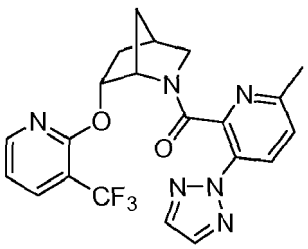
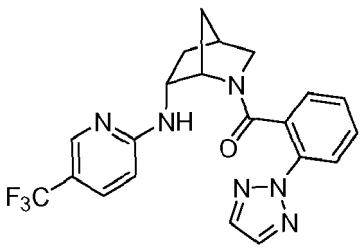
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
36		5	11	322	(2-(2H-1,2,3-triazol-2-yl) phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1] heptan -2-yl)methanone
37		170	265	1800	(3-ethoxy-6-methylpyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1] heptan -2-yl)methanone
38		8	8	690	(2-fluoro-6-(pyrimidin-2-yl) phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1] heptan-2-yl)methanone
39		132	17	108	(2-methoxy-6-(1H-pyrazol-5-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1] heptan -2-yl)methanone
40		16	9	340	(2-methoxy-6-(pyrimidin-2-yl) phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1] heptan -2-yl)methanone
41		4399		>10000	(2-(1,4-dimethyl-1H-pyrazol-5-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1] heptan -2-yl)methanone

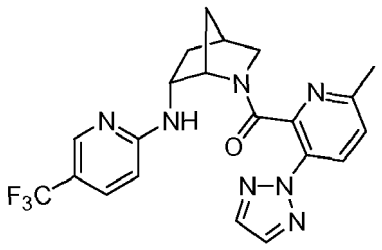
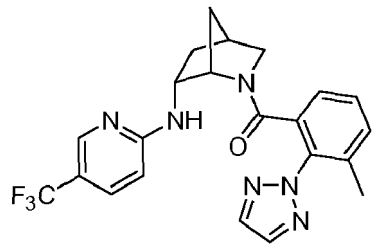
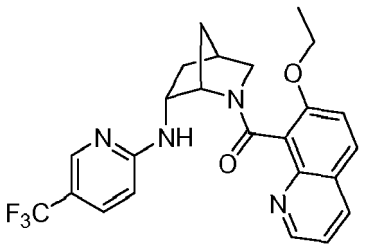
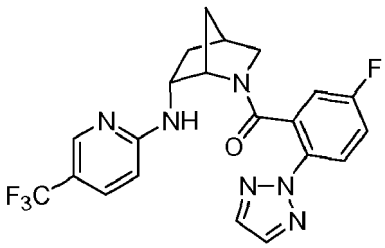
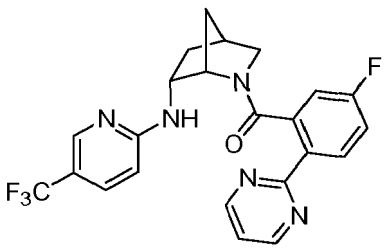
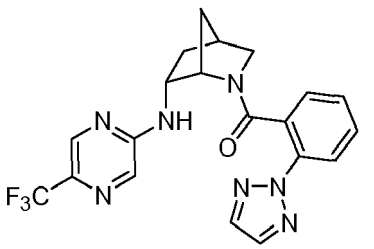
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
42		184	175	5800	(1H-indol-7-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
43		16	8	557	(5-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
44		22	42	2198	(4-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
45		60	55	1500	(2-bromo-3-fluorophenyl)((1S,4R,6 R)-6-((5-(trifluoromethyl) pyridin -2-yl)oxy)-2-azabicyclo [2.2.1]heptan -2-yl)methanone
46		10	12	650	(2-fluoro-6-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
47		7	11	503	((1S,4R,6R)-6-((5-bromopyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl) (2-fluoro-6-(pyrimidin-2-yl) phenyl)methanone

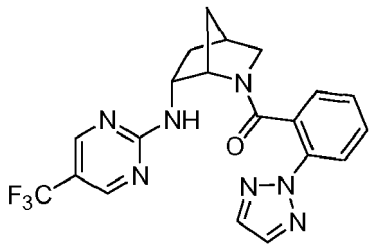
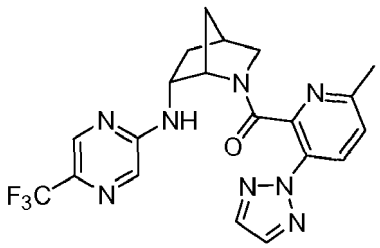
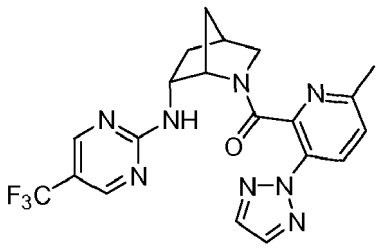
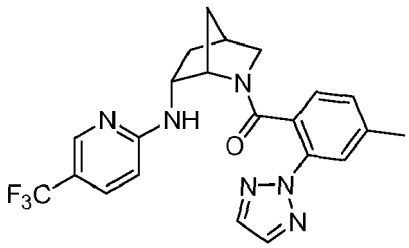
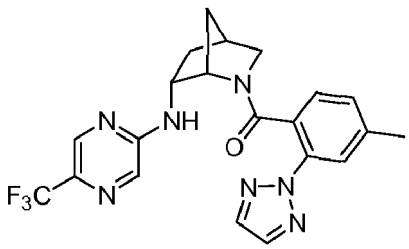
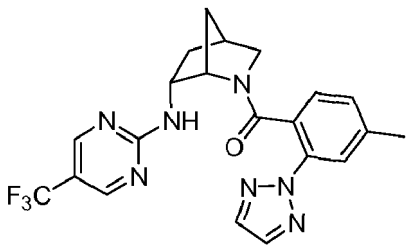
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
48		3	6	972	((1S,4R,6R)-6-((5-bromopyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)(3-fluoro-2-(pyrimidin-2-yl) phenyl)methanone
49		6	6	507	(2-(2H-1,2,3-triazol-2-yl) phenyl)((1S,4R,6R)-6-((5-bromopyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl) methanone
50		7	9	670	((1S,4R,6R)-6-((5-bromopyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)methanone
51		294		676	(2-(2H-1,2,3-triazol-2-yl) phenyl)((1S,4R,6R)-6-((3-(trifluoromethyl)pyridin -2-yl)oxy)-2-azabicyclo[2.2.1] heptan -2-yl)methanone
52		550		4000	(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((3-(trifluoromethyl)pyridin -2-yl)oxy)-2-azabicyclo[2.2.1] heptan -2-yl)methanone
53		3	3	165	(2-(2H-1,2,3-triazol-2-yl) phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin -2-yl)amino)-2-azabicyclo [2.2.1]heptan -2-yl)methanone

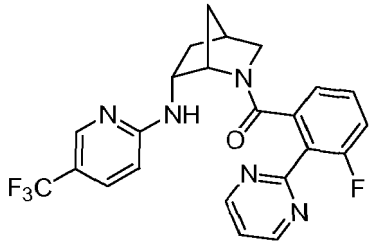
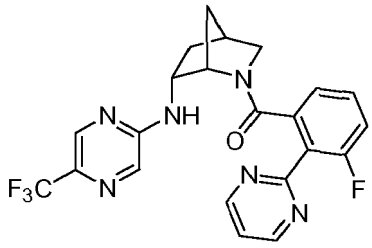
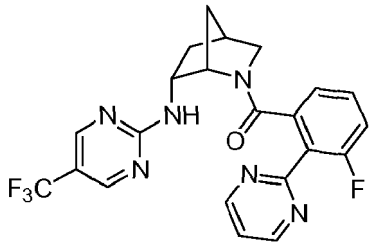
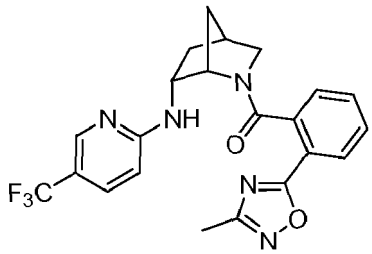
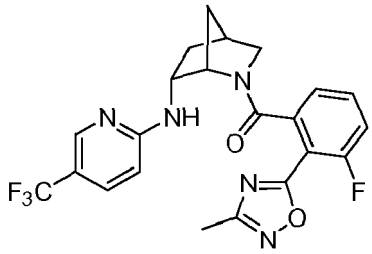
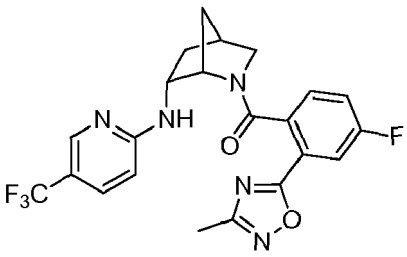
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
54		5	6	132	(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone
55		3	3	46	(3-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone
56		8	10	192	(7-ethoxyquinolin-8-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone
57		6	5	252	(5-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone
58		4	2	181	(5-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone
59		6	9	213	(2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

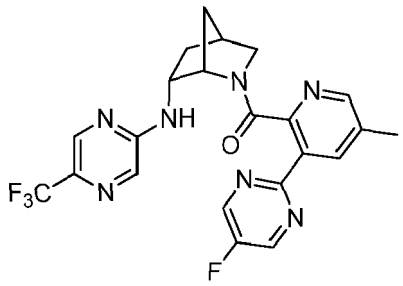
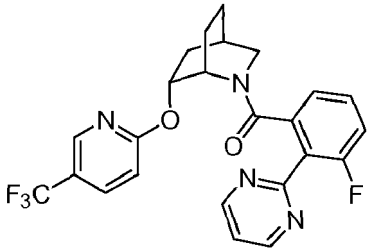
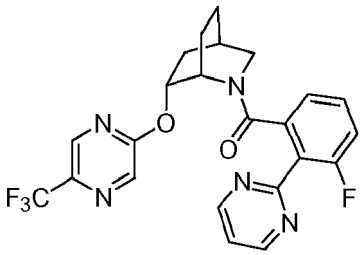
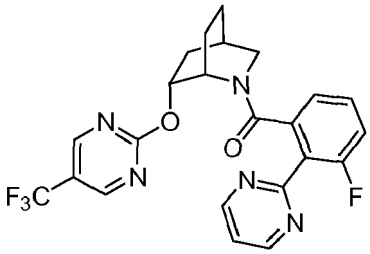
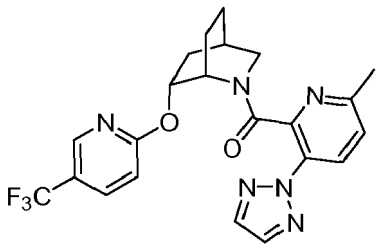
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
60					(2-(2H-1,2,3-triazol-2-yl) phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrimidin-2-yl)amino)-2-azabicyclo [2.2.1]heptan-2-yl)methanone
61					(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo [2.2.1]heptan-2-yl)methanone
62					(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrimidin-2-yl)amino)-2-azabicyclo [2.2.1]heptan-2-yl)methanone
63					(4-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo [2.2.1]heptan-2-yl)methanone
64					(4-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo [2.2.1]heptan-2-yl)methanone
65					(4-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrimidin-2-yl)amino)-2-azabicyclo [2.2.1]heptan-2-yl)methanone

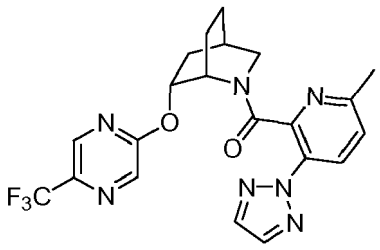
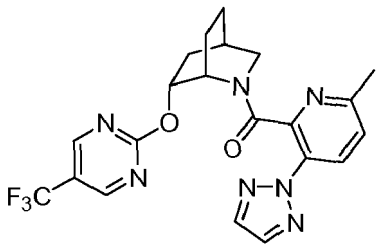
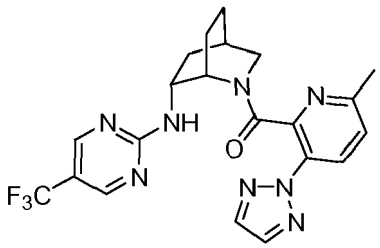
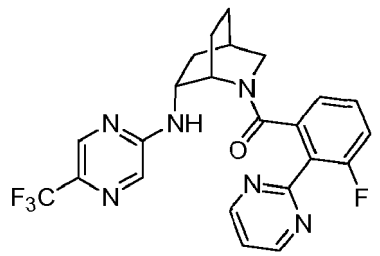
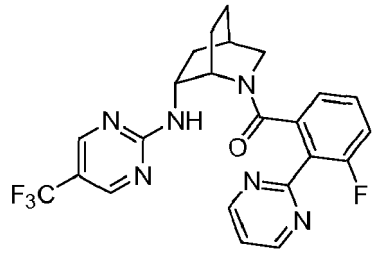
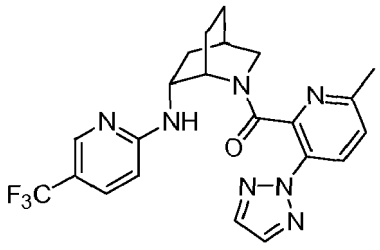
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
66					(3-fluoro-2-(pyrimidin-2-yl) phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone
67					(3-fluoro-2-(pyrimidin-2-yl) phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone
68					(3-fluoro-2-(pyrimidin-2-yl) phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrimidin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone
69					(2-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone
70					(3-fluoro-2-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl) pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl) methanone
71					(4-fluoro-2-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl) pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

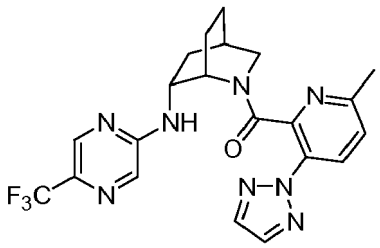
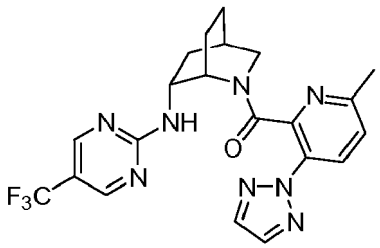
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
72					(3-(5-fluoropyrimidin-2-yl)-5-methylpyridin-2-yl)((1S,4S, 6R)-6-((5-(trifluoromethyl) pyraz in-2-yl)amino)-2-azabicyclo[2.2.1]hept an-2-yl) methanone.
73					(3-fluoro-2-(pyrimidin-2-yl) phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin -2-yl)oxy)-2-azabicyclo[2.2.2] octan-2-yl)methanone
74					(3-fluoro-2-(pyrimidin-2-yl) phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrazin -2-yl)oxy)-2-azabicyclo[2.2.2] octan-2 -yl)methanone
75					(3-fluoro-2-(pyrimidin-2-yl) phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrimi din-2-yl)oxy)-2-azabicyclo [2.2.2]octan-2-yl)methanone
76					(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin -2-yl)oxy)-2-azabicyclo[2.2.2] octan-2-yl)methanone

(continued)

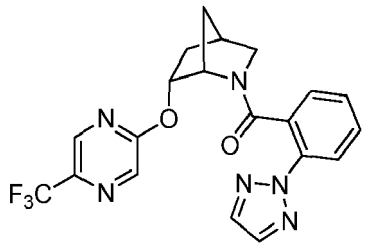
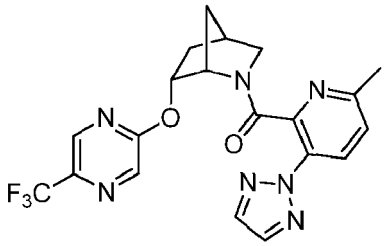
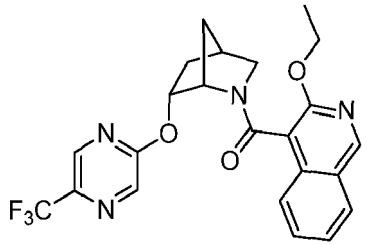
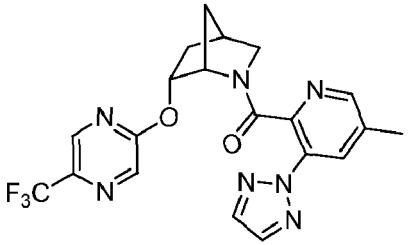
Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
77					(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone
78					(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrimidin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone
79					(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrimidin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone
80					(3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone
81					(3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrimidin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone
82					(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone

(continued)

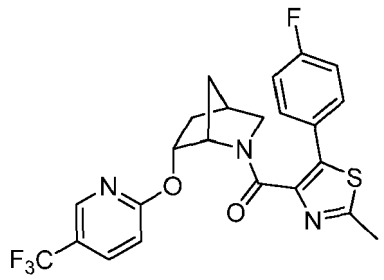
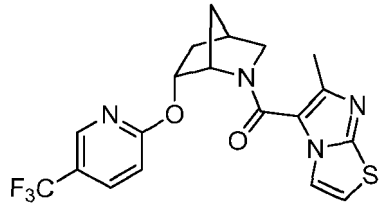
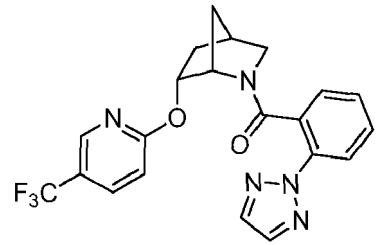
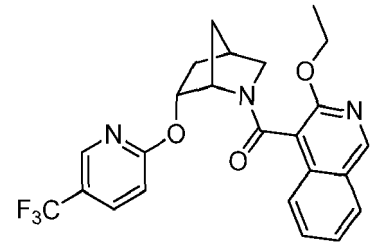
Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
83					(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone
84					(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrimidin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone

[1333] Preferred compounds of the invention are set forth in the table below. Orexin receptor activity of certain compounds of the invention is also set forth in Table 2 below.

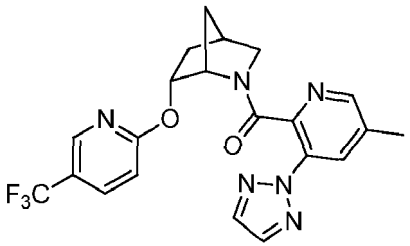
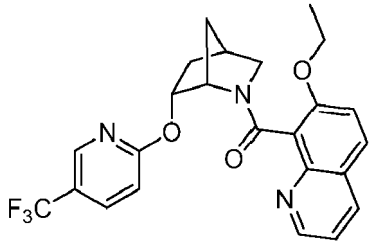
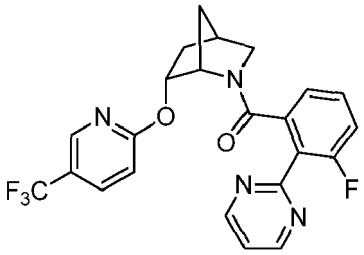
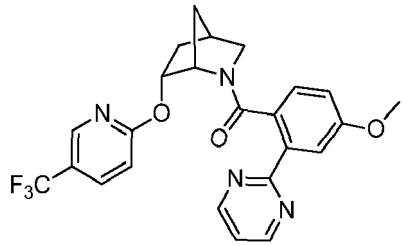
Table 2

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
1		74	120	4700	(R/S)-(2-(2H-1,2,3-triazol-2-yl)phenyl)(6-((5-(trifluoromethyl)pyrazin -2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
2		200	342	10000	(R/S)-(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)(6-((5-(trifluoromethyl)pyrazin -2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
3		63	123	8900	(R/S)-(3-ethoxyisoquinolin-4-yl)((5-(trifluoromethyl)pyrazin -2-yl)oxy)-2-azabicyclo [2.2.1]heptan -2-yl)methanone
4		837		>10000	(R/S)-5-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)(6-((5-(trifluoromethyl)pyrazin -2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone

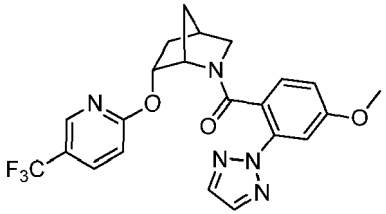
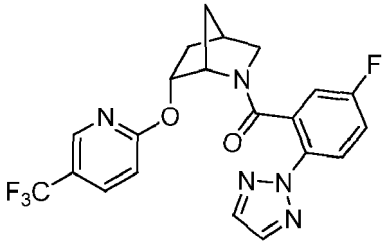
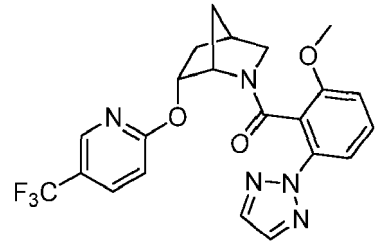
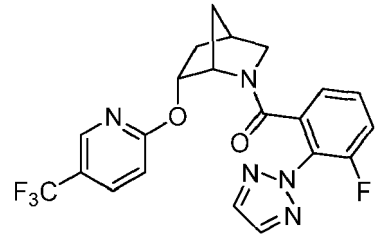
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
5		25	18	779	(R/S)-(5-(4-fluorophenyl)-2-methylthiazol-4-yl)(6-((5-(trifluoromethyl)pyridin -2-yl) oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
6		>10000		>10000	(R/S)-(6-methylimidazo[2,1-b]thiazol-5-yl)(6-((5-(trifluoromethyl)pyridin -2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
7		21	12	800	(R/S)-(2-(2H-1,2,3-triazol-2-yl)phenyl)(6-((5-(trifluoromethyl)pyridin -2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
8		16	15	1450	(R/S)-(3-ethoxyisoquinolin-4-yl)(6-((5-(trifluoromethyl)pyridin -2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone

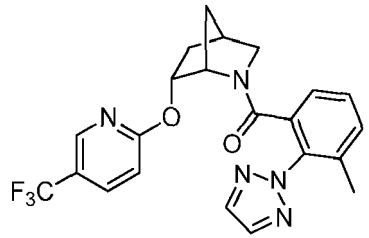
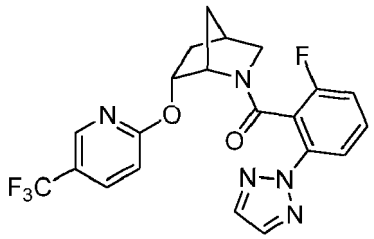
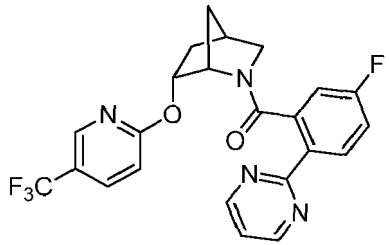
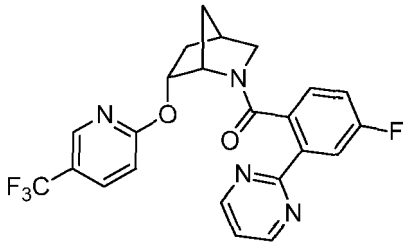
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
9		56	102	2575	(R/S)-(5-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)(6-((5-(trifluoromethyl)pyridin -2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
10		18	27	526	(R/S)-(7-ethoxyquinolin-8-yl)(6-((5-(trifluoromethyl)pyridin -2-yl)oxy)-2-azabicyclo [2.2.1]heptan -2-yl)methanone
11		11	9	1475	(R/S)-(3-fluoro-2-(pyrimidin-2-yl)phenyl)(6-((5-(trifluoromethyl)pyridin -2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
12		44	59	>10000	(R/S)-(4-methoxy-2-(pyrimidin-2-yl)phenyl)(6-((5-(trifluoromethyl)pyridin -2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone

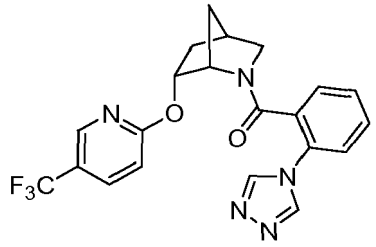
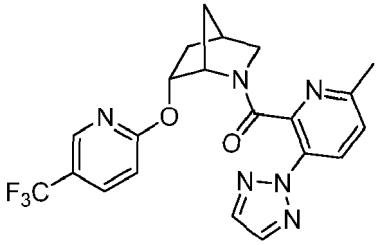
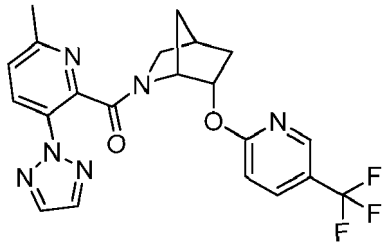
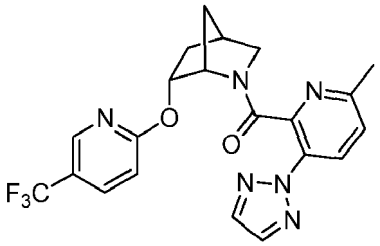
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
13		52	109	>10000	(R/S)-4-methoxy-2-(2H -1,2,3-triazol-2-yl)phenyl)(6-((5-(trifluoromethyl)pyridin -2-yl) oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
14		17	23	882	(R/S)-(5-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)(6-((5-(trifluoromethyl)pyridin -2-yl) oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
15		17	40	229	(R/S)-2-methoxy-6-(2H-1,2,3-triazol-2-yl)phenyl)(6-((5-(trifluoromethyl)pyridin -2-yl) oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
16		8	7	1000	(R/S)-(3-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)(6-((5-(trifluoromethyl)pyridin -2-yl) oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone

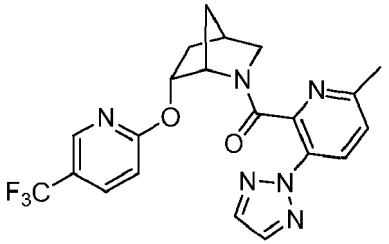
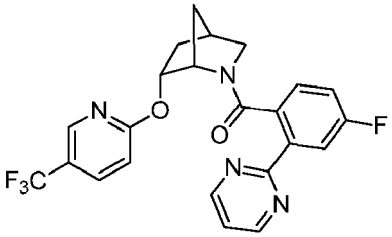
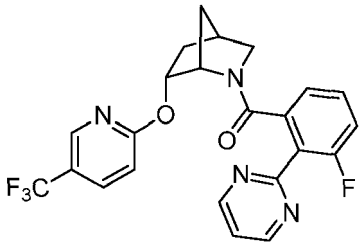
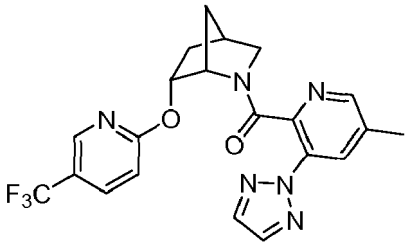
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
17		8	3	234	(R/S)-(3-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)(6-((5-(trifluoromethyl)pyridin -2-yl) oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
18		25	23	1800	(R/S)-(2-fluoro-6-(2H-1,2,3-triazol-2-yl)phenyl)(6-((5-(trifluoromethyl)pyridin -2-yl) oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
19		18	9	945	(R/S)-(5-fluoro-2-(pyrimidin-2-yl)phenyl)(6-((5-(trifluoromethyl)pyridin -2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
20		15	15	2700	(R/S)-(4-fluoro-2-(pyrimidin-2-yl)phenyl)(-6-((5-(trifluoromethyl)pyridin -2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone

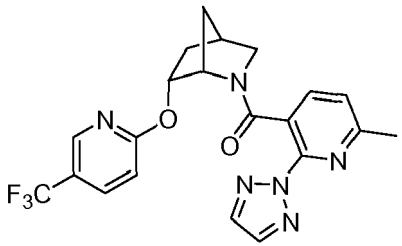
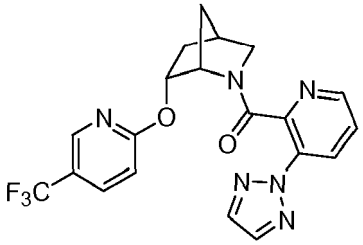
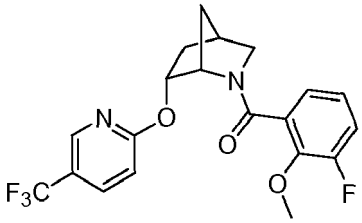
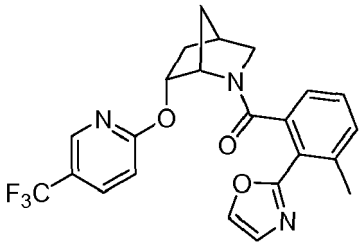
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
21		>10000		>10000	(R/S)-(2-(4H-1,2,4-triazol-4-yl)phenyl)(6-((5-(trifluoromethyl)pyridin -2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
22		25	23	1000	(R/S)-(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)(6-((5-(trifluoromethyl)pyridin -2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
23		>10000		>10000	(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)((1R,4S,6S)-6-((5-(trifluoromethyl) pyridin -2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
24		20	16	692	(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl) pyridin -2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone

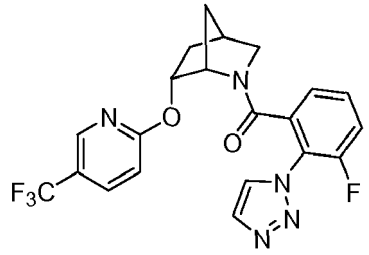
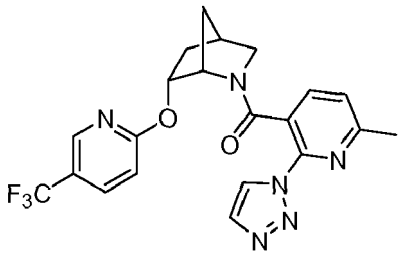
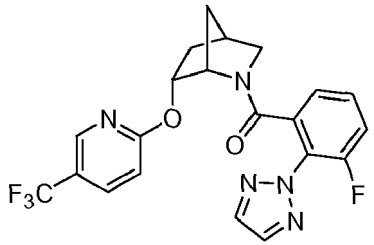
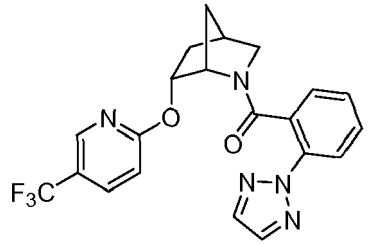
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
25		14	15	483	(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl) pyridin -2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
26		12	15	2100	(4-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin -2-yl) oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
27		6	5	725	(3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin -2-yl) oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
28		32	21	1600	(5-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl) pyridin -2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

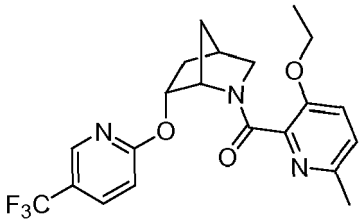
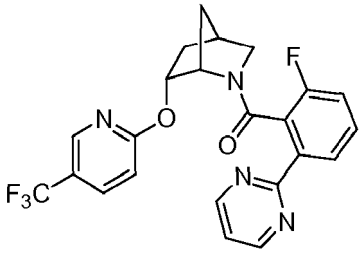
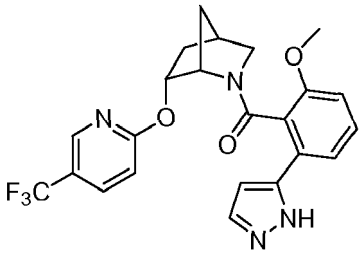
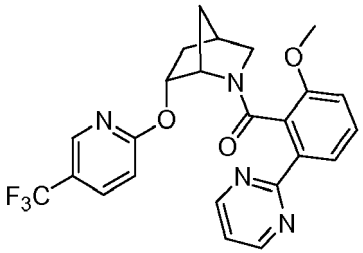
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
29		55	47	>10000	(6-methyl-2-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl) pyridin -2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
30		19	22	1700	(3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin -2-yl) oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
31		707		>10000	(3-fluoro-2-methoxyphenyl)((1S,4R ,6R)-6-((5-(trifluoromethyl)pyridin -2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
32		3	6	149	(3-methyl-2-(oxazol-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin -2-yl) oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone

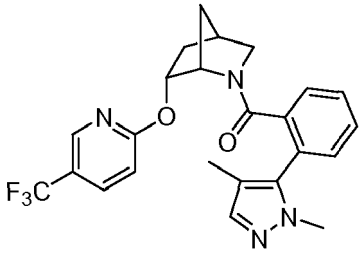
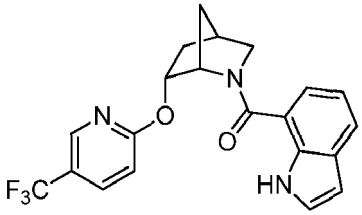
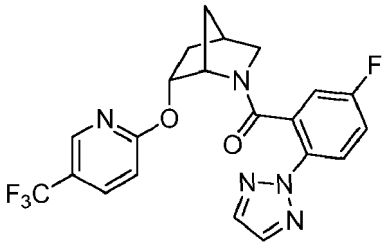
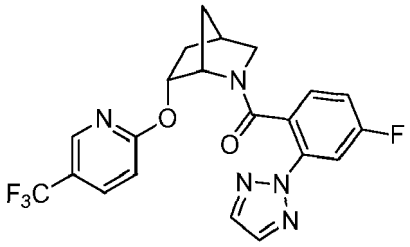
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
33		74	86	3500	(3-fluoro-2-(1H-1,2,3-triazol-1-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin -2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
34		162	368	1050	(6-methyl-2-(1H-1,2,3-triazol-1-yl)pyridin-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl) pyridin -2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
35		8	3	546	(3-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin -2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
36		5	13	343	(2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin -2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

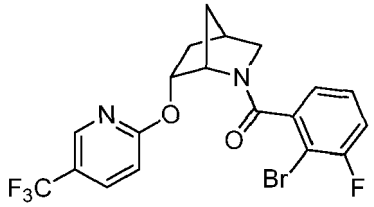
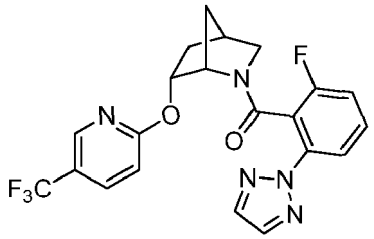
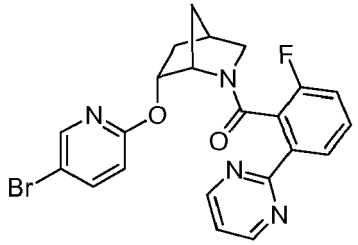
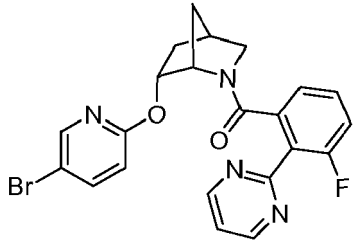
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
37		170	265	1800	(3-ethoxy-6-methylpyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin -2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
38		8	8	633	(2-fluoro-6-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin -2-yl) oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
39		72	17	104	(2-methoxy-6-(1H-pyrazol-5-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin -2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
40		15	9	333	(2-methoxy-6-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin -2-yl) oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone

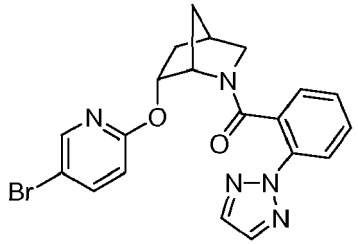
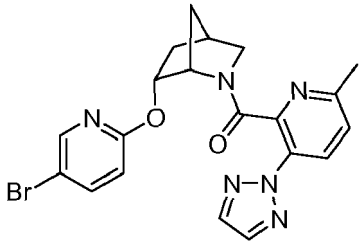
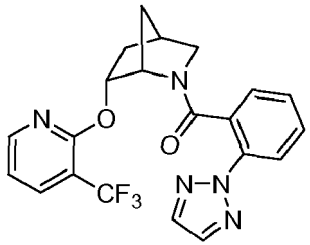
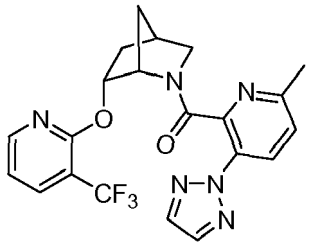
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
41		4400		>10000	(2-(1,4-dimethyl-1H-pyrazol-5-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin -2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
42		184	175	5800	(1H-indol-7-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin -2-yl)oxy)-2-azabicyclo [2.2.1]heptan -2-yl)methanone
43		24	16	550	(5-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin -2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone
44		21	39	2333	(4-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin -2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone

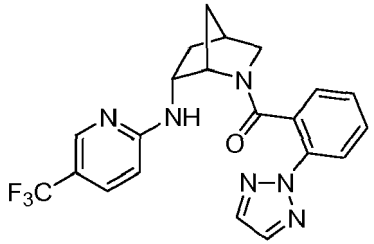
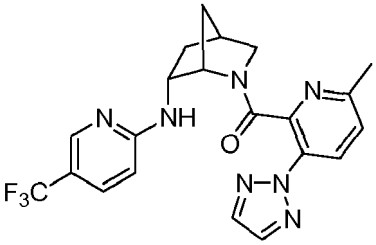
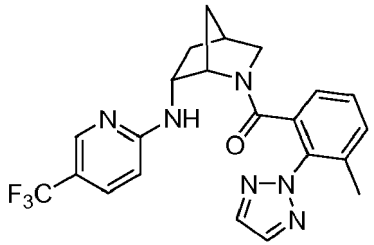
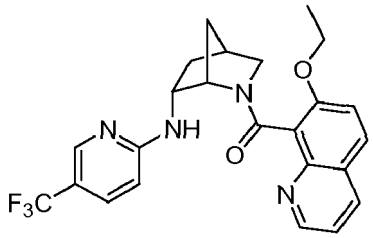
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
45		60	55	1500	(2-bromo-3-fluorophenyl)((1S,4R,6 R)-6-((5-(trifluoromethyl)pyridin -2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
46		10	12	650	(2-fluoro-6-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin -2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
47		6	9	524	((1S,4R,6R)-6-((5-bromopyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)(2-fluoro-6-(pyrimidin-2-yl)phenyl)methanone
48		4	5	903	((1S,4R,6R)-6-((5-bromopyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)(3-fluoro-2-(pyrimidin-2-yl)phenyl)methanone

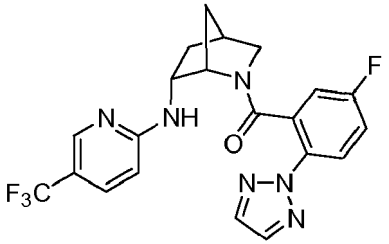
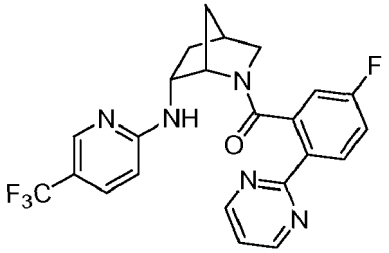
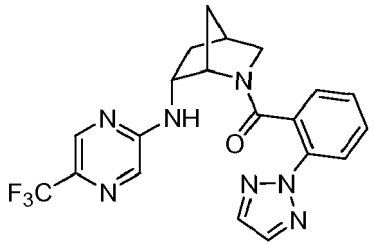
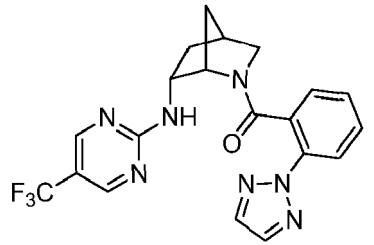
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
49		6	5	443	(2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((5-bromopyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
50		7	10	578	((1S,4R,6R)-6-((5-bromopyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)methanone
51		294		676	(2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((3-(trifluoromethyl)pyridin -2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
52		550		4000	(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((3-(trifluoromethyl) pyridin -2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone

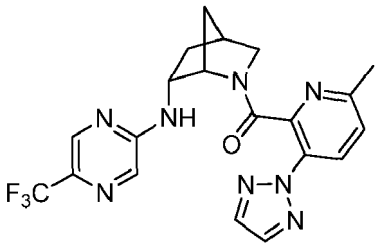
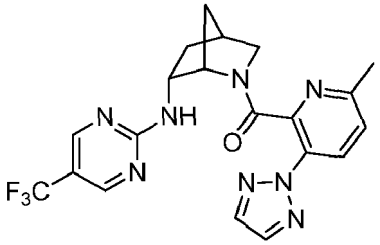
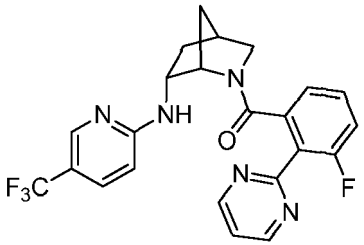
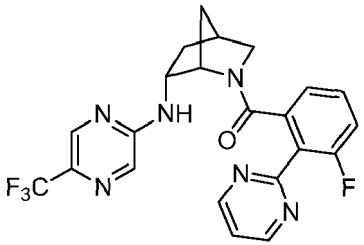
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
53		3	4	169	(2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin -2-yl) amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
54		6	5	126	(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)((1S,4S,6R)-6-((5-(trifluoromethyl) pyridin -2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
55		3	3	46	(3-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin -2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
56		8	10	192	(7-ethoxyquinolin-8-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin -2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone

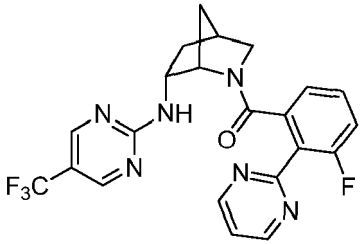
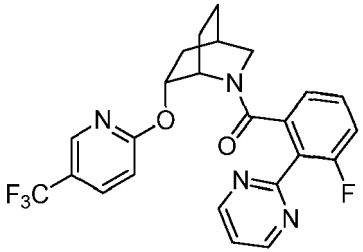
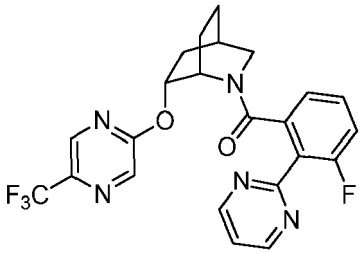
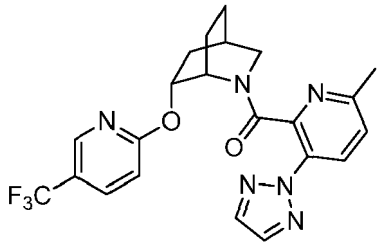
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
57		5	5	225	(5-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin -2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
58		5	3	193	(5-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin -2-yl) amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone
59		6	7	192	(2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin -2-yl) amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
60		20	12	617	(2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrimi din-2-yl) amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone

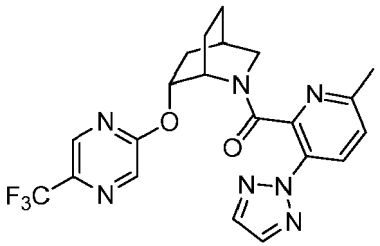
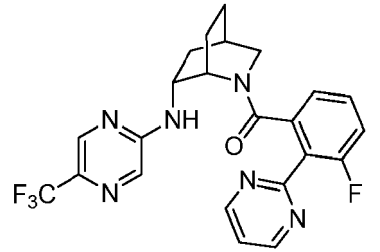
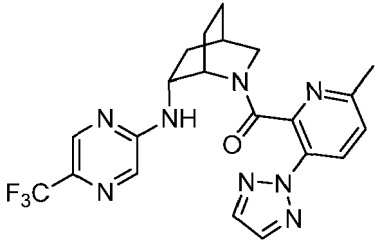
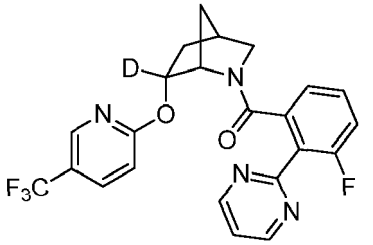
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
61		15	19	248	(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)((1S,4S,6R)-6-((5-(trifluoromethyl) pyrazin -2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
62		28	19	569	(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)((1S,4S,6R)-6-((5-(trifluoromethyl) pyrimi din-2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
66		2	5	181	(3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin -2-yl) amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
67		7	7	264	(3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin -2-yl) amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone

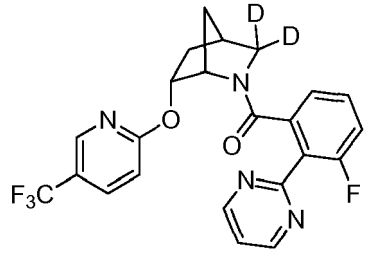
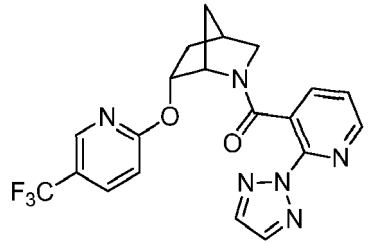
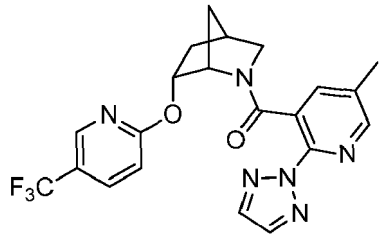
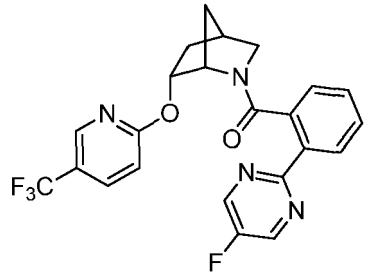
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
68		7	8	612	(3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrimi din-2-yl) amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
73		8	11	575	(3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin -2-yl) oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone
74		16	16	1800	(3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrazin -2-yl) oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone
76		4	3	211	(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl) pyridin -2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone

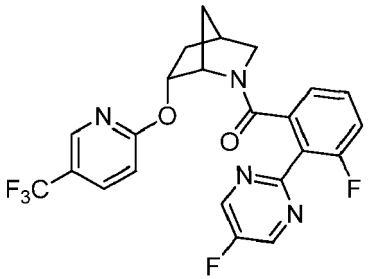
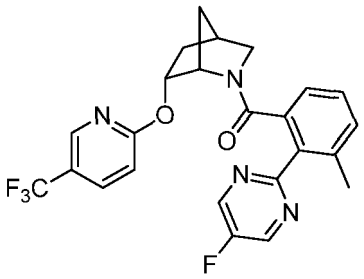
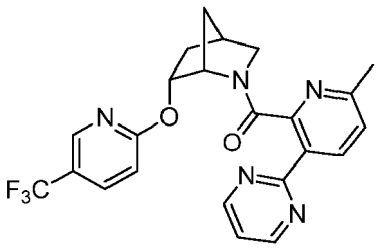
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
77		9	13	1700	(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl) pyrazin -2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone
80		9	7	456	(3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrazin -2-yl) amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone
83		8	5	289	(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl) pyrazin -2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone
85		6	6	910	(3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-(6-^{2}H)-((5-(trifluoromethyl)pyridin -2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone

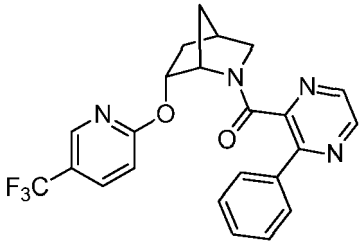
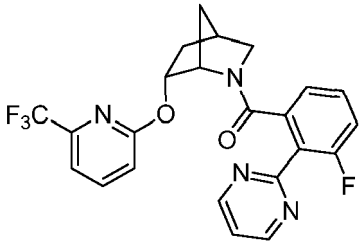
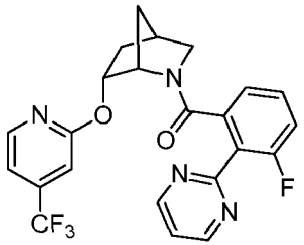
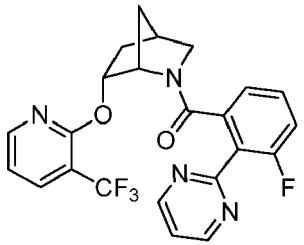
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
86		7	9	946	(3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin -2-yl) oxy)-2-azabicyclo[2.2.1]- (3-^{2}H, ^{2}H)-heptan-2-yl)methanone
87		156	211	>10000	(2-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin -2-yl) oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
88		45	36	>10000	(5-methyl-2-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl) pyridin -2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
89		18	8	1100	(2-(5-fluoropyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin -2-yl) oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

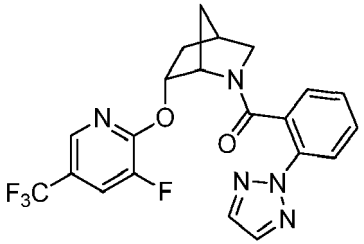
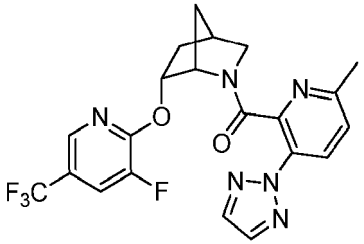
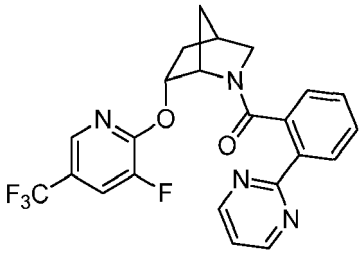
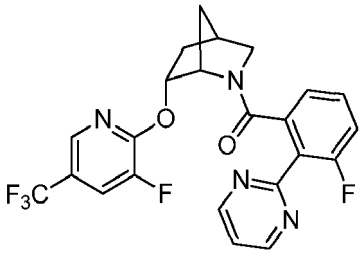
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
90		15	19	2150	(3-fluoro-2-(5-fluoropyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin -2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
91		8	6	331	(2-(5-fluoropyrimidin-2-yl)-3-methylphenyl)((1S,4R,6 R)-6-((5-(trifluoromethyl) pyridin -2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
92		13	19	362	(6-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin -2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone

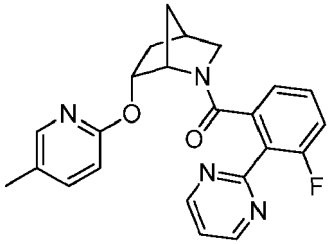
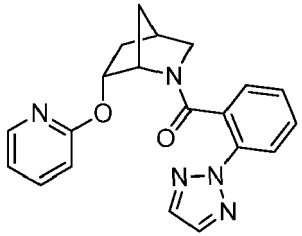
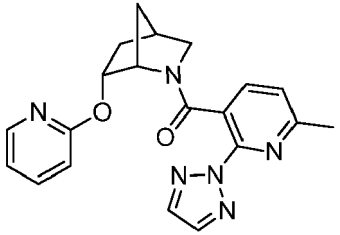
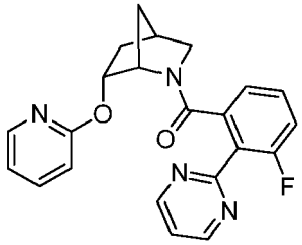
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
93		125	76	3100	(3-phenylpyrazin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin -2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
94		35	30	848	(3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((6-(trifluoromethyl)pyridin -2-yl) oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
95		29	37	137	(3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((4-(trifluoromethyl)pyridin -2-yl) oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
96		320		1700	(3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((3-(trifluoromethyl)pyridin -2-yl) oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

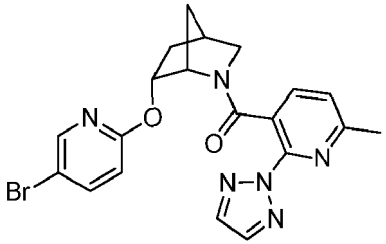
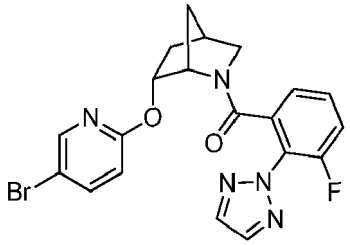
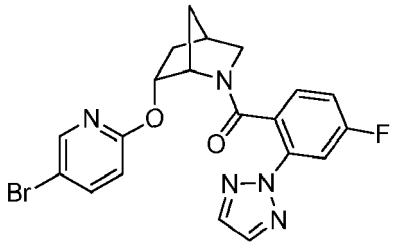
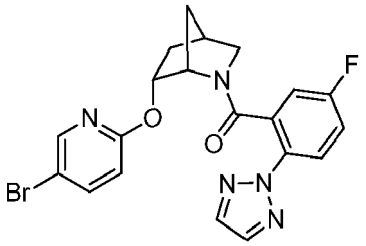
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
97		21	15	1100	(2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((3-fluoro-5-(trifluoromethyl)pyridin -2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
98		37	28	1200	((1S,4R,6R)-6-((3-fluoro-5-(trifluoromethyl)pyridin -2-yl)oxy)-2-azabicyclo[2.2.1] heptan -2-yl)(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)methanone
99		11	10	725	((1S,4R,6R)-6-((3-fluoro-5-(trifluoromethyl)pyridin -2-yl)oxy)-2-azabicyclo[2.2.1] heptan -2-yl)(2-(pyrimidin-2-yl)phenyl)methanone
100		13	12	1600	(3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((3-fluoro-5-(trifluoromethyl)pyridin -2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone

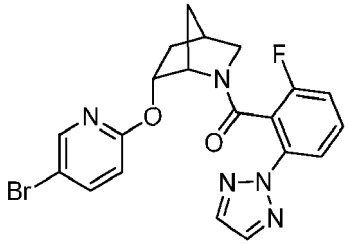
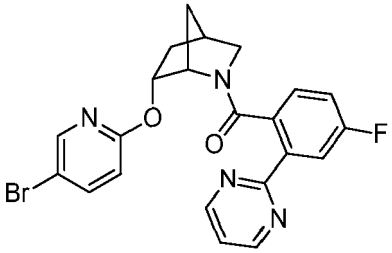
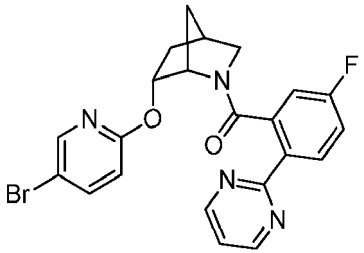
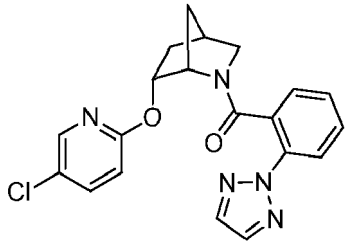
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
101		26	11	710	(3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-methylpyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
102		404		1600	(2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-(pyridin-2-yloxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
103		>10000		>10000	(6-methyl-2-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)((1S,4R,6R)-6-(pyridin-2-yloxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
104		497		5000	(3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-(pyridin-2-yloxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone

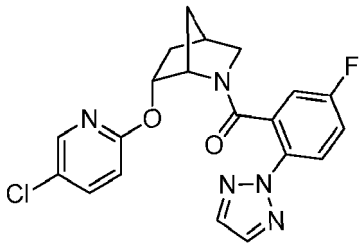
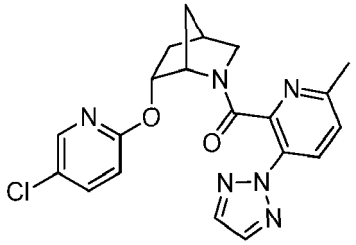
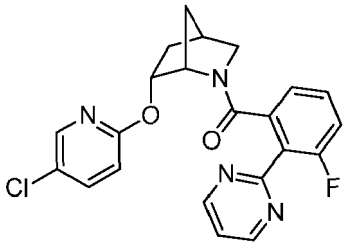
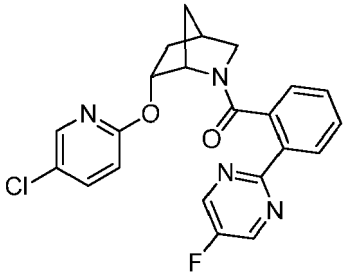
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
105		119	337	>10000	((1S,4R,6R)-6-((5-bromopyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)(6-methyl-2-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)methanone
106		3	4	436	((1S,4R,6R)-6-((5-bromopyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)(3-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone
107		16	26	1960	((1S,4R,6R)-6-((5-bromopyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)(4-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone
108		8	31	776	((1S,4R,6R)-6-((5-bromopyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)(5-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone

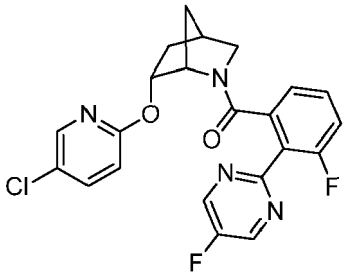
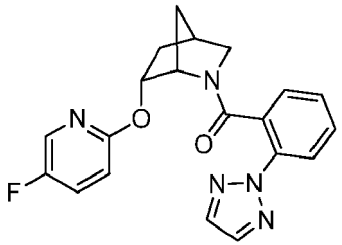
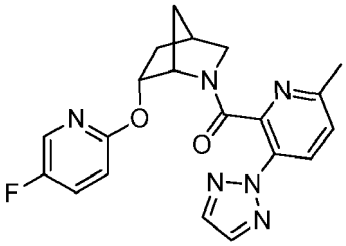
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
109		6	5	442	((1S,4R,6R)-6-((5-bromopyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)(2-fluoro-6-(2H-1,2,3-triazol-2-yl)phenyl)methanone
110		6	11	1200	((1S,4R,6R)-6-((5-bromopyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)(4-fluoro-2-(pyrimidin-2-yl)phenyl)methanone
111		5	5	458	((1S,4R,6R)-6-((5-bromopyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)(5-fluoro-2-(pyrimidin-2-yl)phenyl)methanone
112		8	10	459	(2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((5-chloropyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone

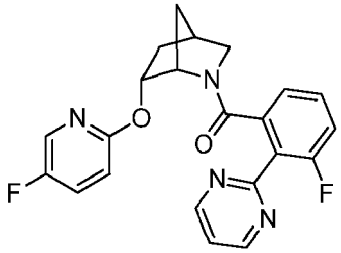
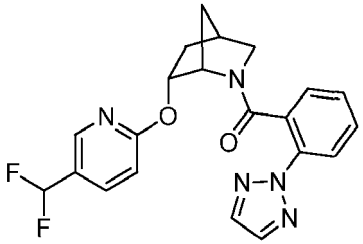
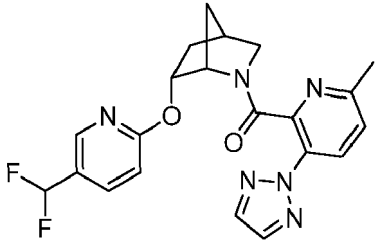
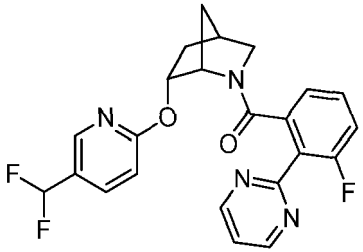
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
113		17	14	984	((1S,4R,6R)-6-((5-chloropyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)(5-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone
114		11	23	668	((1S,4R,6R)-6-((5-chloropyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)methanone
115		7	8	852	((1S,4R,6R)-6-((5-chloropyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)(3-fluoro-2-(pyrimidin-2-yl)phenyl)methanone
116		11	12	939	((1S,4R,6R)-6-((5-chloropyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)(2-(5-fluoropyrimidin-2-yl)phenyl)methanone

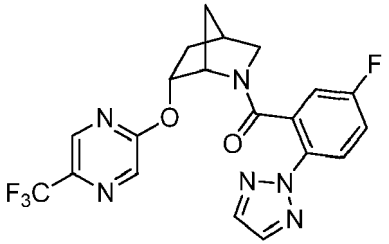
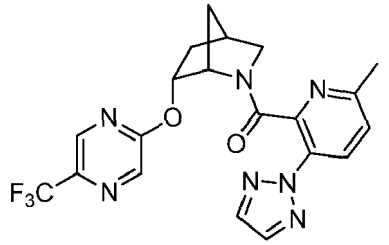
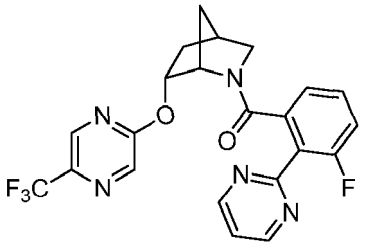
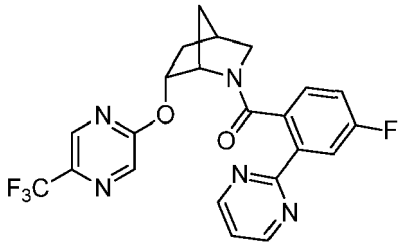
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
117		16	28	1600	((1S,4R,6R)-6-((5-chloropyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)(3-fluoro-2-(5-fluoropyrimidin-2-yl)phenyl)methanone
118		133	105	1600	(2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((5-fluoropyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
119		262		3600	((1S,4R,6R)-6-((5-fluoropyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)methanone

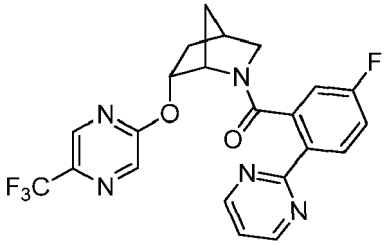
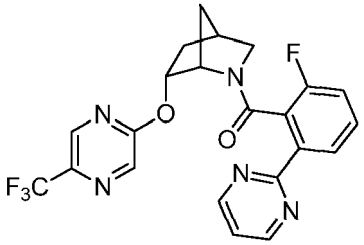
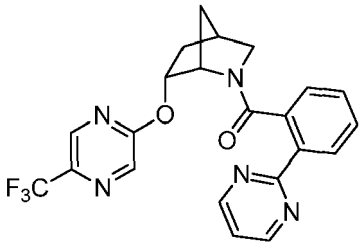
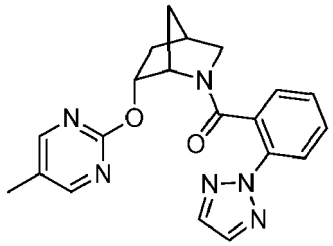
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
120		60	111	4100	(3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-fluoropyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
121		10	11	50	(2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((5-(difluoromethyl)pyridin -2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
122		28	30	218	((1S,4R,6R)-6-((5-(difluoromethyl)pyridin -2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)methanone
123		11	10	149	((1S,4R,6R)-6-((5-(difluoromethyl)pyridin -2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)(3-fluoro-2-(pyrimidin-2-yl)phenyl)methanone

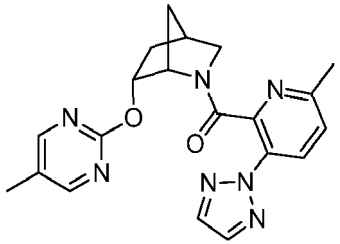
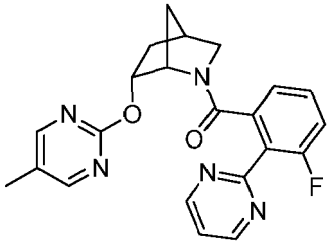
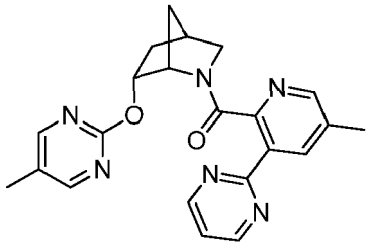
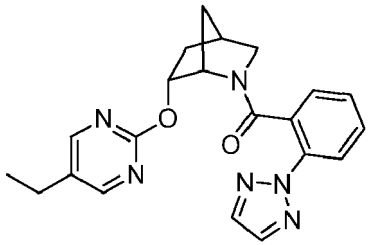
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
124		200	109	4500	(5-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrazin -2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
125		220	88	5500	(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl) pyrazin -2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
126		27	22	4200	(3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrazin -2-yl) oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
127		116	143	>10000	(4-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrazin-2-yl) oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone

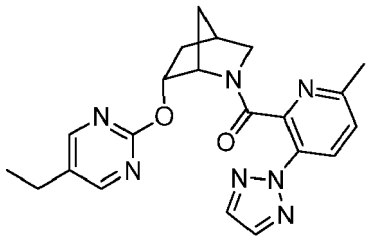
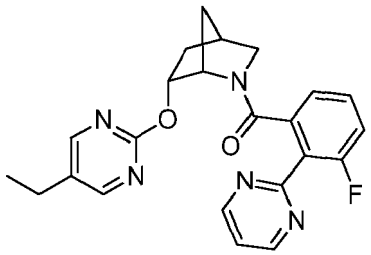
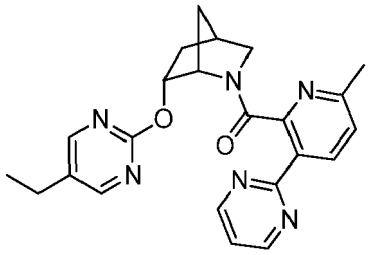
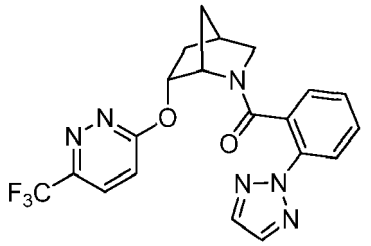
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
128		69	62	3800	(5-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrazin -2-yl) oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
129		53	47	4400	(2-fluoro-6-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrazin -2-yl) oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
130		29	27	3500	(2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrazin -2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
131		140	132	2200	(2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((5-methylpyrimidin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone

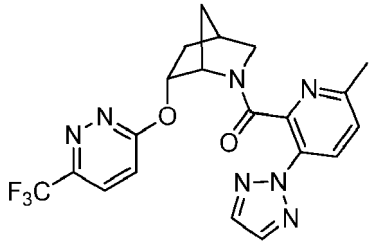
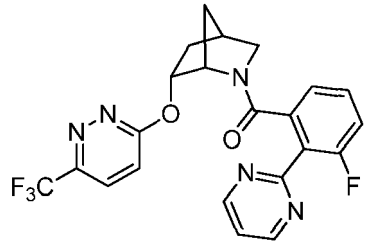
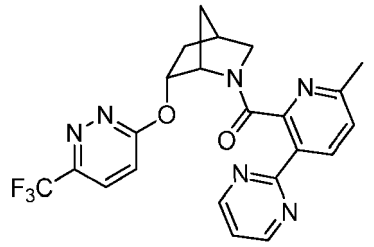
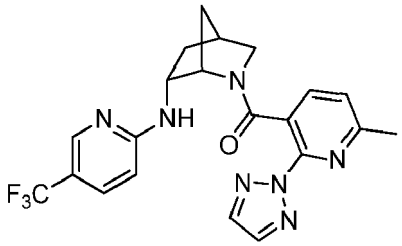
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
132		425		6800	(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-methylpyrimidin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
133		60	102	4200	(3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-methylpyrimidin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
134		668		>10000	(5-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-methylpyrimidin-2-yl) oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
135		61	100	1200	(2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((5-ethylpyrimidin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone

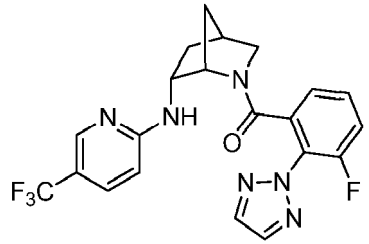
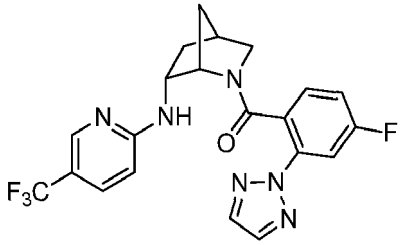
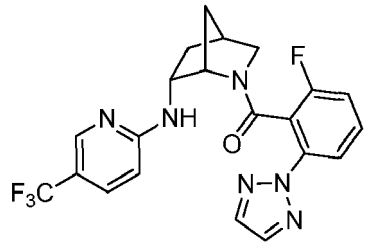
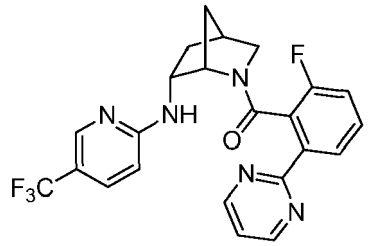
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
136		380		4700	((1S,4R,6R)-6-((5-ethylpyrimidin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)methanone
137		39	65	1700	((1S,4R,6R)-6-((5-ethylpyrimidin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)(3-fluoro-2-(pyrimidin-2-yl)phenyl)methanone
138		300		2700	((1S,4R,6R)-6-((5-ethylpyrimidin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)(6-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)methanone
139		208	150	3700	(2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((6-(trifluoromethyl)pyridaz in-3-yl) oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone

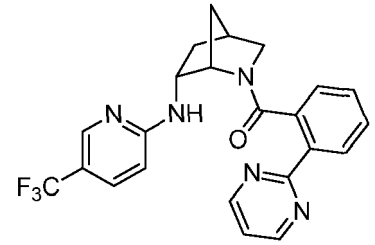
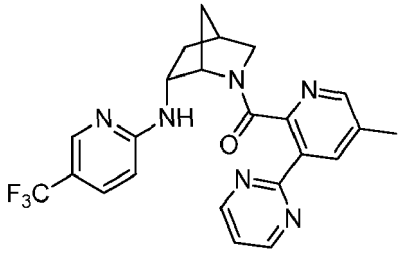
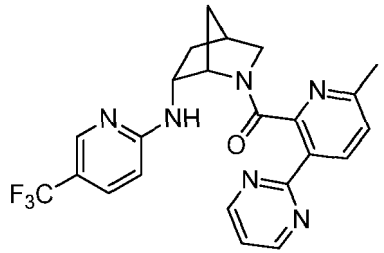
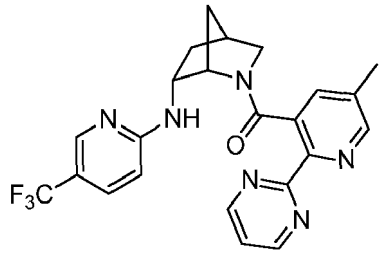
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
140		330		7700	(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((6-(trifluoromethyl) pyridaz in-3-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
141		208	348	>10000	(3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((6-(trifluoromethyl)pyridaz in-3-yl) oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
142		376		7900	(6-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((6-(trifluoromethyl)pyridaz in-3-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
143		24	34	7300	(6-methyl-2-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)((1S,4S,6R)-6-((5-(trifluoromethyl) pyridin -2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone

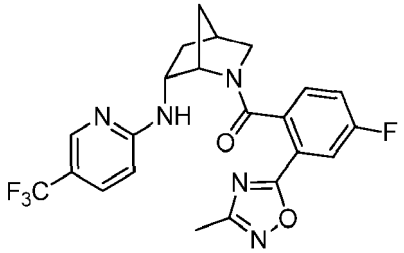
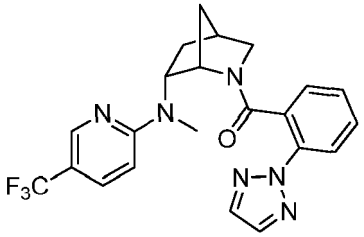
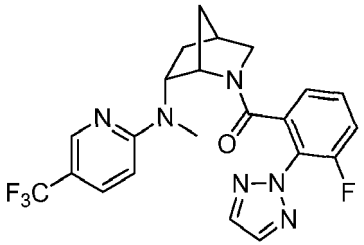
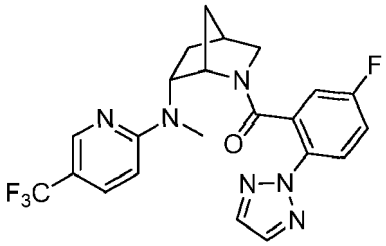
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
144		3	3	133	(3-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin -2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
145		17	7	934	(4-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin -2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
146		6	3	150	(2-fluoro-6-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin -2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone
147		5	6	190	(2-fluoro-6-(pyrimidin-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin -2-yl) amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone

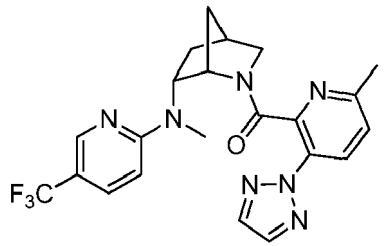
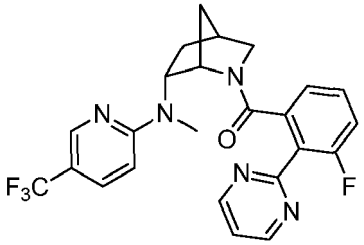
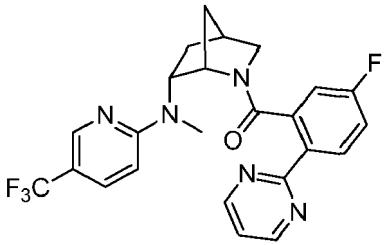
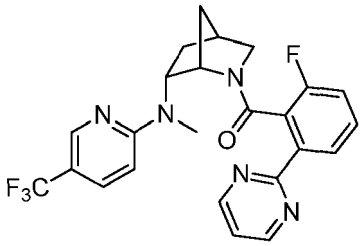
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
148		3	5	189	(2-(pyrimidin-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin -2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
149		14	7	4600	(5-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin -2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
150		13	9	88	(6-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin -2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone
151		21	47	5100	(5-methyl-2-(pyrimidin-2-yl)pyridin-3-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin -2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone

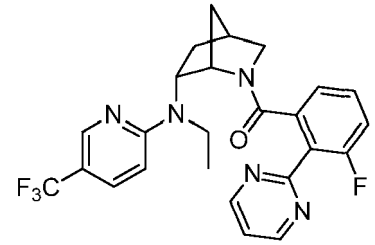
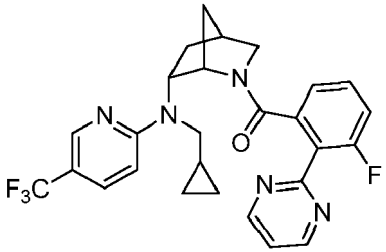
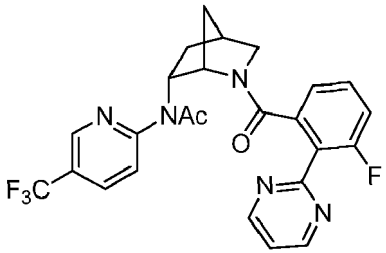
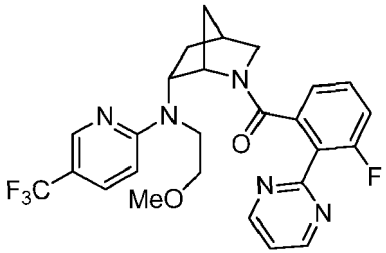
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
152		30	16	1600	(4-fluoro-2-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin -2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl) methanone
153		3	3	342	(2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-(methyl(5-(trifluoromethyl)pyridin -2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
154		4	6	329	(3-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-(methyl(5-(trifluoromethyl) pyridin -2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
155		5	3	303	(5-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-(methyl(5-(trifluoromethyl) pyridin -2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone

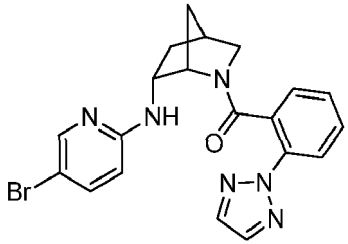
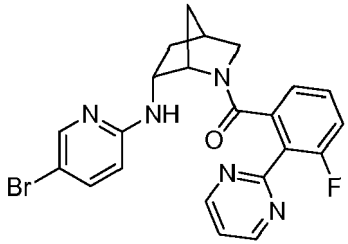
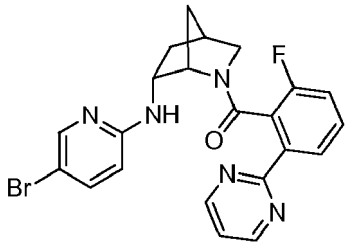
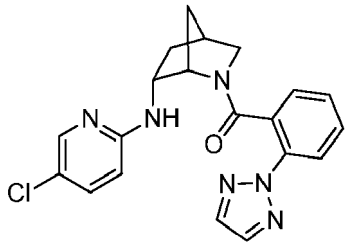
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
156		7	5	274	((1S,4S,6R)-6-(methyl(5-(trifluoromethyl)pyridin -2-yl)amino)-2-azabicyclo[2.2.1] heptan -2-yl)(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)methanone
157		6	3	351	(3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4S,6R)-6-(methyl(5-(trifluoromethyl)pyridin -2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
158		5	2	340	(5-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4S,6R)-6-(methyl(5-(trifluoromethyl)pyridin -2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
159		6	4	209	(2-fluoro-6-(pyrimidin-2-yl)phenyl)((1S,4S,6R)-6-(methyl(5-(trifluoromethyl)pyridin -2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone

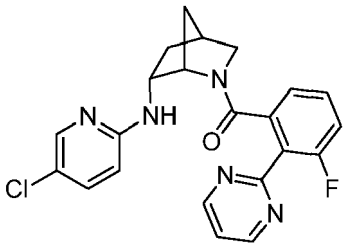
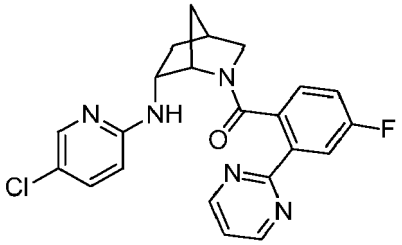
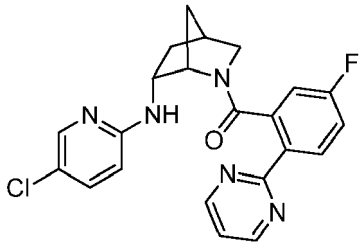
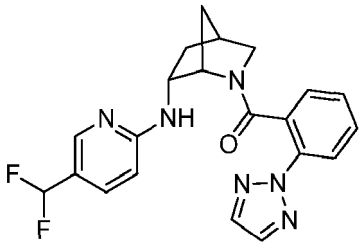
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
160		9	6	208	(2-fluoro-6-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin -2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
161		14	5	384	((1S,4S,6R)-6-((cyclopropylmethyl)(5-(trifluoromethyl)pyridin -2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)(3-fluoro-2-(pyrimidin-2-yl)phenyl)methanone
162		>10000		>10000	N-((1S,4R,6R)-2-(3-fluoro-2-(pyrimidin-2-yl)benzoyl)-2-azabicyclo[2.2.1]heptan -6-yl)-N-(5-(trifluoromethyl)pyridin -2-yl)acetamide
163		19	12	962	(3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4S,6R)-6-((2-methoxyethyl) (5-(trifluoromethyl)pyridin -2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone

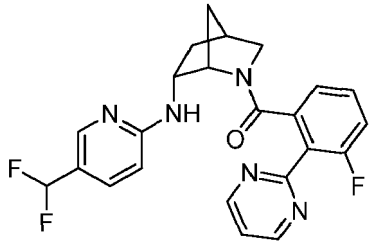
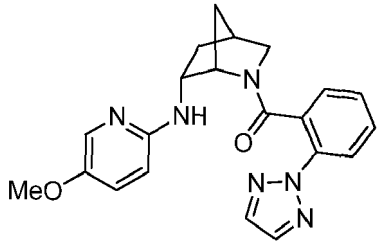
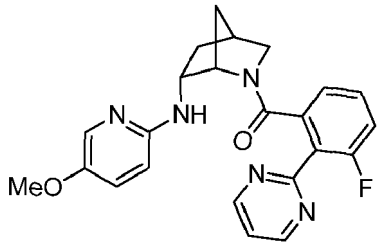
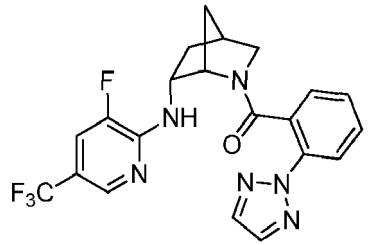
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
166		2	4	236	(2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-bromopyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
167		2	6	239	((1S,4S,6R)-6-((5-bromopyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)(3-fluoro-2-(pyrimidin-2-yl)phenyl)methanone
168		2	4	351	((1S,4S,6R)-6-((5-bromopyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)(2-fluoro-6-(pyrimidin-2-yl)phenyl)methanone
169		3	4	285	(2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-chloropyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone

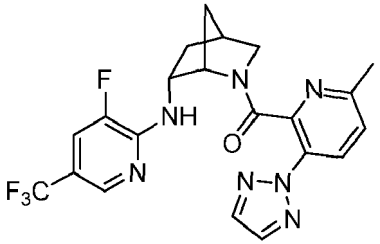
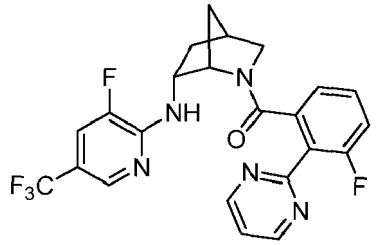
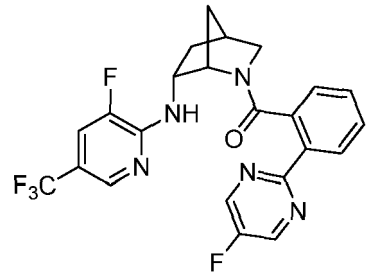
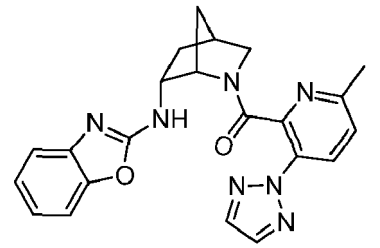
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
170		4	12	321	((1S,4S,6R)-6-((5-chloropyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)(3-fluoro-2-(pyrimidin-2-yl)phenyl)methanone
171		27	25	1900	((1S,4S,6R)-6-((5-chloropyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)(4-fluoro-2-(pyrimidin-2-yl)phenyl)methanone
172		8	7	400	((1S,4S,6R)-6-((5-chloropyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)(5-fluoro-2-(pyrimidin-2-yl)phenyl)methanone
173		55	33	264	(2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-(difluoromethyl)pyridin -2-yl) amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone

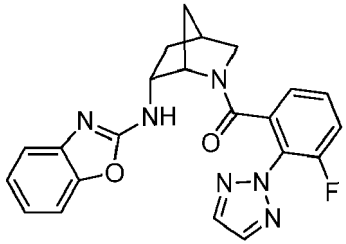
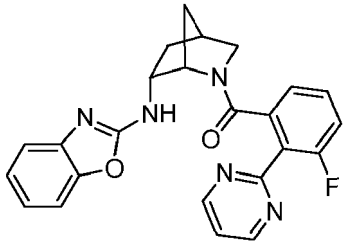
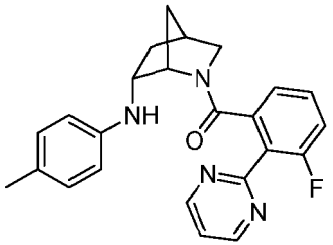
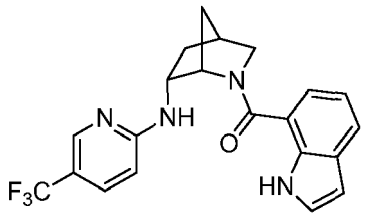
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
174		18	15	230	((1S,4S,6R)-6-((5-(difluoromethyl)pyridin -2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)(3-fluoro-2-(pyrimidin-2-yl)phenyl)methanone
175		170	191	844	(2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-methoxypyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
176		56	52	1300	(3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4S,6R)-6-((5-methoxypyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
177		3	3	200	(2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((3-fluoro-5-(trifluoromethyl)pyridin -2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone

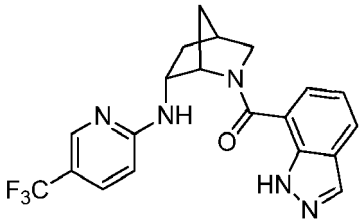
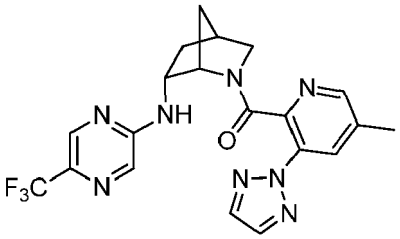
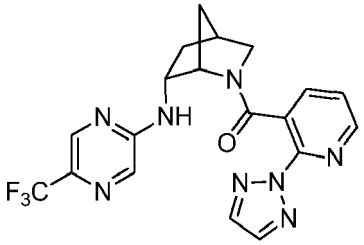
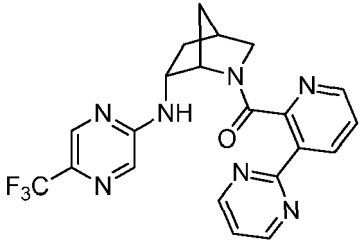
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
178		6	8	112	((1S,4S,6R)-6-((3-fluoro-5-(trifluoromethyl)pyridin -2-yl)amino)-2-azabicyclo[2.2.1] heptan -2-yl)(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)methanone
179		5	5	217	(3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4S,6R)-6-((3-fluoro-5-(trifluoromethyl)pyridin -2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
180		6	5	380	((1S,4S,6R)-6-((3-fluoro-5-(trifluoromethyl)pyridin -2-yl)amino)-2-azabicyclo[2.2.1] heptan -2-yl)(2-(5-fluoropyrimidin-2-yl)phenyl)methanone
181		5	8	163	((1S,4S,6R)-6-(benzo[d]oxazol-2-ylamino)-2-azabicyclo[2.2.1]heptan -2-yl)(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)methanone

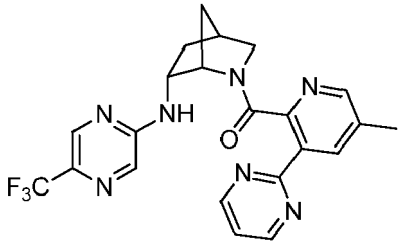
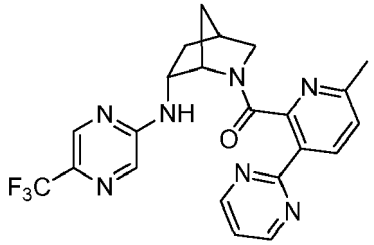
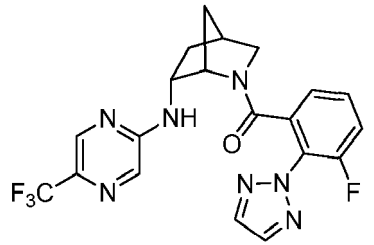
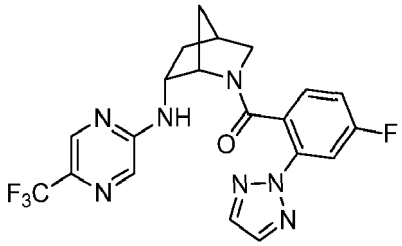
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
182		3	4	218	((1S,4S,6R)-6-(benzo[d]oxazol-2-ylamino)-2-azabicyclo[2.2.1]heptan -2-yl)(3-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone
183		5	7	206	((1S,4S,6R)-6-(benzo[d]oxazol-2-ylamino)-2-azabicyclo[2.2.1]heptan -2-yl)(3-fluoro-2-(pyrimidin-2-yl)phenyl)methanone
184		13	15	337	(3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4S,6R)-6-(p-tolylamino)-2-azabicyclo[2.2.1] heptan -2-yl)methanone
185		27	33	146	(1H-indol-7-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin -2-yl)amino)-2-azabicyclo [2.2.1]heptan -2-yl)methanone

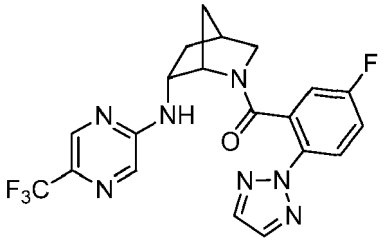
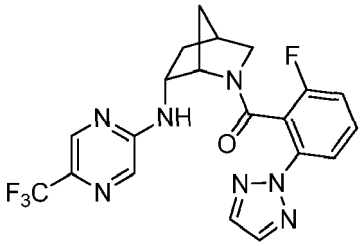
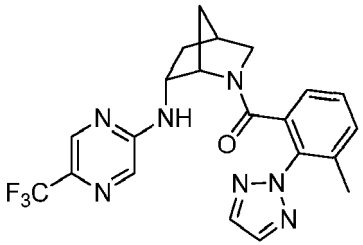
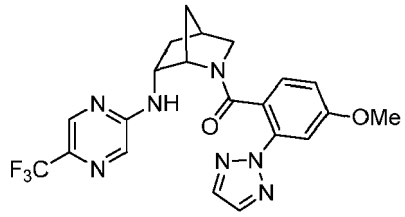
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
186		123	151	2700	(1H-indazol-7-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyridin -2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
187		28	30	1600	(5-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)((1S,4S,6R)-6-((5-(trifluoromethyl) pyrazin -2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
188		191	210	>10000	(2-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin -2-yl) amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
189		14	11	678	(3-(pyrimidin-2-yl)pyridin-2-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin -2-yl) amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone.

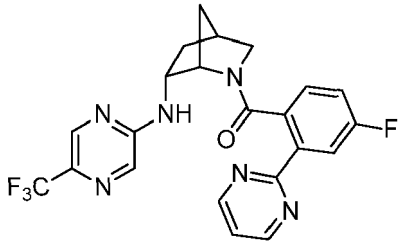
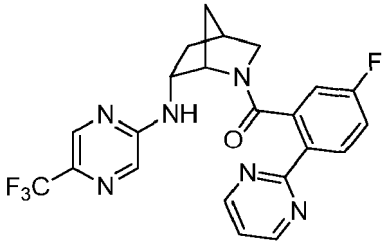
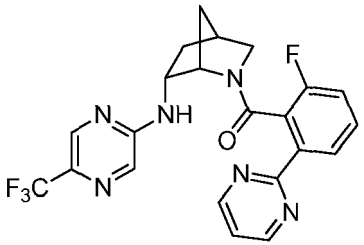
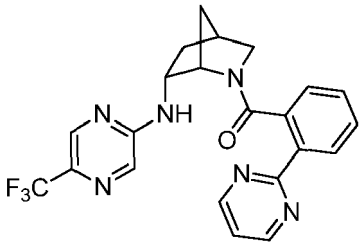
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
190		12	12	>10000	(5-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin -2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
191		15	13	163	(6-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin -2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
192		8	7	249	(3-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin -2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
193		40	65	2000	(4-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin -2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone

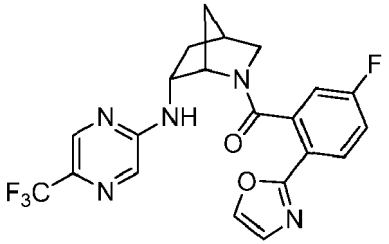
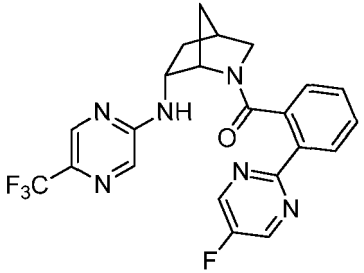
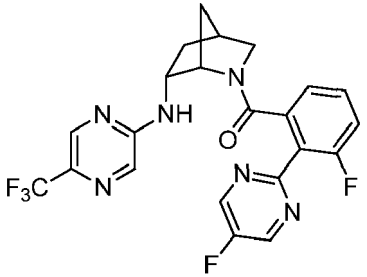
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
194		8	8	241	((5-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin -2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
195		9	8	199	(2-fluoro-6-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin -2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
196		6	4	60	(3-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin -2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
197		93	39	9700	(4-methoxy-2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl) pyrazin -2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone

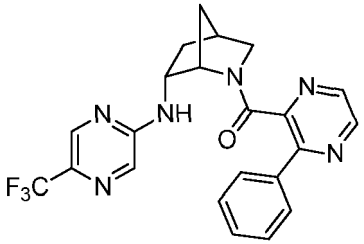
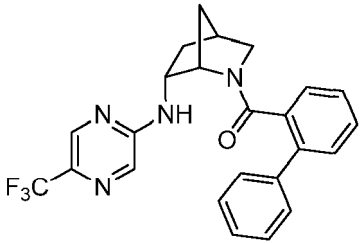
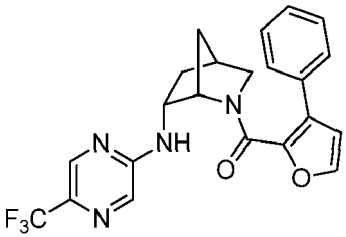
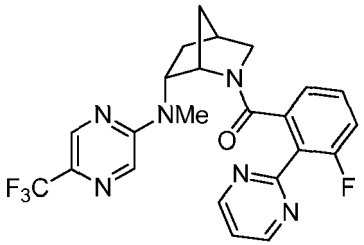
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
198		11	9	1375	(4-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin -2-yl) amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
199		6	8	221	(5-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin -2-yl) amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
200		7	6	240	(2-fluoro-6-(pyrimidin-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin -2-yl) amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
201		6	6	213	(2-(pyrimidin-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin -2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone

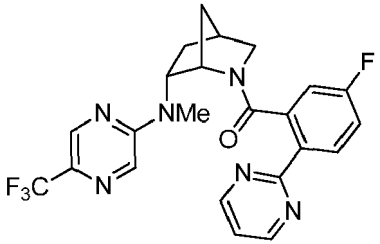
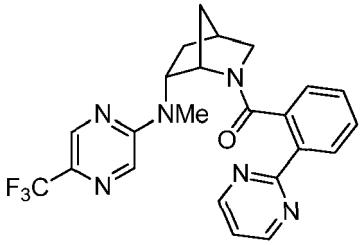
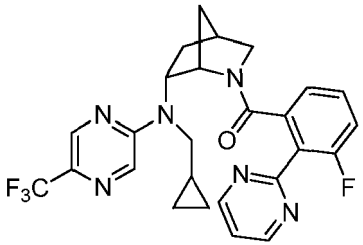
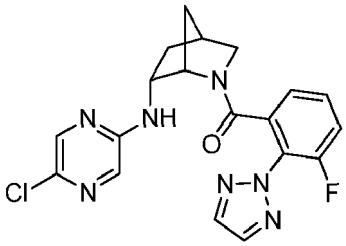
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
202		13	13	302	(5-fluoro-2-(oxazol-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin -2-yl) amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
203		9	9	545	(2-(5-fluoropyrimidin-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin -2-yl) amino)-2-azabicyclo[2.2.1]heptan-2-yl)methanone
204		9	9	960	(3-fluoro-2-(5-fluoropyrimidin-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin -2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone

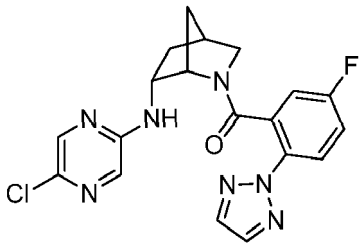
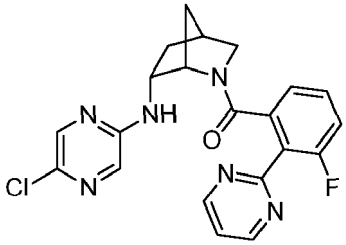
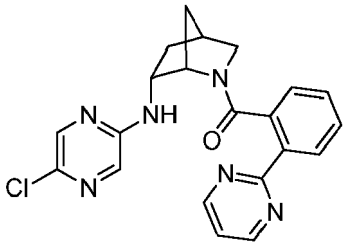
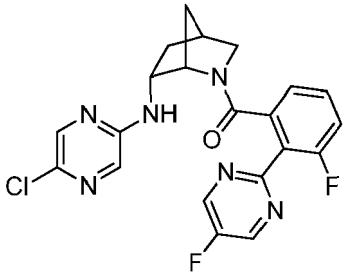
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
205		51	35	846	(3-phenylpyrazin-2-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin -2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
206		8	10	103	[1,1'-biphenyl]-2-yl((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin -2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
207		143	127	611	(3-phenylfuran-2-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrazin -2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
208		7	6	846	(3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4S,6R)-6-(methyl(5-(trifluoromethyl)pyrazin -2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone

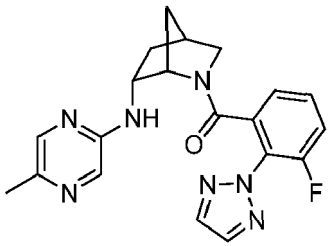
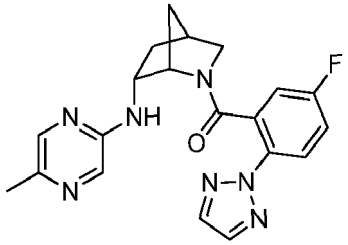
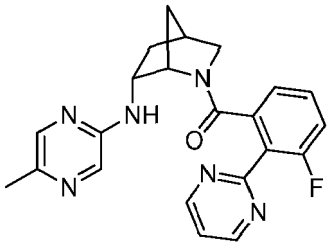
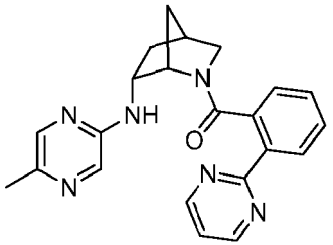
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
209		9	5	753	(5-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4S,6R)-6-(methyl(5-(trifluoromethyl)pyrazin -2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
210		6	5	502	((1S,4S,6R)-6-(methyl(5-(trifluoromethyl)pyrazin -2-yl)amino)-2-azabicyclo[2.2.1] heptan -2-yl)(2-(pyrimidin-2-yl)phenyl)methanone
211		31	16	1300	((1S,4S,6R)-6-((cyclopropylmethyl)(5-(trifluoromethyl)pyrazin -2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)(3-fluoro-2-(pyrimidin-2-yl)phenyl)methanone
212		14	9	607	((1S,4S,6R)-6-((5-chloropyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)(3-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone

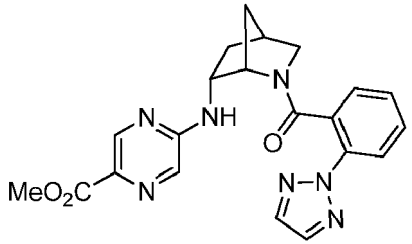
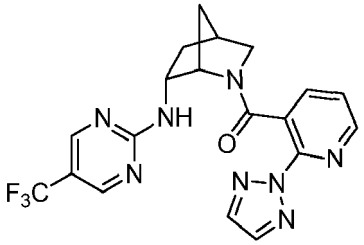
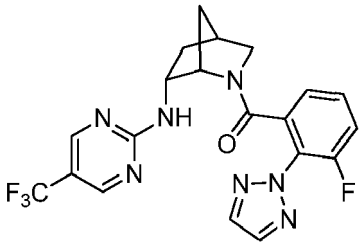
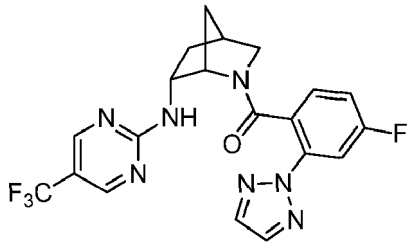
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
213		39	31	871	((1S,4S,6R)-6-((5-chloropyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)(5-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone
214		13	14	708	((1S,4S,6R)-6-((5-chloropyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)(3-fluoro-2-(pyrimidin-2-yl)phenyl)methanone
215		12	13	435	((1S,4S,6R)-6-((5-chloropyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl) (2-(pyrimidin-2-yl)phenyl)methanone
216		9	9	500	((1S,4S,6R)-6-((5-chloropyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)(3-fluoro-2-(5-fluoropyrimidin-2-yl)phenyl)methanone

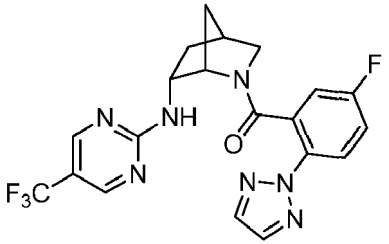
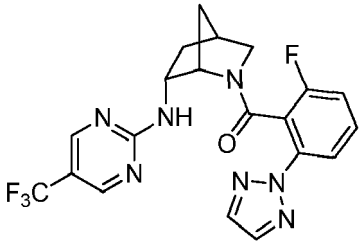
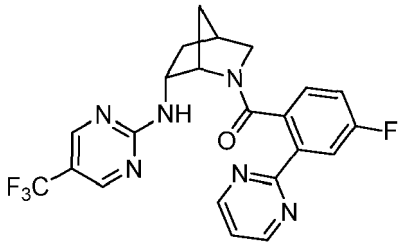
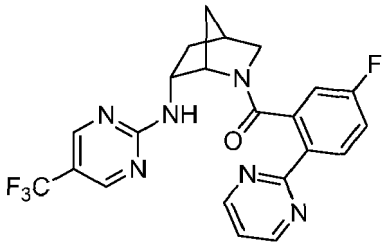
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
217		12	29	390	(3-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-methylpyrazin-2-yl) amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
218		31	49	490	(5-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-methylpyrazin-2-yl) amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
219		20	27	480	(3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4S,6R)-6-((5-methylpyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
220		11	17	284	((1S,4S,6R)-6-((5-methylpyrazin-2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl) (2-(pyrimidin-2-yl)phenyl)methanone

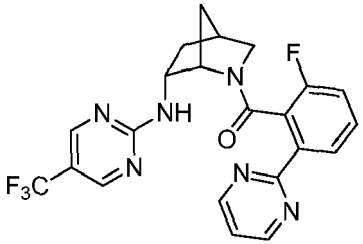
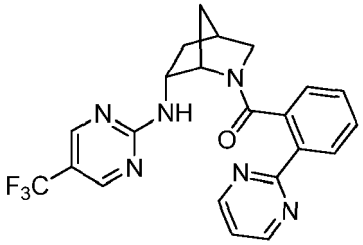
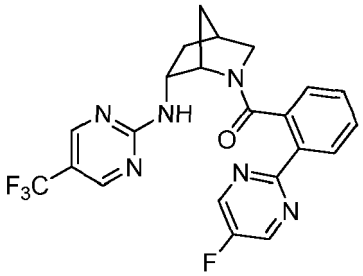
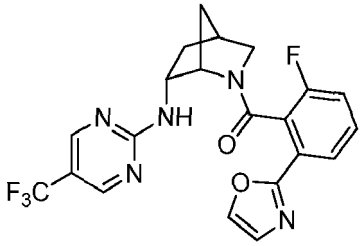
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
221		2100		3000	Methyl 5-(((1S,4S,6R)-2-(2-(2H-1,2,3-triazol-2-yl)benzoyl)-2-azabicyclo[2.2.1] heptan -6-yl)amino)pyrazine-2-carboxylate
222		261		>10000	(2-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrimi din-2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
223		11	6	619	(3-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrimi din-2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
224		37	33	1900	(4-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrimi din-2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone

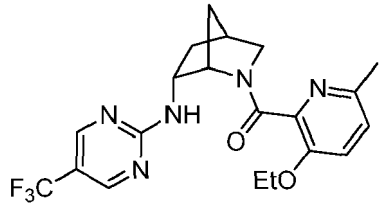
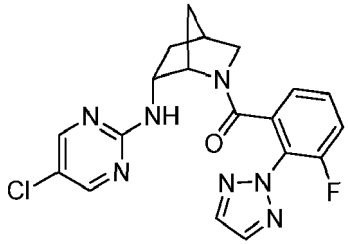
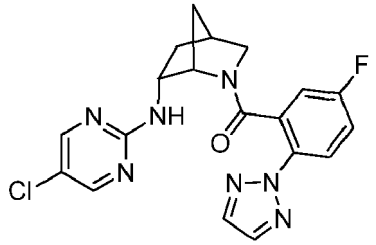
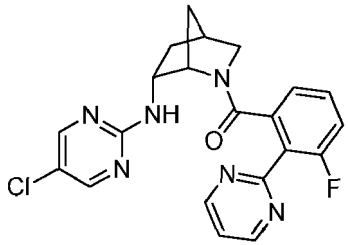
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
225		20	16	800	(5-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrimi din-2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
226		17	19	874	(2-fluoro-6-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl) pyrimidin-2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
227		12	13	3100	(4-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrimi din-2-yl) amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
228		11	9	544	(5-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrimi din-2-yl) amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone

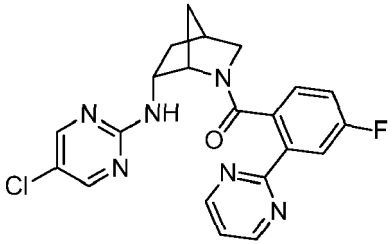
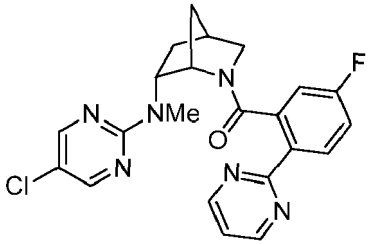
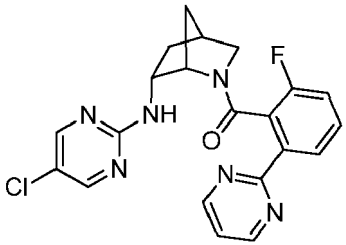
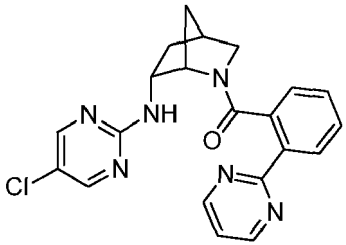
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
229		9	11	724	(2-fluoro-6-(pyrimidin-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrimi din-2-yl) amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
230		4	4	470	(2-(pyrimidin-2-yl)phenyl)((lS,4S,6R)-6-((5-(trifluoromethyl)pyrimi din-2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
231		9	12	1300	(2-(5-fluoropyrimidin-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrimi din-2-yl) amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
232		24	25	1352	(2-fluoro-6-(oxazol-2-yl)phenyl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrimi din-2-yl) amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone

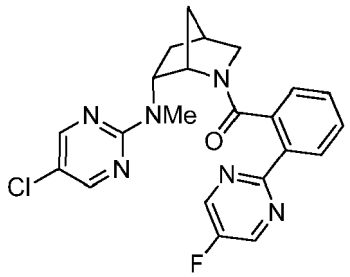
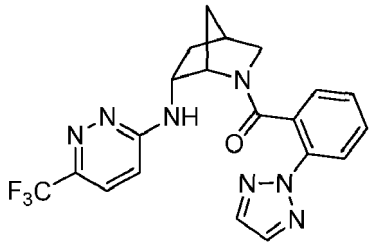
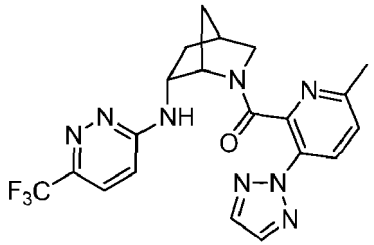
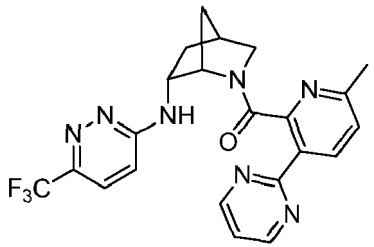
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
233		280		1100	(3-ethoxy-6-methylpyridin-2-yl)((1S,4S,6R)-6-((5-(trifluoromethyl)pyrimi din-2-yl) amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
234		17	12	827	((1S,4S,6R)-6-((5-chloropyrimidin-2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)(3-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone
235		36	41	1300	((1S,4S,6R)-6-((5-chloropyrimidin-2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)(5-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone
236		10	9	1020	((1S,4S,6R)-6-((5-chloropyrimidin-2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)(3-fluoro-2-(pyrimidin-2-yl)phenyl)methanone

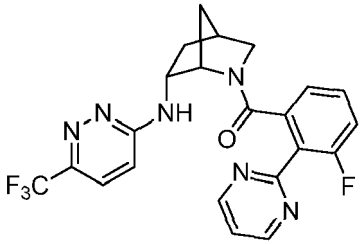
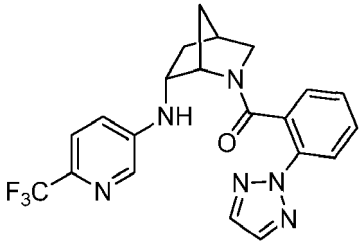
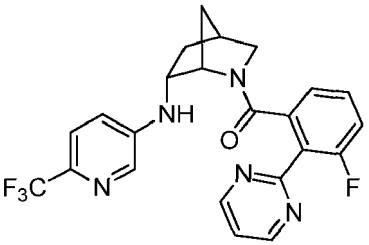
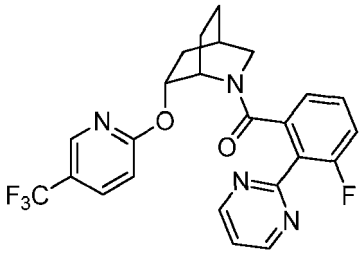
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
237		32	13	1900	((1S,4S,6R)-6-((5-chloropyrimidin-2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)(4-fluoro-2-(pyrimidin-2-yl)phenyl)methanone
238		20	8	991	((1S,4S,6R)-6-((5-chloropyrimidin-2-yl)(methyl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)(5-fluoro-2-(pyrimidin-2-yl)phenyl)methanone
239		23	41	726	((1S,4S,6R)-6-((5-chloropyrimidin-2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)(2-fluoro-6-(pyrimidin-2-yl)phenyl)methanone
240		17	12	831	((1S,4S,6R)-6-((5-chloropyrimidin-2-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)(2-(pyrimidin-2-yl)phenyl)methanone

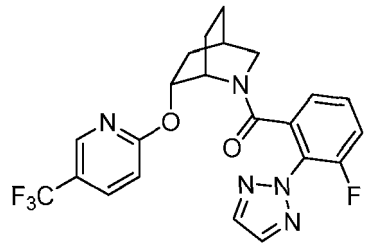
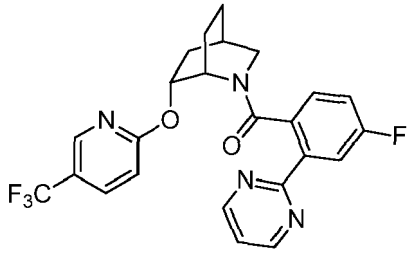
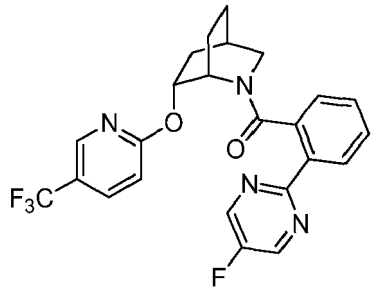
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
241		21	12	971	((1S,4S,6R)-6-((5-chloropyrimidin-2-yl)(methyl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)(2-(5-fluoropyrimidin-2-yl)phenyl)methanone
242		89	113	2100	(2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((6-(trifluoromethyl)pyridaz in-3-yl) amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
243		112	131	1800	(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)((1S,4S,6R)-6-((6-(trifluoromethyl) pyridaz in-3-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
244		114	143	1700	(6-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)((1S,4S,6R)-6-((6-(trifluoromethyl)pyridaz in-3-yl)amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone

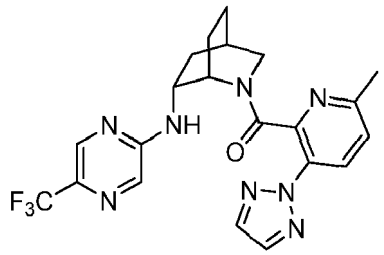
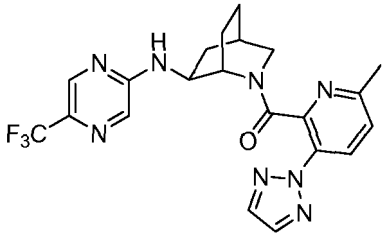
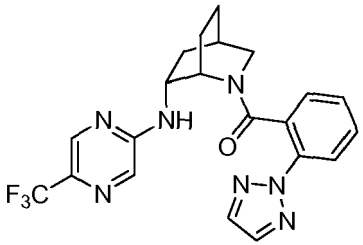
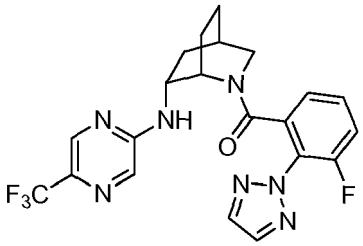
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
245		65	53	4300	(3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4S,6R)-6-((6-(trifluoromethyl)pyridaz in-3-yl) amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
246		194	155	843	(2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4S,6R)-6-((6-(trifluoromethyl)pyridin -3-yl) amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
247		26	31	939	(3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4S,6R)-6-((6-(trifluoromethyl)pyridin -3-yl) amino)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
248		11	14	467	(R/S)-(3-fluoro-2-(pyrimidin-2-yl)phenyl)(6-((5-(trifluoromethyl)pyridin -2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone

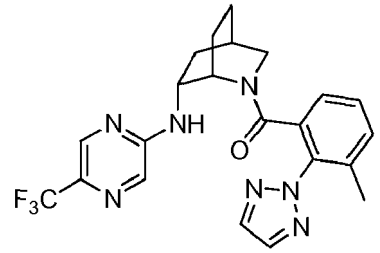
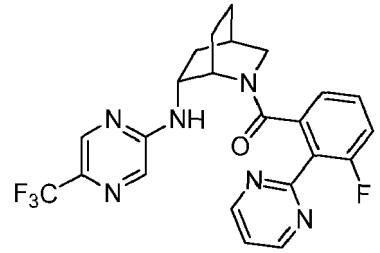
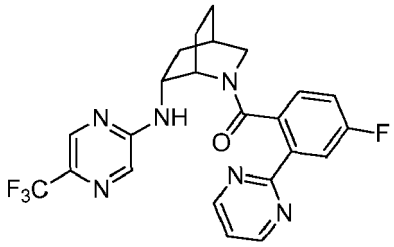
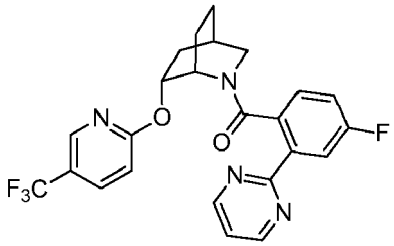
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
249		8	15	758	(R/S)- (3-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)(6-((5-(trifluoromethyl)pyridin -2-yl) oxy)-2-azabicyclo [2.2.2]octan-2-yl)methanone
250		22	24	1800	(R/S)- (4-fluoro-2-(pyrimidin-2-yl)phenyl)(6-((5-(trifluoromethyl)pyridin -2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone
251		18	11	760	(R/S)- (2-(5-fluoropyrimidin-2-yl)phenyl)(6-((5-(trifluoromethyl)pyridin -2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone

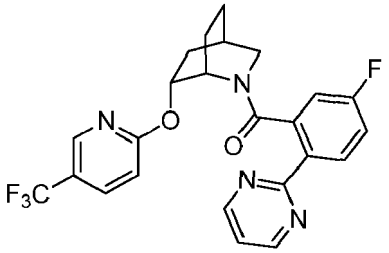
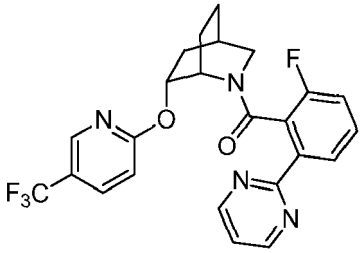
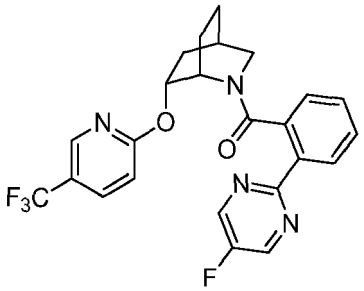
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
252		13	14	312	(R/S)-(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)-6-((5-(trifluoromethyl)pyrazin -2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone
253		>10000		>10000	(R/S)-(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)((1S,4R,6S)-6-((5-(trifluoromethyl)pyrazin -2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone
254		12	10	307	(R/S)-(2-(2H-1,2,3-triazol-2-yl)phenyl)(6-((5-(trifluoromethyl)pyrazin -2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone
255		12	11	1000	(R/S)- (3-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)(6-((5-(trifluoromethyl)pyrazin -2-yl) amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone

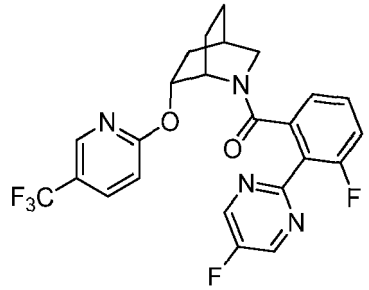
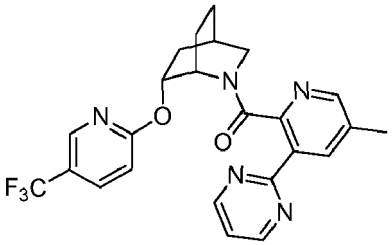
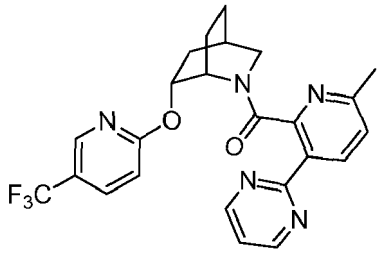
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
256		20	10	348	(R/S)- (3-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)(6-((5-(trifluoromethyl)pyrazin -2-yl) amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone
257		21	24	741	(R/S)- (3-fluoro-2-(pyrimidin-2-yl)phenyl)(6-((5-(trifluoromethyl)pyrazin -2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone
258		26	17	2600	(R/S)- (4-fluoro-2-(pyrimidin-2-yl)phenyl)(6-((5-(trifluoromethyl)pyrazin -2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone
259		16	19	865	(4-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin -2-yl) oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone

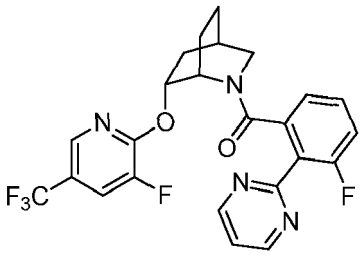
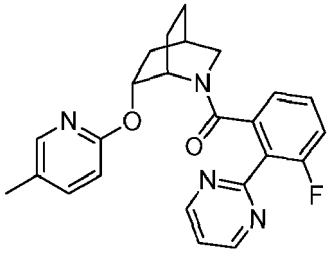
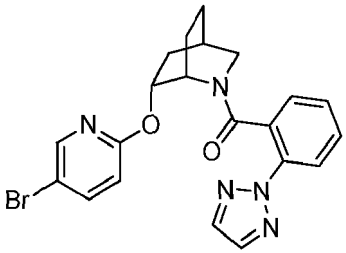
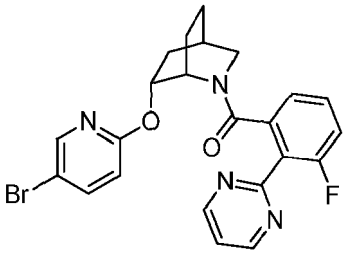
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
260		11	10	294	(5-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin -2-yl) oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone
261		21	9	400	(2-fluoro-6-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin -2-yl) oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone
262		10	10	550	(2-(5-fluoropyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin -2-yl) oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone

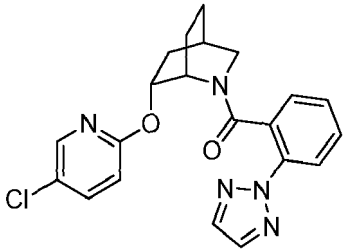
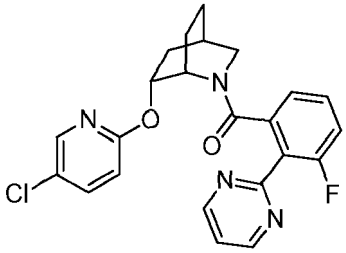
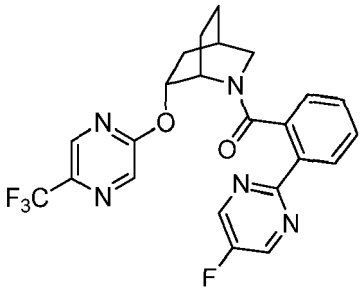
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
263		11	9	1100	(3-fluoro-2-(5-fluoropyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin -2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone
264		10	16	>10000	(5-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin -2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone
265		14	19	306	(6-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin -2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone

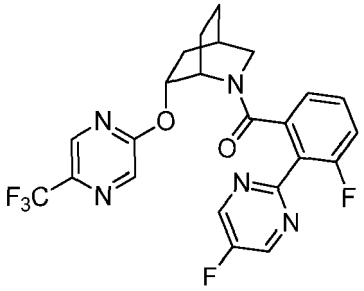
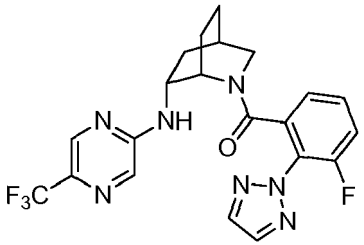
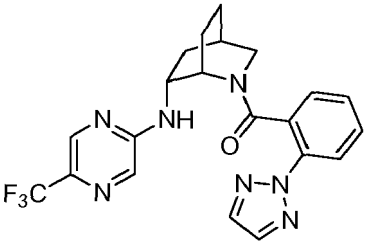
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
266		11	11	654	(3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((3-fluoro-5-(trifluoromethyl)pyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone
267		26	19	1100	(3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-methylpyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone
268		5	4	200	(2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((5-bromopyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone
269		4	5	363	((1S,4R,6R)-6-((5-bromopyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)(3-fluoro-2-(pyrimidin-2-yl)phenyl)methanone

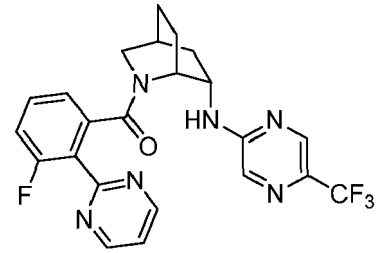
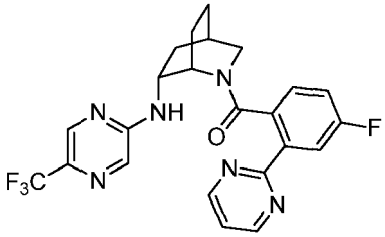
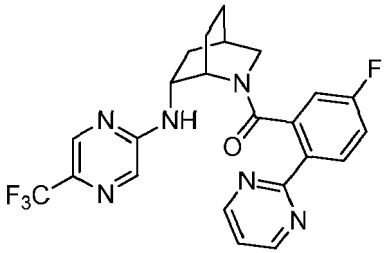
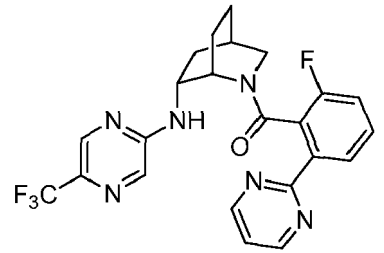
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
270		4	3	200	(2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((5-chloropyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone
271		7	8	452	((1S,4R,6R)-6-((5-chloropyridin-2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)(3-fluoro-2-(pyrimidin-2-yl)phenyl)methanone
272		23	11	1400	(2-(5-fluoropyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrazin -2-yl) oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone

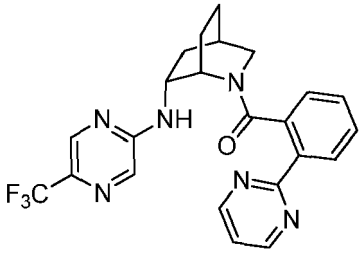
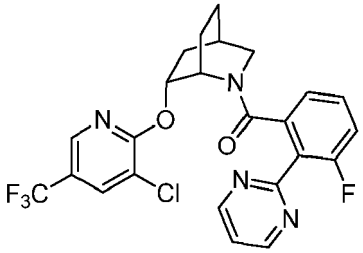
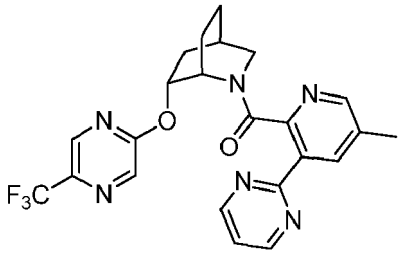
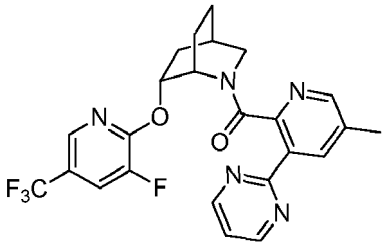
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
273		44	16	3800	(3-fluoro-2-(5-fluoropyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrazin -2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone
274		11	8	534	(3-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrazin -2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone
275		8	5	175	(2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrazin -2-yl) amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone

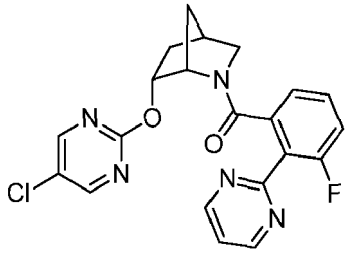
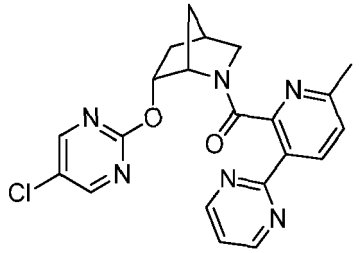
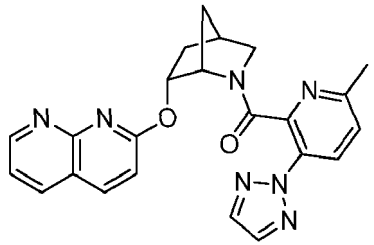
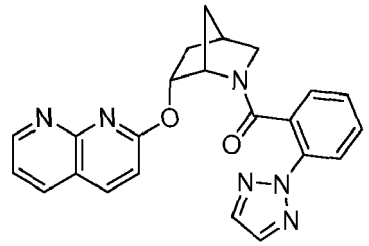
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
276		2700		>10000	(3-fluoro-2-(pyrimidin-2-yl)phenyl)((1R,4S,6S)-6-((5-(trifluoromethyl)pyrazin -2-yl) amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone
277		17	15	998	(4-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrazin -2-yl) amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone
278		14	7	243	(5-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrazin -2-yl) amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone
279		11	13	177	(2-fluoro-6-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrazin -2-yl) amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone

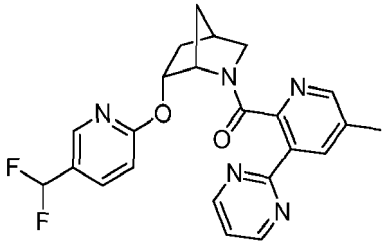
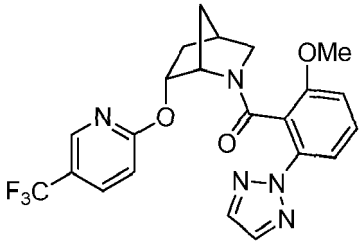
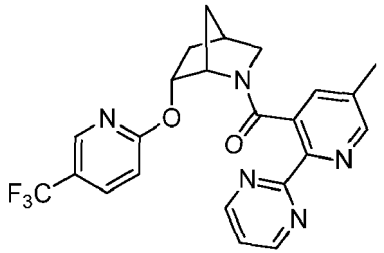
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
280		7	4	189	(2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrazin -2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)methanone
281		5	19	336	((1S,4R,6R)-6-((3-chloro-5-(trifluoromethyl)pyridin -2-yl)oxy)-2-azabicyclo[2.2.2] octan-2-yl)(3-fluoro-2-(pyrimidin-2-yl)phenyl)methanone
282		81	65	>10000	(5-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyrazin -2-yl)oxy)-2-azabicyclo[2.2.2]octan-2-yl)methanone
283		21	27	>10000	((1S,4R,6R)-6-((3-fluoro-5-(trifluoromethyl)pyridin -2-yl)oxy)-2-azabicyclo[2.2.2] octan-2-yl)(5-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)methanone

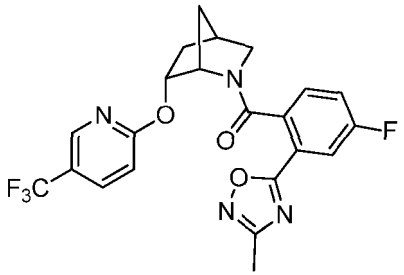
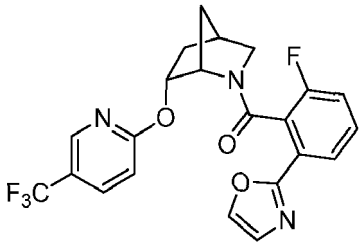
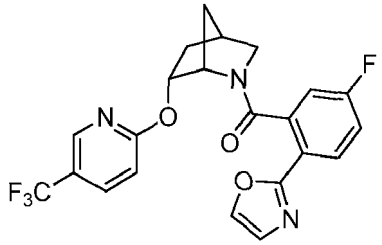
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
284		45	47	5600	((1S,4R,6R)-6-((5-chloropyrimidin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)(3-fluoro-2-(pyrimidin-2-yl)phenyl)methanone
285		117	215	6000	((1S,4R,6R)-6-((5-chloropyrimidin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)(6-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)methanone
286		822		3100	((1S,4R,6R)-6-((1,8-naphthyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)methanone
287		155	226	2700	((1S,4R,6R)-6-((1,8-naphthyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)(2-(2H-1,2,3-triazol-2-yl)phenyl)methanone

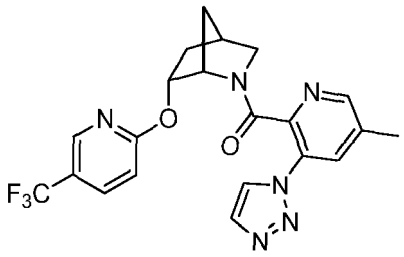
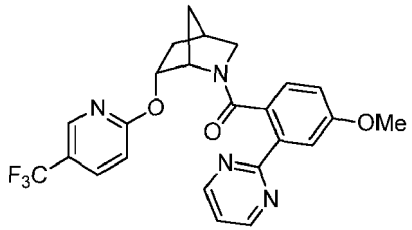
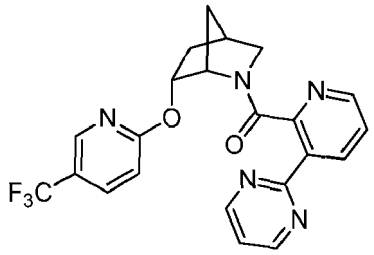
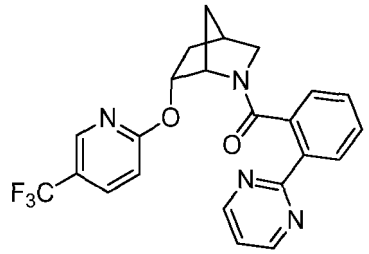
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
288		29	39	5100	((1S,4R,6R)-6-((5-(difluoromethyl)pyridin -2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl) (5-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)methanone
289		14	24	207	(2-methoxy-6-(2H-1,2,3-triazol-2-yl)phenyl)((! S,4R,6R)-6-((5-(trifluoromethyl) pyridin -2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
290		97	188	>10000	(5-methyl-2-(pyrimidin-2-yl)pyridin-3-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin -2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone

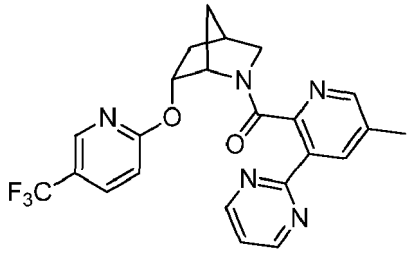
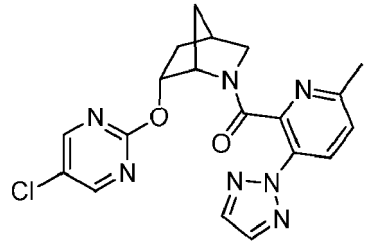
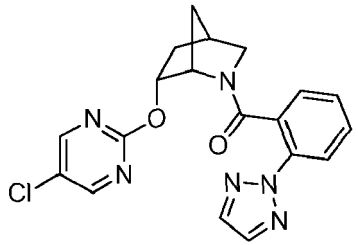
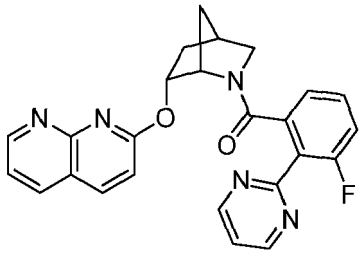
(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
291		43	82	4200	(4-fluoro-2-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin -2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
292		19	40	673	(2-fluoro-6-(oxazol-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin -2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
293		16	26	535	(5-fluoro-2-(oxazol-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin -2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone

(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
294		166	580	1400	(5-methyl-3-(1H-1,2,3-triazol-1-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl) pyridin -2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
295		19	34	5800	(4-methoxy-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin -2-yl) oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
296		8	14	474	(3-(pyrimidin-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin -2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
297		10	10	606	(2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin -2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone

(continued)

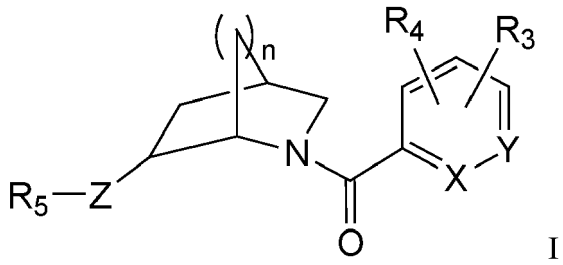
Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
298		24	29	>10000	(5-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)((1S,4R,6R)-6-((5-(trifluoromethyl)pyridin -2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
299					((1S,4R,6R)-6-((5-chloropyrimidin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)methanone
300		92	112	3700	(2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,4R,6R)-6-((5-chloropyrimidin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)methanone
301					((1S,4R,6R)-6-((1,8-naphthyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)(3-fluoro-2-(pyrimidin-2-yl)phenyl)methanone

(continued)

Ex. No.	Compound	rOX1 K_i (nM)	hOX1 K_i (nM)	hOX2 K_i (nM)	Compound Name
302					((1S,4R,6R)-6-((1,8-naphthyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan -2-yl)(6-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)methanone

Claims

1. A compound of formula I



I

or an enantiomer, diastereomer, tautomer or isotopic variant thereof;
or a pharmaceutically acceptable salt or solvate thereof,
for use in therapy,
wherein
X is N or CR_1;
Y is N or CR_2;
R_1 is H, alkoxy, halo, triazolyl, thiazolyl, pyridazinyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl, pyridyl, phenyl or pyrazolyl, wherein triazolyl, thiazolyl, pyridazinyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl, pyridyl, phenyl or pyrazolyl is optionally substituted with up to two substituents selected from the group consisting of halo and alkyl;
R_2 is H, alkyl, alkoxy, or halo;
Z is NH, N-CH_3, N-CH_2CH_3, N-CH_2-cyclopropyl, N-C(=O)CH_3, N-$CH_2CH_2OCH_3$ or O;
R_3 is H, alkyl, alkoxy, halo, triazolyl, thiazolyl, pyridazinyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl, pyridyl, phenyl or pyrazolyl, wherein triazolyl, thiazolyl, pyridazinyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl, pyridyl, phenyl or pyrazolyl is optionally substituted with up to two substituents selected from the group consisting of halo and alkyl;
R_4 is H or alkyl;
or R_3 and R_4, together with the atoms to which they are attached, form a 6-membered aryl ring or a 5- or 6-membered heteroaryl ring;
R_5 is phenyl, pyridyl, pyrazinyl, benzoxazolyl, pyridazinyl, naphthyridinyl or pyrimidinyl, wherein the pyridyl, pyrazinyl, benzoxazolyl, pyridazinyl, naphthyridinyl or pyrimidinyl is optionally substituted with up to two groups selected from the group consisting of halo, alkoxy, hydroxymethyl and alkyl; and
n is 1 or 2,
wherein "alkyl" is a straight- or branched-chain alkyl group having from 1 to 12 carbon atoms in the chain or a mono-cyclic, non-aromatic hydrocarbon group having from 3 to 7 carbon atoms and is optionally substituted with one or more halogen atoms.

2. A pharmaceutical composition comprising a therapeutically effective amount of a compound of formula I as defined in claim 1, or an enantiomer, diastereomer, tautomer or isotopic variant thereof, or a pharmaceutically acceptable salt or solvate thereof, and at a least one pharmaceutically acceptable excipient, for use in therapy.

3. A pharmaceutical composition comprising a therapeutically effective amount of a compound of formula I as defined in claim 1, or an enantiomer, diastereomer, tautomer or isotopic variant thereof, or a pharmaceutically acceptable salt or solvate thereof, and at a least one pharmaceutically acceptable excipient, for use in treating a disease, disorder, or medical condition, wherein the disease, disorder, or medical condition is a sleep disorder, a metabolic disorder, a neurological disorder, arrhythmias, acute heart failure, ulcers, irritable bowel syndrome, diarrhea, gastroesophageal reflux, a mood disorder, a post-traumatic stress disorder, a panic disorder, an attention deficit disorder, cognitive deficiencies, or substance abuse.

4. The pharmaceutical composition for use of claim 3, wherein the disease, disorder, or medical condition is a mood disorder, a post-traumatic stress disorder, a panic disorder, an attention deficit disorder, cognitive deficiencies, or substance abuse.

5. The pharmaceutical composition for use of claim 3, wherein the disease, disorder, or medical condition is a sleep

disorder.

6. The pharmaceutical composition for use of claim 5, wherein the sleep disorder is a sleep-wake transition disorder, insomnia, restless legs syndrome, jet-lag, disturbed sleep, or a sleep disorder secondary to neurological disorders.

7. The pharmaceutical composition for use of claim 3, wherein the disease, disorder, or medical condition is a metabolic disorder.

8. The pharmaceutical composition for use of claim 7, wherein the metabolic disorder is overweight, obesity, insulin resistance, type II diabetes, hyperlipidemia, gallstones, angina, hypertension, breathlessness, tachycardia, infertility, sleep apnea, back and joint pain, varicose veins, or osteoarthritis.

9. The pharmaceutical composition for use of claim 3, wherein the disease, disorder, or medical condition is a neurological disorder.

10. The pharmaceutical composition for use of claim 9, wherein the neurological disorder is Parkinson's disease, Alzheimer's disease, Tourette's syndrome, catatonia, anxiety, delirium, or dementia.

11. A pharmaceutical composition comprising a therapeutically effective amount of a compound of formula I as defined in claim 1, or an enantiomer, diastereomer, tautomer or isotopic variant thereof, or a pharmaceutically acceptable salt or solvate thereof, and at a least one pharmaceutically acceptable excipient, for oral administration.

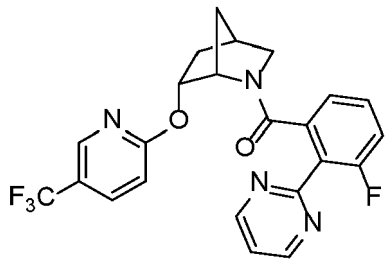
12. The pharmaceutical composition of claim 11 in the form of a tablet, a capsule, a solution, an emulsion, or a suspension.

13. The pharmaceutical composition of claim 11 in the form of a tablet.

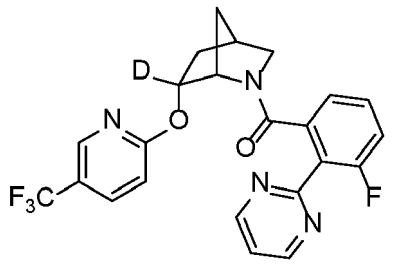
14. The pharmaceutical composition of claim 13 wherein the excipients are selected from inert diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavoring agents, coloring agents and preservative agents.

15. The pharmaceutical composition of claim 14, wherein inert fillers are selected from sodium and calcium carbonate, sodium and calcium phosphate, lactose, starch, sugar, glucose, methyl cellulose, magnesium stearate, mannitol and sorbitol.

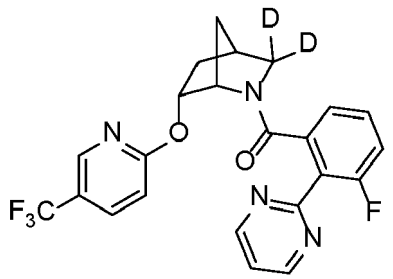
16. The compound or pharmaceutical composition for use of claims 1-10, or the pharmaceutical composition of claims 11-15, wherein the compound is

	(3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl) pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

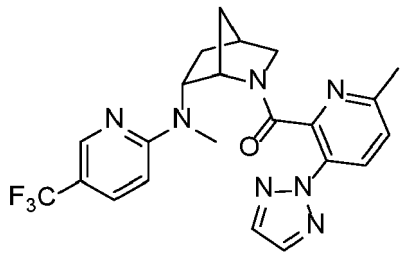
17. The compound or pharmaceutical composition for use of claims 1-10, or the pharmaceutical composition of claims 11-15, wherein the compound is

	(3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-(6-^{2}H)-((5-(trifluoromethyl) pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanone.

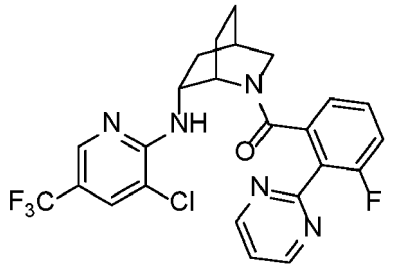
18. The compound or pharmaceutical composition for use of claims 1-10, or the pharmaceutical composition of claims 11-15, wherein the compound is

	(3-fluoro-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluoromethyl) pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]- (3-^{2}H, ^{2}H)-heptan-2-yl)methanone.

19. The compound or pharmaceutical composition for use of claims 1-10, or the pharmaceutical composition of claims 11-15, wherein the compound is

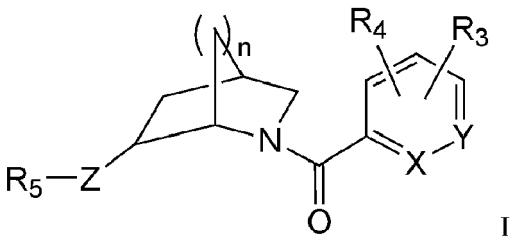
	((1S,4S,6R)-6-(methyl(5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)methanone.

20. The compound or pharmaceutical composition for use of claims 1-10, or the pharmaceutical composition of claims 11-15, wherein the compound is

	((1S,4R,6R)-6-((3-chloro-5-(trifluoromethyl)pyridin-2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl)(3-fluoro-2-(pyrimidin-2-yl)phenyl)methanone.

Patentansprüche

1. Verbindung der Formel I



I

oder ein Enantiomer, ein Diastereomer, ein Tautomer oder eine Isotopenvariante davon;
oder ein pharmazeutisch unbedenkliches Salz oder Solvat davon,
zur Verwendung bei der Therapie,
wobei

X für N oder CR_1 steht;
Y für N oder CR_2 steht;
R_1 für H, Alkoxy, Halogen, Triazolyl, Thiazolyl, Pyridazinyl, Pyrimidinyl, Oxazolyl, Isoxazolyl, Oxadiazolyl, Pyridyl, Phenyl oder Pyrazolyl steht, wobei Triazolyl, Thiazolyl, Pyridazinyl, Pyrimidinyl, Oxazolyl, Isoxazolyl, Oxadiazolyl, Pyridyl, Phenyl oder Pyrazolyl gegebenenfalls durch bis zu zwei Substituenten, die aus der Gruppe bestehend aus Halogen und Alkyl ausgewählt sind, substituiert ist;
R_2 für H, Alkyl, Alkoxy oder Halogen steht;
Z für NH, N-CH_3, N-CH_2CH_3, N-CH_2-Cyclopropyl, N-C(=O)CH_3, N-$CH_2CH_2OCH_3$ oder O steht;
R_3 für H, Alkyl, Alkoxy, Halogen, Triazolyl, Thiazolyl, Pyridazinyl, Pyrimidinyl, Oxazolyl, Isoxazolyl, Oxadiazolyl, Pyridyl, Phenyl oder Pyrazolyl steht, wobei Triazolyl, Thiazolyl, Pyridazinyl, Pyrimidinyl, Oxazolyl, Isoxazolyl, Oxadiazolyl, Pyridyl, Phenyl oder Pyrazolyl gegebenenfalls durch bis zu zwei Substituenten, die aus der Gruppe bestehend aus Halogen und Alkyl ausgewählt sind, substituiert ist;
R_4 für H oder Alkyl steht; oder R_3 und R_4 zusammen mit den Atomen, an die sie gebunden sind, einen 6-gliedrigen Arylring oder einen 5- oder 6-gliedrigen Heteroarylring bilden;
R_5 für Phenyl, Pyridyl, Pyrazinyl, Benzoxazolyl, Pyridazinyl, Naphthyridinyl oder Pyrimidinyl steht, wobei Pyridyl, Pyrazinyl, Benzoxazolyl, Pyridazinyl, Naphthyridinyl oder Pyrimidinyl gegebenenfalls durch bis zu zwei Gruppen, die aus der Gruppe bestehend aus Halogen, Alkoxy, Hydroxymethyl und Alkyl ausgewählt sind, substituiert ist; und
n für 1 oder 2 steht,

wobei "Alkyl" für eine gerad- oder verzweigtkettige Alkylgruppe mit 1 bis 12 Kohlenstoffatomen in der Kette oder eine monocyclische nichtaromatische Kohlenwasserstoffgruppe mit 3 bis 7 Kohlenstoffatomen steht und gegebenenfalls durch ein oder mehrere Halogenatome substituiert ist.

2. Pharmazeutische Zusammensetzung, umfassend eine therapeutisch wirksame Menge einer Verbindung der Formel I gemäß Anspruch 1 oder ein Enantiomer, ein Diastereomer, ein Tautomer oder eine Isotopenvariante davon oder ein pharmazeutisch unbedenkliches Salz oder Solvat davon und mindestens einen pharmazeutisch unbedenklichen Hilfsstoff zur Verwendung bei der Therapie.

3. Pharmazeutische Zusammensetzung, umfassend eine therapeutisch wirksame Menge einer Verbindung der Formel I gemäß Anspruch 1 oder ein Enantiomer, ein Diastereomer, ein Tautomer oder eine Isotopenvariante davon oder ein pharmazeutisch unbedenkliches Salz oder Solvat davon und mindestens einen pharmazeutisch unbedenklichen Hilfsstoff zur Verwendung bei der Behandlung einer Erkrankung, einer Störung oder eines medizinischen Leidens, wobei es sich bei der Erkrankung, der Störung bzw. dem medizinischen Leiden um eine Schlafstörung, eine Stoffwechselstörung, eine neurologische Störung, Arrhythmien, akute Herzinsuffizienz, Geschwüre, Reizdarmsyndrom, Diarrhoe, gastroösophagealen Rückfluss, eine Gemütsstörung, eine akute Belastungsreaktion, eine Panikstörung, eine Aufmerksamkeitsdefizitstörung, kognitive Defizite oder Substanzmissbrauch handelt.

4. Pharmazeutische Zusammensetzung zur Verwendung nach Anspruch 3, wobei es sich bei der Erkrankung, der Störung bzw. dem medizinischen Leiden um eine Gemütsstörung, eine akute Belastungsreaktion, eine Panikstörung,

eine Aufmerksamkeitsdefizitstörung, kognitive Defizite oder Substanzmissbrauch handelt.

5. Pharmazeutische Zusammensetzung zur Verwendung nach Anspruch 3, wobei es sich bei der Erkrankung, der Störung bzw. dem medizinischen Leiden um eine Schlafstörung handelt.

6. Pharmazeutische Zusammensetzung zur Verwendung nach Anspruch 5, wobei es sich bei der Schlafstörung um eine Störung des Schlaf-Wach-Übergangs, Schlaflosigkeit, Syndrom der unruhigen Beine, Jetlag, gestörten Schlaf oder eine Schlafstörung als Folge von neurologischen Störungen handelt.

7. Pharmazeutische Zusammensetzung zur Verwendung nach Anspruch 3, wobei es sich bei der Erkrankung, der Störung bzw. dem medizinischen Leiden um eine Stoffwechselstörung handelt.

8. Pharmazeutische Zusammensetzung zur Verwendung nach Anspruch 7, wobei es sich bei der Stoffwechselstörung um Übergewicht, Obesitas, Insulinresistenz, Typ-II-Diabetes, Hyperlipidämie, Gallensteine, Angina, Hypertonie, Kurzatmigkeit, Tachykardie, Unfruchtbarkeit, Schlafapnoe, Rücken- und Gelenkschmerzen, Krampfadern oder Osteoarthritis handelt.

9. Pharmazeutische Zusammensetzung zur Verwendung nach Anspruch 3, wobei es sich bei der Erkrankung, der Störung bzw. dem medizinischen Leiden um eine neurologische Störung handelt.

10. Pharmazeutische Zusammensetzung zur Verwendung nach Anspruch 9, wobei sich bei der neurologischen Störung um Parkinson-Krankheit, Alzheimer-Krankheit, Tourette-Syndrom, Katatonie, Angst, Delirium oder Demenz handelt.

11. Pharmazeutische Zusammensetzung, umfassend eine therapeutisch wirksame Menge einer Verbindung der Formel I gemäß Anspruch 1 oder ein Enantiomer, ein Diastereomer, ein Tautomer oder eine Isotopenvariante davon oder ein pharmazeutisch unbedenkliches Salz oder Solvat davon und mindestens einen pharmazeutisch unbedenklichen Hilfsstoff, zur oralen Verabreichung.

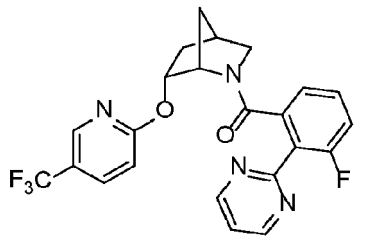
12. Pharmazeutische Zusammensetzung nach Anspruch 11 in Form einer Tablette, einer Kapsel, einer Lösung, in der Emulsion oder einer Suspension.

13. Pharmazeutische Zusammensetzung nach Anspruch 11 in Form einer Tablette.

14. Pharmazeutische Zusammensetzung nach Anspruch 13, wobei die Hilfsstoffe aus inerten Verdünnungsmitteln, Sprengmitteln, Bindemitteln, Schmiermitteln, Süßungsmitteln, Geschmacksstoffen, Farbmitteln und Konservierungsstoffen ausgewählt sind.

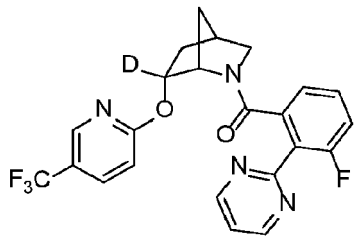
15. Pharmazeutische Zusammensetzung nach Anspruch 14, wobei inerte Füllstoffe aus Natrium- und Calciumcarbonat, Natrium- und Calciumphosphat, Lactose, Stärke, Zucker, Glucose, Methylcellulose, Magnesiumstearat, Mannitol und Sorbitol ausgewählt sind.

16. Verbindung oder pharmazeutische Zusammensetzung zur Verwendung nach den Ansprüchen 1-10 oder pharmazeutische Zusammensetzung nach den Ansprüchen 11-15, wobei es sich bei der Verbindung um

	(3-Fluor-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluormethyl)-pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)methanon

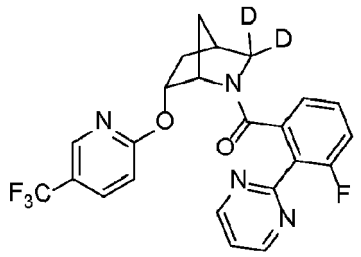
handelt.

17. Verbindung oder pharmazeutische Zusammensetzung zur Verwendung nach den Ansprüchen 1-10 oder pharmazeutische Zusammensetzung nach den Ansprüchen 11-15, wobei es sich bei der Verbindung um

	(3-Fluor-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-(6-^{2}H)-((5-(trifluormethyl)-pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl) methanon

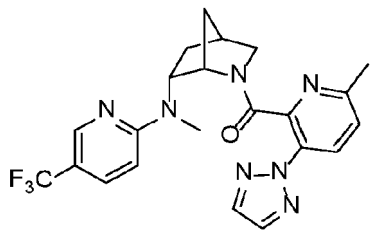
handelt.

18. Verbindung oder pharmazeutische Zusammensetzung zur Verwendung nach den Ansprüchen 1-10 oder pharmazeutische Zusammensetzung nach den Ansprüchen 11-15, wobei es sich bei der Verbindung um

	(3-Fluor-2-(pyrimidin-2-yl)phenyl)((1S,4R,6R)-6-((5-(trifluormethyl)-pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]-(3-^{2}H,^{2}H)-heptan-2-yl)methanon

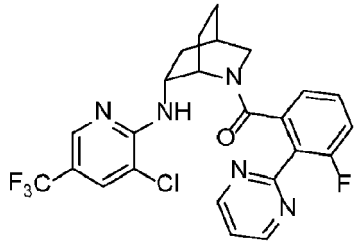
handelt.

19. Verbindung oder pharmazeutische Zusammensetzung zur Verwendung nach den Ansprüchen 1-10 oder pharmazeutische Zusammensetzung nach den Ansprüchen 11-15, wobei es sich bei der Verbindung um

	((1S,4S,6R)-6-(Methyl(5-(trifluormethyl)pyridin-2-yl)amino)-2-azabicyclo-[2.2.1]heptan-2-yl) (6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)methanon

handelt.

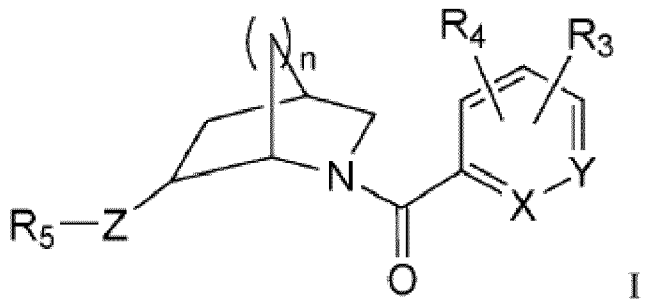
20. Verbindung oder pharmazeutische Zusammensetzung zur Verwendung nach den Ansprüchen 1-10 oder pharmazeutische Zusammensetzung nach den Ansprüchen 11-15, wobei es sich bei der Verbindung um

	((1S,4R,6R)-6-((3-Chlor-5-(trifluormethyl)pyridin-2-yl)amino)-2-azabicyclo-[2.2.2]octan-2-yl) (3-fluor-2-(pyrimidin-2-yl)phenyl)-methanon

handelt.

Revendications

1. Composé de formule I



I

ou énantiomère, diastéréoisomère, forme tautomère ou variante isotopique correspondant(e) ;
ou sel ou solvate pharmaceutiquement acceptable correspondant ;
pour une utilisation en thérapie,
X étant N ou CR_1 ;
Y étant N ou CR_2 ;
R_1 étant H, alcoxy, halogéno, triazolyle, thiazolyle, pyridazinyle, pyrimidinyle, oxazolyle, isoxazolyle, oxadiazolyle, pyridinyle, phényle ou pyrazolyle, dans lequel triazolyle, thiazolyle, pyridazinyle, pyrimidinyle, oxazolyle, isoxazolyle, oxadiazolyle, pyridinyle, phényle ou pyrazolyle est éventuellement substitué par jusqu'à deux substituants choisis dans le groupe constitué par halogéno et alkyle ;
R_2 étant H, alkyle, alcoxy, ou halogéno ;
Z étant NH, N-CH_3, N-CH_2CH_3, N-CH_2-cyclopropyle, N-C(=O)CH_3, N-$CH_2CH_2OCH_3$ ou O ;
R_3 étant H, alkyle, alcoxy, halogéno, triazolyle, thiazolyle, pyridazinyle, pyrimidinyle, oxazolyle, isoxazolyle, oxadiazolyle, pyridinyle, phényle ou pyrazolyle, dans lequel triazolyle, thiazolyle, pyridazinyle, pyrimidinyle, oxazolyle, isoxazolyle, oxadiazolyle, pyridinyle, phényle ou pyrazolyle est éventuellement substitué par jusqu'à deux substituants choisis dans le groupe constitué par halogéno et alkyle ;
R_4 étant H ou alkyle ;
ou R_3 et R_4, conjointement avec les atomes auxquels ils sont fixés, formant un cycle aryle à 6 chaînons ou un cycle hétéroaryle à 5 ou 6 chaînons ;
R_5 étant phényle, pyridinyle, pyrazinyle, benzoxazolyle, pyridazinyle, naphtyridinyle ou pyrimidinyle, le pyridinyle, pyrazinyle, benzoxazolyle, pyridazinyle, naphtyridinyle ou pyrimidinyle étant éventuellement substitué par jusqu'à deux groupes choisis dans le groupe constitué par halogéno, alcoxy, hydroxyméthyle et alkyle ; et
n étant 1 ou 2,
« alkyle » étant un groupe alkyle à chaîne droite ou ramifiée possédant de 1 à 12 atomes de carbone dans la chaîne ou un groupe hydrocarboné monocyclique, non aromatique possédant de 3 à 7 atomes de carbone et étant éventuellement substitué par un ou plusieurs atomes d'halogène.

2. Composition pharmaceutique comprenant une quantité thérapeutiquement efficace d'un composé de formule I tel que défini dans la revendication 1, ou un énantiomère, diastéréoisomère, une forme tautomère ou une variante isotopique correspondant(e), ou un sel ou un solvate pharmaceutiquement acceptable correspondant, et au moins un excipient pharmaceutiquement acceptable, pour une utilisation en thérapie.

3. Composition pharmaceutique comprenant une quantité thérapeutiquement efficace d'un composé de formule I tel que défini dans la revendication 1, ou un énantiomère, diastéréoisomère, une forme tautomère ou une variante isotopique correspondant (e), ou un sel ou un solvate pharmaceutiquement acceptable correspondant, et au moins un excipient pharmaceutiquement acceptable, pour une utilisation dans le traitement d'une maladie, d'un trouble ou d'un état médical, la maladie, le trouble ou l'état médical étant un trouble du sommeil, un trouble métabolique, un trouble neurologique, des arythmies, une insuffisance cardiaque aiguë, des ulcères, le syndrome du côlon irritable, la diarrhée, le reflux gastro-œsophagien, un trouble de l'humeur, un trouble de stress post-traumatique, un trouble panique, un trouble du déficit de l'attention, des déficiences cognitives ou un abus de substance.

4. Composition pharmaceutique pour une utilisation selon la revendication 3, la maladie, le trouble ou l'état médical étant un trouble de l'humeur, un trouble de stress post-traumatique, un trouble panique, un trouble du déficit de l'attention, des déficiences cognitives ou un abus de substance.

5. Composition pharmaceutique pour une utilisation selon la revendication 3, la maladie, le trouble ou l'état médical étant un trouble du sommeil.

6. Composition pharmaceutique pour une utilisation selon la revendication 5, le trouble du sommeil étant un trouble de la transition veille-sommeil, une insomnie, un syndrome des jambes sans repos, un décalage horaire, un sommeil perturbé ou un trouble du sommeil secondaire à des troubles neurologiques.

7. Composition pharmaceutique pour une utilisation selon la revendication 3, la maladie, le trouble ou l'état médical étant un trouble métabolique.

8. Composition pharmaceutique pour une utilisation selon la revendication 7, le trouble métabolique étant le surpoids, l'obésité, la résistance à l'insuline, le diabète de type II, l'hyperlipidémie, des calculs biliaires, l'angine, l'hypertension, l'essoufflement, la tachycardie, l'infertilité, l'apnée du sommeil, des douleurs dorsales et articulaires, des varices ou l'arthrose.

9. Composition pharmaceutique pour une utilisation selon la revendication 3, la maladie, le trouble ou l'état médical étant un trouble neurologique.

10. Composition pharmaceutique pour une utilisation selon la revendication 9, le trouble neurologique étant la maladie de Parkinson, la maladie d'Alzheimer, le syndrome de Gilles de la Tourette, une catatonie, l'anxiété, un délire ou une démence.

11. Composition pharmaceutique comprenant une quantité thérapeutiquement efficace d'un composé de formule I tel que défini dans la revendication 1, ou un énantiomère, diastéréoisomère, une forme tautomère ou une variante isotopique correspondant(e), ou un sel ou un solvate pharmaceutiquement acceptable correspondant, et au moins un excipient pharmaceutiquement acceptable, pour une administration orale.

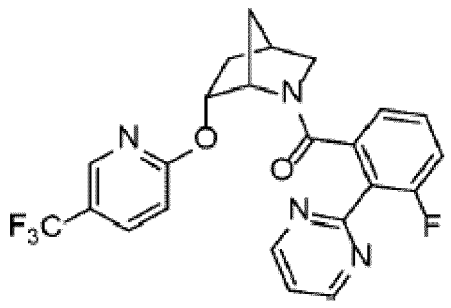
12. Composition pharmaceutique selon la revendication 11 sous la forme d'un comprimé, d'une capsule, d'une solution, d'une émulsion ou d'une suspension.

13. Composition pharmaceutique selon la revendication 11 sous la forme d'un comprimé.

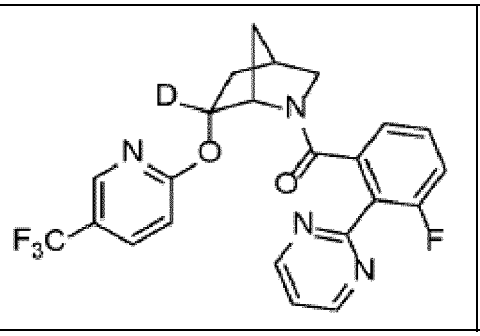
14. Composition pharmaceutique selon la revendication 13, les excipients étant choisis parmi des diluants inertes, des agents désintégrants, des agents liants, des agents lubrifiants, des agents édulcorants, des agents aromatisants, des agents colorants et des agents conservateurs.

15. Composition pharmaceutique selon la revendication 14, des charges inertes étant choisies parmi le carbonate de sodium et de calcium, le phosphate de sodium et de calcium, le lactose, l'amidon, un sucre, le glucose, une méthylcellulose, le stéarate de magnésium, le mannitol et le sorbitol.

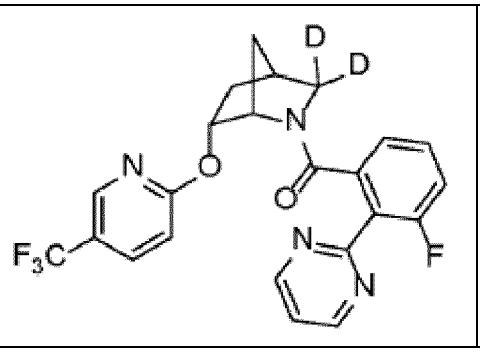
16. Composé ou composition pharmaceutique pour une utilisation selon les revendications 1 à 10, ou composition pharmaceutique selon les revendications 11 à 15, le composé étant

	(3-fluoro-2-(pyrimidin-2-yl)phényl)((1S,4R,6R)-6-((5-(trifluorométhyl) pyridin-2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)méthanone.

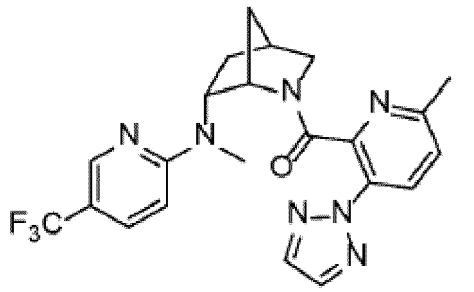
17. Composé ou composition pharmaceutique pour une utilisation selon les revendications 1 à 10, ou composition pharmaceutique selon les revendications 11 à 15, le composé étant

	(3-fluoro-2-(pyrimidin-2-yl)phényl)((1S,4R,6R)-(6-^{2}H)-((5-(trifluorométhyl)pyridin -2-yl)oxy)-2-azabicyclo[2.2.1]heptan-2-yl)méthanone.

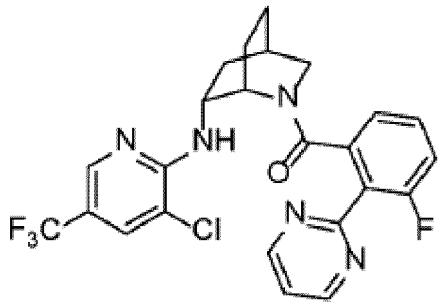
18. Composé ou composition pharmaceutique pour une utilisation selon les revendications 1 à 10, ou composition pharmaceutique selon les revendications 11 à 15, le composé étant

	(3-fluoro-2-(pyrimidin-2-yl)phényl)((1S,4R,6R)-6-((5-(trifluorométhyl) pyridin -2-yl)oxy)-2-azabicyclo[2.2.1]-(3-^{2}H,^{2}H)-heptan-2-yl) méthanone.

19. Composé ou composition pharmaceutique pour une utilisation selon les revendications 1 à 10, ou composition pharmaceutique selon les revendications 11 à 15, le composé étant

	((1S,4S,6R)-6-(méthyl(5-(trifluorométhyl)pyridin -2-yl)amino)-2-azabicyclo[2.2.1]heptan-2-yl)(6-méthyl-3-(2H-1,2,3-triazol-2-yl) pyridin-2-yl)méthanone.

20. Composé ou composition pharmaceutique pour une utilisation selon les revendications 1 à 10, ou composition pharmaceutique selon les revendications 11 à 15, le composé étant

	((1S,4R,6R)-6-((3-chloro-5-(trifluorométhyl)pyridin -2-yl)amino)-2-azabicyclo[2.2.2]octan-2-yl) (3-fluoro-2-(pyrimidin-2-yl)phényl) méthanone.

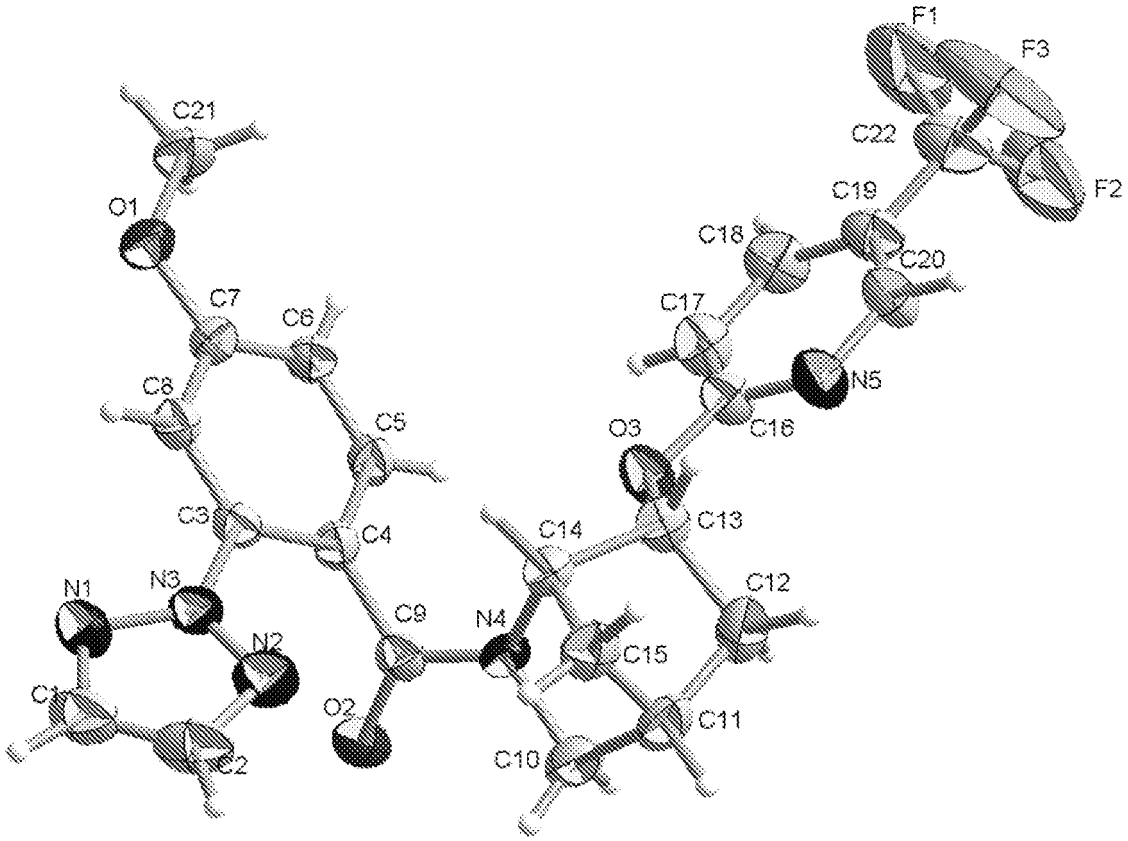
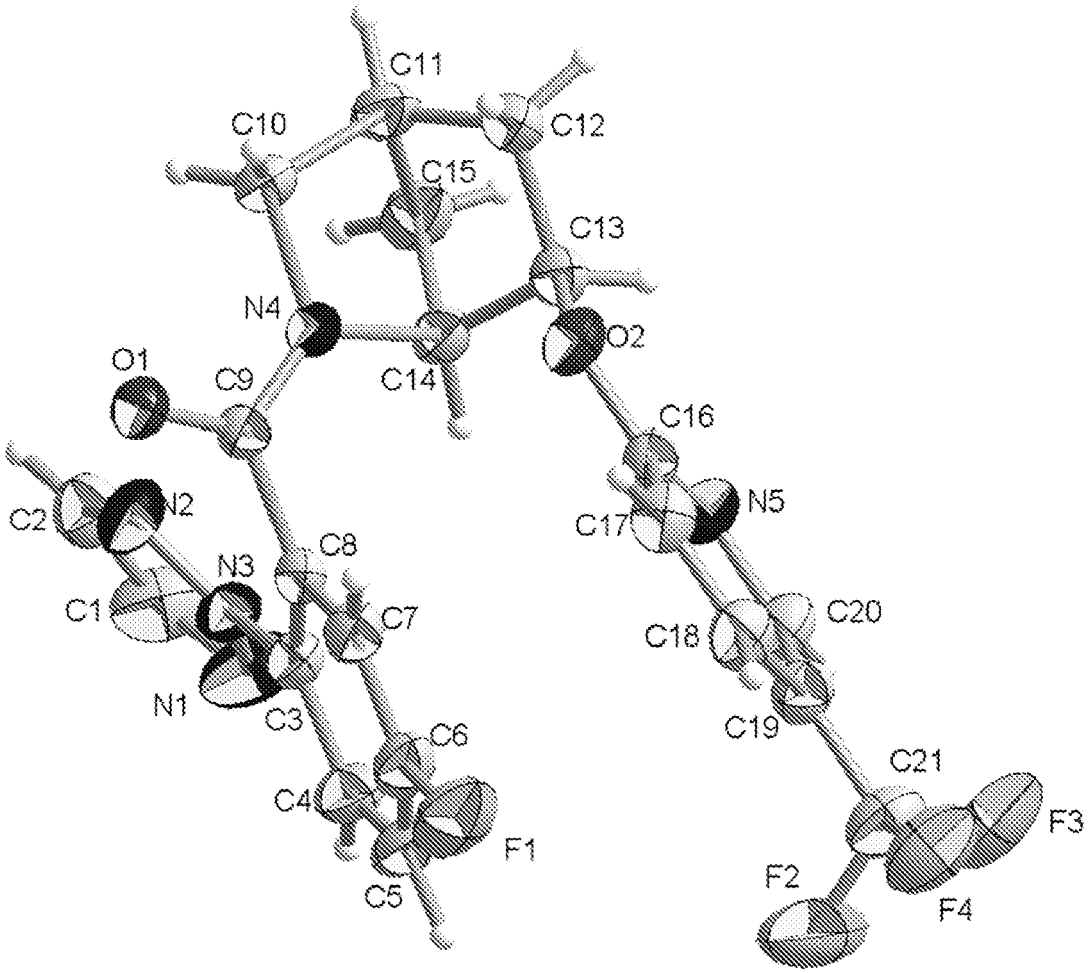

F1
F3
C21
C22
F2
O1
C19
C18
C20
C7
C6
C17
N5
C8
C5
O3
C16
C3
C4
C14
C13
N1
N3
C9
N4
C12
N2
C15
C1
O2
C11
C2
C10

Figure 1


C11
C10
C12
C15
C13
N4
O2
O1
C9
C14
C16
N2
C2
N5
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C8
N3
C1
C7
C18
C20
N1
C3
C19
C6
C21
C4
F3
F1
F2
C5
F4

Figure 2

REFERENCES CITED IN THE DESCRIPTION

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