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(54) **TMEM16A MODULATORS**

TMEM16A HEMMER

MODULATEURS DE TMEM16A

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- **TINA MORWICK ET AL: "Hit to Lead Account of the Discovery of Bisbenzamide and Related Ureidobenzamide Inhibitors of Rho Kinase", JOURNAL OF MEDICINAL CHEMISTRY, vol. 53, no. 2, 28 January 2010 (2010-01-28), pages 759-777, XP055572362, US ISSN: 0022-2623, DOI: 10.1021/jm9014263**

Description

[0001] The present invention relates to novel compounds which have activity as positive modulators of the calcium-activated chloride channel (CaCC), TMEM16A. The invention also relates to methods of preparing the compounds and pharmaceutical compositions containing them as well as these compounds for use in treating diseases and conditions modulated by TMEM16A, particularly respiratory diseases and conditions.

[0002] Humans can inhale up to 12,000 L of air each day and with it comes the potential for airborne pathogens (such as bacteria, viruses and fungal spores) to enter the airways. To protect against these airborne pathogens, the lung has evolved innate defence mechanisms to minimise the potential for infection and colonisation of the airways. One such mechanism is the mucus clearance system, whereby secreted mucus is propelled up and out of the airways by the coordinated beating of cilia together with cough clearance. This ongoing 'cleansing' of the lung constantly removes inhaled particles and microbes thereby reducing the risk of infection.

[0003] In recent years it has become clear that the hydration of the mucus gel is critical to enable mucus clearance (Boucher 2007; Matsui *et al,* 1998). In a normal, healthy airway, the mucus gel is typically 97% water and 3% w/v solids under which conditions the mucus is cleared by mucociliary action. The hydration of the airway mucosa is regulated by the coordinated activity of a number of ion channels and transporters. The balance of anion (Cl^- / HCO_3^-) secretion mediated via the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) and the Calcium Activated Chloride Conductance (CaCC; TMEM16A) and Na^+ absorption through the epithelial Na^+ channel (ENaC) determine the hydration status of the airway mucosa. As ions are transported across the epithelium, water is osmotically obliged to follow and thus fluid is either secreted or absorbed.

[0004] In respiratory diseases such as chronic bronchitis and cystic fibrosis, the % solids of the mucus gel is increased as the hydration is reduced and mucus clearance is reduced (Boucher, 2007). In cystic fibrosis, where loss of function mutations in CFTR attenuates ability of the airway to secrete fluid, the % solids can be increased to 15% which is believed to contribute towards the plugging of small airways and failure of mucus clearance. Strategies to increase the hydration of the airway mucus include either the stimulation of anion and thereby fluid secretion or the inhibition of Na^+ absorption. To this end, stimulating the activity of TMEM16A channels will increase anion secretion and therefore increase fluid accumulation in the airway mucosa, hydrate mucus and enhance mucus clearance mechanisms.

[0005] TMEM16A, also referred to as Anoctamin-1 (Ano1), is the molecular identity of calcium-activated chloride channels (Caputo *et al,* 2008; Yang *et al,* 2008). TMEM16A channels open in response to elevation of intracellular calcium levels and allow the bidirectional flux of chloride, bicarbonate and other anions across the cell membrane. Functionally TMEM16A channels have been proposed to modulate transepithelial ion transport, gastrointestinal peristalsis, nociception and cell migration/proliferation (Pedemonte & Galietta, 2014).

[0006] TMEM16A channels are expressed by the epithelial cells of different organs including the lungs, liver, kidney, pancreas and salivary glands. In the airway epithelium TMEM16A is expressed at high levels in mucus producing goblet cells, ciliated cells and in submucosal glands. Physiologically TMEM16A is activated by stimuli which mobilise intracellular calcium, particularly purinergic agonists (ATP, UTP), which are released by the respiratory epithelium in response to cyclical shear stress caused by breathing and other mechanical stimuli such as cough. In addition to increasing anion secretion leading to enhanced hydration of the airways, activation of TMEM16A plays an important role in bicarbonate secretion. Bicarbonate secretion is reported to be an important regulator of mucus properties and in controlling airway lumen pH and hence the activity of native antimicrobials such as defensins (Pezzulo *et al,* 2012).

[0007] Indirect modulation of TMEM16A, via elevation of intracellular calcium, has been clinically explored eg. denufosol (Kunzelmann & Mall, 2003). Although encouraging initial results were observed in small patient cohorts this approach did not deliver clinical benefit in larger patient cohorts (Accurso *et al* 2011; Kellerman *et al* 2008). This lack of clinical effect was ascribed to only a transient elevation in anion secretion, the result of a short half-life of denufosol on the surface of the epithelium and receptor/pathway desensitisation, and unwanted effects of elevating intracellular calcium such as increased release of mucus from goblet cells (Moss, 2013). Compounds which act directly upon TMEM16Ato enhance channel opening at low levels of calcium elevation are expected to durably enhance anion secretion and mucociliary clearance in patients and improve innate defence. As TMEM16A activity is independent of CFTR function, TMEM16A positive modulators have the potential to deliver clinical benefit to all CF patients and non-CF respiratory diseases characterised by mucus congestion including chronic bronchitis and severe asthma.

[0008] TMEM16A modulation has been implicated as a therapy for dry mouth (xerostomia), resultant from salivary gland dysfunction in Sjorgen's syndrome and radiation therapy, dry eye, cholestasis and gastrointestinal motility disorders.

[0009] WO 2008/002671 describes compounds which are inhibitors of MMP-13.

[0010] EP 1403235 describes N-arylphenylacetamide derivatives and medical compositions containing the same.

[0011] WO 2013/030802 describes compounds which are inhibitors of PGDF receptor mediated biological activity.

[0012] WO 2017/083971 describes compounds which are of use in the treatment of influenza A virus infections by inhibition or downregulation of the Wnt/β-catenin signalling pathway. WO 2016/029136 describes compounds which are useful for increasing levels of APOBEC3G and are therefore useful in treating HIV-1 infection or cancer.

[0013] Journal of Medicinal Chemistry, vol. 53, no. 2, 28 January 2010, pages 759-777 describes the hit validation and lead generation process for bisbenzimide and related ureidobenzamide inhibitors of Rho kinase.

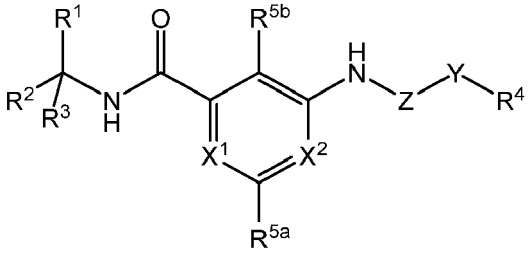
[0014] US 2016/272577 describes compounds which are inhibitors of the endothelial differentiation gene receptor 2 (EDG2) and are useful for treating diseases such as atherosclerosis, myocardial infarction and heart failure.

[0015] WO 2009/080203 describes a composition containing at least one amino benzamide derivative for controlling animal parasites.

[0016] US 2006/0069132 describes azolecarboxamide herbicides.

[0017] The present inventors have developed novel compounds which are positive modulators of TMEM16A and which are therefore of use in the treatment of diseases and conditions in which modulation of TMEM16A plays a role, particularly respiratory diseases and conditions.

[0018] In a first aspect of the present invention there is provided a compound of general formula (I) including all tautomeric forms all enantiomers and isotopic variants and salts and solvates thereof:



(I)

wherein:

R^1 is H, CN, $C(O)OR^{12}$, C_{1-3} alkyl, C_{2-3} alkenyl or C_{2-3} alkynyl, any of which alkyl, alkenyl or alkynyl groups are optionally substituted with one or more substituents, suitably one substituent, selected from fluoro, OR^{12}, $N(R^{12})_2$, $C(O)OR^{12}$, $C(O)N(R^{12})_2$, $C(O)R^{12}$ and $N(R^{13})C(O)R^{12}$;
wherein each R^{12} and R^{13} is independently selected from H, C_{1-6} alkyl and C_{1-6} fluoroalkyl
R^2 is H or C_{1-6} alkyl optionally substituted with OR^{12};
R^3 is:

C_{1-10} alkyl, C_{2-10} alkenyl or C_{2-10} alkynyl, any of which is optionally substituted with one or more substituents, suitably one substituent, selected from fluoro, CN, R^{14} OR^{14}, OR^{15}, $N(R^{15})_2$, $C(O)OR^{15}$, $C(O)N(R^{15})_2$, $N(R^{16})C(O)R^{15}$, $N(R^{15})S(O)_2R^{14}$, $N(R^{15})S(O)_2R^{16}$ and $N(R^{15})C(O)OR^{16}$;or

a 3- to 7-membered carbocyclic or heterocyclic ring system or a 6- to 10 membered aryl or 5- to 10-membered heteroaryl ring system, either of which is optionally substituted with one or more substituents selected from halo, CN, C_{1-4} alkyl, C_{1-4} haloalkyl, OR^{17} and $N(R^{17})_2$;

wherein R^{14} is a 6- to 10-membered aryl or 5- to 10-membered heteroaryl ring system or a 3- to 7-membered carbocyclic or heterocyclic ring system, any of which is optionally substituted with one or more substituents selected from halo, C_{1-4} alkyl, C_{1-4} haloalkyl, OR^{17} and $N(R^{17})_2$; wherein each R^{17} is independently H, C_{1-4} alkyl or C_{1-4} haloalkyl;
each R^{15} and R^{16} is independently H, C_{1-6} alkyl or C_{1-6} haloalkyl; or

R^2 and R^3 together with the carbon atom to which they are attached combine to form a 3-to 10-membered carbocyclic or heterocyclic ring system optionally substituted with one or more substituents selected from halo, CN, OR^9, $N(R^9)_2$, $C(O)OR^9$, $C(O)N(R^9)_2$, $C(O)R^9$, $N(R^9)C(O)R^9$ and C_{1-4} alkyl optionally substituted with halo, OR^9 or $N(R^9)_2$; or

R^1, R^2 and R^3 together with the carbon atom to which they are attached combine to form a bridged 5- to 10-membered carbocyclic or heterocyclic ring system or phenyl, any of which is optionally substituted with one or more substituents selected from halo, CN, OR^9, $N(R^9)_2$, $C(O)OR^9$, $C(O)N(R^9)_2$, $C(O)R^9$, $N(R^9)C(O)R^9$ and C_{1-4} alkyl optionally substituted with halo, OR^9 or $N(R^9)_2$;

each R^9 is independently selected from H, C_{1-6} alkyl or C_{1-6} haloalkyl;

X^1 is N;

X^2 is CR^8;
R^8 is H, halo, OH, $O(C_{1-4}$ alkyl), CN or NH_2;

Y is a bond or a straight C_{1-6} alkylene chain which is optionally substituted with one or more substituents R^{18}, wherein two substituents R^{18} may be attached to the same or to different carbon atoms;
wherein each R^{18} is independently C_{1-3} alkyl or C_{1-3} haloalkyl in which a $-CH_2-$ is optionally replaced with -NH- or -O- and wherein two R^{18} groups may combine with the atom or atoms to which they are attached to form a 3- to 6-membered carbocyclic or heterocyclic ring system;

Z is -C(O)- or -C(O)NH-;

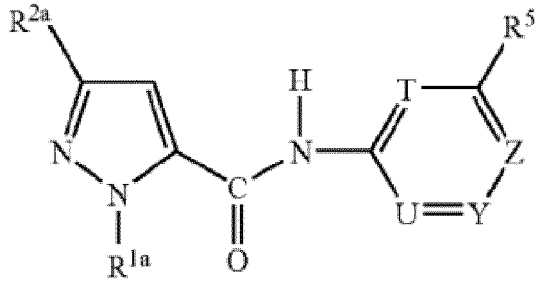
R^4 is a 6- to 14-membered aryl, 5- to 14-membered heteroaryl or a 5- to 10-membered carbocyclic ring system, any of which is optionally substituted with one or more substituents selected from:

halo, CN, nitro, R^{19}, OR^{19}, OR^6, SR^6, NR^6R^7, $C(O)R^6$, $C(O)R^{19}$, $C(O)OR^6$, $C(O)N(R^6)(R^7)$, $N(R^7)C(O)R^6$;
C_{1-6} alkyl or $O(C_{1-6}$ alkyl) either of which is optionally substituted with one or more substituents selected from halo, CN, nitro, R^{19}, OR^6, SR^6, NR^6R^7, $C(O)R^6$ $C(O)OR^6$, $C(O)N(R^6)(R^7)$ and $N(R^7)C(O)R^6$; and when R^4 is not fully aromatic in character, oxo;

wherein R^{19} is 5- or 6-membered aryl or heteroaryl ring system or a 3- to 7-membered carbocyclic or heterocyclic ring system, any of which is optionally substituted with one or more substituents selected from halo, C_{1-4} alkyl, C_{1-4} haloalkyl, OH, $O(C_{1-4}$ alkyl), $O(C_{1-4}$ haloalkyl);
R^6 is H, C_{1-6} alkyl, C_{1-6} haloalkyl, benzyl, 3- to 7-membered carbocyclyl or 3- to 7-membered heterocyclyl;
R^7 is H, C_{1-6} alkyl or C_{1-6} haloalkyl; or
R^6 and R^7 together with the nitrogen atom to which they are attached may form a 4 to 7-membered heterocyclic ring optionally containing one or more further heteroatoms and optionally substituted with one or more substituents selected from oxo and halo; and

each of R^{5a} and R^{5b} is independently H, C_{1-4} alkyl or halo;
provided that:

when X^2 is CH, Z is -C(O)- and Y is a bond, R^4 is not a 5- to 10-membered heteroaryl ring linked to Y via a nitrogen atom, and
wherein the compounds of formula (A):



(A)

wherein R^{1a} is ethyl; R^{2a} is *tert*-butyl; T, U and Y are CH and Z is N; and R^5 is C(O)NHEt, $C(O)NH(CH_2)_2CH_3$, $C(O)NH(CH_2)_2CH_2F$, $C(O)NH(CH_2)_3CH_3$, $C(O)NH(CH_2)_3CH_2F$, $C(O)NHCH_2C{\equiv}CH$ or $C(O)NHCH_2CH{=}CH_2$ are disclaimed and any tautomeric forms, enantiomers and isotopic variants and salts and solvates of the compounds of Formula (A) are not disclaimed.

[0019] In a further aspect of the present invention there is provided a compound as defined in claim 14 for use in medicine.

[0020] In the present specification, except where the context requires otherwise due to express language or necessary implication, the word "comprises", or variations such as "comprises" or "comprising" is used in an inclusive sense i.e. to specify the presence of the stated features but not to preclude the presence or addition of further features in various embodiments of the invention.

[0021] In the present specification, references to "pharmaceutical use" refer to use for administration to a human or an animal, in particular a human or a mammal, for example a domesticated or livestock mammal, for the treatment or prophylaxis of a disease or medical condition. The term "pharmaceutical composition" refers to to a composition which is suitable for pharmaceutical use and "pharmaceutically acceptable" refers to an agent which is suitable for use in a pharmaceutical composition. Other similar terms should be construed accordingly.

[0022] In the present specification, the term "C_{1-6}" alkyl refers to a straight or branched fully saturated hydrocarbon group having from 1 to 6 carbon atoms. The term encompasses methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl and t-butyl. Other alkyl groups, for example C_{1-10} alkyl are as defined above but contain different numbers of carbon atoms.

[0023] The term "C_{2-6}" alkenyl refers to a straight or branched hydrocarbon group having from 1 to 6 carbon atoms and at least one carbon-carbon double bond. The term encompasses ethenyl, propen-1-yl, propen-2-yl, buten-1-yl and buten-2-yl. Other alkenyl groups, for example C_{2-10} alkenyl are as defined above but contain different numbers of carbon atoms.

[0024] The term "C_{2-6}" alkynyl refers to a straight or branched hydrocarbon group having from 1 to 6 carbon atoms and at least one carbon-carbon triple bond. The term encompasses ethynyl, propyn-1-yl, propyn-2-yl, butyn-1-yl and butyn-2-yl. Other alkynyl groups, for example C_{2-10} alkynyl are as defined above but contain different numbers of carbon atoms.

[0025] The term "C_{1-6} alkylene" refers to a straight or branched fully saturated hydrocarbon chain having from 1 to 6 carbon atoms. Examples of alkylene groups include -CH_2-, -CH_2CH_2-, CH(CH_3)-CH_2-, $CH_2CH(CH_3)$-, -$CH_2CH_2CH_2$-, -$CH_2CH(CH_2CH_3)$- and - $CH_2CH(CH_2CH_3)CH_2$-. Other alkylene groups, for example C_{1-3} alkylene are as defined above except that they contain the specified number (e.g. 1 to 3) carbon atoms.

[0026] The terms "carbocyclic" and "carbocyclyl" refer to a non-aromatic hydrocarbon ring system containing from 3 to 10 ring carbon atoms, unless otherwise indicated, and optionally one or more double bond. The carbocyclic group may be a single ring or may contain two or three rings which may be fused or bridged, where carbon atoms in a bridge are included in the number of ring carbon atoms. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopentenyl and cyclohexenyl as well as bridged systems such as bicyclo[1.1.1]pentyl, bicyclo-[2.2.1]heptyl, bicyclo-[2.2.2]octyl and adamantyl.

[0027] In the context of the present specification, the terms "heterocyclic" and "heterocyclyl" refer to a non-aromatic ring system containing 3 to 10 ring atoms including at least one heteroatom selected from N, O and S. The heterocyclic group may be a single ring or may contain two or three rings which may be fused or bridged, where bridge atoms are included in the number of ring atoms. Examples include tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl and thiomorpholinyl, as well as fused systems such as cyclopropyl-fused pyrrolidine.

[0028] The terms "aryl" and "aromatic" in the context of the present specification refer to a ring system with aromatic character having from 5 to 14 ring carbon atoms and containing up to three rings. Where an aryl group contains more than one ring, not all rings must be fully aromatic in character. Examples of aromatic moieties are benzene, naphthalene, fluorene, tetrahydronaphthalene, indane and indene.

[0029] The terms "heteroaryl" and "heteroaromatic" in the context of the specification refer to a ring system with aromatic character having from 5 to 14 ring atoms, at least one of which is a heteroatom selected from N, O and S, and containing up to three rings. Where a heteroaryl group contains more than one ring, not all rings must be aromatic in character. Examples of heteroaryl groups include pyridine, pyrimidine, indole, indazole, thiophene, benzothiophene, benzoxazole, benzofuran, dihydrobenzofuran, tetrahydrobenzofuran, benzimidazole, benzimidazoline, quinoline and indolene.

[0030] The term "oxo" refers to a C=O substituent, where the carbon atom is a ring atom of a carbocyclyl, heterocyclyl group or a ring of an aryl or heteroaryl group which is not aromatic in character.

[0031] The term "halogen" refers to fluorine, chlorine, bromine or iodine and the term "halo" to fluoro, chloro, bromo or iodo groups. Similarly, "halide" refers to fluoride, chloride, bromide or iodide.

[0032] The term "C_{1-6} haloalkyl" as used herein refers to a C_{1-6} alkyl group as defined above in which one or more of the hydrogen atoms is replaced by a halo group. Any number of hydrogen atoms may be replaced, up to perhalo substitution. Examples include trifluoromethyl, chloroethyl and 1,1-difluoroethyl. A fluoroalkyl group is a haloalkyl group in which halo is fluoro.

[0033] The term "isotopic variant" refers to isotopically-labelled compounds which are identical to those recited in formula (I) but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number most commonly found in nature, or in which the proportion of an atom

having an atomic mass or mass number found less commonly in nature has been increased (the latter concept being referred to as "isotopic enrichment"). Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, fluorine, iodine and chlorine such as 2H (deuterium), 3H, 11C, 13C, 14C, 18F, 1231 or 1251 (e.g. 3H, 11C, 14C, 18F, 1231 or 1251), which may be naturally occurring or non-naturally occurring isotopes.

[0034] The compounds of general formula (I) are modulators of TMEM16A and therefore, in a further aspect of the invention, there is provided a compound of general formula (I) as defined above for use in the treatment or prophylaxis of diseases and conditions affected by modulation of TMEM16A.

[0035] The diseases and conditions affected by modulation of TMEM16A include respiratory diseases and conditions, dry mouth (xerostomia), intestinal hypermobility, cholestasis and ocular conditions.

[0036] There is also provided:

- A compound of general formula (I) for use in the treatment or prophylaxis of respiratory diseases and conditions.
- A compound of general formula (I) for use in the treatment or prophylaxis of dry mouth (xerostomia).
- A compound of general formula (I) for use in the treatment or prophylaxis of intestinal hypermobility.
- A compound of general formula (I) for use in the treatment or prophylaxis of cholestasis.
- A compound of general formula (I) for use in the treatment or prophylaxis of ocular conditions.

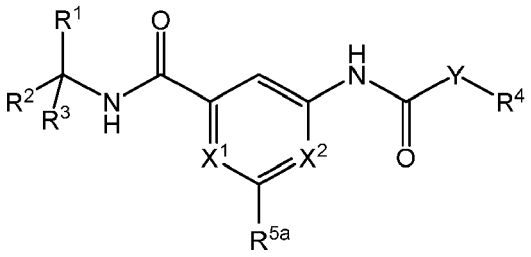
[0037] Respiratory diseases and conditions which may be treated or prevented by the compounds of general formula (I) include cystic fibrosis, chronic obstructive pulmonary disease (COPD), chronic bronchitis, emphysema, bronchiectasis, including non-cystic fibrosis bronchiectasis, asthma and primary ciliary dyskinesia.

[0038] Dry mouth (xerostomia) which may be treated or prevented by the compounds of general formula (I) may result from Sjorgens syndrome, radiotherapy treatment and xerogenic drugs.

[0039] Intestinal hypermobility which may be treated or prevented by the compounds of general formula (I) may be associated with gastric dyspepsia, gastroparesis, chronic constipation and irritable bowel syndrome.

[0040] Ocular conditions which may be treated or prevented by the compounds of by the compounds of general formula (I) include dry eye disease.

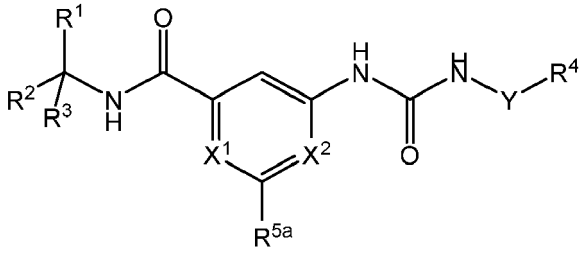
[0041] In some cases, in the compound of general formula (I), Z is -C(O)- and R^{5b} is H, such that the compound is of formula (Iz):



(Iz)

wherein R^1, R^2, R^3, R^4, R^{5a} and Y are as defined for general formula (I).

[0042] In some cases, in the compound of general formula (I), Z is -C(O)NH-, and R^{5b} is H such that the compound is of general formula (Iy):



(Iy)

wherein R^1, R^2, R^3, R^4, R^{5a} and Y are as defined for general formula (I).

[0043] In some compounds of general formula (Iz), Y is not a bond.

[0044] In some suitable compounds of the present invention, R^1 is H, CN, $C(O)OR^{12}$ or methyl, ethyl or ethynyl optionally substituted with one or more substituents selected from fluoro, OR^{12}, $N(R^{12})_2$, $C(O)OR^{12}$, $C(O)N(R^{12})_2$, $C(O)R^{12}$ and $N(R^{13})C(O)R^{12}$;
wherein each R^{12} and R^{13} is independently as defined above but is more suitably H or C_{1-4} alkyl.

[0045] More suitably, R^1 is H, CN, C(O)OH, C(O)OMe or methyl, ethyl or ethynyl any of which may be unsubstituted or substituted with one or more substituents selected from fluoro, OH, methoxy, $C(O)OC_{1-4}$ alkyl, $NHC(O)C_{1-4}$ alkyl, $C(O)NHC_{1-4}$ alkyl, NHC_{1-4} alkyl and NHC_{1-4} fluoroalkyl.

[0046] In some more suitable compounds, R^1 is H, CN, ethynyl or methyl either of which may be unsubstituted or substituted with OH; especially H, CN or methyl.

[0047] In some suitable compounds of the present invention:

R^2 is methyl or ethyl, particularly methyl; and
R^3 is C_{1-4} alkyl, or more suitably C_{1-3} alkyl, for example methyl, ethyl or isopropyl; any of which is optionally substituted with one or more substituents selected from hydroxyl, methoxy, ethoxy, $-C(O)O-(C_{1-4}$ alkyl) and $-N(H)C(O)O-(C_{1-4}$ alkyl).

[0048] More suitably in this case, R^3 is unsubstituted or substituted with a single substituent selected from methoxy, ethoxy and $-N(H)C(O)O-(C_{1-4}$ alkyl), particularly methoxy or and $- N(H)C(O)O-(C_{1-4}$ alkyl).

[0049] In these compounds, R^1 is suitably methyl.

[0050] In other suitable compounds of the present invention, R^2 is H or C_{1-4} alkyl, more suitably H, methyl or ethyl, especially H or methyl.

[0051] In some suitable compounds of the present invention, R^3 is C_{1-10} alkyl, more suitably C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl, any of which is optionally substituted as described above.

[0052] More suitably, R^3 is C_{1-10} alkyl, more suitably C_{1-6} alkyl, or C_{2-3} alkynyl.

[0053] More suitably, when R^3 is an alkyl, alkenyl or alkynyl group, it is unsubstituted or substituted with a single substituent selected from fluoro, R^{14} OR^{14}, OR^{15}, $C(O)OR^{15}$, $N(R^{16})S(O)_2R^{15}$ and $N(R^{16})C(O)OR^{15}$; wherein R^{14}, R^{15} and R^{16} are as described above.

[0054] In these compounds, it is still more suitable for R^{14} to be selected from phenyl, pyridyl and a 5- or 6-membered heterocyclic ring, especially a nitrogen containing ring and more especially a 6-membered nitrogen containing ring such as morpholine, piperidine or piperazine. More suitably, R^{15} is selected from H, or C_{1-4} alkyl. R^{16} is suitably H.

[0055] Examples of such R^3 groups include:

methyl or ethyl optionally substituted with OH, F, phenyl, O-phenyl, morpholine, $NHS(O)_2C_{1-4}$ alkyl or $NHC(O)C_{1-4}$ alkyl;
propynyl, for example prop-1-ynyl, and ethynyl.

[0056] In other suitable compounds, R^3 is a 3- to 7-membered carbocyclic or heterocyclic ring system, in particular a C_{3-7} cycloalkyl group, for example cyclopropyl, which may be substituted as defined above but is more suitably unsubstituted.

[0057] In still other suitable compounds of general formula (I), R^3 is a 6- to 10 membered aryl or 5- to 10-membered heteroaryl ring system, either of which is optionally substituted as defined above.

[0058] More suitably in this case, R^3 is phenyl or a 5- or 6-membered heteroaryl group optionally substituted as defined above, in particular phenyl or pyridyl.

[0059] Such R^3 groups may be unsubstituted or substituted as defined above, with particularly suitable substituents being selected from OR^{17} and $N(R^{17})_2$, wherein each R^{17} is independently as defined above but is more suitably H or methyl.

[0060] In some particularly suitable compounds of the present invention, R^1 is methyl or CN and R^2 and R^3 are both methyl.

[0061] In some suitable compounds of the present invention, R^2 and R^3 combine with the carbon atom to which they are attached to form a carbocyclic or heterocyclic ring system.

[0062] Suitable carbocyclic rings formed by R^2 and R^3 include: cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl; and bridged systems such as bicyclo[1.1.1]pentyl, bicyclo-[2.2.1]heptyl, bicyclo-[2.2.2]octyl and adamantyl, (provided that the atom to which R^2 and R^3 are attached is not a bridge atom).

[0063] More suitable carbocyclic rings formed by R^2 and R^3 include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

[0064] Suitable heterocyclic rings formed by R^2 and R^3 include; tetrahydropyran-yl, for example tetrahydropyran-4-yl; tetrahydrofuranyl, for example tetrahydrofuran-3-yl; oxetanyl, for example oxetan-3-yl; piperidinyl, for example piperidin-2-yl and piperidin-4-yl; morpholinyl, piperazinyl and cyclopropyl-fused pyrrolidine.

[0065] More suitable heterocyclic rings formed by R^2 and R^3 include; tetrahydropyran-yl, for example tetrahydropyran-

4-yl; tetrahydrofuranyl, for example tetrahydrofuran-3-yl; oxetanyl, for example oxetan-3-yl; piperidinyl, for example piperidin-2-yl and piperidin-4-yl; and cyclopropyl-fused pyrrolidine.

[0066] Any of the ring systems formed by R^2 and R^3 may be substituted as described above. In some cases, the ring system is unsubstituted or are substituted with a single substituent selected from OR^9 and $C(O)OR^9$, where R^9 is as defined above but is suitably C_{1-4} alkyl, for example *tert*-butyl.

[0067] In alternative suitable compounds, the carbocyclic or heterocyclic ring system formed by R^2 and R^3 may be unsubstituted or substituted with one or more substituents, for example 1 or 2 substituents, selected from halo, OR^9, $C(O)OR^9$, unsubstituted C_{1-4} alkyl and C_{1-4} alkyl substituted with halo or OR^9, more suitably with 1 or 2 substituents selected from fluoro, OR^9, $C(O)OR^9$, unsubstituted C_{1-4} alkyl and C_{1-4} alkyl substituted with fluoro or OR^9.

[0068] In particular, the carbocyclic or heterocyclic ring system formed by R^2 and R^3 may be unsubstituted or substituted with one or more substituents, for example 1 or 2 substituents, selected from fluoro, OH, $C(O)O(C_{1-4}$ alkyl), unsubstituted C_{1-4} alkyl or C_{1-4} alkyl substituted with OH.

[0069] In some compounds where R^2 and R^3 form a carbocyclic or heterocyclic ring system, R^1 is H;

[0070] In other such compounds, R^1 is methyl.

[0071] In other such compounds, R^1 is methyl substituted with OH.

[0072] In still other such compounds, R^1 is CN.

[0073] In still other such compounds, R^1 is ethynyl.

[0074] In still other such compounds, R^1 is $C(O)OR^{12}$, for example $C(O)OCH_3$.

[0075] In particularly suitable compounds where R^2 and R^3 form a carbocyclic or heterocyclic ring system: R^1 is H or cyano and R^2 and R^3 form a 5- or 6-membered carbocyclic or heterocyclic ring system, particularly a 6-membered ring system, for example cyclohexyl or tetrahydropyranyl, such as tetrahydropyran-4yl.

[0076] In still other suitable compounds of the present invention, R^1, R^2 and R^3 combine with the carbon atom to which they are attached to form a bridged carbocyclic or heterocyclic ring system, especially a carbocyclic system such as bicyclo[1.1.1]pentanyl, bicyclo[2.1.1]hexanyl, bicyclo-[2.2.1]heptanyl, bicyclo-[2.2.2]octanyl or adamantyl.

[0077] In some cases, the carbocyclic system may be selected from 3-bicyclo[1.1.1]pentanyl, bicyclo-[2.2.1]heptanyl, bicyclo-[2.2.2]octanyl and 1-adamantyl.

[0078] In other cases, the carbocyclic ring system may be selected from bicyclo[1.1.1]pentanyl, bicyclo[2.1.1]hexanyl and adamantyl, especially, 3-bicyclo[1.1.1]pentanyl, 1-bicyclo[2.1.1]hexanyl and 1-adamantyl,

[0079] Suitably, the ring system is unsubstituted or substituted with a single substituent selected from OR^9 and $C(O)OR^9$, where R^9 is as defined above but is suitably H, methyl or ethyl, especially H or methyl and more particularly methyl. More suitably, the ring system is unsubstituted.

[0080] Alternatively, the ring system may be unsubstituted or substituted with one or more substituents, suitably one or two substituents and more suitably with a single substituent selected from fluoro, cyano, C_{1-4} alkyl, OR^9 and $C(O)OR^9$, where R^9 is as defined above but is suitably H, methyl or ethyl, especially H or methyl and more particularly methyl.

[0081] In still other suitable compounds of the present invention, R^1, R^2 and R^3 combine with the carbon atom to which they are attached to form a phenyl group which may be substituted as defined above but is more suitably unsubstituted.

[0082] In the compounds of general formula (I), X^1 is N and X^2 is CR^8, where R^8 is as defined above. In particular, X^1 is N and X^2 is CH.

[0083] Suitably in such compounds, when -Z is C(O)- and Y is a bond, R^4 is not a 5- to 10-membered heteroaryl ring system which is attached to the linker Y via a ring nitrogen atom.

[0084] In such compounds, R^4 is suitably phenyl having an OH substituent at the 2- or 3-position and optionally one or more further substituents as defined above.

[0085] More suitably, R^4 is phenyl having an OH substituent at the 2-position and optionally one or more further substituents as defined above.

[0086] In some suitable compounds of this type, Z is -C(O)- and Y is not a bond. Thus, Y may be a straight C_{1-6} alkylene chain optionally substituted with one or more substituents R^{18} as defined above.

[0087] In these compounds, suitably when one of R^1 and R^2 is H and the other of R^1 and R^2 is H or methyl, R^3 is not substituted or unsubstituted phenyl.

[0088] In the compounds of the present invention, R^8 is suitably H or halo, for example H or fluoro. In alternative suitable compounds, R^8 is H, halo, OH, methoxy or ethoxy, especially H, fluoro, chloro, OH or methoxy.

[0089] As described above, in more suitable compounds of the present invention, Z is -C(O)- or C(O)NH and that the compound is of general formula (Iz) or (Iy).

[0090] In some more suitable compounds of the present invention, Y is C_{1-3} alkylene, still more suitably $-CH_2-$, $-CH(CH_3)CH_2-$ or $-CH_2CH_2-$. More suitably, Y is $-CH_2-$ or $-CH_2CH_2-$ and in particularly suitable compounds, Y is $-CH_2-$.

[0091] In other suitable compounds of the invention, Y is a bond.

[0092] In other suitable compounds of the present invention, Y is a straight C_{1-3} alkylene optionally substituted with one or more substituents R^{18}, wherein R^{18} is as defined above and wherein two substituents R^{18} may be attached to the same or to different carbon atoms.

[0093] Suitably in such compounds, each R^{18} is independently methyl or ethyl or two R^{18} groups attached to the same carbon atom combine to form a cyclopropyl, cyclobutyl or cyclopentyl ring.

[0094] Still more suitably, Y is a bond or -C_{1-3} alkylene-.

[0095] Examples of linkers Y include a bond, -CH_2-, -CH(CH3)-, -CH_2CH_2- and

.

[0096] In other suitable compounds of general formula (I), Y is -CH_2-, -CH_2CH_2-, -$CH(CH_3)CH_2$-, -CH2CH(CH3)- or -CH2CH2CH2-, especially -CH2- or -CH_2CH_2- and more especially -CH_2-.

[0097] In some suitable compounds of general formulae (I), R^{5b} is H or halo, for example fluoro.

[0098] More usually, R^{5b} is H such that the compound is a compound of general formula (Iz) or (Iy) above.

[0099] In some suitable compounds of general formulae (I), (Iz) and (Iy), R^{5a} is H, C_{1-4} alkyl or halo, for example fluoro.

[0100] In some suitable compounds of general formulae (I), (Iz) and (Iy), R^{5a} is methyl or ethyl, especially methyl.

[0101] In other suitable compounds of general formula (I), (Iz) and (Iy), R^{5a} is halo, especially fluoro

[0102] More usually in compounds of general formulae (I), (Iz), and (Iy), R^{5a} is H.

[0103] In still other suitable compounds of the invention, R^5 is halo, especially fluoro.

[0104] In typical compounds of general formula (I), both R^{5a} and R^{5b} are H.

[0105] In the compounds of the present invention R^4 is a 6-14-membered aryl, 5-14-membered heteroaryl or a 5- to 10-membered carbocyclic ring system, any of which is optionally substituted as defined above. More suitably, R^4 is 6-10-membered aryl, 5- to 10-membered heteroaryl or a 5- to 10-membered carbocyclic ring system, any of which is optionally substituted with one or more substituents as described above.

[0106] In some more suitable compounds of general formula (I), R^4 is a 6- to 11-membered aryl group, for example a group selected from phenyl, naphthyl, indanyl, 1,2,3,4-tetrahydronaphthyl and benzocycloheptanyl, any of which is optionally substituted as described above.

[0107] In other more suitable compounds of general formula (I), R^4 is a 5- to 10-membered heteroaryl group, for example a group selected from pyridyl, quinolinyl, quinoxalinyl, indazolyl, indolyl, benzoxazolyl, dihydrobenzofuranyl, furyl and thienyl, any of which is optionally substituted as described above.

[0108] In other more suitable compounds of general formula (I), R^4 is a carbocyclyl group, for example a group selected from cyclohexyl and adamantyl, any of which is unsubstituted or substituted as described above.

[0109] In some suitable compounds of the present invention, R^4 is phenyl optionally substituted with one or more substituents as described above.

[0110] Alternatively, R^4 is 5-10-membered heteroaryl optionally substituted with one or more substituents as described above. More suitably in this case R^4 is pyridyl, pyrrolyl, thienyl, furyl, benzoxazolyl, imidazolyl, indolyl or indazolyl.

[0111] In some suitable compounds, R^4 is substituted with one or more substituents selected from:

halo, CN;
OR^6, NR^6R^7, $C(O)OR^6$, $C(O)N(R^6)(R^7)$;
C_{1-6} alkyl optionally substituted with one or more substituents selected from halo, CN, OR^6, NR^6R^7, $C(O)OR^6$ and $C(O)N(R^6)(R^7)$;

wherein R^6 is H, C_{1-6} alkyl, C_{1-6} haloalkyl, 3-7 membered carbocyclyl or 3-7 membered heterocyclyl;
R^7 is H, C_{1-6} alkyl or C_{1-6} haloalkyl; or
R^6 and R^7 together with the nitrogen atom to which they are attached may form a 5- or 6-membered heterocyclic ring optionally containing one or more further heteroatoms and optionally substituted with one or more oxo substituents.

[0112] In other suitable compounds, wherein R^4 is an aryl group, it is more suitably unsubstituted or substituted with one or more substituents selected from:

halo, CN, R^{19}, OR^{19};
OR^6, $C(O)OR^6$;
C_{1-4} alkyl or $O(C_{1-4}$ alkyl) optionally substituted with one or more substituents selected from halo, CN, R^{19}, OR^{19}, OR^6 and NR^6R^7;
wherein R^6, R^7 and R^{19} are as defined above.

[0113] More suitably, however, R^6 is H, C_{1-4} alkyl or C_{1-4} haloalkyl or, for a moiety NR^6R^7, R^6 and R^7 combine with the nitrogen atom to which they are attached to form a 5- or 6-membered heterocyclic ring, optionally containing one or more further heteroatoms and optionally substituted with one or more halo substituents.

[0114] R^{19} is more suitably a 3- to 6- membered carbocyclyl group or phenyl, either or which is optionally substituted with one or more substituents selected from halo, methyl and methoxy.

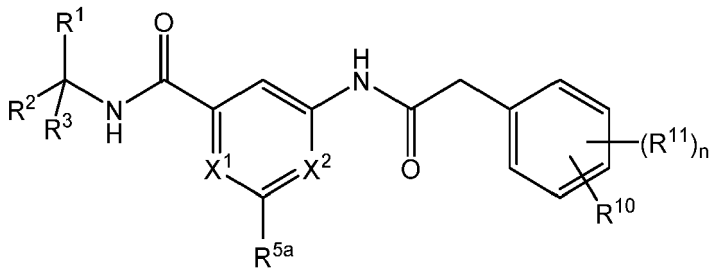
[0115] In particularly suitable compounds, R^4 is phenyl substituted with an OH group at either the 2- or the 3-position and optionally with one or more further substituents as defined for general formula (I), more suitably with one or more further substituents, for example one further substituent, selected from those defined immediately above.

[0116] When R^4 is a bicyclic aryl group it is more suitably unsubstituted or substituted with one or two substituents selected from OH and halo.

[0117] When R^4 is a heteroaryl group, it is more suitably unsubstituted or substituted with one or more substituents selected from OH and halo.

[0118] When R^4 is a carbocyclic group it is more suitably unsubstituted or substituted with one or more substituents selected from OH and halo. Still more suitably, it is unsubstituted.

[0119] In particularly suitable compounds of the present invention, Y is-CH_2-, R^4 is phenyl and the compound is a compound of general formula (Ia):

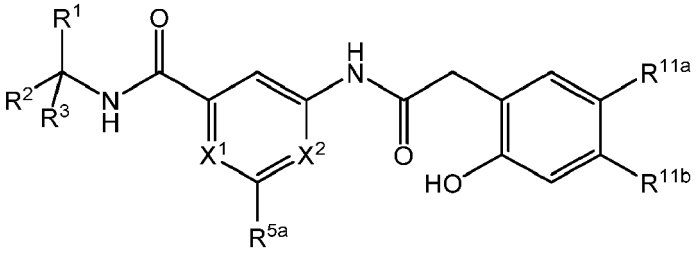


(Ia)

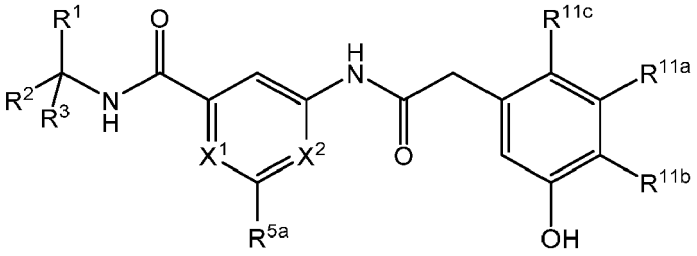
wherein

R^1, R^2, R^3, R^{5a}, X^1 and X^2 are as defined for general formula (I);
R^{10} is H, OH, halo, C_{1-6} alkyl, -O(C_{1-6} alkyl);
each R^{11} is independently H, halo, OH, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, -O(C_{1-6} alkyl) or C(O)O-(C_{1-6} alkyl); and
n is 1 or 2.

[0120] Still more suitably, the compound is a compound of general formula (Ib) or (Ic):



(Ib)

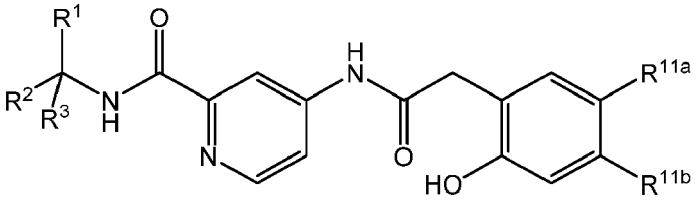


(Ic)

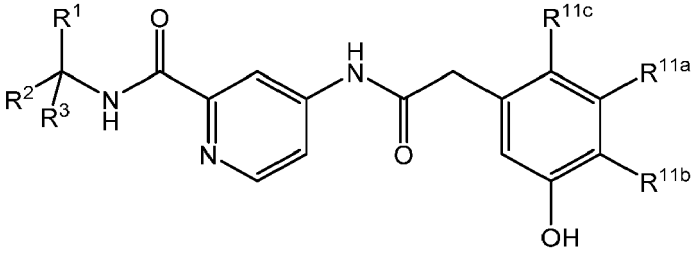
wherein

R^1, R^2, R^3, R^{5a}, X^1 and X^2 are as defined for general formula (I);
R^{11a} is H, halo, C_{1-4} alkyl, C_{1-4} haloalkyl or $C(O)O(C_{1-4}$ alkyl);
R^{11b} is H, halo, C_{1-4} alkyl or C_{1-4} haloalkyl; and
R^{11c} is H, halo, CN, C_{1-4} alkyl or C_{1-4} haloalkyl.

[0121] In particularly suitable compounds of general formula (Ib), one or both of R^{11a} and R^{11b} is H.
[0122] In some such compounds of general formula (Ib), R^{11a} is H, halo, C_{1-4} alkyl or $C(O)O(C_{1-4}$ alkyl) and R^{11b} is H.
[0123] More suitably, R^{11a} is H, chloro, C_{1-4} alkyl or $C(O)OCH_3$ and R^{11b} is H.
[0124] In some compounds of general formula (Ib) R^{11a} is chloro and R^{11b} is H.
[0125] In other such compounds of general formula (Ib), R^{11a} is H and R^{11b} is H, halo or C_{1-6} haloalkyl.
[0126] More suitably, R^{11a} is H and R^{11b} is H, chloro, bromo or trifluoromethyl.
[0127] Alternatively, in other particularly suitable compounds of general formula (Ib) both R^{11a} and R^{11b} are halo, particularly chloro or bromo.
[0128] In some particularly suitable compounds of general formula (Ic), R^{11a} is H.
[0129] More suitably in compounds of general formula (Ic), R^{11b} is C_{1-4} alkyl or C_{1-4} halo alkyl, for example *t*-butyl.
[0130] In the compounds of general formulae (Ia) and (Ib) suitable R^1, R^2, R^3, R^5, X^1 and X^2 groups are as set out above for the compounds of general formula (I). However, still more suitably, X^1 is N, X^2 is CH and R^{5b} is H such that the compounds is of general formula (Id) or (Ie):



(Id)



(Ie)

wherein R^1, R^2, R^3, R^{11a}, R^{11b} and R^{11c} are as defined above for compounds of general formulae (Ib) and (Ic).
[0131] Particularly suitable groups R^{11a} and R^{11b} for general formula (Id) are as described above for general formula (Ib) and particularly suitable groups R^{11a} and R^{11b} for general formula (Ie) are as described above for general formula (Ic).
[0132] Suitable compounds of general formula (I) include:
Specific examples of compounds of general formula (I) include the following:

(* denotes a reference compound that is not claimed)
N-tert-Butyl-4-[[2-(2-hydroxyphenyl)acetyl]amino]pyridine-2-carboxamide (Compound 1);
N-(1,1-Dimethylpropyl)-3-[[2-(2-hydroxyphenyl)acetyl]amino]benzamide (Compound 1.1*);
N-(1-Adamantyl)-3-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]benzamide (Compound 1.2*);
N-(1-Adamantyl)-4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide(Compound 1.3);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(3-methoxy-1,1-dimethylpropyl)pyridine-2-carboxamide (Compound 1.4);
3-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1,1-dimethyl propyl)benzamide (Compound 1.5*);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1-methylcyclobutyl)pyridine-2-carboxamide (Compound 1.6);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1-methylcyclohexyl)pyridine-2-carboxamide (Compound 1.7);
tert-Butyl N-[3-[[4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carbonyl]amino]-3-methyl-butyl]carbamate (Compound 1.8);
3-[[2-(2-Hydroxyphenyl)acetyl]amino]-N-(2-methoxy-1,1-dimethyl-ethyl)benzamide (Compound 1.9*);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-cyclohexyl-pyridine-2-carboxamide (Compound 1.10);
N-tert-Butyl-3-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]benzamide (Compound 2*);
N-tert-Butyl-3-[[2-(5-fluoro-2-hydroxy-phenyl)acetyl]amino]benzamide (Compound 2.1*);
N-tert-Butyl-3-[[2-(3-fluoro-2-hydroxy-phenyl)acetyl]amino]benzamide (Compound 2.2*);
N-tert-Butyl-3-[[2-(4-fluoro-2-hydroxy-phenyl)acetyl]amino]benzamide (Compound 2.3*);
N-tert-Butyl-3-[[2-(2,6-dihydroxy phenyl)acetyl]amino]benzamide (Compound 2.4*);
N-tert-Butyl-3-[3-(2-hydroxyphenyl)propanamido]benzamide (Compound 2.5*);
N-tert-Butyl-3-[[2-(2-hydroxy-6-methoxy-phenyl)acetyl]amino] benzamide (Compound 2.6*);
N-tert-Butyl-3-[2-(2-hydroxyphenyl)propanamido]benzamide (Compound 2.7*);
N-tert-Butyl-3-[[2-(2-hydroxy-3-methoxy-phenyl)acetyl]amino] benzamide (Compound 2.8*);
N-tert-Butyl-3-[[2-(3,5-difluoro-2-hydroxy-phenyl)acetyl]amino] benzamide (Compound 2.9*);
3-[[2-(5-Bromo-2-hydroxy-phenyl) acetyl]amino]-N-tert-butyl-benzamide (Compound 2.10*);
N-tert-Butyl-3-[[2-(2,3-difluoro-6-hydroxy-phenyl)acetyl]amino] benzamide (Compound 2.11*);
N-tert-Butyl-3-[[2-(4,5-difluoro-2-hydroxy-phenyl)acetyl]amino] benzamide (Compound 2.12*);
N-(1,1-Dimethylpropyl)-3-[[2-(4-fluoro-2-hydroxy-phenyl)acetyl]amino] benzamide (Compound 2.13*);
N-tert-Butyl-3-[[2-(2-hydroxy-4-methoxy-phenyl)acetyl]amino]benzamide (Compound 2.14*);
N-tert-Butyl-3-[[2-(2-fluoro-6-hydroxy-phenyl)acetyl]amino]benzamide (Compound 2.15*);
N-tert-Butyl-3-[[2-(2,3-dihydroxyphenyl) acetyl]amino]benzamide (Compound 2.16*);
N-tert-Butyl-3-[[2-[2-hydroxy-5-(trifluoro methyl)phenyl]acetyl]amino]benzamide (Compound 2.17*);
Methyl 3-[2-[3-(tert-butylcarbamoyl)anilino]-2-oxo-ethyl]-4-hydroxy-benzoate (Compound 2.18*);
N-tert-Butyl-3-[[2-[2-hydroxy-4-(trifluoro methyl)phenyl]acetyl]amino]benzamide (Compound 2.19*);
N-tert-Butyl-4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 3);
N-(1,1-Dimethylpropyl)-4-[[2-(4-fluoro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 3.1a);
N-tert-Butyl-4-[[2-(4-fluoro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 3.2a);
N-tert-Butyl-4-[[2-(2-chloro-6-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 3.3a);
4-[[2-(4-Bromo-5-chloro-2-hydroxy-phenyl)acetyl]amino]-N-tert-butyl-pyridine-2-carboxamide (Compound 3.4a);
4-[[2-(5-tert-Butyl-2-hydroxy-phenyl)acetyl]amino]-N-(1-cyanocyclobutyl)pyridine-2-carboxamide (Compound 3.5a);
4-[[2-(5-tert-Butyl-2-hydroxy-phenyl)acetyl]amino]-N-(1-methyl cyclobutyl)pyridine-2-carboxamide (Compound 3.6a);
N-tert-butyl-4-[2-(2,5-dibromo-3-fluoro-6-hydroxyphenyl)acetamido]pyridine-2-carboxamide (Compound 3.7a);
N-tert-Butyl-4-[[2-[2-hydroxy-5-(trifluoromethyl)phenyl]acetyl]amino]pyridine-2-carboxamide (Compound 3.5b);
N-tert-Butyl-4-[[2-(4-chloro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 3.6b);
N-tert-Butyl-4-[[2-[2-hydroxy-4-(trifluoro methyl)phenyl]acetyl]amino]pyridine-2-carboxamide (Compound 3.7b);
N-tert-Butyl-4-[[2-(2-hydroxy-5-methoxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 3.8b);
N-tert-Butyl-4-[(6-hydroxyindane-1-carbonyl)amino]pyridine-2-carboxamide (Compound 3.9b);
N-tert-Butyl-4-[(7-hydroxyindane-1-carbonyl)amino]pyridine-2-carboxamide (Compound 3.10b);
N-tert-Butyl-4-[[2-(2,5-dibromo-3-chloro-6-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 3.11b);
N-tert-Butyl-4-[[2-(3-hydroxyphenyl) acetyl]amino]pyridine-2-carboxamide (Compound 3.12b);
N-tert-Butyl-4-[[2-(2-fluoro-5-hydroxy-phenyl) acetyl]amino]pyridine-2-carboxamide (Compound 3.13b);
N-tert-Butyl-4-[[2-(4-chloro-3-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 3.14b);
N-tert-Butyl-4-[[2-(2-chloro-3-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 3.15b);
N-tert-Butyl-4-[[2-(2-chloro-5-hydroxy-phenyl) acetyl]amino]pyridine-2-carboxamide (Compound 3.16b);
N-tert-Butyl-4-[[2-(3-chloro-5-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 3.17b);

N-tert-Butyl-3-[[2-(3-hydroxyphenyl)acetyl]amino]benzamide (Compound 4*);
N-tert-Butyl-3-[[2-(1H-indazol-3-yl)acetyl]amino]benzamide (Compound 4.1*);
N-tert-Butyl-3-[[2-(5-fluoro-1H-indol-3-yl)acetyl]amino]benzamide (Compound 4.2*);
N-tert-Butyl-3-[[2-(2-hydroxyphenyl)acetyl]amino] benzamide (Compound 4.3*);
N-tert-Butyl-3-[[2-(7-fluoro-2-methyl-1H-indol-3-yl)acetyl]amino]benzamide (Compound 4.4*);
N-tert-Butyl-3-[[2-(1H-indol-3-yl)acetyl]amino]benzamide (Compound 4.5*);
N-tert-Butyl-3-[(2-phenylacetyl) amino]benzamide (Compound 4.6*);
N-tert-Butyl-3-[[2-(2-fluoro-6-methoxy-phenyl)acetyl]amino]benzamide (Compound 4.7*);
N-tert-Butyl-3-[[2-(2,3-difluoro-6-methoxy-phenyl)acetyl]amino]benzamide (Compound 4.8*);
N-tert-Butyl-3-[[2-[2-methoxy-4-(trifluoro methyl)phenyl]acetyl]amino]benzamide (Compound 4.9*);
N-tert-Butyl-4-[[2-(2-thienyl)acetyl]amino]pyridine-2-carboxamide (Compound 5);
4-[[2-(2-Adamantyl)acetyl]amino]-N-tert-butyl-pyridine-2-carboxamide (Compound 5.1);
N-tert-Butyl-4-[[2-(4-fluoro-2-methoxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 5.2);
N-tert-Butyl-4-[[2-(5-chloro-2-fluoro-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 5.3);
N-tert-Butyl-4-[[2-(2-furyl)acetyl]amino] pyridine-2-carboxamide (Compound 5.4);
N-tert-Butyl-4-[[2-(3-chlorophenyl) acetyl]amino]pyridine-2-carboxamide (Compound 5.5);
N-tert-Butyl-4-[[2-(1H-indol-3-yl)acetyl] amino]pyridine-2-carboxamide (Compound 5.6);
N-tert-Butyl-4-[[2-(o-tolyl)acetyl] amino]pyridine-2-carboxamide (Compound 5.7);
N-tert-Butyl-4-[[2-(3,4-dichlorophenyl) acetyl]amino]pyridine-2-carboxamide (Compound 5.8);
N-tert-Butyl-4-[[2-(3-fluorophenyl)acetyl] amino]pyridine-2-carboxamide (Compound 5.9);
N-tert-Butyl-4-[[2-(5-chloro-2-methoxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 5.10);
N-tert-Butyl-4-[[2-(p-tolyl)acetyl] amino]pyridine-2-carboxamide (Compound 5.11);
N-tert-Butyl-4-[[2-(2-fluorophenyl) acetyl]amino]pyridine-2-carboxamide (Compound 5.12);
N-tert-Butyl-4-[[2-(4-fluorophenyl) acetyl]amino]pyridine-2-carboxamide (Compound 5.13);
N-tert-Butyl-4-[[2-(m-tolyl)acetyl] amino]pyridine-2-carboxamide (Compound 5.14);
4-[[2-(1,3-Benzoxazol-6-yl)acetyl] amino]-N-tert-butyl-pyridine-2-carboxamide (Compound 5.15);
N-tert-Butyl-4-[[2-(2-chloro-3-pyridyl) acetyl]amino]pyridine-2-carboxamide (Compound 5.16);
N-tert-Butyl-4-[[2-(2,6-dichlorophenyl) acetyl]amino]pyridine-2-carboxamide (Compound 5.17);
N-tert-Butyl-4-[[2-(4-chloro-3-fluoro-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 5.18);
N-tert-Butyl-4-[[2-(3,5-dichloro phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 5.19);
N-tert-Butyl-4-[[2-(2-chlorophenyl) acetyl]amino]pyridine-2-carboxamide (Compound 5.20);
N-tert-Butyl-4-[[2-(3-chloro-4-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 5.21);
N-tert-Butyl-4-(indane-1-carbonyl amino)pyridine-2-carboxamide (Compound 5.22);
N-tert-Butyl-4-[(2-quinoxalin-6-ylacetyl) amino]pyridine-2-carboxamide (Compound 5.23);
N-tert-Butyl-4-[[2-(2-naphthyl) acetyl]amino]pyridine-2-carboxamide (Compound 5.24);
N-tert-Butyl-4-(2,3-dihydrobenzofuran-3-carbonylamino)pyridine-2-carboxamide (Compound 5.25);
N-tert-Butyl-4-(6,7,8,9-tetrahydro-5H-benzo[7]annulene-5-carbonylamino) pyridine-2-carboxamide (Compound 5.26);
N-tert-Butyl-4-(tetralin-1-carbonylamino) pyridine-2-carboxamide (Compound 5.27);
N-tert-Butyl-4-[[2-(6-quinolyl)acetyl] amino]pyridine-2-carboxamide (Compound 5.29);
N-tert-butyl-4-[[1-(3-chlorophenyl) cyclopropanecarbonyl]amino]pyridine-2-carboxamide (Compound 5.31);
N-tert-Butyl-4-[[2-(2,3-dihydro-1,4-benzodioxin-6-yl)acetyl]amino]pyridine-2-carboxamide (Compound 5.32);
N-(1,1-Dimethylprop-2-ynyl)-4-[(2-isochroman-1-ylacetyl)amino]pyridine-2-carboxamide (Compound 5.33);
4-[[2-(4,4-Difluorocyclohexyl)acetyl]amino]-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide (Compound 5.34);
N-(1,1-Dimethylprop-2-ynyl)-4-[[2-[4-(trifluoromethyl)phenyl]acetyl]amino]pyridine-2-carboxamide (Compound 5.35);
N-(1,1-Dimethylprop-2-ynyl)-4-[[2-[3-(trifluoromethyl)-1H-pyrazol-4-yl]acetyl] amino] pyridine-2-carboxamide (Compound 5.36);
N-(1,1-Dimethylprop-2-ynyl)-4-[[2-[3-(trifluoromethyl)phenyl]acetyl]amino]pyridine-2-carboxamide (Compound 5.37);
N-(1,1-Dimethylprop-2-ynyl)-4-[[2-[2-(trifluoromethyl)phenyl]acetyl]amino]pyridine-2-carboxamide (Compound 5.38);
4-[[2-(2,3-Dihydro-1,4-benzoxazin-4-yl)acetyl]amino]-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide (Compound 5.39);
N-tert-Butyl-4-[[2-(5-cyano-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 6);
3-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1,1,2,2-tetramethylpropyl) benzamide (Compound 7*);
3-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(1,1-dimethylbutyl)benzamide (Compound 7.1*);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(1,1-dimethylbutyl)pyridine-2-carboxamide (Compound 7.2);

3-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-cyclohexyl-benzamide (Compound 7.3*);
3-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-tetrahydropyran-4-yl-benzamide (Compound 7.4*);
3-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(1,1,2-trimethylpropyl)benzamide (Compound 7.5*);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(1,1,2-trimethylpropyl)pyridine-2-carboxamide (Compound 7.6);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-isopropyl-pyridine-2-carboxamide (Compound 7.7);
3-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(4-methyltetrahydropyran-4-yl)benzamide (Compound 7.8*);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(4-methyltetrahydropyran-4-yl)pyridine-2-carboxamide (Compound 7.9);
3-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(1-methylcyclobutyl)benzamide (Compound 7.10*);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-tetrahydropyran-4-yl-pyridine-2-carboxamide (Compound 7.11);
4-[2-(5-Chloro-2-hydroxyphenyl)acetamido]-N-[(1s,4s)-4-hydroxycyclohexyl]pyridine-2-carboxamide (Compound 7.12);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-sec-butyl-pyridine-2-carboxamide (Compound 7.13);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(2-hydroxy-1,1,2-trimethylpropyl)pyridine-2-carboxamide (Compound 7.14);
N-(3-Bicyclo[1.1.1]pentanyl)-4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 7.15);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(1-cyanocyclobutyl)pyridine-2-carboxamide (Compound 7.16);
tert-Butyl-3-[[3-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]benzoyl]amino] piperidine-1-carboxylate (Compound 8*);
tert-Butyl-3-[[4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carbonyl]amino]piperidine-1-carboxylate (Compound 8.1);
tert-Butyl 4-[[3-[[2-(5-chloro-2-hydroxy-phenyl) acetyl]amino]benzoyl]amino]-4-methylpiperidine-1-carboxylate (Compound 8.2*);
tert-Butyl (1r,5s,6s)-6-{4-[2-(5-chloro-2-hydroxyphenyl)acetamido]pyridine-2-amido}-3-azabicyclo[3.1.0]hexane-3-carboxylate (Compound 8.3);
N-tert-Butyl-3-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]-4-fluoro-benzamide (Compound 9*);
N-tert-Butyl-3-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]-5-methyl-benzamide (Compound 9.1*);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1,1-dimethylpropyl)pyridine-2-carboxamide (Compound 9.2);
N-tert-Butyl-4-[[2-(5-tert-butyl-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 10);
N-tert-Butyl-5-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]-2-hydroxy-benzamide (Compound 11*);
N-tert-Butyl-3-[[2-(5-cyano-2-hydroxy-phenyl)acetyl]amino]benzamide (Compound 12*);
Methyl 3-[2-[[2-(tert-butylcarbamoyl)-4-pyridyl]amino]-2-oxo-ethyl]-4-hydroxy-benzoate (Compound 13);
N-tert-Butyl-3-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]-4-hydroxy-benzamide (Compound 14*);
N-tert-Butyl-4-[[2-(2-hydroxy-5-methyl-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 15);
N-tert-Butyl-3-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]-4-methoxy-benzamide (Compound 16*);
N-tert-Butyl-5-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]-2-fluoro-benzamide (Compound 17*);
N-tert-Butyl-3-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]-5-fluoro-benzamide (Compound 18*);
N-tert-Butyl-4-[[2-(3-hydroxy-2-pyridyl)acetyl]amino]pyridine-2-carboxamide (Compound 19);
N-tert-Butyl-4-[[2-(5-fluoro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 20);
N-tert-Butyl-4-[[(1R) or (1S)-indane-1-carbonyl]amino]pyridine-2-carboxamide (Compound 21a);
N-tert-Butyl-4-[[(1R) or (1S)-indane-1-carbonyl]amino]pyridine-2-carboxamide (Compound 21b) ;
N-tert-Butyl-4-[(2-phenylacetyl)amino]pyridine-2-carboxamide (Compound 22);
4-(3,3-Dimethylbutanoylamino)-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide (Compound 22.1);
4-[(2-Cyclopentylacetyl)amino]-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide (Compound 22.2);
4-[[2-(3-Chloro-4-pyridyl)acetyl]amino]-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide (Compound 22.3);
4-[[2-(4-Chlorophenyl)acetyl]amino]-N-(1-cyanocyclopropyl)pyridine-2-carboxamide (Compound 23);
4-[[2-(3-Chlorophenyl)acetyl] amino]-N-(1-cyanocyclo propyl)pyridine-2-carboxamide (Compound 23.1);
4-[[2-(2-Chloro-5-fluoro-phenyl) acetyl] amino]-N-(1-cyanocyclo propyl)pyridine-2-carboxamide (Compound 23.2);
N-tert-Butyl-4-(indane-2-carbonyl amino)pyridine-2-carboxamide (Compound 23.3);
N-tert-Butyl-4-[[2-[2-(difluoromethoxy) phenyl]acetyl]amino]pyridine-2-carboxamide (Compound 23.4);
N-tert-Butyl-4-[[2-[2-(difluoromethyl) phenyl]acetyl]amino]pyridine-2-carboxamide (Compound 23.5);
N-tert-Butyl-4-[[2-(3,4-difluorophenyl) acetyl]amino]pyridine-2-carboxamide (Compound 23.6);
N-tert-Butyl-4-[[2-(3,5-difluorophenyl) acetyl]amino]pyridine-2-carboxamide (Compound 23.7);
N-tert-Butyl-4-[[2-(2,3-difluorophenyl) acetyl]amino]pyridine-2-carboxamide (Compound 23.8);
4-[[2-(2-Chlorophenyl)acetyl]amino]-N-tetrahydropyran-4-yl-pyridine-2-carboxamide (Compound 23.9);
N-(1-Cyanocyclobutyl)-4-[[2-(6-quinolyl) acetyl]amino]pyridine-2-carboxamide (Compound 23.11);
N-tert-Butyl-4-[[2-[2-(trifluoromethyl) phenyl]acetyl]amino]pyridine-2-carboxamide (Compound 23.12);

4-[[2-(2-Bromophenyl)acetyl]amino]-N-tert-butyl-pyridine-2-carboxamide (Compound 23.13);
N-tert-Butyl-4-[[2-(2-cyanophenyl) acetyl]amino]pyridine-2-carboxamide (Compound 23.14);
4-[[2-(2-Chlorophenyl)acetyl]amino]-N-(4-cyanotetrahydropyran-4-yl)pyridine-2-carboxamide (Compound 23.15);
N-(4-Cyanotetrahydropyran-4-yl)-4-[[2-(6-quinolyl)acetyl]amino]pyridine-2-carboxamide (Compound 23.16);
4-[[2-(2-Chloro-5-methoxy-phenyl)acetyl] amino]-N-(1-cyanocyclopropyl)pyridine-2-carboxamide (Compound 24);
N-(3-Bicyclo[1.1.1]pentanyl)-4-[[2-(5-tert-butyl-2-hydroxy-phenyl)acetyl]amino] pyridine-2-carboxamide (Compound 25);
-[[2-(5-tert-Butyl-2-hydroxy-phenyl)acetyl]amino]-N-(4-cyanotetrahydropyran-4-yl)pyridine-2-carboxamide (Compound 25.1);
N-tert-Butyl-4-[[2-(2-hydroxy-5-phenyl-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 26);
N-tert-Butyl-4-[[2-[5-chloro-2-hydroxy-4-(pyrrolidin-1-ylmethyl)phenyl]acetyl] amino]pyridine-2-carboxamide (Compound 27);
N-tert-Butyl-4-[[2-[4-[(tert-butylamino)methyl]-5-chloro-2-hydroxyphenyl]acetyl]amino]pyridine-2-carboxamide (Compound 27.1);
N-tert-Butyl-4-[[2-[5-chloro-2-hydroxy-4-(morpholinomethyl)phenyl]acetyl]amino]pyridine-2-carboxamide (Compound 27.2);
N-tert-Butyl-4-[[2-[5-chloro-4-[(3,3-difluoropyrrolidin-1-yl)methyl]-2-hydroxyphenyl]acetyl]amino]pyridine-2-carboxamide (Compound 27.3);
N-tert-butyl-4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]-5-fluoro-pyridine-2-carboxamide (Compound 28);
N-tert-Butyl-4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]-3-fluoro-pyridine-2-carboxamide (Compound 28.1);
4-[[2-(2-Chlorophenyl)acetyl]amino]-N-(1-cyanocyclobutyl)pyridine-2-carboxamide (Compound 30);
4-[[2-(2-Chlorophenyl)acetyl]amino]-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide (Compound 30.1);
4-[[2-(2-Chlorophenyl)acetyl]amino]-N-(4-fluoro-1-bicyclo[2.1.1]hexanyl)pyridine-2-carboxamide (Compound 30.2);
4-[[2-(2-Chlorophenyl)acetyl]amino]-N-(1-cyclopropyl-1-methyl-ethyl)pyridine-2-carboxamide (Compound 30.3);
4-[[2-(2-Chlorophenyl)acetyl]amino]-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide (Compound 30.3a);
4-[[2-(2-Chlorophenyl)acetyl]amino]-N-(1-methyl-3-bicyclo[1.1.1] pentanyl)pyridine-2-carboxamide (Compound 30.4);
4-[[2-(2-Chlorophenyl)acetyl]amino]-N-(1-cyano-3-bicyclo[1.1.1]pentanyl) pyridine-2-carboxamide (Compound 30.5);
4-[[2-(2-Chlorophenyl)acetyl]amino]-N-(2,2-difluorocyclopropyl)pyridine-2-carboxamide (Compound 30.6);
4-[[2-(2-Chlorophenyl)acetyl]amino]-N-(1-cyanocyclopropyl)pyridine-2-carboxamide (Compound 30.7);
4-[[2-(2-Clorophenyl)acetyl]amino]-N-(1-methylcyclopropyl)pyridine-2-carboxamide (Compound 30.8);
4-[[2-(2-Chlorophenyl)acetyl]amino]-N-(3-fluoro-1-bicyclo[1.1.1]pentanyl)pyridine-2-carboxamide (Compound 30.9);
4-[[2-(2-Chlorophenyl)acetyl]amino]-N-(2-fluoro-1,1-dimethyl-ethyl)pyridine-2-carboxamide (Compound 30.10);
4-[[2-(2-Chlorophenyl)acetyl]amino]-N-(4-ethynyltetrahydropyran-4-yl)pyridine-2-carboxamide (Compound 30.11);
4-[[2-(2-Chlorophenyl)acetyl]amino]-N-(1-cyanocyclopentyl)pyridine-2-carboxamide (Compound 30.12);
4-[[2-(2-Chlorophenyl)acetyl]amino]-N-(2,2-difluoro-1,1-dimethyl-ethyl)pyridine-2-carboxamide (Compound 30.13);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(4-cyanotetrahydropyran-4-yl)pyridine-2-carboxamide (Compound 31);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1-ethynylcyclopentyl)pyridine-2-carboxamide (Compound 31.2);
4-[2-(5-Chloro-2-hydroxyphenyl)acetamido]-N-[(1s,2s)-2-hydroxycyclohexyl] pyridine-2-carboxamide (Compound 31.3);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[(1S,2S)-2-hydroxycyclo hexyl]pyridine-2-carboxamide or
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[(1R,2R)-2-hydroxycyclohexyl]pyridine-2-carboxamide (Compound 31.3a);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(4-ethynyltetrahydropyran-4-yl)pyridine-2-carboxamide (Compound 31.4);
N-[(6-Amino-2-pyridyl)methyl]-4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl] amino]pyridine-2-carboxamide (Compound 32);
12-[[4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carbonyl] amino]dodecanoic acid (Compound 32.1);
4-[[2-(5-Chloro-2-hydroxy-phenyl) acetyl]amino]-N-(3-pyridylmethyl)pyridine-2-carboxamide (Compound 32.2);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(2-pyridylmethyl)pyridine-2-carboxamide (Compound 32.3);
4-[[2-(5-Chloro-2-hydroxy-phenyl) acetyl]amino]-N-(4-pyridylmethyl)pyridine-2-carboxamide (Compound 32.4);
4-[[2-(5-Chloro-2-hydroxy-phenyl) acetyl]amino]-N-[(2-hydroxyphenyl) methyl]pyridine-2-carboxamide (Compound 32.5);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(1,1-dimethyl-2-morpholinoethyl)pyridine-2-carboxamide (Com-

pound 32.6);
4-[[2-(5-Chloro-2-hydroxy-phenyl) acetyl]amino]-N-(2-hydroxy-1,1-dimethylethyl)pyridine-2-carboxamide (Compound 32.7);
4-[[2-(5-Chloro-2-hydroxy-phenyl) acetyl] amino]-N-(3,3-difluoro-4-piperidyl)pyridine-2-carboxamide (Compound 32.8);
4-[[2-(5-Chloro-2-hydroxy-phenyl) acetyl]amino]-N-(1H-imidazol-2-yl)pyridine-2-carboxamide (Compound 32.9);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[(1R,2R)-2-hydroxycyclopentyl] pyridine-2-carboxamide (Compound 33);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide (Compound 34);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[3-(hydroxymethyl) tetrahydrofuran-3-yl]pyridine-2-carboxamide (Compound 35);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[(3R)-3-(hydroxymethyl)tetrahydro furan-3-yl]pyridine-2-carboxamide or 4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]-N-[(3S)-3-(hydroxymethyl)tetrahydrofuran-3-yl]pyridine-2-carboxamide (Compound 35a);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[(3R)-3-(hydroxymethyl)tetrahydro furan-3-yl]pyridine-2-carboxamide or 4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]-N-[(3S)-3-(hydroxymethyl)tetrahydrofuran-3-yl]pyridine-2-carboxamide (Compound 35b);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(4-hydroxy-4-methyl-cyclohexyl) pyridine-2-carboxamide as a 6:4 mixture of stereoisomers (Compound 35.1);
4-[[2-(5-Chloro-2-hydroxy-phenyl) acetyl]amino]-N-[(1s,2r)-2-(hydroxy methyl)cyclohexyl]pyridine-2-carboxamide (Compound 35.2);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-[(1s,3r)-3-hydroxycyclopentyl] pyridine-2-carboxamide (Compound 35.3);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-[2-hydroxy-1-(hydroxy methyl)-1-methyl-ethyl]pyridine-2-carboxamide (Compound 35.4);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(3-hydroxycyclohexyl)pyridine-2-carboxamide as a mixture of stereoisomers (Compound 35.6);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(3-phenoxypropyl)pyridine-2-carboxamide (Compound 35.7);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(1-methylcyclo propyl)pyridine-2-carboxamide (Compound 35.8);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-[1-methyl-1-(2-pyridyl) ethyl]pyridine-2-carboxamide (Compound 35.9);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(3-phenylpropyl)pyridine-2-carboxamide (Compound 35.10);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-[2-hydroxy-1-(2-pyridyl)ethyl] pyridine-2-carboxamide (Compound 35.11);
4-[[2-(5-Chloro-2-hydroxy-phenyl) acetyl]amino]-N-[(5-methoxy-2-pyridyl)methyl]pyridine-2-carboxamide (Compound 35.12);
Ethyl 3-[[4-[[2-(5-chloro-2-hydroxy-phenyl) acetyl]amino]pyridine-2-carbonyl]amino]-3-methyl-butanoate (Compound 35.13);
4-[[2-(5-Chloro-2-hydroxy-phenyl) acetyl]amino]-N-(3-hydroxy-1,1-dimethylpropyl)pyridine-2-carboxamide (Compound 35.14);
N-Benzyl-4-[[2-(5-chloro-2-hydroxy-phenyl) acetyl]amino]pyridine-2-carboxamide (Compound 35.15);
4-[[2-(5-Chloro-2-hydroxy-phenyl) acetyl]amino]-N-phenyl-pyridine-2-carboxamide (Compound 35.16);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-[(1S,2S)-2-hydroxycyclopentyl]pyridine-2-carboxamide (Compound 35.17);
4-[[2-(5-Chloro-2-hydroxy-phenyl) acetyl]amino]-N-[(1R,2S)-2-hydroxy cyclopentyl]pyridine-2-carboxamide (Compound 35.18);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-[(1S,2R)-2-hydroxy cyclopentyl]pyridine-2-carboxamide (Compound 35.19);
3-[[2-(5-Fluoro-2-hydroxy-phenyl)acetyl] amino]-N-(1-methylcyclohexyl)benzamide (Compound 35.20*);
N-(1,1-Dimethylprop-2-ynyl)-3-[[2-(5-fluoro-2-hydroxy-phenyl)acetyl]amino]benzamide (Compound 35.21*);
N-Cyclohexyl-3-[[2-(5-fluoro-2-hydroxy-phenyl)acetyl]amino]benzamide (Compound 35.22*);
3-[[2-(5-Fluoro-2-hydroxy-phenyl)acetyl] amino]-N-[3-(hydroxymethyl)tetrahydro furan-3-yl]benzamide (Compound 35.23*);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1-ethynylcyclohexyl)pyridine-2-carboxamide (Compound 35.24);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[1-(hydroxymethyl)cyclobutyl]pyridine-2-carboxamide (Com-

pound 35.25);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[3-(hydroxymethyl)oxetan-3-yl]pyridine-2-carboxamide (Compound 35.26);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1-cyano-2-methoxy-1-methylethyl)pyridine-2-carboxamide (Compound 35.27);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[(1-hydroxycyclobutyl)methyl]pyridine-2-carboxamide (Compound 35.28);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide (Compound 36);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1-cyano-1,2-dimethyl-propyl)pyridine-2-carboxamide (Compound 37);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1-methylcyclopentyl)pyridine-2-carboxamide (Compound 38);
N-(4-tert-Butylcyclohexyl)-4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 39);
N-tert-Butyl-4-[[2-(2-chloro-3-fluoro-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 40);
N-tert-Butyl-4-[[2-(2-chloro-5-fluoro-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 40.1);
N-(4-Cyanotetrahydropyran-4-yl)-3-[[2-(5-fluoro-2-hydroxy-phenyl)acetyl]amino] benzamide (Compound 41*);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[4-(2-hydroxyethyl) tetrahydropyran-4-yl]pyridine-2-carboxamide (Compound 42);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[1,1-dimethyl-3-(2,2,2-trifluoro ethylamino)propyl]pyridine-2-carboxamide (Compound 43);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(4-fluoro-1-bicyclo[2.1.1] hexanyl)pyridine-2-carboxamide (Compound 44);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[3-(2,2-dimethylpropanoyl amino)-1,1-dimethyl-propyl]pyridine-2-carboxamide (Compound 45);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1-cyano-2-hydroxy-1-methylethyl)pyridine-2-carboxamide (Compound 46);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[(1S)-1-cyano-2-hydroxy-1-methylethyl]pyridine-2-carboxamide or 4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]-N-[(1R)-1-cyano-2-hydroxy-1-methyl-ethyl]pyridine-2-carboxamide (Compound 46a);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[(1S)-1-cyano-2-hydroxy-1-methylethyl]pyridine-2-carboxamide or 4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]-N-[(1R)-1-cyano-2-hydroxy-1-methyl-ethyl]pyridine-2-carboxamide (Compound 46b);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(3-cyanotetrahydrofuran-3-yl)pyridine-2-carboxamide (Compound 47);
Methyl2-[4-[[4-[[2-(5-chloro-2-hydroxy-phenyl) acetyl]amino]pyridine-2-carbonyl]amino]tetrahydropyran-4-yl]acetate (Compound 47.1);
Methyl 4-[[4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carbonyl] amino]tetrahydropyran-4-carboxylate (Compound 47.2);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(3-cyanooxetan-3-yl)pyridine-2-carboxamide (Compound 47.3);
4-[[2-(5-Fluoro-2-hydroxy-phenyl)acetyl]amino]-N-(1-methylcyclobutyl)pyridine-2-carboxamide (Compound 48);
N-(4-Cyanotetrahydropyran-4-yl)-4-[[2-(5-fluoro-2-hydroxy-phenyl)acetyl]amino] pyridine-2-carboxamide (Compound 48.1);
N-[3-(tert-Butylamino)-1,1-dimethyl-3-oxo-propyl]-4-[[2-(5-chloro-2-hydroxy-phenyl) acetyl]amino]pyridine-2-carboxamide (Compound 49);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[3-(methanesulfonamido)-1,1-dimethyl -propyl]pyridine-2-carboxamide (Compound 50);
N-(3-Acetamido-1,1-dimethyl-propyl)-4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl] amino]pyridine-2-carboxamide (Compound 51);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[4-(hydroxymethyl)tetrahydro pyran-4-yl]pyridine-2-carboxamide (Compound 53);
N-tert-Butyl-4-[[2-[3-(1-hydroxyethyl)phenyl]acetyl]amino]pyridine-2-carboxamide (Compound 54);
N-tert-Butyl-5-chloro-4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 55);
N-tert-Butyl-4-[[2-[5-chloro-2-[(4-methoxyphenyl)methoxy]phenyl]acetyl] amino]pyridine-2-carboxamide (Compound 56);
N-tert-butyl-4-[[(1S) or (1R)-4-chloro-7-hydroxy-indane-1-carbonyl]amino]pyridine-2-carboxamide (Compound 57a);
N-tert-butyl-4-[[(1S) or (1R)-4-chloro-7-hydroxy-indane-1-carbonyl]amino]pyridine-2-carboxamide (Compound 57b);

N-tert-Butyl-4-[[2-(2-cyclopropylphenyl)acetyl]amino]pyridine-2-carboxamide (Compound 58);
4-[[2-(3-Bromo-5-chloro-2-hydroxy-phenyl)acetyl]amino]-N-tert-butyl-pyridine-2-carboxamide (Compound 59);
N-(4-Fluoro-1-bicyclo[2.1.1]hexanyl)-4-[[2-(2-fluorophenyl)acetyl]amino]pyridine-2-carboxamide (Compound 60);
N-(1-Cyano-2-hydroxy-1-methyl-ethyl)-4-[[2-(2-fluorophenyl)acetyl]amino]pyridine-2-carboxamide (Compound 60.1);
N-(1,1-Dimethylprop-2-ynyl)-4-[[2-(2-fluorophenyl)acetyl]amino]pyridine-2-carboxamide (Compound 60.2);
N-tert-Butyl-4-[[2-(5-chloro-2-hydroxy-3-isopropyl-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 61);
N-tert-Butyl-4-[[2-[5-chloro-2-hydroxy-3-(1-methoxyethyl)phenyl]acetyl]amino] pyridine-2-carboxamide (Compound 62);
4-[[2-(6-Quinolyl)acetyl]amino]-N-tetrahydropyran-4-yl-pyridine-2-carboxamide (Compound 63);
4-(Benzylcarbamoylamino)-N-tert-butyl-pyridine-2-carboxamide (Compound 64);
N-tert-Butyl-4-(cyclohexylmethylcarbamoyl amino)pyridine-2-carboxamide (Compound 64.1);
N-tert-Butyl-4-(2-phenylethylcarbamoyl amino)pyridine-2-carboxamide (Compound 64.2);
N-tert-Butyl-4-[[(1R)-1-phenylethyl]carbamoyl amino]pyridine-2-carboxamide (Compound 64.3);
N-tert-Butyl-4-[[(1S)-1-phenylethyl] carbamoylamino]pyridine-2-carboxamide (Compound 64.4);
N-tert-Butyl-4-[(2-chlorophenyl) methylcarbamoylamino]pyridine-2-carboxamide (Compound 64.5);
N-tert-butyl-4-(1H-indol-3-ylcarbamoyl amino)pyridine-2-carboxamide (Compound 64.6);
N-tert-Butyl-4-[(3-chlorophenyl)methyl carbamoylamino]pyridine-2-carboxamide (Compound 64.7);
N-tert-butyl-4-[(4-chlorophenyl)methyl carbamoylamino]pyridine-2-carboxamide (Compound 64.8);
N-tert-Butyl-4-[(2-hydroxyphenyl)carbamoylamino]pyridine-2-carboxamide (Compound 65);
N-tert-Butyl-4-[(2-methoxyphenyl)methylcarbamoylamino]pyridine-2-carboxamide (Compound 65.1);
N-tert-Butyl-4-[(2-hydroxyphenyl)methylcarbamoylamino]pyridine-2-carboxamide (Compound 65.2);
N-tert-Butyl-4-[(3-hydroxyphenyl)methylcarbamoylamino]pyridine-2-carboxamide (Compound 65.3);
N-tert-Butyl-4-[(4-hydroxyphenyl)methylcarbamoylamino]pyridine-2-carboxamide (Compound 65.4);
N-tert-Butyl-4-[[2-[2-hydroxy-5-(1-hydroxyethyl)phenyl]acetyl]amino]pyridine-2-carboxamide (Compound 66);
N-tert-Butyl-4-[[2-[2-hydroxy-5-[1-(2,2,2-trifluoroethylamino)ethyl]phenyl] acetyl]amino]pyridine-2-carboxamide (Compound 67);
N-tert-Butyl-4-[[2-[3-(cyanomethyl)phenyl]acetyl]amino]pyridine-2-carboxamide (Compound 68);
N-tert-Butyl-4-[[2-[3-(methoxymethyl)phenyl]acetyl]amino]pyridine-2-carboxamide (Compound 69);
N-tert-Butyl-4-[[2-[2-hydroxy-5-(morpholinomethyl)phenyl]acetyl]amino]pyridine-2-carboxamide (Compound 70);
3-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(3-cyanotetrahydrofuran-3-yl)benzamide (Compound 71*);
3-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1-methylcyclohexyl)benzamide (Compound 71.1*);
4-[[2-(5-Fluoro-2-hydroxy-phenyl)acetyl]amino]-N-[3-(hydroxymethyl)tetrahydro furan-3-yl]pyridine-2-carboxamide (Compound 72);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[1-(hydroxymethyl)-2-methoxy-1-methyl-ethyl]pyridine-2-carboxamide (Compound 73);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1,1-dimethylbut-2-ynyl) pyridine-2-carboxamide (Compound 73.1);
3-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1,1-dimethylprop-2-ynyl)benzamide (Compound 74*);
3-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[3-(hydroxymethyl)tetra hydrofuran-3-yl]benzamide (Compound 74.1*);
N-tert-Butyl-4-[[2-[2-hydroxy-5-(3-hydroxypropyl)phenyl]acetyl]amino]pyridine-2-carboxamide (Compound 75);
4-[[2-(5-Chloro-4-fluoro-2-hydroxy-phenyl)acetyl]amino]-N-(1-methylcyclo butyl)pyridine-2-carboxamide (Compound 76);
4-[[2-(2,5-Difluorophenyl)acetyl]amino]-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide (Compound 77);
4-[[2-(2,5-Difluorophenyl)acetyl]amino]-N-(4-fluoro-1-bicyclo[2.1.1]hexanyl) pyridine-2-carboxamide (Compound 77.1);
4-[[2-(4-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide (Compound 78);
N-(1,1-Dimethylprop-2-ynyl)-4-[[2-[2-hydroxy-4-(trifluoromethyl)phenyl]acetyl] amino]pyridine-2-carboxamide (Compound 78.1);
N-(1,1-Dimethylprop-2-ynyl)-4-[[2-[2-hydroxy-5-(trifluoromethyl)phenyl]acetyl] amino]pyridine-2-carboxamide (Compound 78.2);
4-[(2-Chroman-4-ylacetyl)amino]-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide (Compound 79);
N-(1,1 -Dimethylprop-2-ynyl)-4-[[2-(1 -isopropyl-3,5-dimethyl-pyrazol-4-yl)acetyl] amino]pyridine-2-carboxamide (Compound 79.1);
N-(1,1-Dimethylprop-2-ynyl)-4-[[2-(1H-indazol-4-yl)acetyl]amino]pyridine-2-carboxamide (Compound 79.2);
N-(1,1-Dimethylprop-2-ynyl)-4-[[2-(1H-indol-7-yl)acetyl]amino]pyridine-2-carboxamide (Compound 79.3);

3-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(4-cyanotetrahydropyran-4-yl) benzamide (Compound 80*);
N-(1-Cyano-1-methyl-ethyl)-4-[[2-(5-fluoro-2-hydroxy-phenyl)acetyl]amino] pyridine-2-carboxamide (Compound 81);
N-(1-Cyano-2-hydroxy-1-methyl-ethyl)-4-[[2-(5-fluoro-2-hydroxy-phenyl)acetyl]amino] pyridine-2-carboxamide (Compound 81.1);
4-[[2-(5-Fluoro-2-hydroxy-phenyl)acetyl]amino]-N-isopropyl-pyridine-2-carboxamide (Compound 81.2);
N-(1,1-Dimethylprop-2-ynyl)-4-[[2-(5-fluoro-2-hydroxy-phenyl)acetyl]amino] pyridine-2-carboxamide (Compound 81.3);
N-(4-Fluoro-1-bicyclo[2.1.1]hexanyl)-4-[[2-(5-fluoro-2-hydroxy-phenyl)acetyl]amino] pyridine-2-carboxamide (Compound 81.4);
4-[[2-(5-Fluoro-2-hydroxy-phenyl)acetyl]amino]-N-[1-(hydroxymethyl)cyclobutyl] pyridine-2-carboxamide (Compound 81.5);
N-tert-Butyl-6-[[2-(5-chloro-2-methoxy-phenyl)acetyl]amino]pyrimidine-4-carboxamide (Compound 82*);
N-(1-Cyano-1-methyl-ethyl)-4-(thiophene-3-carbonylamino)pyridine-2-carboxamide (Compound 83);
N-(1-Cyano-1-methyl-ethyl)-4-[(2-cyclohexylacetyl) amino]pyridine-2-carboxamide (Compound 83.1);
N-(1-Cyano-1-methyl-ethyl)-4-(cyclohexane carbonylamino)pyridine-2-carboxamide (Compound 83.2);
N-(1-Cyano-1-methyl-ethyl)-4-[(3,3-difluorocyclo pentanecarbonyl)amino]pyridine-2-carboxamide (Compound 83.3);
N-(1-Cyano-1-methyl-ethyl)-4-[(1-methylcyclo pentanecarbonyl)amino]pyridine-2-carboxamide (Compound 83.4);
N-(1-Cyano-1-methyl-ethyl)-4-(3-cyclohexyl propanoylamino)pyridine-2-carboxamide (Compound 83.5);
4-(2-{Bicyclo[2.2.1]heptan-2-yl}acetamido)-N-(1-cyano-1-methylethyl)pyridine-2-carboxamide (Compound 83.6);
N-(1-Cyano-1-methyl-ethyl)-4-[[2-(1-methylcyclo hexyl)acetyl]amino]pyridine-2-carboxamide (Compound 83.7);
N-[2-[(1-Cyano-1-methyl-ethyl)carbamoyl]-4-pyridyl]-2-cyclopropyl-pyrimidine-5-carboxamide (Compound 83.8);
N-[2-[(1-Cyano-1-methyl-ethyl)carbamoyl]-4-pyridyl]-3-isobutyl-isoxazole-5-carboxamide (Compound 83.9);
N-(1-Cyano-1-methyl-ethyl)-4-[[2-(4,4-difluorocyclo hexyl)acetyl]amino]pyridine-2-carboxamide (Compound 83.10);
4-[(1-Benzylcyclopropanecarbonyl)amino]-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide (Compound 83.11);
N-(1-Cyano-1-methyl-ethyl)-4-[3-(2-methoxy-4-pyridyl)propanoylamino]pyridine-2-carboxamide (Compound 83.13);
4-[(5-tert-Butyl-2-methyl-pyrazole-3-carbonyl)amino]-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide (Compound 83.14);
N-(1-Cyano-1-methyl-ethyl)-4-[(2-pyrazol-1-ylbenzoyl)amino]pyridine-2-carboxamide (Compound 83.15);
N-[2-[(1-Cyano-1-methyl-ethyl)carbamoyl]-4-pyridyl]-6-(trifluoromethyl)pyridine-2-carboxamide (Compound 83.16);
N-[2-[(1-Cyano-1-methyl-ethyl)carbamoyl]-4-pyridyl]-3-oxo-4H-1,4-benzoxazine-7-carboxamide (Compound 83.17);
N-[2-[(1-Cyano-1-methyl-ethyl)carbamoyl]-4-pyridyl]-1-ethyl-indole-2-carboxamide (Compound 83.18);
N-(1-Cyano-1-methyl-ethyl)-4-[[2-(2,2,2-trifluoroethyl)pyrazole-3-carbonyl]amino]pyridine-2-carboxamide (Compound 83.19);
N-[2-[(1-Cyano-1-methyl-ethyl)carbamoyl]-4-pyridyl]-3-phenyl-isoxazole-4-carboxamide (Compound 83.20);
4-[(1-Benzylpyrazole-4-carbonyl)amino]-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide (Compound 83.21);
N-(1-Cyano-1-methyl-ethyl)-4-[(2-methyl-5-phenyl-pyrazole-3-carbonyl)amino]pyridine-2-carboxamide (Compound 83.22);
N-(1-Cyano-1-methyl-ethyl)-4-[[2-(3-methyl-1,2,4-oxadiazol-5-yl)benzoyl]amino]pyridine-2-carboxamide (Compound 83.23);
N-(1-Cyano-1-methyl-ethyl)-4-[(3-methyl-1-phenyl-pyrazole-4-carbonyl)amino]pyridine-2-carboxamide (Compound 83.24);
N-[2-[(1-Cyano-1-methyl-ethyl)carbamoyl]-4-pyridyl]-2-phenoxy-pyridine-3-carboxamide (Compound 83.25);
N-(1-Cyano-1-methyl-ethyl)-4-[[2,5-dimethyl-1-(2-thienylmethyl)pyrrole-3-carbonyl]amino]pyridine-2-carboxamide (Compound 83.26);
N-[2-[(1-Cyano-1-methyl-ethyl)carbamoyl]-4-pyridyl]-5-(2-methoxyphenyl)isoxazole-3-carboxamide (Compound 83.27);
N-[2-[(1-Cyano-1-methyl-ethyl)carbamoyl]-4-pyridyl]-4-methyl-2-phenyl-thiazole-5-carboxamide (Compound 83.28);
4-[(4-Acetamidobenzoyl)amino]-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide (Compound 83.29);
N-[2-[(1-Cyano-1-methyl-ethyl)carbamoyl]-4-pyridyl]-1,3-benzothiazole-7-carboxamide (Compound 83.30);
N-(1-Cyano-1-methyl-ethyl)-4-[3-(4-fluorophenyl) butanoylamino]pyridine-2-carboxamide (Compound 83.31);
N-[2-[(1-Cyano-1-methyl-ethyl)carbamoyl]-4-pyridyl]-1-methyl-2-oxo-quinoline-3-carboxamide (Compound 83.32);
N-tert-Butyl-3-[[2-(2-hydroxycyclohexyl)acetyl]amino]benzamide (Compound 84*);

N-tert-Butyl-6-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]pyrimidine-4-carboxamide (Compound 85*);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[1-cyano-2-methoxy-1-(methoxy methyl)ethyl]pyridine-2-carboxamide (Compound 86);
4-[[2-(3-Amino-4-tert-butyl-phenyl)acetyl]amino]-N-tert-butyl-pyridine-2-carboxamide (Compound 87);
4-[[2-(2-Amino-4-tert-butyl-phenyl)acetyl]amino]-N-tert-butyl-pyridine-2-carboxamide (Compound 88);
N-tert-Butyl-4-[[2-(4-tert-butyl-3-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 89);
N-tert-Butyl-4-[[2-(4-tert-butyl-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 90);
N-tert-Butyl-4-[[2-(4-tert-butyl-2-fluoro-5-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 91);
4-[[2-(4-Chloro-3-hydroxy-phenyl)acetyl]amino]-N-(4-cyanotetrahydropyran-4-yl)pyridine-2-carboxamide (Compound 92);
4-[[2-(4-Chloro-3-hydroxy-phenyl)acetyl]amino]-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide (Compound 92.1);
4-[[2-(4-Chloro-3-hydroxy-phenyl)acetyl]amino]-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide (Compound 92.2);
4-[[2-(4-Chloro-3-hydroxy-phenyl)acetyl]amino]-N-[(1s,2s)-2-hydroxycyclopentyl]pyridine-2-carboxamide (Compound 92.3);
4-[[2-(4-tert-Butyl-3-hydroxy-phenyl)acetyl]amino]-N-[3-(hydroxymethyl) tetrahydrofuran-3-yl]pyridine-2-carboxamide (Compound 93);
4-[[2-(4-tert-Butyl-3-hydroxy-phenyl)acetyl]amino]-N-[(2S)-2-hydroxycyclohexyl]pyridine-2-carboxamide (Compound 93.1);
4-[[2-(4-tert-Butyl-3-hydroxy-phenyl)acetyl]amino]-N-[(2S)-2-hydroxycyclopentyl]pyridine-2-carboxamide (Compound 93.2);
4-[[2-(4-tert-Butyl-3-hydroxy-phenyl)acetyl]amino]-N-(4-cyanotetrahydropyran-4-yl)pyridine-2-carboxamide (Compound 93.3);
4-[[2-(4-tert-Butyl-3-hydroxy-phenyl)acetyl]amino]-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide (Compound 93.4);
4-[[2-(4-tert-Butyl-3-hydroxy-phenyl)acetyl]amino]-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide (Compound 93.5);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1-methyl-1-phenyl-ethyl) pyridine-2-carboxamide (Compound 94);and salts and solvates of any of the above.

[0133] In some particularly suitable novel compounds of the invention, X^1 is N and X^2 is CH.

[0134] Examples of novel compounds according to the invention are:

(* denotes a reference compound that is not claimed)
N-tert-Butyl-4-[[2-(2-hydroxyphenyl)acetyl]amino]pyridine-2-carboxamide (Compound 1);
N-(1,1-Dimethylpropyl)-3-[[2-(2-hydroxyphenyl)acetyl]amino]benzamide (Compound 1.1*);
N-(1-Adamantyl)-3-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]benzamide (Compound 1.2*);
N-(1-Adamantyl)-4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide(Compound 1.3);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(3-methoxy-1,1-dimethylpropyl)pyridine-2-carboxamide (Compound 1.4);
3-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1,1-dimethyl propyl)benzamide (Compound 1.5*);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1-methylcyclobutyl)pyridine-2-carboxamide (Compound 1.6);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1-methylcyclohexyl)pyridine-2-carboxamide (Compound 1.7);
tert-Butyl N-[3-[[4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carbonyl]amino]-3-methyl-butyl]carbamate (Compound 1.8);
3-[[2-(2-Hydroxyphenyl)acetyl]amino]-N-(2-methoxy-1,1-dimethyl-ethyl)benzamide (Compound 1.9*);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-cyclohexyl-pyridine-2-carboxamide (Compound 1.10);
N-tert-Butyl-3-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]benzamide (Compound 2*);
N-tert-Butyl-3-[[2-(5-fluoro-2-hydroxy-phenyl)acetyl]amino]benzamide (Compound 2.1*);
N-tert-Butyl-3-[[2-(3-fluoro-2-hydroxy-phenyl)acetyl]amino]benzamide (Compound 2.2*);
N-tert-Butyl-3-[[2-(4-fluoro-2-hydroxy-phenyl)acetyl]amino]benzamide (Compound 2.3*);
N-tert-Butyl-3-[[2-(2,6-dihydroxy phenyl)acetyl]amino]benzamide (Compound 2.4*);
N-tert-Butyl-3-[3-(2-hydroxyphenyl)propanamido]benzamide (Compound 2.5*);
N-tert-Butyl-3-[[2-(2-hydroxy-6-methoxy-phenyl)acetyl]amino] benzamide (Compound 2.6*);
N-tert-Butyl-3-[2-(2-hydroxyphenyl)propanamido]benzamide (Compound 2.7*);
N-tert-Butyl-3-[[2-(2-hydroxy-3-methoxy-phenyl)acetyl]amino] benzamide (Compound 2.8*);
N-tert-Butyl-3-[[2-(3,5-difluoro-2-hydroxy-phenyl)acetyl]amino] benzamide (Compound 2.9*);

3-[[2-(5-Bromo-2-hydroxy-phenyl) acetyl]amino]-N-tert-butyl-benzamide (Compound 2.10*);
N-tert-Butyl-3-[[2-(2,3-difluoro-6-hydroxy-phenyl)acetyl]amino]benzamide (Compound 2.11*);
N-tert-Butyl-3-[[2-(4,5-difluoro-2-hydroxy-phenyl)acetyl]amino] benzamide (Compound 2.12*);
N-(1,1-Dimethylpropyl)-3-[[2-(4-fluoro-2-hydroxy-phenyl)acetyl]amino] benzamide (Compound 2.13*);
N-tert-Butyl-3-[[2-(2-hydroxy-4-methoxy-phenyl)acetyl]amino]benzamide (Compound 2.14*);
N-tert-Butyl-3-[[2-(2-fluoro-6-hydroxy-phenyl)acetyl]amino]benzamide (Compound 2.15*);
N-tert-Butyl-3-[[2-(2,3-dihydroxyphenyl) acetyl]amino]benzamide (Compound 2.16*);
N-tert-Butyl-3-[[2-[2-hydroxy-5-(trifluoro methyl)phenyl]acetyl]amino]benzamide (Compound 2.17*);
Methyl 3-[2-[3-(tert-butylcarbamoyl)anilino]-2-oxo-ethyl]-4-hydroxy-benzoate (Compound 2.18*);
N-tert-Butyl-3-[[2-[2-hydroxy-4-(trifluoro methyl)phenyl]acetyl]amino]benzamide (Compound 2.19*);
N-tert-Butyl-4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 3);
N-(1,1-Dimethylpropyl)-4-[[2-(4-fluoro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 3.1a);
N-tert-Butyl-4-[[2-(4-fluoro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 3.2a);
N-tert-Butyl-4-[[2-(2-chloro-6-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 3.3a);
4-[[2-(4-Bromo-5-chloro-2-hydroxy-phenyl)acetyl]amino]-N-tert-butyl-pyridine-2-carboxamide (Compound 3.4a);
4-[[2-(5-tert-Butyl-2-hydroxy-phenyl)acetyl]amino]-N-(1-cyanocyclobutyl)pyridine-2-carboxamide (Compound 3.5a);
4-[[2-(5-tert-Butyl-2-hydroxy-phenyl)acetyl]amino]-N-(1-methyl cyclobutyl)pyridine-2-carboxamide (Compound 3.6a);
N-tert-butyl-4-[2-(2,5-dibromo-3-fluoro-6-hydroxyphenyl)acetamido]pyridine-2-carboxamide (Compound 3.7a);
N-tert-Butyl-4-[[2-[2-hydroxy-5-(trifluoromethyl)phenyl]acetyl]amino]pyridine-2-carboxamide (Compound 3.5b);
N-tert-Butyl-4-[[2-(4-chloro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 3.6b);
N-tert-Butyl-4-[[2-[2-hydroxy-4-(trifluoro methyl)phenyl]acetyl]amino]pyridine-2-carboxamide (Compound 3.7b);
N-tert-Butyl-4-[[2-(2-hydroxy-5-methoxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 3.8b);
N-tert-Butyl-4-[(6-hydroxyindane-1-carbonyl)amino]pyridine-2-carboxamide (Compound 3.9b);
N-tert-Butyl-4-[(7-hydroxyindane-1-carbonyl)amino]pyridine-2-carboxamide (Compound 3.10b);
N-tert-Butyl-4-[[2-(2,5-dibromo-3-chloro-6-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 3.11b);
N-tert-Butyl-4-[[2-(3-hydroxyphenyl) acetyl]amino]pyridine-2-carboxamide (Compound 3.12b);
N-tert-Butyl-4-[[2-(2-fluoro-5-hydroxy-phenyl) acetyl]amino]pyridine-2-carboxamide (Compound 3.13b);
N-tert-Butyl-4-[[2-(4-chloro-3-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 3.14b);
N-tert-Butyl-4-[[2-(2-chloro-3-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 3.15b);
N-tert-Butyl-4-[[2-(2-chloro-5-hydroxy-phenyl) acetyl]amino]pyridine-2-carboxamide (Compound 3.16b);
N-tert-Butyl-4-[[2-(3-chloro-5-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 3.17b);
N-tert-Butyl-3-[[2-(3-hydroxyphenyl)acetyl]amino]benzamide (Compound 4*);
N-tert-Butyl-3-[[2-(1H-indazol-3-yl)acetyl]amino]benzamide (Compound 4.1*);
N-tert-Butyl-3-[[2-(5-fluoro-1H-indol-3-yl)acetyl]amino]benzamide (Compound 4.2*);
N-tert-Butyl-3-[[2-(2-hydroxyphenyl)acetyl]amino] benzamide (Compound 4.3*)
N-tert-Butyl-4-[[2-(2-thienyl)acetyl]amino]pyridine-2-carboxamide (Compound 5);
4-[[2-(2-Adamantyl)acetyl]amino]-N-tert-butyl-pyridine-2-carboxamide (Compound 5.1);
N-tert-Butyl-4-[[2-(4-fluoro-2-methoxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 5.2);
N-tert-Butyl-4-[[2-(5-chloro-2-fluoro-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 5.3);
N-tert-Butyl-4-[[2-(2-furyl)acetyl]amino] pyridine-2-carboxamide (Compound 5.4);
N-tert-Butyl-4-[[2-(3-chlorophenyl) acetyl]amino]pyridine-2-carboxamide (Compound 5.5);
N-tert-Butyl-4-[[2-(1H-indol-3-yl)acetyl] amino]pyridine-2-carboxamide (Compound 5.6);
N-tert-Butyl-4-[[2-(o-tolyl)acetyl] amino]pyridine-2-carboxamide (Compound 5.7);
N-tert-Butyl-4-[[2-(3,4-dichlorophenyl) acetyl]amino]pyridine-2-carboxamide (Compound 5.8);
N-tert-Butyl-4-[[2-(3-fluorophenyl)acetyl] amino]pyridine-2-carboxamide (Compound 5.9);
N-tert-Butyl-4-[[2-(5-chloro-2-methoxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 5.10);
N-tert-Butyl-4-[[2-(p-tolyl)acetyl] amino]pyridine-2-carboxamide (Compound 5.11);
N-tert-Butyl-4-[[2-(2-fluorophenyl) acetyl]amino]pyridine-2-carboxamide (Compound 5.12);
N-tert-Butyl-4-[[2-(4-fluorophenyl) acetyl]amino]pyridine-2-carboxamide (Compound 5.13);
N-tert-Butyl-4-[[2-(m-tolyl)acetyl] amino]pyridine-2-carboxamide (Compound 5.14);
4-[[2-(1,3-Benzoxazol-6-yl)acetyl] amino]-N-tert-butyl-pyridine-2-carboxamide (Compound 5.15);
N-tert-Butyl-4-[[2-(2-chloro-3-pyridyl) acetyl]amino]pyridine-2-carboxamide (Compound 5.16);
N-tert-Butyl-4-[[2-(2,6-dichlorophenyl) acetyl]amino]pyridine-2-carboxamide (Compound 5.17);
N-tert-Butyl-4-[[2-(4-chloro-3-fluoro-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 5.18);
N-tert-Butyl-4-[[2-(3,5-dichloro phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 5.19);

N-tert-Butyl-4-[[2-(2-chlorophenyl) acetyl]amino]pyridine-2-carboxamide (Compound 5.20);
N-tert-Butyl-4-[[2-(3-chloro-4-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 5.21);
N-tert-Butyl-4-(indane-1-carbonyl amino)pyridine-2-carboxamide (Compound 5.22);
N-tert-Butyl-4-[(2-quinoxalin-6-ylacetyl) amino]pyridine-2-carboxamide (Compound 5.23);
N-tert-Butyl-4-[[2-(2-naphthyl) acetyl]amino]pyridine-2-carboxamide (Compound 5.24);
N-tert-Butyl-4-(2,3-dihydrobenzofuran-3-carbonylamino)pyridine-2-carboxamide (Compound 5.25);
N-tert-Butyl-4-(6,7,8,9-tetrahydro-5H-benzo[7]annulene-5-carbonylamino) pyridine-2-carboxamide (Compound 5.26);
N-tert-Butyl-4-(tetralin-1-carbonylamino) pyridine-2-carboxamide (Compound 5.27);
N-tert-Butyl-4-[[2-(6-quinolyl)acetyl] amino]pyridine-2-carboxamide (Compound 5.29);
N-tert-butyl-4-[[1-(3-chlorophenyl) cyclopropanecarbonyl]amino]pyridine-2-carboxamide (Compound 5.31);
N-tert-Butyl-4-[[2-(2,3-dihydro-1,4-benzodioxin-6-yl)acetyl]amino]pyridine-2-carboxamide (Compound 5.32);
N-(1,1-Dimethylprop-2-ynyl)-4-[(2-isochroman-1-ylacetyl)amino]pyridine-2-carboxamide (Compound 5.33);
4-[[2-(4,4-Difluorocyclohexyl)acetyl]amino]-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide (Compound 5.34);
N-(1,1-Dimethylprop-2-ynyl)-4-[[2-[4-(trifluoromethyl)phenyl]acetyl]amino]pyridine-2-carboxamide (Compound 5.35);
N-(1,1-Dimethylprop-2-ynyl)-4-[[2-[3-(trifluoromethyl)-1H-pyrazol-4-yl]acetyl] amino] pyridine-2-carboxamide (Compound 5.36);
N-(1,1-Dimethylprop-2-ynyl)-4-[[2-[3-(trifluoromethyl)phenyl]acetyl]amino]pyridine-2-carboxamide (Compound 5.37);
N-(1,1-Dimethylprop-2-ynyl)-4-[[2-[2-(trifluoromethyl)phenyl]acetyl]amino]pyridine-2-carboxamide (Compound 5.38);
4-[[2-(2,3-Dihydro-1,4-benzoxazin-4-yl)acetyl]amino]-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide (Compound 5.39);
N-tert-Butyl-4-[[2-(5-cyano-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 6);
3-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1,1,2,2-tetramethylpropyl) benzamide (Compound 7*);
3-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(1,1-dimethylbutyl)benzamide (Compound 7.1*);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(1,1-dimethylbutyl)pyridine-2-carboxamide (Compound 7.2);
3-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-cyclohexyl-benzamide (Compound 7.3*);
3-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-tetrahydropyran-4-yl-benzamide (Compound 7.4*);
3-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(1,1,2-trimethylpropyl)benzamide (Compound 7.5*);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(1,1,2-trimethylpropyl)pyridine-2-carboxamide (Compound 7.6);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-isopropyl-pyridine-2-carboxamide (Compound 7.7);
3-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(4-methyltetrahydropyran-4-yl)benzamide (Compound 7.8*);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(4-methyltetrahydropyran-4-yl)pyridine-2-carboxamide (Compound 7.9);
3-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(1-methylcyclobutyl)benzamide (Compound 7.10*);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-tetrahydropyran-4-yl-pyridine-2-carboxamide (Compound 7.11);
4-[2-(5-Chloro-2-hydroxyphenyl)acetamido]-N-[(1s,4s)-4-hydroxycyclohexyl]pyridine-2-carboxamide (Compound 7.12);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-sec-butyl-pyridine-2-carboxamide (Compound 7.13);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(2-hydroxy-1,1,2-trimethylpropyl)pyridine-2-carboxamide (Compound 7.14);
N-(3-Bicyclo[1.1.1]pentanyl)-4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 7.15);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(1-cyanocyclobutyl)pyridine-2-carboxamide (Compound 7.16);
tert-Butyl-3-[[3-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]benzoyl]amino] piperidine-1-carboxylate (Compound 8*);
tert-Butyl-3-[[4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carbonyl]amino]piperidine-1-carboxylate (Compound 8.1);
tert-Butyl 4-[[3-[[2-(5-chloro-2-hydroxy-phenyl) acetyl]amino]benzoyl]amino]-4-methylpiperidine-1-carboxylate (Compound 8.2*);
tert-Butyl (1r,5s,6s)-6-{4-[2-(5-chloro-2-hydroxyphenyl)acetamido]pyridine-2-amido}-3-azabicyclo[3.1.0]hexane-3-carboxylate (Compound 8.3);
N-tert-Butyl-3-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]-4-fluoro-benzamide (Compound 9*);
N-tert-Butyl-3-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]-5-methyl-benzamide (Compound 9.1*);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1,1-dimethylpropyl)pyridine-2-carboxamide (Compound 9.2);
N-tert-Butyl-4-[[2-(5-tert-butyl-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 10);

N-tert-Butyl-5-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]-2-hydroxy-benzamide (Compound 11*);
N-tert-Butyl-3-[[2-(5-cyano-2-hydroxy-phenyl)acetyl]amino]benzamide (Compound 12*);
Methyl 3-[2-[[2-(tert-butylcarbamoyl)-4-pyridyl]amino]-2-oxo-ethyl]-4-hydroxy-benzoate (Compound 13);
N-tert-Butyl-3-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]-4-hydroxy-benzamide (Compound 14*);
N-tert-Butyl-4-[[2-(2-hydroxy-5-methyl-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 15);
N-tert-Butyl-3-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]-4-methoxy-benzamide (Compound 16*);
N-tert-Butyl-5-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]-2-fluoro-benzamide (Compound 17*);
N-tert-Butyl-3-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]-5-fluoro-benzamide (Compound 18*);
N-tert-Butyl-4-[[2-(3-hydroxy-2-pyridyl)acetyl]amino]pyridine-2-carboxamide (Compound 19);
N-tert-Butyl-4-[[2-(5-fluoro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 20);
N-tert-Butyl-4-[[(1R) or (1S)-indane-1-carbonyl]amino]pyridine-2-carboxamide (Compound 21a);
N-tert-Butyl-4-[[(1R) or (1S)-indane-1-carbonyl]amino]pyridine-2-carboxamide (Compound 21b);
N-tert-Butyl-4-[(2-phenylacetyl)amino]pyridine-2-carboxamide (Compound 22);
4-(3,3-Dimethylbutanoylamino)-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide (Compound 22.1);
4-[(2-Cyclopentylacetyl)amino]-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide (Compound 22.2);
4-[[2-(3-Chloro-4-pyridyl)acetyl]amino]-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide (Compound 22.3);
4-[[2-(4-Chlorophenyl)acetyl]amino]-N-(1-cyanocyclopropyl)pyridine-2-carboxamide (Compound 23);
4-[[2-(3-Chlorophenyl)acetyl] amino]-N-(1-cyanocyclo propyl)pyridine-2-carboxamide (Compound 23.1);
4-[[2-(2-Chloro-5-fluoro-phenyl) acetyl] amino]-N-(1-cyanocyclo propyl)pyridine-2-carboxamide (Compound 23.2);
N-tert-Butyl-4-(indane-2-carbonyl amino)pyridine-2-carboxamide (Compound 23.3);
N-tert-Butyl-4-[[2-[2-(difluoromethoxy) phenyl]acetyl]amino]pyridine-2-carboxamide (Compound 23.4);
N-tert-Butyl-4-[[2-[2-(difluoromethyl) phenyl]acetyl]amino]pyridine-2-carboxamide (Compound 23.5);
N-tert-Butyl-4-[[2-(3,4-difluorophenyl) acetyl]amino]pyridine-2-carboxamide (Compound 23.6);
N-tert-Butyl-4-[[2-(3,5-difluorophenyl) acetyl]amino]pyridine-2-carboxamide (Compound 23.7);
N-tert-Butyl-4-[[2-(2,3-difluorophenyl) acetyl]amino]pyridine-2-carboxamide (Compound 23.8);
4-[[2-(2-Chlorophenyl)acetyl]amino]-N-tetrahydropyran-4-yl-pyridine-2-carboxamide (Compound 23.9);
N-(1-Cyanocyclobutyl)-4-[[2-(6-quinolyl) acetyl]amino]pyridine-2-carboxamide (Compound 23.11);
N-tert-Butyl-4-[[2-[2-(trifluoromethyl) phenyl]acetyl]amino]pyridine-2-carboxamide (Compound 23.12);
4-[[2-(2-Bromophenyl)acetyl]amino]-N-tert-butyl-pyridine-2-carboxamide (Compound 23.13);
N-tert-Butyl-4-[[2-(2-cyanophenyl) acetyl]amino]pyridine-2-carboxamide (Compound 23.14);
4-[[2-(2-Chlorophenyl)acetyl]amino]-N-(4-cyanotetrahydropyran-4-yl)pyridine-2-carboxamide (Compound 23.15);
N-(4-Cyanotetrahydropyran-4-yl)-4-[[2-(6-quinolyl)acetyl]amino]pyridine-2-carboxamide (Compound 23.16);
4-[[2-(2-Chloro-5-methoxy-phenyl)acetyl] amino]-N-(1-cyanocyclopropyl)pyridine-2-carboxamide (Compound 24);
N-(3-Bicyclo[1.1.1]pentanyl)-4-[[2-(5-tert-butyl-2-hydroxy-phenyl)acetyl]amino] pyridine-2-carboxamide (Compound 25);
-[[2-(5-tert-Butyl-2-hydroxy-phenyl)acetyl]amino]-N-(4-cyanotetrahydropyran-4-yl)pyridine-2-carboxamide (Compound 25.1);
N-tert-Butyl-4-[[2-(2-hydroxy-5-phenyl-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 26);
N-tert-Butyl-4-[[2-[5-chloro-2-hydroxy-4-(pyrrolidin-1-ylmethyl)phenyl]acetyl] amino]pyridine-2-carboxamide (Compound 27);
N-tert-Butyl-4-[[2-[4-[(tert-butylamino)methyl]-5-chloro-2-hydroxyphenyl]acetyl]amino]pyridine-2-carboxamide (Compound 27.1);
N-tert-Butyl-4-[[2-[5-chloro-2-hydroxy-4-(morpholinomethyl)phenyl]acetyl]amino]pyridine-2-carboxamide (Compound 27.2);
N-tert-Butyl-4-[[2-[5-chloro-4-[(3,3-difluoropyrrolidin-1-yl)methyl]-2-hydroxyphenyl]acetyl]amino]pyridine-2-carboxamide (Compound 27.3);
N-tert-butyl-4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]-5-fluoro-pyridine-2-carboxamide (Compound 28);
N-tert-Butyl-4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]-3-fluoro-pyridine-2-carboxamide (Compound 28.1);
4-[[2-(2-Chlorophenyl)acetyl]amino]-N-(1-cyanocyclobutyl)pyridine-2-carboxamide (Compound 30);
4-[[2-(2-Chlorophenyl)acetyl]amino]-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide (Compound 30.1);
4-[[2-(2-Chlorophenyl)acetyl]amino]-N-(4-fluoro-1-bicyclo[2.1.1]hexanyl)pyridine-2-carboxamide (Compound 30.2);
4-[[2-(2-Chlorophenyl)acetyl]amino]-N-(1-cyclopropyl-1-methyl-ethyl)pyridine-2-carboxamide (Compound 30.3);
4-[[2-(2-Chlorophenyl)acetyl]amino]-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide (Compound 30.3a);
4-[[2-(2-Chlorophenyl)acetyl]amino]-N-(1-methyl-3-bicyclo[1.1.1] pentanyl)pyridine-2-carboxamide (Compound 30.4);
4-[[2-(2-Chlorophenyl)acetyl]amino]-N-(1-cyano-3-bicyclo[1.1.1]pentanyl) pyridine-2-carboxamide (Compound 30.5);
4-[[2-(2-Chlorophenyl)acetyl]amino]-N-(2,2-difluorocyclopropyl)pyridine-2-carboxamide (Compound 30.6);

4-[[2-(2-Chlorophenyl)acetyl]amino]-N-(1-cyanocyclopropyl)pyridine-2-carboxamide (Compound 30.7);
4-[[2-(2-Clorophenyl)acetyl]amino]-N-(1-methylcyclopropyl)pyridine-2-carboxamide (Compound 30.8);
4-[[2-(2-Chlorophenyl)acetyl]amino]-N-(3-fluoro-1-bicyclo[1.1.1]pentanyl)pyridine-2-carboxamide (Compound 30.9);
4-[[2-(2-Chlorophenyl)acetyl]amino]-N-(2-fluoro-1,1-dimethyl-ethyl)pyridine-2-carboxamide (Compound 30.10);
4-[[2-(2-Chlorophenyl)acetyl]amino]-N-(4-ethynyltetrahydropyran-4-yl)pyridine-2-carboxamide (Compound 30.11);
4-[[2-(2-Chlorophenyl)acetyl]amino]-N-(1-cyanocyclopentyl)pyridine-2-carboxamide (Compound 30.12);
4-[[2-(2-Chlorophenyl)acetyl]amino]-N-(2,2-difluoro-1,1-dimethyl-ethyl)pyridine-2-carboxamide (Compound 30.13);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(4-cyanotetrahydropyran-4-yl)pyridine-2-carboxamide (Compound 31);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1-ethynylcyclopentyl)pyridine-2-carboxamide (Compound 31.2);
4-[2-(5-Chloro-2-hydroxyphenyl)acetamido]-N-[(1s,2s)-2-hydroxycyclohexyl] pyridine-2-carboxamide (Compound 31.3);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[(1S,2S)-2-hydroxycyclo hexyl]pyridine-2-carboxamide or 4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[(1R,2R)-2-hydroxycyclohexyl]pyridine-2-carboxamide (Compound 31.3a);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(4-ethynyltetrahydropyran-4-yl)pyridine-2-carboxamide (Compound 31.4);
N-[(6-Amino-2-pyridyl)methyl]-4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl] amino]pyridine-2-carboxamide (Compound 32);
12-[[4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carbonyl] amino]dodecanoic acid (Compound 32.1);
4-[[2-(5-Chloro-2-hydroxy-phenyl) acetyl]amino]-N-(3-pyridylmethyl)pyridine-2-carboxamide (Compound 32.2);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(2-pyridylmethyl)pyridine-2-carboxamide (Compound 32.3);
4-[[2-(5-Chloro-2-hydroxy-phenyl) acetyl]amino]-N-(4-pyridylmethyl)pyridine-2-carboxamide (Compound 32.4);
4-[[2-(5-Chloro-2-hydroxy-phenyl) acetyl]amino]-N-[(2-hydroxyphenyl) methyl]pyridine-2-carboxamide (Compound 32.5);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(1,1-dimethyl-2-morpholinoethyl)pyridine-2-carboxamide (Compound 32.6);
4-[[2-(5-Chloro-2-hydroxy-phenyl) acetyl]amino]-N-(2-hydroxy-1,1-dimethylethyl)pyridine-2-carboxamide (Compound 32.7);
4-[[2-(5-Chloro-2-hydroxy-phenyl) acetyl] amino]-N-(3,3-difluoro-4-piperidyl)pyridine-2-carboxamide (Compound 32.8);
4-[[2-(5-Chloro-2-hydroxy-phenyl) acetyl]amino]-N-(1H-imidazol-2-yl)pyridine-2-carboxamide (Compound 32.9);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[(1R,2R)-2-hydroxycyclopentyl] pyridine-2-carboxamide (Compound 33);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide (Compound 34);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[3-(hydroxymethyl) tetrahydrofuran-3-yl]pyridine-2-carboxamide (Compound 35);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[(3R)-3-(hydroxymethyl)tetrahydro furan-3-yl]pyridine-2-carboxamide or 4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]-N-[(3S)-3-(hydroxymethyl)tetrahydrofuran-3-yl]pyridine-2-carboxamide (Compound 35a);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[(3R)-3-(hydroxymethyl)tetrahydro furan-3-yl]pyridine-2-carboxamide or 4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]-N-[(3S)-3-(hydroxymethyl)tetrahydrofuran-3-yl]pyridine-2-carboxamide (Compound 35b);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(4-hydroxy-4-methyl-cyclohexyl) pyridine-2-carboxamide as a 6:4 mixture of stereoisomers (Compound 35.1);
4-[[2-(5-Chloro-2-hydroxy-phenyl) acetyl]amino]-N-[(1s,2r)-2-(hydroxy methyl)cyclohexyl]pyridine-2-carboxamide (Compound 35.2);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-[(1s,3r)-3-hydroxycyclopentyl] pyridine-2-carboxamide (Compound 35.3);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-[2-hydroxy-1-(hydroxy methyl)-1-methyl-ethyl]pyridine-2-carboxamide (Compound 35.4);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(3-hydroxycyclohexyl)pyridine-2-carboxamide as a mixture of stereoisomers (Compound 35.6);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(3-phenoxypropyl)pyridine-2-carboxamide (Compound 35.7);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(1-methylcyclo propyl)pyridine-2-carboxamide (Compound

35.8);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-[1-methyl-1-(2-pyridyl) ethyl]pyridine-2-carboxamide (Compound 35.9);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(3-phenylpropyl)pyridine-2-carboxamide (Compound 35.10);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-[2-hydroxy-1-(2-pyridyl)ethyl] pyridine-2-carboxamide (Compound 35.11);
4-[[2-(5-Chloro-2-hydroxy-phenyl) acetyl]amino]-N-[(5-methoxy-2-pyridyl)methyl]pyridine-2-carboxamide (Compound 35.12);
Ethyl 3-[[4-[[2-(5-chloro-2-hydroxy-phenyl) acetyl]amino]pyridine-2-carbonyl]amino]-3-methyl-butanoate (Compound 35.13);
4-[[2-(5-Chloro-2-hydroxy-phenyl) acetyl]amino]-N-(3-hydroxy-1,1-dimethylpropyl)pyridine-2-carboxamide (Compound 35.14);
N-Benzyl-4-[[2-(5-chloro-2-hydroxy-phenyl) acetyl]amino]pyridine-2-carboxamide (Compound 35.15);
4-[[2-(5-Chloro-2-hydroxy-phenyl) acetyl]amino]-N-phenyl-pyridine-2-carboxamide (Compound 35.16);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-[(1S,2S)-2-hydroxycyclopentyl]pyridine-2-carboxamide (Compound 35.17);
4-[[2-(5-Chloro-2-hydroxy-phenyl) acetyl]amino]-N-[(1R,2S)-2-hydroxy cyclopentyl]pyridine-2-carboxamide (Compound 35.18);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-[(1S,2R)-2-hydroxy cyclopentyl]pyridine-2-carboxamide (Compound 35.19);
3-[[2-(5-Fluoro-2-hydroxy-phenyl)acetyl] amino]-N-(1-methylcyclohexyl)benzamide (Compound 35.20*);
N-(1,1-Dimethylprop-2-ynyl)-3-[[2-(5-fluoro-2-hydroxy-phenyl)acetyl]amino]benzamide (Compound 35.21*);
N-Cyclohexyl-3-[[2-(5-fluoro-2-hydroxy-phenyl)acetyl]amino]benzamide (Compound 35.22*);
3-[[2-(5-Fluoro-2-hydroxy-phenyl)acetyl] amino]-N-[3-(hydroxymethyl)tetrahydro furan-3-yl]benzamide (Compound 35.23*);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1-ethynylcyclohexyl)pyridine-2-carboxamide (Compound 35.24);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[1-(hydroxymethyl)cyclobutyl]pyridine-2-carboxamide (Compound 35.25);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[3-(hydroxymethyl)oxetan-3-yl]pyridine-2-carboxamide (Compound 35.26);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1-cyano-2-methoxy-1-methylethyl)pyridine-2-carboxamide (Compound 35.27);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[(1-hydroxycyclobutyl)methyl]pyridine-2-carboxamide (Compound 35.28);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide (Compound 36);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1-cyano-1,2-dimethyl-propyl)pyridine-2-carboxamide (Compound 37);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1-methylcyclopentyl)pyridine-2-carboxamide (Compound 38);
N-(4-tert-Butylcyclohexyl)-4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 39);
N-tert-Butyl-4-[[2-(2-chloro-3-fluoro-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 40);
N-tert-Butyl-4-[[2-(2-chloro-5-fluoro-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 40.1);
N-(4-Cyanotetrahydropyran-4-yl)-3-[[2-(5-fluoro-2-hydroxy-phenyl)acetyl]amino] benzamide (Compound 41*);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[4-(2-hydroxyethyl) tetrahydropyran-4-yl]pyridine-2-carboxamide (Compound 42);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[1,1-dimethyl-3-(2,2,2-trifluoro ethylamino)propyl]pyridine-2-carboxamide (Compound 43);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(4-fluoro-1-bicyclo[2.1.1] hexanyl)pyridine-2-carboxamide (Compound 44);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[3-(2,2-dimethylpropanoyl amino)-1,1-dimethyl-propyl]pyridine-2-carboxamide (Compound 45);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1-cyano-2-hydroxy-1-methylethyl)pyridine-2-carboxamide (Compound 46);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[(1S)-1-cyano-2-hydroxy-1-methylethyl]pyridine-2-carboxamide or 4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]-N-[(1R)-1-cyano-2-hydroxy-1-methyl-ethyl]pyridine-2-carboxamide (Compound 46a);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[(1S)-1-cyano-2-hydroxy-1-methylethyl]pyridine-2-carboxamide

or 4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]-N-[(1R)-1-cyano-2-hydroxy-1-methyl-ethyl]pyridine-2-carboxamide (Compound 46b);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(3-cyanotetrahydrofuran-3-yl)pyridine-2-carboxamide (Compound 47);
Methyl2-[4-[[4-[[2-(5-chloro-2-hydroxy-phenyl) acetyl]amino]pyridine-2-carbonyl]amino]tetrahydropyran-4-yl]acetate (Compound 47.1);
Methyl 4-[[4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carbonyl] amino]tetrahydropyran-4-carboxylate (Compound 47.2);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(3-cyanooxetan-3-yl)pyridine-2-carboxamide (Compound 47.3);
4-[[2-(5-Fluoro-2-hydroxy-phenyl)acetyl]amino]-N-(1-methylcyclobutyl)pyridine-2-carboxamide (Compound 48);
N-(4-Cyanotetrahydropyran-4-yl)-4-[[2-(5-fluoro-2-hydroxy-phenyl)acetyl]amino] pyridine-2-carboxamide (Compound 48.1);
N-[3-(tert-Butylamino)-1,1-dimethyl-3-oxo-propyl]-4-[[2-(5-chloro-2-hydroxy-phenyl) acetyl]amino]pyridine-2-carboxamide (Compound 49);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[3-(methanesulfonamido)-1,1-dimethyl -propyl]pyridine-2-carboxamide (Compound 50);
N-(3-Acetamido-1,1-dimethyl-propyl)-4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl] amino]pyridine-2-carboxamide (Compound 51);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[4-(hydroxymethyl)tetrahydro pyran-4-yl]pyridine-2-carboxamide (Compound 53);
N-tert-Butyl-4-[[2-[3-(1-hydroxyethyl)phenyl]acetyl]amino]pyridine-2-carboxamide (Compound 54);
N-tert-Butyl-5-chloro-4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 55);
N-tert-Butyl-4-[[2-[5-chloro-2-[(4-methoxyphenyl)methoxy]phenyl]acetyl] amino]pyridine-2-carboxamide (Compound 56);
N-tert-butyl-4-[[(1S) or (1R)-4-chloro-7-hydroxy-indane-1-carbonyl]amino]pyridine-2-carboxamide (Compound 57a);
N-tert-butyl-4-[[(1S) or (1R)-4-chloro-7-hydroxy-indane-1-carbonyl]amino]pyridine-2-carboxamide (Compound 57b);
N-tert-Butyl-4-[[2-(2-cyclopropylphenyl)acetyl]amino]pyridine-2-carboxamide (Compound 58);
4-[[2-(3-Bromo-5-chloro-2-hydroxy-phenyl)acetyl]amino]-N-tert-butyl-pyridine-2-carboxamide (Compound 59);
N-(4-Fluor0-1-bicyclo[2.1.1]hexanyl)-4-[[2-(2-fluorophenyl)acetyl]amino]pyridine-2-carboxamide (Compound 60);
N-(1-Cyano-2-hydroxy-1-methyl-ethyl)-4-[[2-(2-fluorophenyl)acetyl]amino]pyridine-2-carboxamide (Compound 60.1);
N-(1,1-Dimethylprop-2-ynyl)-4-[[2-(2-fluorophenyl)acetyl]amino]pyridine-2-carboxamide (Compound 60.2);
N-tert-Butyl-4-[[2-(5-chloro-2-hydroxy-3-isopropyl-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 61);
N-tert-Butyl-4-[[2-[5-chloro-2-hydroxy-3-(1-methoxyethyl)phenyl]acetyl]amino] pyridine-2-carboxamide (Compound 62);
4-[[2-(6-Quinolyl)acetyl]amino]-N-tetrahydropyran-4-yl-pyridine-2-carboxamide (Compound 63);
4-(Benzylcarbamoylamino)-N-tert-butyl-pyridine-2-carboxamide (Compound 64);
N-tert-Butyl-4-(cyclohexylmethylcarbamoyl amino)pyridine-2-carboxamide (Compound 64.1);
N-tert-Butyl-4-(2-phenylethylcarbamoyl amino)pyridine-2-carboxamide (Compound 64.2);
N-tert-Butyl-4-[[(1R)-1-phenylethyl]carbamoyl amino]pyridine-2-carboxamide (Compound 64.3);
N-tert-Butyl-4-[[(1S)-1-phenylethyl] carbamoylamino]pyridine-2-carboxamide (Compound 64.4);
N-tert-Butyl-4-[(2-chlorophenyl) methylcarbamoylamino]pyridine-2-carboxamide (Compound 64.5);
N-tert-butyl-4-(1H-indol-3-ylcarbamoyl amino)pyridine-2-carboxamide (Compound 64.6);
N-tert-Butyl-4-[(3-chlorophenyl)methyl carbamoylamino]pyridine-2-carboxamide (Compound 64.7);
N-tert-butyl-4-[(4-chlorophenyl)methyl carbamoylamino]pyridine-2-carboxamide (Compound 64.8);
N-tert-Butyl-4-[(2-hydroxyphenyl)carbamoylamino]pyridine-2-carboxamide (Compound 65);
N-tert-Butyl-4-[(2-methoxyphenyl)methylcarbamoylamino]pyridine-2-carboxamide (Compound 65.1);
N-tert-Butyl-4-[(2-hydroxyphenyl)methylcarbamoylamino]pyridine-2-carboxamide (Compound 65.2);
N-tert-Butyl-4-[(3-hydroxyphenyl)methylcarbamoylamino]pyridine-2-carboxamide (Compound 65.3);
N-tert-Butyl-4-[(4-hydroxyphenyl)methylcarbamoylamino]pyridine-2-carboxamide (Compound 65.4);
N-tert-Butyl-4-[[2-[2-hydroxy-5-(1-hydroxyethyl)phenyl]acetyl]amino]pyridine-2-carboxamide (Compound 66);
N-tert-Butyl-4-[[2-[2-hydroxy-5-[1-(2,2,2-trifluoroethylamino)ethyl]phenyl] acetyl]amino]pyridine-2-carboxamide (Compound 67);
N-tert-Butyl-4-[[2-[3-(cyanomethyl)phenyl]acetyl]amino]pyridine-2-carboxamide (Compound 68);
N-tert-Butyl-4-[[2-[3-(methoxymethyl)phenyl]acetyl]amino]pyridine-2-carboxamide (Compound 69);
N-tert-Butyl-4-[[2-[2-hydroxy-5-(morpholinomethyl)phenyl]acetyl]amino]pyridine-2-carboxamide (Compound 70);

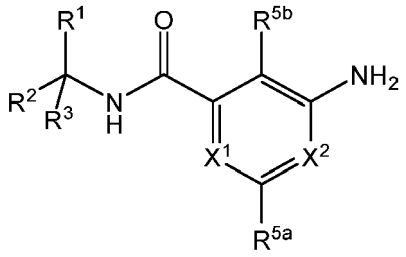
3-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(3-cyanotetrahydrofuran-3-yl)benzamide (Compound 71*);
3-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1-methylcyclohexyl)benzamide (Compound 71.1*);
4-[[2-(5-Fluoro-2-hydroxy-phenyl)acetyl]amino]-N-[3-(hydroxymethyl)tetrahydro furan-3-yl]pyridine-2-carboxamide (Compound 72);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[1-(hydroxymethyl)-2-methoxy-1-methyl-ethyl]pyridine-2-carboxamide (Compound 73);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1,1-dimethylbut-2-ynyl) pyridine-2-carboxamide (Compound 73.1);
3-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1,1-dimethylprop-2-ynyl)benzamide (Compound 74*);
3-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[3-(hydroxymethyl)tetra hydrofuran-3-yl]benzamide (Compound 74.1*);
N-tert-Butyl-4-[[2-[2-hydroxy-5-(3-hydroxypropyl)phenyl]acetyl]amino]pyridine-2-carboxamide (Compound 75);
4-[[2-(5-Chloro-4-fluoro-2-hydroxy-phenyl)acetyl]amino]-N-(1-methylcyclo butyl)pyridine-2-carboxamide (Compound 76);
4-[[2-(2,5-Difluorophenyl)acetyl]amino]-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide (Compound 77);
4-[[2-(2,5-Difluorophenyl)acetyl]amino]-N-(4-fluoro-1-bicyclo[2.1.1]hexanyl) pyridine-2-carboxamide (Compound 77.1);
4-[[2-(4-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1,1-dimethylprop-2-ynyl) pyridine-2-carboxamide (Compound 78);
N-(1,1-Dimethylprop-2-ynyl)-4-[[2-[2-hydroxy-4-(trifluoromethyl)phenyl]acetyl] amino]pyridine-2-carboxamide (Compound 78.1);
N-(1,1-Dimethylprop-2-ynyl)-4-[[2-[2-hydroxy-5-(trifluoromethyl)phenyl]acetyl] amino]pyridine-2-carboxamide (Compound 78.2);
4-[(2-Chroman-4-ylacetyl)amino]-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide (Compound 79);
N-(1,1 -Dimethylprop-2-ynyl)-4-[[2-(1 -isopropyl-3,5-dimethyl-pyrazol-4-yl)acetyl] amino]pyridine-2-carboxamide (Compound 79.1);
N-(1,1-Dimethylprop-2-ynyl)-4-[[2-(1H-indazol-4-yl)acetyl]amino]pyridine-2-carboxamide (Compound 79.2);
N-(1,1-Dimethylprop-2-ynyl)-4-[[2-(1H-indol-7-yl)acetyl]amino]pyridine-2-carboxamide (Compound 79.3);
3-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(4-cyanotetrahydropyran-4-yl) benzamide (Compound 80*);
N-(1-Cyano-1-methyl-ethyl)-4-[[2-(5-fluoro-2-hydroxy-phenyl)acetyl]amino] pyridine-2-carboxamide (Compound 81);
N-(1-Cyano-2-hydroxy-1-methyl-ethyl)-4-[[2-(5-fluoro-2-hydroxy-phenyl)acetyl]amino] pyridine-2-carboxamide (Compound 81.1);
4-[[2-(5-Fluoro-2-hydroxy-phenyl)acetyl]amino]-N-isopropyl-pyridine-2-carboxamide (Compound 81.2);
N-(1,1-Dimethylprop-2-ynyl)-4-[[2-(5-fluoro-2-hydroxy-phenyl)acetyl]amino] pyridine-2-carboxamide (Compound 81.3);
N-(4-Fluoro-1-bicyclo[2.1.1]hexanyl)-4-[[2-(5-fluoro-2-hydroxy-phenyl)acetyl]amino] pyridine-2-carboxamide (Compound 81.4);
4-[[2-(5-Fluoro-2-hydroxy-phenyl)acetyl]amino]-N-[1-(hydroxymethyl)cyclobutyl] pyridine-2-carboxamide (Compound 81.5);
N-tert-Butyl-6-[[2-(5-chloro-2-methoxy-phenyl)acetyl]amino]pyrimidine-4-carboxamide (Compound 82*);
N-(1-Cyano-1-methyl-ethyl)-4-(thiophene-3-carbonylamino)pyridine-2-carboxamide (Compound 83);
N-(1-Cyano-1-methyl-ethyl)-4-[(2-cyclohexylacetyl) amino]pyridine-2-carboxamide (Compound 83.1);
N-(1-Cyano-1-methyl-ethyl)-4-(cyclohexane carbonylamino)pyridine-2-carboxamide (Compound 83.2);
N-(1-Cyano-1-methyl-ethyl)-4-[(3,3-difluorocyclo pentanecarbonyl)amino]pyridine-2-carboxamide (Compound 83.3);
N-(1-Cyano-1-methyl-ethyl)-4-[(1-methylcyclo pentanecarbonyl)amino]pyridine-2-carboxamide (Compound 83.4);
N-(1-Cyano-1-methyl-ethyl)-4-(3-cyclohexyl propanoylamino)pyridine-2-carboxamide (Compound 83.5);
4-(2-{Bicyclo[2.2.1]heptan-2-yl}acetamido)-N-(1-cyano-1-methylethyl)pyridine-2-carboxamide (Compound 83.6);
N-(1-Cyano-1-methyl-ethyl)-4-[[2-(1-methylcyclo hexyl)acetyl]amino]pyridine-2-carboxamide (Compound 83.7);
N-[2-[(1-Cyano-1-methyl-ethyl)carbamoyl]-4-pyridyl]-2-cyclopropyl-pyrimidine-5-carboxamide (Compound 83.8);
N-[2-[(1-Cyano-1-methyl-ethyl)carbamoyl]-4-pyridyl]-3-isobutyl-isoxazole-5-carboxamide (Compound 83.9);
N-(1-Cyano-1-methyl-ethyl)-4-[[2-(4,4-difluorocyclo hexyl)acetyl]amino]pyridine-2-carboxamide (Compound 83.10);
4-[(1-Benzylcyclopropanecarbonyl)amino]-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide (Compound 83.11);
N-(1-Cyano-1-methyl-ethyl)-4-[3-(2-methoxy-4-pyridyl)propanoylamino]pyridine-2-carboxamide (Compound 83.13);
4-[(5-tert-Butyl-2-methyl-pyrazole-3-carbonyl)amino]-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide (Com-

pound 83.14);
N-(1-Cyano-1-methyl-ethyl)-4-[(2-pyrazol-1-ylbenzoyl)amino]pyridine-2-carboxamide (Compound 83.15);
N-[2-[(1-Cyano-1-methyl-ethyl)carbamoyl]-4-pyridyl]-6-(trifluoromethyl)pyridine-2-carboxamide (Compound 83.16);
N-[2-[(1-Cyano-1-methyl-ethyl)carbamoyl]-4-pyridyl]-3-oxo-4H-1,4-benzoxazine-7-carboxamide (Compound 83.17);
N-[2-[(1-Cyano-1-methyl-ethyl)carbamoyl]-4-pyridyl]-1-ethyl-indole-2-carboxamide (Compound 83.18);
N-(1-Cyano-1-methyl-ethyl)-4-[[2-(2,2,2-trifluoroethyl)pyrazole-3-carbonyl]amino]pyridine-2-carboxamide (Compound 83.19);
N-[2-[(1-Cyano-1-methyl-ethyl)carbamoyl]-4-pyridyl]-3-phenyl-isoxazole-4-carboxamide (Compound 83.20);
4-[(1-Benzylpyrazole-4-carbonyl)amino]-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide (Compound 83.21);
N-(1-Cyano-1-methyl-ethyl)-4-[(2-methyl-5-phenyl-pyrazole-3-carbonyl)amino]pyridine-2-carboxamide (Compound 83.22);
N-(1-Cyano-1-methyl-ethyl)-4-[[2-(3-methyl-1,2,4-oxadiazol-5-yl)benzoyl]amino]pyridine-2-carboxamide (Compound 83.23);
N-(1-Cyano-1-methyl-ethyl)-4-[(3-methyl-1-phenyl-pyrazole-4-carbonyl)amino]pyridine-2-carboxamide (Compound 83.24);
N-[2-[(1-Cyano-1-methyl-ethyl)carbamoyl]-4-pyridyl]-2-phenoxy-pyridine-3-carboxamide (Compound 83.25);
N-(1-Cyano-1-methyl-ethyl)-4-[[2,5-dimethyl-1-(2-thienylmethyl)pyrrole-3-carbonyl]amino]pyridine-2-carboxamide (Compound 83.26);
N-[2-[(1-Cyano-1-methyl-ethyl)carbamoyl]-4-pyridyl]-5-(2-methoxyphenyl)isoxazole-3-carboxamide (Compound 83.27);
N-[2-[(1-Cyano-1-methyl-ethyl)carbamoyl]-4-pyridyl]-4-methyl-2-phenyl-thiazole-5-carboxamide (Compound 83.28);
4-[(4-Acetamidobenzoyl)amino]-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide (Compound 83.29);
N-[2-[(1-Cyano-1-methyl-ethyl)carbamoyl]-4-pyridyl]-1,3-benzothiazole-7-carboxamide (Compound 83.30);
N-(1-Cyano-1-methyl-ethyl)-4-[3-(4-fluorophenyl) butanoylamino]pyridine-2-carboxamide (Compound 83.31);
N-[2-[(1-Cyano-1-methyl-ethyl)carbamoyl]-4-pyridyl]-1-methyl-2-oxo-quinoline-3-carboxamide (Compound 83.32);
N-tert-Butyl-3-[[2-(2-hydroxycyclohexyl)acetyl]amino]benzamide (Compound 84*);
N-tert-Butyl-6-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]pyrimidine-4-carboxamide (Compound 85*);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[1-cyano-2-methoxy-1-(methoxy methyl)ethyl]pyridine-2-carboxamide (Compound 86);
4-[[2-(3-Amino-4-tert-butyl-phenyl)acetyl]amino]-N-tert-butyl-pyridine-2-carboxamide (Compound 87);
4-[[2-(2-Amino-4-tert-butyl-phenyl)acetyl]amino]-N-tert-butyl-pyridine-2-carboxamide (Compound 88);
N-tert-Butyl-4-[[2-(4-tert-butyl-3-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 89);
N-tert-Butyl-4-[[2-(4-tert-butyl-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 90);
N-tert-Butyl-4-[[2-(4-tert-butyl-2-fluoro-5-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 91);
4-[[2-(4-Chloro-3-hydroxy-phenyl)acetyl]amino]-N-(4-cyanotetrahydropyran-4-yl)pyridine-2-carboxamide (Compound 92);
4-[[2-(4-Chloro-3-hydroxy-phenyl)acetyl]amino]-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide (Compound 92.1);
4-[[2-(4-Chloro-3-hydroxy-phenyl)acetyl]amino]-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide (Compound 92.2);
4-[[2-(4-Chloro-3-hydroxy-phenyl)acetyl]amino]-N-[(1s,2s)-2-hydroxycyclopentyl]pyridine-2-carboxamide (Compound 92.3);
4-[[2-(4-tert-Butyl-3-hydroxy-phenyl)acetyl]amino]-N-[3-(hydroxymethyl) tetrahydrofuran-3-yl]pyridine-2-carboxamide (Compound 93);
4-[[2-(4-tert-Butyl-3-hydroxy-phenyl)acetyl]amino]-N-[(2S)-2-hydroxycyclohexyl]pyridine-2-carboxamide (Compound 93.1);
4-[[2-(4-tert-Butyl-3-hydroxy-phenyl)acetyl]amino]-N-[(2S)-2-hydroxycyclopentyl]pyridine-2-carboxamide (Compound 93.2);
4-[[2-(4-tert-Butyl-3-hydroxy-phenyl)acetyl]amino]-N-(4-cyanotetrahydropyran-4-yl)pyridine-2-carboxamide (Compound 93.3);
4-[[2-(4-tert-Butyl-3-hydroxy-phenyl)acetyl]amino]-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide (Compound 93.4);
4-[[2-(4-tert-Butyl-3-hydroxy-phenyl)acetyl]amino]-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide (Compound 93.5);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1-methyl-1-phenyl-ethyl) pyridine-2-carboxamide (Compound 94); and

salts and solvates of any of the above.

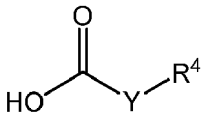
[0135] The compound of general formula (I) may be prepared as described below and the processes for its preparation form a further aspect of the invention.

[0136] A compound of general formula (I) in which Z is -C(O)- may be prepared from a compound of general formula (II):



(II)

wherein R^1, R^2, R^3, R^{5a} and R^{5b}, X^1 and X^2 are as defined for general formula (I);
by reaction with a compound of general formula (III):



(III)

wherein R^4 and Y are as defined for general formula (I).

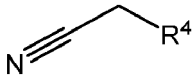
[0137] The reaction is suitably conducted in the presence of a coupling reagent and this method is particularly suitable for compounds of general formula (I) in which X^1 is N and X^2 is CR^8, wherein R^8 is halo, and Y is a bond or alkylene.

[0138] One example of a suitable coupling reagent is a carbodiimide such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) and a triazole such as 1-hydroxy-7-azabenzotriazole (HOAt) or hydroxybenzotriazole (HOBt). Suitably, the reaction is conducted under basic conditions, for example in the presence of an amine such as diisopropylethylamine (DIPEA) and in an organic solvent such as DMF.

[0139] Alternatively, the coupling reagent may be propylphosphonic anhydride (T3P®). When T3P® is used as the coupling reagent, the reaction may be conducted under basic conditions, for example in the presence of an amine such as diisopropylethylamine (DIPEA) or triethylamine (TEA) and in an organic solvent such as dioxane.

[0140] Other known peptide coupling agents such as O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU), O-(Benzotriazol-1-yl)- N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU), O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU), O-(7-Azabenzotriazol-1-yl)- N,N,N',N'-tetramethyluronium tetrafluoroborate (TATU), (Benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP), (Benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP) etc may also be used.

[0141] Compounds of general formula (III) are commercially available or may be prepared by methods known to those of skill in the art. For example, compounds of general formula (III) in which Y is $-CH_2-$ may be synthesised from nitriles of general formula (XXIII):

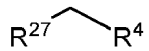


(XXIII)

wherein R^4 is as defined for general formula (I);
by reaction with an aqueous base, for example a metal hydroxide such as lithium hydroxide, followed by acidification, for example with hydrochloric acid.

[0142] The reaction is suitably carried out in an aqueous solution and is heated to reflux temperature.

[0143] A nitrile of general formula (XXIII) may be prepared from a compound of general formula (XXIV):

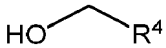


(XXIV)

wherein R^4 is as defined for general formula (I) and R^{27} is halo, for example fluoro, chloro or bromo, especially chloro; by reaction with a cyanide salt such as sodium cyanide.

[0144] The reaction may be carried out at a temperature of about 15 to 25°C, typically at room temperature, in an organic solvent such as *N*,*N*-dimethylformamide.

[0145] A compound of general formula (XXIV) can be prepared by halogenation a compound of general formula (XXV):

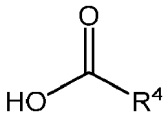


(XXV)

wherein R^4 is as defined for general formula (I).
by reaction with a halogenating agent.

[0146] Suitable halogenating agents for use in the reaction will depend upon which halo group R^{27} is required. For example, when R^{27} is chloro, the halogenating agent may be thionyl chloride. The reaction may be carried out at a temperature of about 15 to 25°C, typically at room temperature, in an organic solvent such as dichloromethane.

[0147] A compound of general formula (XXV) may be obtained by reduction of a compound of general formula (III) in which Y is a bond, ie which has the formula:

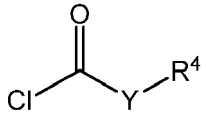


(XXVI)

wherein R^4 is as defined for general formula (I).

[0148] The reduction may be carried out using any suitable reducing agent, for example borane-THF and is suitably conducted at elevated temperature, for example 30-60°C, typically about 50°C.

[0149] In an alternative method for the preparation of a compound of general formula (I), a compound of general formula (II) as defined above may be reacted with an acid chloride of general formula (IV):



(IV)

wherein R^4 and Y are as defined for general formula (I).

[0150] The reaction is suitably conducted under basic conditions, for example in the presence of an amine such as DIPEA.

[0151] This method is particularly suitable for compounds in which Y is a bond or alkylene.

[0152] The acid chloride of general formula (IV) may be commercially available or may be obtained from the carboxylic acid of general formula (III) by reaction with a chlorinating agent, for example thionyl chloride.

[0153] Compounds of general formula (III) are known and are either commercially available or may be prepared by methods known to those of skill in the art.

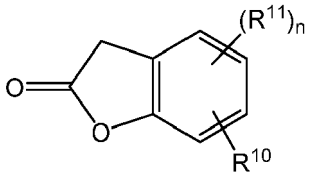
[0154] Alternatively, for compounds of general formula (I) in which Z is -C(O)NH-, the compound of general formula (II) may be reacted with a compound of general formula (XIV):

$O=C=N-Y-R^4$ (XIV)

wherein R^4 and Y are as defined for general formula (I).

[0155] Suitably, the reaction is carried out in an anhydrous organic solvent such as *N,N*-dimethylformamide at elevated temperature, for example about 70 to 85 °C.

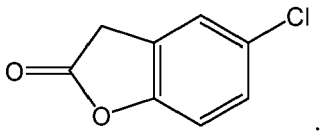
[0156] An alternative method for the preparation of a compound of general formula (Ia) or (Ib) is by reacting a compound of general formula (II) with a compound of general formula (XIII):



(XIII)

wherein R^{10}, R^{11} and n are as defined for a compound of general formula (Ia).

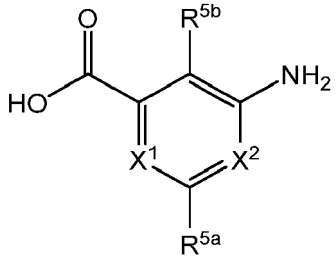
[0157] For example, to prepare a compound of general formula (Ib) in which R^{11a} is Cl and R^{11b} is H, the compound of general formula (XIII) may be 5-chloro-2(*3H*)-benzofuranone, which has the structure:



[0158] The reaction may be carried out in an organic solvent such as toluene, typically at elevated temperature, for example about 90 to 120 °C, for example about 100 to 110°C and under pressurised conditions such as in a sealed tube.

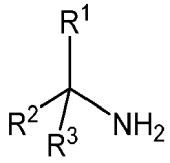
[0159] Compounds of general formulae (XIII) and (XIV) are known and are either commercially available or may be prepared by methods known to those of skill in the art.

[0160] The compound of general formula (II) may be formed by the reaction of a compound of general formula (VIII):



(VIII)

wherein R^{5a}, R^{5b}, X^1 and X^2 are as defined for general formula (I);
with a compound of general formula (VII):

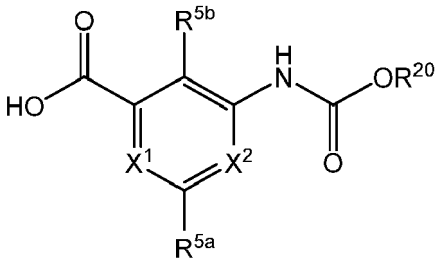


(VII)

wherein R^1, R^2 and R^3 are as defined for general formula (I).

[0161] Suitably the reaction is conducted in the presence of a coupling agent as described above for the reaction between the compounds of general formulae (II) and (III). TBTU is a particularly suitable coupling agent for this reaction, although EDCI and HOAt or HOBt may also be used.

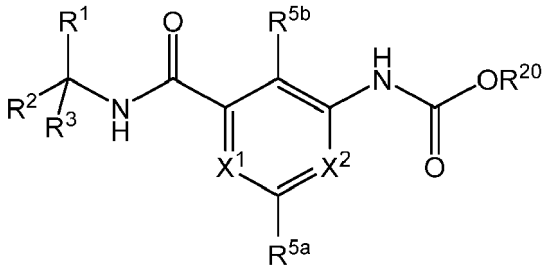
[0162] In some cases, the compound of general formula (VIII) may be protected as a carbamate ester of general formula (VI):



(VI)

wherein R^{5a}, R^{5b}, X^1 and X^2 are as defined for general formula (I); and R^{20} is C_{1-8} alkyl or benzyl.

[0163] In this case, the reaction with the compound of general formula (VII) produces a carbamate ester of general formula (V):



(V)

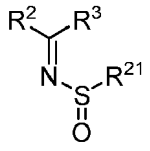
wherein R^1, R^2, R^3, R^{5a}, R^{5b}, X^1 and X^2 are as defined for general formula (I); and R^{20} is as defined for general formula (VI).

[0164] The carbamate protecting group may be removed by hydrolysis, suitably acid hydrolysis, for example using hydrochloric acid and may be conducted in an organic solvent such as dichloromethane.

[0165] Compounds of general formulae (VI), (VII) and (VIII) are known and are commercially available or may be prepared by methods known to those of skill in the art.

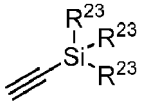
[0166] For example, a compound of general formula (VIII) in which X^2 is C-Cl may be prepared from a compound of general formula (VIII) in which X^2 is CH by reaction with a chlorinating agent such as N-chlorosuccinimide. Suitably, the reaction takes place in an organic solvent such as *N*,*N*-dimethylformamide at elevated temperature, for example about 50 to 70°C.

[0167] Also, a compound of general formula (VII) in which R^1 is ethynyl and R^2 and R^2 together form a carbocyclic or heterocyclic ring may be prepared by reacting a compound of general formula (XVII):



(XVII)

wherein R^2 and R^3 form a carbocyclic or heterocyclic ring and R^{21} is C_{3-8} alkyl, for example t-butyl;
with a compound of general formula (XVIII):

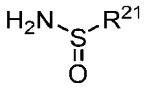


(XVIII)

wherein each R^{23} is independently C_{1-3} alkyl, suitably in the presence of an aluminium catalyst and a base; followed by deprotection using an acid.

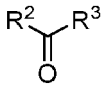
[0168] Suitable bases include strong bases such as n-butyl lithium and a suitable acid for the deprotection step is hydrochloric acid, suitably in an organic solvent such as dioxane.

[0169] The compound of general formula (XVII) may be prepared by reaction of a compound of general formula (XIX):



(XIX)

wherein R^{21} is as defined for general formula (XVII);
with a compound of general formula (XX):



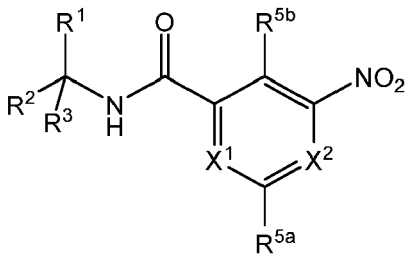
(XX)

wherein R^2 and R^3 form a carbocyclic or heterocyclic ring.

[0170] Suitably, the reaction is catalysed with titanium (IV) catalyst, for example titanium (IV) ethoxide.

[0171] Compounds of general formulae (XIX) and (XX) are known and are readily available.

[0172] An Alternative method for the preparation of a compound of general formula (II) is by reduction of a compound of general formula (IX):

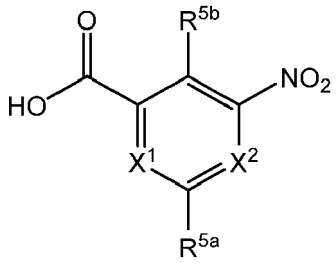


(IX)

wherein R^1, R^2, R^3, R^{5a}, R^{5b}, X^1 and X^2 are as defined for general formula (I);
for example by hydrogenation over a palladium catalyst.

[0173] The hydrogenation is typically carried out in an alcoholic solvent such as ethanol at a temperature of about 15 to 25 °C, for example at room temperature.

[0174] Compounds of general formula (IX) may be obtained by reaction of a compound of general formula (VIIIa):

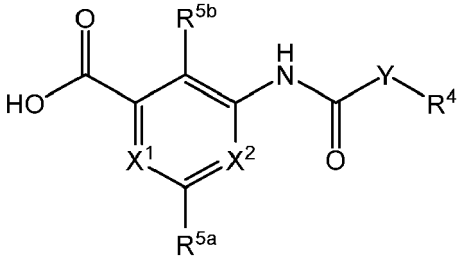


(VIIIa)

wherein R^{5a}, R^{5b}, X^1 and X^2 are as defined for general formula (I);
with an amine of general formula (VII)

[0175] The reaction may be carried out in the presence of a coupling agent, for example one of the coupling agents described above for the reaction between the compounds of general formulae (II) and (III).

[0176] An alternative method for the preparation of a compound of general formula (I) is by reacting a compound of general formula (X):



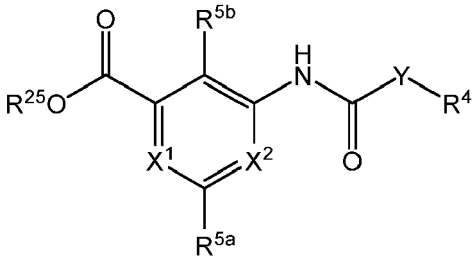
(X)

wherein X^1, X^2, Y, R^4, R^{5a} and R^{5b} are as defined for general formula (I);
with a compound of general formula (VII) as defined above.

[0177] This method is particularly suitable for compounds in which X^1 is N and X^2 is CR^8, wherein R^8 is H, OH or $O(C_{1-4}$ alkyl) and/or R^{5a} is H or F.

[0178] Suitably the reaction is conducted under basic conditions, for example in the presence of an amine such as DIPEA or TEA, and in the presence of a coupling agent as described above for the reaction between the compounds of general formulae (II) and (III). EDCI and HOAt or HOBt is a suitable coupling agent for this reaction, as are HATU TBTU and HBTU.

[0179] A compound of general formula (X) may be prepared by deprotecting a compound of general formula (XI):



(XI)

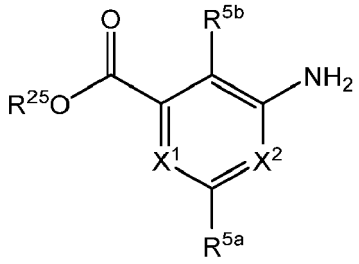
wherein X^1, X^2, Y, R^4, R^{5a} and R^{5b} are as defined for general formula (I); and R^{25} is C_{1-8} alkyl or benzyl.

[0180] One example of a suitable deprotecting agent is boron tribromide, although other methods of deprotecting carboxylic acid are known in the art and/or are discussed below.

[0181] This method using boron tribromide for deprotection is particularly suitable when the target compound is a compound of general formula (I) in which R^4 is substituted with OH, for example a compound of general formula (Ib), (Ic), (d) or (Ie) or a compound of general formula (Ia) in which R^{10} and/or one or more R^{11} groups is/are OH. In such compounds, the OH group on the R^4 moiety in the compound of general formula (XI) may be protected as a group OR^{26}, where R^{26} is C_{1-8} alkyl or benzyl. This protecting group can also be removed using boron tribromide. Similarly, boron tribromide deprotection is also suitable for the preparation of a compound of general formula (X) in which X^2 is CR^8, wherein R^8 is OH.

[0182] On the other hand, if in the required compound of general formula (I) is a compound comprising an alkoxy group, for example a compound in which R^4 is substituted with a group such as $O(C_{1-6}$ alkyl) or in which X^2 is $C(OC_{1-4}$ alkyl), it is preferable that the deprotection is carried out by hydrolysis, particularly base hydrolysis, for example using an alkali metal hydroxide such as lithium hydroxide. This ensures that the $C(O)OR^{25}$ group is hydrolysed to C(O)OH without effecting alkoxy substituents in other parts of the molecule.

[0183] A compound of general formula (XI) may be prepared from a compound of general formula (XII):



(XII)

wherein X^1 and X^2, R^{5a} and R^{5b} are as defined for general formula (I); and R^{25} is as defined for general formula (XI); by reaction with a compound of general formula (III) as defined above or by reaction with a compound of general formula (IV) as defined above or by reaction with a compound of general formula (XIII), for example 5-chloro-2(3H)-benzofuranone, which gives a compound of general formula (Ib) in which R^{11a} is chloro and R^{11b} is H.

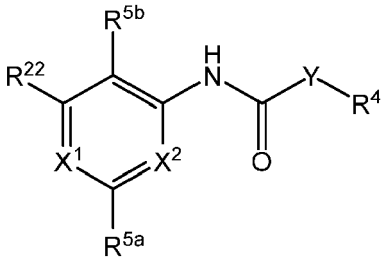
[0184] The reaction with the compound of general formula (III) is suitably carried out under basic conditions, for example in the presence of an amine such as DIPEA or TEA and a coupling agent is used as described above for the reaction between the compounds of general formulae (II) and (III). EDCI with HOAt or HOBt is a particularly suitable coupling agent.

[0185] The reaction with the compound of general formula (IV) will usually be conducted in an organic solvent such as dichloromethane. The compound of general formula (IV) may be generated *in situ* by reacting a compound of general formula (III) with thionyl chloride.

[0186] The reaction with the compound of general formula (XIII) may be carried out in an organic solvent such as toluene, typically at elevated temperature, for example about 90 to 120 °C, for example about 100 to 110°C and under pressurised conditions such as in a sealed tube.

[0187] Compounds of general formula (XII) are known and are either commercially available or may be prepared by methods known to those of skill in the art.

[0188] In a further alternative method, a compound of general formula (I) may be prepared by the reaction of a compound of general formula (XV):

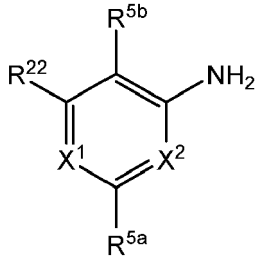


(XV)

wherein X^1, X^2, Y, R^4, R^{5a} and R^{5b} are as defined for general formula (I) and R^{22} is halo, suitably chloro or bromo;

with an amine of general formula (VII) as defined above and carbon monoxide in the presence of a phosphorus ligand such as XantPhos and a palladium catalyst.

[0189] A compound of general formula (XV) may be prepared by reacting a compound of general formula (XVI):



(XVI)

wherein X^1, X^2, R^{5a} and R^{5b} are as defined for general formula (I) and R^{22} is as defined for general formula (XV); with a compound of general formula (IV) as defined above or with a compound of general formula (III) above in the presence of a coupling agent such as HATU.

[0190] The reaction may be carried out under an inert atmosphere in an organic solvent such as *N*,*N*-dimethylformamide at a temperature of about 15 to 25 °C, suitably at room temperature.

[0191] When a compound of general formula (IV) is used, it may be produced *in situ* by reaction of a compound of general formula (III) with thionyl chloride.

[0192] Alternatively, the compound of general formula (XVI) may be reacted with a lactone of general formula (XIII).

[0193] Compounds of general formula (XVI) are well known and are either commercially available or may be prepared by methods familiar to those of skill in the art.

[0194] Compounds of general formula (I) may be prepared in as protected derivatives. For example, a compound of general formula (I) in which R^4 has an OH substituent may be prepared from an equivalent compound of general formula (I) in which the OH is protected, for example as a C_{1-6} alkoxy, benzyloxy or substituted benzyloxy group, wherein the benzyloxy group may be substituted with C_{1-6} alkoxy or halo. The protecting group may be present in the precursors of general formulae (III), (IV), (X), (XI), (XIII), (XIV) and (XV) and may be removed using aqueous acid, for example aqueous hydrochloric acid or by hydrogenation, for example under a hydrogen atmosphere in the presence of a metal catalyst such as palladium on carbon.

[0195] Compounds of general formula (I) may also be converted to other compounds of general formula (I).

[0196] A compound of general formula (I) or (Ia) in which R^4 is an aryl or heteroaryl ring system substituted with one or more -O(C_{1-6} alkyl) substituents may be converted to a compound of general formula (I) or (Ia) in which the -O(C_{1-6} alkyl) substituents are replaced by OH substituents by reaction with boron tribromide. This method is useful for preparing a compounds of general formulae (Ib), (Ic), (Id) and (Ie).

[0197] A compound of general formula (I) or (Ia) in which R^4 is an aryl or heteroaryl ring system substituted with OH may also be prepared by reaction of an equivalent compound of general formula (I) in which R^4 is an aryl or heteroaryl ring system substituted with NH_2 by a diazotisation reaction with nitrous acid, generated *in situ* from sodium nitrite and a strong acid such as sulfuric acid. The resulting diazonium salt reacts with water to form an OH substituent on the R^4 group in a reaction which is suitably catalysed by copper (I), for example in the form of copper (I) oxide.

[0198] A compound of general formula (I) or (Ia) in which R^4 is an aryl or heteroaryl ring system substituted with NH_2 may be prepared by the reduction of an equivalent compound of general formula (I) in which R^4 is an aryl or heteroaryl ring system substituted with nitro. Typically, the reduction is achieved by hydrogenation, suitably catalysed with palladium.

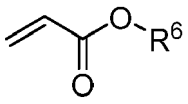
[0199] A compound of general formula (I) or (Ia) in which R^4 is an aryl or heteroaryl ring system substituted with nitro may be prepared by nitration of equivalent compound of general formula (I), for example using concentrated nitric acid mixed with sulfuric acid. Alternatively, nitration may be carried out at an earlier stage of the process. For example, nitration may be carried out on a compound of general formula (III) or general formula (IV) and these nitrated derivatives may then be converted to compounds of general formula (I). A compound of general formula (I) in which R^4 is an aryl or heteroaryl group with a halide substituent may be converted to a compound of general formula (I) in which the halide substituent is replaced with CN, $C(O)R^6$, $C(O)OR^6$, $C(O)N(R^6)(R^7)$, $N(R^7)C(O)R^6$, R^{19} or C_{1-6} alkyl optionally substituted with one or more substituents selected from halo, CN, nitro, cycloalkyl, OR^6, SR^6, NR^6R^7, $C(O)R^6$ $C(O)OR^6$, $C(O)N(R^6)(R^7)$ and $N(R^7)C(O)R^6$, wherein R^6 and R^7 are as defined above for general formula (I) by using a palladium catalysed carbon-carbon coupling reaction, for example a Heck, Suzuki-Miyaura, Stille, Hiyama or Songoshira reaction.

This may be followed, if required, by a further process, for example hydrogenation to reduce alkenyl to alkyl groups.

[0200] For example, a compound of general formula (I) in which R^4 has a halo substituent can be converted to an analogue in which R^4 has a cyano substituent by reaction with a metal cyanide salt, for example zinc cyanide. The reaction is suitably catalysed by a palladium/phosphine complex such as tetrakis(triphenylphosphine)palladium(0).

[0201] A compound of general formula (I) in which R^4 has a $C(O)R^6$ substituent may be prepared from the equivalent halo substituted compound by a palladium/phosphine catalysed reaction with a 1-vinyloxyalkane or a vinyloxysilane. Suitably, the reaction with the vinyloxyalkane is carried out in the presence of a base such as triethylamine and is conducted at elevated temperature, for example about 90 to 120°C, under pressurised conditions, for example in a sealed tube. Reaction with a vinyloxysilane may be carried out in the presence of zinc fluoride and in an anhydrous solvent such as *N,N*-dimethylformamide at elevated temperature, for example about 60 to 80°C, under pressurised conditions such as in a sealed tube. If required, the carbonyl group can be reduced to an OH group, for example using a hydride reducing agent such as sodium borohydride.

[0202] Similarly, compounds of general formula (I) in which R^4 has a halo substituent can be converted to compounds in which R^4 is substituted with CH_2CH_2-$C(O)OR^6$ by a palladium/phosphine catalysed reaction with a compound of general formula (XXII):



(XXII)

wherein R^6 is as defined for general formula (I) but is more suitably not hydrogen; followed by catalytic hydrogenation.

[0203] The reaction with the compound of general formula (XXII) may be conducted under a nitrogen atmosphere in the presence of a base such as triethylamine and at elevated temperature, for example about 60 to 80°C.

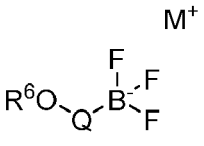
[0204] Hydrogenation may be catalysed by palladium or palladium/carbon.

[0205] The resultant compounds in R^6 is other than hydrogen can be converted to compounds in which R^6 is hydrogen by hydrolysis, typically base hydrolysis, for example using an aqueous alkali metal hydroxide such as lithium hydroxide.

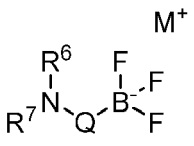
[0206] The product of general formula (I) in which R^4 is substituted with CH_2CH_2-C(O)OH can be reduced to give compounds of general formula (I) in which R^4 is substituted with CH_2CH_2-CH_2OH. Suitably, the acid can be first converted into a mixed anhydride with an appropriate alkyl chloroformate regent such as methyl chloroformate followed by *in situ* reduction to the desired alcohol with an appropriate reducing agent such as sodium borohydride. The reaction may be conducted in the presence of a base such as triethylamine.

[0207] Compounds of general formula (I) in which R^4 has a $C(O)OR^6$ substituent, where R^6 is not H, may be prepared from compounds of general formula (I) in which R^4 is substituted with halo in a palladium/phosphine catalysed reaction with carbon monoxide and an appropriate alcohol. The catalyst may be generated from a pre-catalyst, suitably a third generation Buchwald precatalyst such as XantPhos. The carbon monoxide may be prepared by reacting formic acid with an agent such as methane sulfonyl chloride and a base such as triethylamine. The $C(O)OR^6$ group can be converted to C(O)OH by hydrolysis, for example base hydrolysis using an alkali metal hydroxide such as lithium hydroxide

[0208] Compounds of general formula (I) in which R^4 has a halo substituent can be converted to compounds of general formula (I) in which R^4 is substituted with C_{1-6} alkyl substituted with OR^6 or NR^6R^7 where R^6 and R^7 are as defined for general formula (I) in a palladium catalysed reaction with a compound of formula (XXa) or (XXb):



(XXa)



(XXb)

wherein R^6 and R^7 are as defined for general formula (I), M^+ is a metal ion, suitably a potassium ion, and Q is C_{1-6} alkylene, suitably -CH_2-.

[0209] Suitably, the reaction is conducted under mildly basic conditions, for example in the presence of sodium carbonate at elevated temperature, for example about 70 to 90 °C.

[0210] Compounds of general formula (I) where R^4 is aryl substituted with halo can be converted to compounds of general formula (I) where R^4 is aryl substituted with aryl by reaction with the appropriate aryl boronic acid. The reaction is suitably catalysed by a palladium/phosphine catalyst such as 1,1'-Bis(diphenylphosphino)ferrocenedichloropalladi-

um(II). Suitably, the reaction is carried out in an organic solvent such as 1,4-dioxane and is conducted at elevated temperature, for example about 90 to 120°C under pressurised conditions, for example in a sealed tube.

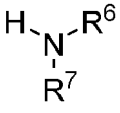
[0211] Compounds of general formula (I) in which R^4 is phenyl can be alkylated using a Friedel Crafts type alkylation by reaction with the appropriate alcohol or alkyl halide in the presence of a strong Lewis acid catalyst, for example sulfuric acid. The position of alkylation will depend upon the position of other substituents in the ring. For example, when R^4 is 2-fluoro-5-hydroxyphenyl, alkylation will occur at the 4-position as illustrated in Example 91.

[0212] In the compounds of general formula (I), replacement of a halo with a methyl group can be achieved via a Suzuki-Miyaura coupling (Grey, et al, Tetrahedron Letters, 41(32), 6237-6240; 2000); installation of nitrile can be achieved as described by Willardsen et al in Journal of Medicinal Chemistry, 47(16), 4089-4099; 2004. Installation of ester and amides may be via carbonylation as described by Veryser et al in React. Chem. Eng., 2016,1, 142-146.

[0213] The R^4 group of compounds of general formula (I) in which R^4 is an aryl or heteroaryl ring system substituted with a group OR^6 can be halogenated by reaction with halogenating agent, for example an N-halo succinimide or bromine.

[0214] The reaction with an N-halo succinimide may be conducted in a polar organic solvent such as acetonitrile and at elevated temperature, for example about 50 to 70°C. A reaction with bromine can take place in solution in a solvent such as acetic acid and at reduced temperature, for example about -5 to 5°C.

[0215] Compounds of general formula (I) in which R^4 is substituted with $C(O)R^{6'}$, where $R^{6'}$ is C_{1-6} alkyl or haloalkyl can be converted to compounds of general formula (I) in which R^4 is substituted with $C(R^{6'})$-NR^6R^7, wherein R^6 and R^7 are as defined for general formula (I), by reaction with a compound of formula (XXI):



(XXI)

wherein R^6 and R^7 are as defined for general formula (I);
under reducing conditions, for example in the presence of a borohydride such as sodium triacetoxyborohydride. The reaction may be carried out in an organic solvent, for example a halogenated solvent such as dichloroethane or dichloromethane, in the presence of an appropriate acid catalyst such as acetic acid and the reaction temperature may be about 15 to 25°C, typically room temperature.

[0216] A compound of general formula (I) in which R^4 is substituted with haloalkyl can be converted to an analogue in which R^4 is substituted with cyanoalkyl by reaction with a group I or group II metal cyanide salt, for example sodium cyanide in the presence of tetrabutylammonium bromide. The reaction is suitably conducted at a temperature of about 15 to 80°C. In some cases, the reaction may take a room temperature. The reaction solvent may be an aqueous solvent, typically a mixture of water and an organic solvent such as dichloromethane.

[0217] Reactions for interconverting the substituent groups on R^4 can also be carried out at an earlier stage of the process. For example, compounds of general formulae (III), (IV), (VI), (X), (XI) or (XV) can also be interconverted in the same way as compounds of general formula (I).

[0218] In compounds in which R^1 is C(O)OH or R^1 or R^3 is substituted with C(O)OH or in which R^4 has a substituent comprising a C(O)OH group, the C(O)OH group can be reduced to an OH group using any suitable method. Hydride reducing agents such as lithium aluminium hydride are particularly suitable.

[0219] In compounds of general formula (I) comprising an alkyl group substituted with a primary or secondary amino group $N(R)_2$, the amino group can be converted to a group -N(R)-C(O)-alkyl (where R is a group R^6, R^{12} or R^{15} depending on the position of the amino group in the molecule) a by reaction with a carboxylic acid in the presence of a coupling agent or with a base followed by an anhydride.

[0220] Primary and secondary amine groups in these compounds can be converted to a group - N(R)-C(O)O-alkyl by reaction with a carboxylic anhydride. The process can be reversed by treatment of the compound containing an alkyloxycarbonyl amino substituent with an acid or with boron tribromide to yield a primary or secondary amine.

[0221] Compounds of general formula (I) in which R^3 is $N(R^{15})S(O)_2R^{14}$ or $N(R^{15})S(O)_2R^{16}$ can be prepared from compounds of general formula (I) in which R^3 $N(R^{15})_2$ by reaction with a sulfonyl halide $W\text{-}S(O)_2R^{14}$ or $W\text{-}S(O)_2R^{16}$, where W is halide, especially chloride and R^{14}, R^{15} and R^{16} are as defined above.

[0222] Compounds of general formula (I) in which R^1, R^3 or R^4 comprise a group C(O)OR', where R' is R^6, R^7, R^{12} or R^{15} as appropriate, can be converted to compounds containing a group $C(O)N(R')_2$ by reaction with appropriate amine in the presence of a coupling reagent.

[0223] Other interconversions of the various substituent groups can be carried out by methods familiar to those of skill in the art.

[0224] The compounds of the present invention will generally be administered as part of a pharmaceutical composition and therefore the invention further provides a pharmaceutical composition comprising a compound of general formula ((I), (Iz), (Iy), (Ia), (Ib), (Ic), (Id) or (Ie) together with a pharmaceutically acceptable excipient.

[0225] The pharmaceutical composition may be formulated for oral, rectal, nasal, bronchial (inhaled), topical (including dermal, transdermal, eye drops, buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration and may be prepared by any methods well known in the art of pharmacy.

[0226] The composition may be prepared by bringing into association the above defined active agent with the excipient. In general, the formulations are prepared by uniformly and intimately bringing into association the active agent with liquid carriers or finely divided solid carriers or both, and then if necessary shaping the product. The invention extends to methods for preparing a pharmaceutical composition comprising bringing a compound of general formula (I) in conjunction or association with a pharmaceutically acceptable carrier or vehicle.

[0227] Formulations for oral administration in the present invention may be presented as: discrete units such as capsules, sachets or tablets each containing a predetermined amount of the active agent; as a powder or granules; as a solution or a suspension of the active agent in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water in oil liquid emulsion; or as a bolus etc.

[0228] For compositions for oral administration (e.g. tablets and capsules), the term "acceptable carrier" includes vehicles such as common excipients e.g. binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, polyvinylpyrrolidone (Povidone), methylcellulose, ethylcellulose, sodium carboxymethylcellulose, hydroxypropylmethylcellulose, sucrose and starch; fillers and carriers, for example corn starch, gelatin, lactose, sucrose, microcrystalline cellulose, kaolin, mannitol, dicalcium phosphate, sodium chloride and alginic acid; and lubricants such as magnesium stearate, sodium stearate and other metallic stearates, glycerol stearate, stearic acid, silicone fluid, talc waxes, oils and colloidal silica. Flavouring agents such as peppermint, oil of wintergreen, cherry flavouring and the like can also be used. It may be desirable to add a colouring agent to make the dosage form readily identifiable. Tablets may also be coated by methods well known in the art.

[0229] A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active agent in a free flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface-active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active agent.

[0230] Other formulations suitable for oral administration include lozenges comprising the active agent in a flavoured base, usually sucrose and acacia or tragacanth; pastilles comprising the active agent in an inert base such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active agent in a suitable liquid carrier.

[0231] For topical application to the skin, compounds of general formula (I) may be made up into a cream, ointment, jelly, solution or suspension etc. Cream or ointment formulations that may be used for the drug are conventional formulations well known in the art, for example, as described in standard text books of pharmaceutics such as the British Pharmacopoeia.

[0232] Topical administration to the lung may be achieved by use of an aerosol formulation. Aerosol formulations typically comprise the active ingredient suspended or dissolved in a suitable aerosol propellant, such as a chlorofluorocarbon (CFC) or a hydrofluorocarbon (HFC). Suitable CFC propellants include trichloromonofluoromethane (propellant 11), dichlorotetrafluoromethane (propellant 114), and dichlorodifluoromethane (propellant 12). Suitable HFC propellants include tetrafluoroethane (HFC-134a) and heptafluoropropane (HFC-227). The propellant typically comprises 40%-99.5% e.g. 40%-90% by weight of the total inhalation composition. The formulation may comprise excipients including co-solvents (e.g. ethanol) and surfactants (e.g. lecithin, sorbitan trioleate and the like). Other possible excipients include polyethylene glycol, polyvinylpyrrolidone, glycerine and the like. Aerosol formulations are packaged in canisters and a suitable dose is delivered by means of a metering valve (e.g. as supplied by Bespak, Valois or 3M or alternatively by Aptar, Coster or Vari).

[0233] Topical administration to the lung may also be achieved by use of a non-pressurised formulation such as an aqueous solution or suspension. These may be administered by means of a nebuliser e.g. one that can be hand-held and portable or for home or hospital use (ie non-portable). The formulation may comprise excipients such as water, buffers, tonicity adjusting agents, pH adjusting agents, surfactants and co-solvents. Suspension liquid and aerosol formulations (whether pressurised or unpressurised) will typically contain the compound of the invention in finely divided form, for example with a D_{50} of 0.5-10 μm e.g. around 1-5 μm. Particle size distributions may be represented using D_{10}, D_{50} and D_{90} values. The D_{50} median value of particle size distributions is defined as the particle size in microns that divides the distribution in half. The measurement derived from laser diffraction is more accurately described as a volume distribution, and consequently the D_{50} value obtained using this procedure is more meaningfully referred to as a Dv_{50} value (median for a volume distribution). As used herein Dv values refer to particle size distributions measured using laser diffraction. Similarly, D_{10} and D_{90} values, used in the context of laser diffraction, are taken to mean Dv_{10} and Dv_{90}

values and refer to the particle size whereby 10% of the distribution lies below the D_{10} value, and 90% of the distribution lies below the D_{90} value, respectively.

[0234] Topical administration to the lung may also be achieved by use of a dry-powder formulation. A dry powder formulation will contain the compound of the disclosure in finely divided form, typically with a mass mean diameter (MMAD) of 1-10 μm or a D_{50} of 0.5-10 μm e.g. around 1-5 μm. Powders of the compound of the invention in finely divided form may be prepared by a micronization process or similar size reduction process. Micronization may be performed using a jet mill such as those manufactured by Hosokawa Alpine. The resultant particle size distribution may be measured using laser diffraction (e.g. with a Malvern Mastersizer 2000S instrument). The formulation will typically contain a topically acceptable diluent such as lactose, glucose or mannitol (preferably lactose), usually of comparatively large particle size e.g. a mass mean diameter (MMAD) of 50 μm or more, e.g. 100 μm or more or a D_{50} of 40-150 μm. As used herein, the term "lactose" refers to a lactose-containing component, including α-lactose monohydrate, β-lactose monohydrate, α-lactose anhydrous, β-tactose anhydrous and amorphous lactose. Lactose components may be processed by micronization, sieving, milling, compression, agglomeration or spray drying. Commercially available forms of lactose in various forms are also encompassed, for example Lactohale® (inhalation grade lactose; DFE Pharma), InhaLac®70 (sieved lactose for dry powder inhaler; Meggle), Pharmatose® (DFE Pharma) and Respitose® (sieved inhalation grade lactose; DFE Pharma) products. In one embodiment, the lactose component is selected from the group consisting of α-lactose monohydrate, α-lactose anhydrous and amorphous lactose. Preferably, the lactose is α-lactose monohydrate.

[0235] Dry powder formulations may also contain other excipients. Thus in one embodiment a dry powder formulation according the present disclosure comprises magnesium or calcium stearate. Such formulations may have superior chemical and/or physical stability especially when such formulations also contain lactose.

[0236] A dry powder formulation is typically delivered using a dry powder inhaler (DPI) device. Example dry powder delivery systems include SPINHALER®, DISKHALER®, TURBOHALER®, DISKUS®, SKYEHALER®, ACCUHALER® and CLICKHALER®. Further examples of dry powder delivery systems include ECLIPSE®, NEXT®, ROTAHALER®, HANDIHALER®, AEROLISER®, CYCLOHALER®, BREEZHALER®/NEOHALER®, MONODOSE®, FLOWCAPS®, TWINCAPS®, X-CAPS®, TURBOSPIN®, ELPENHALER®, MIATHALER®, TWISTHALER®, NOVOLIZER®, PRESSAIR®, ELLIPTA®, ORIEL® dry powder inhaler, MICRODOSE®, PULVINAL®, EASYHALER®, ULTRAHALER®, TAIFUN®, PULMOJET®, OMNIHALER®, GYROHALER®, TAPER®, CONIX®, XCELOVAIR® and PROHALER®.

[0237] In one embodiment a compound of general formula (I) is provided as a micronized dry powder formulation, for example comprising lactose of a suitable grade.

[0238] Thus, as an aspect of the invention there is provided a pharmaceutical composition comprising a compound of general formula (I) in particulate form in combination with particulate lactose, said composition optionally comprising magnesium stearate.

[0239] In one embodiment a compound of general formula (I) is provided as a micronized dry powder formulation, comprising lactose of a suitable grade and magnesium stearate, filled into a device such as DISKUS®. Suitably, such a device is a multidose device, for example the formulation is filled into blisters for use in a multi-unit dose device such as DISKUS®.

[0240] In another embodiment a compound of general formula (I) is provided as a micronized dry powder formulation, for example comprising lactose of a suitable grade, filled into hard shell capsules for use in a single dose device such as AEROLISER®.

[0241] In another embodiment a compound of general formula (I) is provided as a micronized dry powder formulation, comprising lactose of a suitable grade and magnesium stearate, filled into hard shell capsules for use in a single dose device such as AEROLISER®.

[0242] In another embodiment a compound of general formula (I) is provided as a fine powder for use in an inhalation dosage form wherein the powder is in fine particles with a D_{50} of 0.5-10 μm e.g. around 1-5 μm, that have been produced by a size reduction process other than jet mill micronisation e.g. spray drying, spray freezing, microfluidisation, high pressure homogenisation, super critical fluid crystallisation, ultrasonic crystallisation or combinations of these methods thereof, or other suitable particle formation methods known in the art that are used to produce fine particles with an aerodynamic particle size of 0.5-10 μm. The resultant particle size distribution may be measured using laser diffraction (e.g. with a Malvern Mastersizer 2000S instrument). The particles may either comprise the compound alone or in combination with suitable other excipients that may aid the processing. The resultant fine particles may form the final formulation for delivery to humans or may optionally be further formulated with other suitable excipients to facilitate delivery in an acceptable dosage form.

[0243] The compound of the invention may also be administered rectally, for example in the form of suppositories or enemas, which include aqueous or oily solutions as well as suspensions and emulsions and foams. Such compositions are prepared following standard procedures, well known by those skilled in the art. For example, suppositories can be prepared by mixing the active ingredient with a conventional suppository base such as cocoa butter or other glycerides. In this case, the drug is mixed with a suitable nonirritating excipient which is solid at ordinary temperatures but liquid at

the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

[0244] Generally, for compositions intended to be administered topically to the eye in the form of eye drops or eye ointments, the total amount of the compound of general formula (I) will be about 0.0001 to less than 4.0% (w/w).

[0245] Preferably, for topical ocular administration, the compositions administered according to general formula (I) will be formulated as solutions, suspensions, emulsions and other dosage forms. Aqueous solutions are generally preferred, based on ease of formulation, as well as a patient's ability to administer such compositions easily by means of instilling one to two drops of the solutions in the affected eyes. However, the compositions may also be suspensions, viscous or semi-viscous gels, or other types of solid or semi-solid compositions. Suspensions may be preferred for compounds that are sparingly soluble in water.

[0246] An alternative for administration to the eye is intravitreal injection of a solution or suspension of the compound of general formula (I). In addition, the compound of general formula (I) may also be introduced by means of ocular implants or inserts.

[0247] The compositions administered according to general formula (I) may also include various other ingredients, including, but not limited to, tonicity agents, buffers, surfactants, stabilizing polymer, preservatives, co-solvents and viscosity building agents. Suitable pharmaceutical compositions of general formula (I) include a compound of the invention formulated with a tonicity agent and a buffer. The pharmaceutical compositions of general formula (I) may further optionally include a surfactant and/or a palliative agent and/or a stabilizing polymer.

[0248] Various tonicity agents may be employed to adjust the tonicity of the composition, preferably to that of natural tears for ophthalmic compositions. For example, sodium chloride, potassium chloride, magnesium chloride, calcium chloride, simple sugars such as dextrose, fructose, galactose, and/or simply polyols such as the sugar alcohols mannitol, sorbitol, xylitol, lactitol, isomaltitol, maltitol, and hydrogenated starch hydrolysates may be added to the composition to approximate physiological tonicity. Such an amount of tonicity agent will vary, depending on the particular agent to be added. In general, however, the compositions will have a tonicity agent in an amount sufficient to cause the final composition to have an ophthalmically acceptable osmolality (generally about 150-450 mOsm, preferably 250-350 mOsm and most preferably at approximately 290 mOsm). In general, the tonicity agents of the invention will be present in the range of 2 to 4% w/w. Preferred tonicity agents of the invention include the simple sugars or the sugar alcohols, such as D-mannitol.

[0249] An appropriate buffer system (e.g. sodium phosphate, sodium acetate, sodium citrate, sodium borate or boric acid) may be added to the compositions to prevent pH drift under storage conditions. The particular concentration will vary, depending on the agent employed. Preferably however, the buffer will be chosen to maintain a target pH within the range of pH 5 to 8, and more preferably to a target pH of pH 5 to 7.

[0250] Surfactants may optionally be employed to deliver higher concentrations of compound of general formula (I). The surfactants function to solubilise the compound and stabilise colloid dispersion, such as micellar solution, microemulsion, emulsion and suspension. Examples of surfactants which may optionally be used include polysorbate, poloxamer, polyosyl 40 stearate, polyoxyl castor oil, tyloxapol, Triton, and sorbitan monolaurate. Preferred surfactants to be employed in the invention have a hydrophile/lipophile/balance "HLB" in the range of 12.4 to 13.2 and are acceptable for ophthalmic use, such as TritonX114 and tyloxapol.

[0251] Additional agents that may be added to the ophthalmic compositions of compounds of general formula (I) are demulcents which function as a stabilising polymer. The stabilizing polymer should be an ionic/charged example with precedence for topical ocular use, more specifically, a polymer that carries negative charge on its surface that can exhibit a zetapotential of (-)10-50 mV for physical stability and capable of making a dispersion in water (i.e. water soluble). A preferred stabilising polymer of the invention would be polyelectrolyte, or polyelectrolytes if more than one, from the family of cross-linked polyacrylates, such as carbomers and Pemulen®, specifically Carbomer 974p (polyacrylic acid), at 0.1-0.5% w/w.

[0252] Other compounds may also be added to the ophthalmic compositions of the compound of general formula (I) to increase the viscosity of the carrier. Examples of viscosity enhancing agents include, but are not limited to: polysaccharides, such as hyaluronic acid and its salts, chondroitin sulfate and its salts, dextrans, various polymers of the cellulose family; vinyl polymers; and acrylic acid polymers.

[0253] Topical ophthalmic products are typically packaged in multidose form. Preservatives are thus required to prevent microbial contamination during use. Suitable preservatives include: benzalkonium chloride, chlorobutanol, benzododecinium bromide, methyl paraben, propyl paraben, phenylethyl alcohol, edentate disodium, sorbic acid, polyquaternium-1, or other agents known to those skilled in the art. Such preservatives are typically employed at a level of from 0.001 to 1.0% w/v. Unit dose compositions of general formula (I) will be sterile, but typically unpreserved. Such compositions, therefore, generally will not contain preservatives.

[0254] Parenteral formulations will generally be sterile.

[0255] The medical practitioner, or other skilled person, will be able to determine a suitable dosage for the compound of general formula (I), (Ia) or (Ib) and hence the amount of the compound of the invention that should be included in any

particular pharmaceutical formulation (whether in unit dosage form or otherwise).

[0256] Compounds of general formula (I) may be used in combination with one or more other active agents which are useful in the treatment or prophylaxis of respiratory diseases and conditions.

[0257] An additional active agent of this type may be included in the pharmaceutical composition described above but alternatively it may be administered separately, either at the same time as the compound of general formula (I) or at an earlier or later time.

[0258] Therefore, in a further aspect of the present invention there is provided a product comprising a compound of general formula (I) and an additional agent useful in the treatment or prevention of respiratory conditions as a combined preparation for simultaneous, sequential or separate use in the treatment of a disease or condition affected by modulation of TMEM16A and especially a respiratory disease or condition, for example one of the diseases and conditions mentioned above.

[0259] There is also provided a compound of general formula (I) in combination with an additional agent useful in the treatment or prevention of respiratory conditions as a combined preparation for simultaneous, sequential or separate use in the treatment of a disease or condition affected by modulation of TMEM16A and especially a respiratory disease or condition, for example one of the diseases and conditions mentioned above.

[0260] Suitable additional active agents which may be included in a pharmaceutical composition or a combined preparation with the compounds of general formula (I) include:

β2 adrenoreceptor agonists such as metaproterenol, isoproterenol, isoprenaline, albuterol, salbutamol, formoterol, salmeterol, indacaterol, terbutaline, orciprenaline, bitolterol mesylate, pirbuterol, olodaterol, vilanterol and abediterol;
antihistamines, for example histamine H_1 receptor antagonists such as loratadine, cetirizine, desloratadine, levocetirizine, fexofenadine, astemizole, azelastine and chlorpheniramine or H_4 receptor antagonists;
dornase alpha;
corticosteroids such as prednisone, prednisolone, flunisolide, triamcinolone acetonide, beclomethasone dipropionate, budesonide, fluticasone propionate mometasone furoate and fluticasone furoate;
Leukotriene antagonists such as montelukast and zafirlukast;
anticholinergic compounds, particularly muscarinic antagonists such as ipratropium, tiotropium, glycopyrrolate, aclidinium and umeclidinium;
CFTR repair therapies (e.g. CFTR potentiators, correctors or amplifiers) such as Ivacaftor, QBW251, VX659, VX445, VX561/CPT-656, VX152, VX440, GLP2737, GLP2222, GLP2451, PTI438, PTI801, PTI808, FDL-169 and FDL-176and CFTR correctors such as Lumacaftor and Tezacaftor;
ENaC modulators, particularly ENaC inhibitors;
Antibiotics;
Airway hydrating agents (osmoloytes) such as hypertonic saline and mannitol (Bronchitol®); and
Mucolytic agents eg. N-acetyl cytsteine.

[0261] When the additional active agent is an ENaC modulator, it may be an ENaC inhibitor such as amiloride, VX-371, AZD5634, QBW276, SPX-101, BI443651 and ETD001. Other suitable ENaC blockers are disclosed in our applications WO 2017/221008, WO 2018/096325, PCT/GB2018/052982 and GB 1808093.7 and any of the example compounds of those applications may be used in combination with the compounds of general formula (I). Particularly suitable compounds for use in combination with the compounds of general formula (I) include compounds having a cation selected from:

2-[({3-amino-5*H*-pyrrolo[2,3-b]pyrazin-2-yl}formamido) ethyl]-6-(4-{bis[(2S,3R,4R,5R)-2,3,4,5,6-pentahydroxyhexyl]amino}piperidine-1-carbonyl)-1,3-diethyl-1*H*-1,3-benzodiazol-3-ium;
2-[({3-amino-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl}formamido) methyl]-6-{[2-(4-{bis[(2S,3R,4R,5R)-2,3,4,5,6-pentahydroxyhexyl]amino}piperidin-1-yl)ethyl]carbamoyl}-1,3-diethyl-1*H*-1,3-benzodiazol-3-ium;
2-[({3-amino-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl}formamido)methyl]-5-[4-({bis[(2*S*,3*R*,4*R*,5*R*)-2,3,4,5,6-pentahydroxyhexyl]amino)methyl)piperidine-1-carbonyl]-1,3-diethyl-1*H*-1,3-benzodiazol-3-ium;
2-[({3-amino-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl}formamido)methyl]-6-[(3*R*)-3-{bis[(2*S*,3*R*,4*R*,5*R*)-2,3,4,5,6-pentahydroxyhexyl]amino}pyrrolidine-1-carbonyl]-1,3-diethyl-1*H*-1,3-benzodiazol-3-ium;
2-[({3-amino-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl}formamido)methyl]-6-[(3*S*)-3-{bis[(2*S*,3*R*,4*R*,5*R*)-2,3,4,5,6-pentahydroxyhexyl]amino}pyrrolidine-1-carbonyl]-1,3-diethyl-1*H*-1,3-benzodiazol-3-ium;
2-[({3-amino-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl}formamido)methyl]-1,3-diethyl-6-{[(1*r*,4*r*)-4-{bis[(2*S*,3*R*,4*R*,5*R*)-2,3,4,5,6-pentahydroxyhexyl]amino}cyclohexyl]carbamoyl}-1*H*-1,3-benzodiazol-3-ium;
2-[({3-amino-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl}formamido)methyl]-1,3-diethyl-6-{[(1*s*,4*s*)-4-{bis[(2*S*,3*R*,4*R*,5*R*)-2,3,4,5,6-pentahydroxyhexyl]amino}cyclohexyl]carbamoyl}-1*H*-1,3-benzodiazol-3-ium;
and a suitable anion, for example halide, sulfate, nitrate, phosphate, formate, acetate, trifluoroacetate, fumarate,

citrate, tartrate, oxalate, succinate, mandelate, methane sulfonate or p-toluene sulfonate.

[0262] The invention is illustrated by the following non-limiting Examples and to the drawing in which:
FIGURE 1 is an example trace from a whole-cell patch clamp (Qpatch) TMEM16A potentiator assay as used in Biological Example 95 and illustrates the methodology used in the assay. In Figure 1: S is Saline; V is Vehicle; #1 is Test Compound concentration #1; #2 is Test Compound concentration 2; #3 is Test Compound concentration 3; #4 is Test Compound concentration 4; #5 is Test Compound concentration #5; and R is Reference. The arrow in column V represents the baseline current, I_{BL}. The arrows in each of the columns #1, #2, #3, #4, #5 and R represent $I_{[\#1]}$, $I_{[\#2]}$, $I_{[\#3]}$, $I_{[\#4]}$, $I_{[\#5]}$ and $I_{[Ref]}$, which are the peak currents during the incubation periods for test compounds conentrations #1 to #5 and the Reference.

EXAMPLES

[0263] The invention is illustrated by the following Examples.

General Conditions:

[0264] Mass spectra were run on LC-MS systems using electrospray ionization. These were run using either a Waters Acquity uPLC® system with Waters PDA and ELS detectors or Shimadzu LCMS-2010EV systems. [M+H]+ refers to mono-isotopic molecular weights. NMR spectra were recorded on a Bruker Avance III HD 500 MHz with a 5mm Broad Band Inverse probe, a Bruker Avance III HD 250 MHz or a 400MHz Avance III HD Nanobay fitted with a 5mm Broad Band Observed SmartProbe using the solvent as internal deuterium lock. Spectra were recorded at room temperature unless otherwise stated and were referenced using the solvent peak.

[0265] Referring to the examples that follow, compounds of the preferred embodiments were synthesized using the methods described herein, or other methods, which are known in the art.

[0266] The various starting materials, intermediates, and compounds of the preferred embodiments may be isolated and purified, where appropriate, using conventional techniques such as precipitation, filtration, crystallization, evaporation, distillation, and chromatography. Unless otherwise stated, all starting materials are obtained from commercial suppliers and used without further purification. Salts may be prepared from compounds by known salt-forming procedures.

[0267] Compounds were purified by flash column chromatography on normal phase silica on Biotage® Isolera systems using the appropriate SNAP cartridge and gradient. Alternatively, compounds were purified on reverse phase silica using Biotage® Isolera systems with the appropriate SNAP C18 cartridges and reverse phase eluent or by preparative HPLC (if stated otherwise).

Preparative HPLC using acidic pH, early elution method

[0268] Purifications by were performed on a Gilson LC system using Waters Sunfire C18 columns (30 mm x 100 mm, 10 μM; temperature: RT) and a gradient of 10-95% B (A= 0.1% formic acid in water; B= 0.1% formic acid in acetonitrile) over 14.44 min then 95% B for 2.11 min, with an injection volume of 1500 μL and a flow rate of 40 mL/min. UV spectra were recorded at 215 nm using a Gilson detector.

Preparative HPLC using acidic pH, standard elution method

[0269] Purifications by preparative HPLC (acidic pH, standard elution method) were performed on a Gilson LC system using Waters Sunfire C18 columns (30 mm x 100 mm, 10 μM; temperature: RT) and a gradient of 30-95% B (A= 0.1% formic acid in water; B= 0.1% formic acid in acetonitrile) over 11 min then 95% B for 2.11 min, with an injection volume of 1500 μL and a flow rate of 40 mL/min. UV spectra were recorded at 215 nm using a Gilson detector.

Preparative HPLC using basic pH, early elution method

[0270] Purifications by preparative HPLC (basic pH, early elution method) were performed on a Gilson LC system using Waters Xbridge C18 columns (30 mm x 100 mm, 10 μM; temperature: RT) and a gradient of 10-95% (A= 0.2% ammonium hydroxide in water; B= 0.2% ammonium hydroxide in acetonitrile) over 14.44 min then 95% B for 2.11 min, with an injection volume of 1500 μL and a flow rate of 40 mL/min. UV spectra were recorded at 215 nm using a Gilson detector.

Preparative HPLC using basic pH, standard elution method

[0271] Purifications by preparative HPLC (basic pH, standard elution method) were performed on a Gilson LC system using Waters Xbridge C18 columns (30 mm x 100 mm, 10 μM; temperature: RT) and a gradient of 30-95% (A= 0.2% ammonium hydroxide in water; B= 0.2% ammonium hydroxide in acetonitrile) over 11 min then 95% B for 2.11 min, with an injection volume of 1500 μL and a flow rate of 40 mL/min. UV spectra were recorded at 215 nm using a Gilson detector.
[0272] If not indicated otherwise, the analytical HPLC conditions are as follows:

Method A

[0273]

Column:	Phenomenex Kinetix-XB C18 2.1 × 100 mm, 1.7μm
Column Temp	40 °C
Eluents:	A: H20 0.1% formic acid, B: acetonitrile, 0.1% formic acid
Flow Rate:	0.6 mL/min
Gradient:	0-5.3mins 5-100%B, 5.3-5.8mins 100%B, 5.8-5.82mins 100-5%B, 5.82-7.00mins 5%B

Method B

[0274]

Column:	Waters UPLC ® CSH™ C18 2.1 × 100mm 1.7μm
Column Temp	40 °C
Eluents:	A: 2mM amm. Bicarbonate, buffered to pH10, B: acetonitrile
Flow Rate:	0.6 mL/min
Gradient:	0-5.3mins 5-100%B, 5.3-5.8mins 100%B, 5.8-5.82mins 100-5%B, 5.82-7.00mins 5%B

Method C

[0275]

Column:	Waters UPLC ® BEH™ C18 2.1 × 100mm 1.7μm
Column Temp	40 °C
Eluents:	A: 2mM ammonium bicarbonate, buffered to pH10, B: acetonitrile
Flow Rate:	0.6 mL/min
Gradient:	0-5.3mins 5-100%B, 5.3-5.8mins 100%B, 5.8-5.82mins 100-5%B, 5.82-7.00mins 5%B

Method D

[0276]

Column:	Waters Atlantis dC18 2.1 × 100mm 3μm
Column Temp	40 °C
Eluents:	A: H20 +0.1% formic acid, B: acetonitrile+ 0.1% formic acid
Flow Rate:	0.6 mL/min
Gradient:	0-5mins 5-100%B, 5-5.4mins 100%B, 5.4-5.42mins 100-5%B, 5.42-7.00mins 5%B

Method E

[0277]

Column:	Kinetex Core-Shell C18 2.1 × 50mm 5μm
Column Temp	40 °C
Eluents:	A: H20+0.1% formic acid, B: acetonitrile+ 0.1% formic acid
Flow Rate:	1.2 mL/min
Gradient:	0-1.20mins 5-100%B, 1.20-1.30mins 100%B, 1.30-1.31mins 100-5%B

Method F

[0278]

Column:	Phenomenex Gemini-NX C18 2 x 50mm 3μm
Column Temp	40 °C
Eluents:	A: 2mM ammonium bicarbonate, buffered to pH10, B: acetonitrile
Flow Rate:	1 mL/min
Gradient:	0-1.80mins 1-100%B, 1.80-2.10mins 100%B, 2.10-2.30mins 100-1%B

[0279] The following examples are intended to illustrate the invention and are not to be construed as being limitations thereon. Temperatures are given in degrees centigrade. If not mentioned otherwise, all evaporations are performed *in vacuo,* preferably between about 15 mm Hg and 100 mm Hg (= 20-133 mbar). The structure of final products, intermediates and starting materials is confirmed by standard analytical methods, e.g., microanalysis and spectroscopic characteristics, e.g., MS, IR, and NMR. Abbreviations used are those conventional in the art. If not defined, the terms have their generally accepted meanings.

Abbreviation

[0280]

aq.	aqueous
br	broad
d	doublet
dd	doublet of doublets
DCM	dichloromethane
DIPEA	diisopropylethylamine
DMF	N,N-dimethylformamide
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EtOAc	ethyl acetate
HOAt	1-hydroxy-7-azabenzotriazole
HATU	2-(7-aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HPLC	high pressure liquid chromatography
MeCN	acetonitrile
MeOH	methanol
MS	mass spectrometry
m	multiplet
min	minute(s)
mL	milliliter(s)
m/z	mass to charge ratio
NCS	N-chlorosuccinimide
NMR	nuclear magnetic resonance
PTFE	polytetrafluoroethylene
Rt	retention time
s	singlet
t	triplet
TBME	methyl tert-butyl ether
TBTU	N,N,N',N'-tetramethyl-O-(benzotriazol-1-yl)uronium tetrafluoroborate
TEA	triethylamine

TFA trifluoroacetic acid
THF tetrahydrofuran
T3P® 1,2. propylphosphonic anhydride

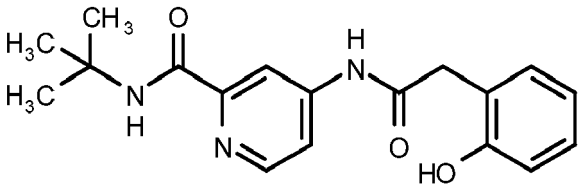
Preparation of Examples

[0281] (* denotes a reference compound that is not claimed)

Example 1

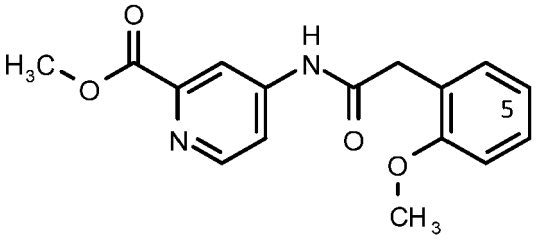
N-tert-Butyl-4-[[2-(2-hydroxyphenyl)acetyl]amino]pyridine-2-carboxamide

[0282]



Step 1: Methyl 4-[[2-(2-methoxyphenyl)acetyl]amino]pyridine-2-carboxylate

[0283]



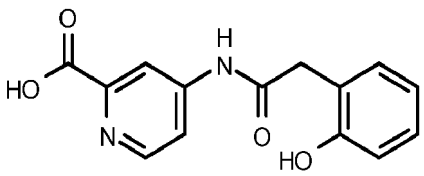
[0284] To a solution of 2-(2-methoxyphenyl)acetic acid (218 mg, 1.31 mmol) in DMF (4 mL) was added HOAt (179 mg, 1.31 mmol), EDCI (328 mg, 1.71 mmol), DIPEA (574 μL, 3.29 mmol) and methyl 4-aminopyridine-2-carboxylate (200 mg, 1.31 mmol) and the mixture was stirred at room temperature for 6 hours 15 minutes. The resulting mixture was partitioned between H_2O (30 mL) and DCM (30 mL) and the two phases separated. The aqueous was further extracted with DCM (30 mL) and the combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by chromatography on silica eluting with EtOAc in heptane to afford the titled compound as a pale yellow gum.

[0285] 1H NMR (500 MHz, Chloroform-d) δ 8.58 (d, J = 5.5 Hz, 1H), 8.10 (s, 1H), 7.92 (dd, J = 5.5, 2.2 Hz, 1H), 7.84 (d, J = 2.1 Hz, 1H), 7.37 - 7.32 (m, 1H), 7.29 (dd, J = 7.4, 1.5 Hz, 1H), 7.04 - 6.97 (m, 2H), 3.98 (s, 3H), 3.97 (s, 3H), 3.75 (s, 2H).

[0286] LC-MS (Method E): Rt 0.96 mins; MS m/z 301.1 = [M+H]+ (99% @ 215nm)

Step 2: 4-[[2-(2-Hydroxyphenyl)acetyl]amino]pyridine-2-carboxylic acid

[0287]



[0288] A solution of methyl 4-[[2-(2-methoxyphenyl)acetyl]amino]pyridine-2-carboxylate (step 1) (119 mg, 0.4 mmol)

in DCM (1.2 mL) was cooled to 0°C and treated with 1M BBr3 in DCM (2.38 mL, 2.38 mmol) over 15 minutes and stirred at 0°C for 1 hr. After warming to room temperature and the reaction was stirred was further 19 hours. A further portion of 1M BBr3 in DCM (1.19 mL, 1.19 mmol) was added at room temperature and stirring continued for a further 72 hours. Water (25 mL) was slowly added to the reaction mixture and then the biphasic solution was concentrated *in vacuo* to yield the titled compound as a brown solid.

[0289] 1H NMR (500 MHz, Methanol-d4) δ 8.68 - 8.60 (m, 2H), 8.39 (dd, J = 6.7, 2.4 Hz, 1H), 7.18 (dd, J = 7.7, 1.6 Hz, 1H), 7.15 - 7.10 (m, 1H), 6.85 - 6.79 (m, 2H), 3.84 (s, 2H). (Compound purity 85%).

[0290] LC-MS (Method E): Rt 0.74 mins; MS m/z 273.0 = [M+H]+ (92% @ 215nm)

Step 3: N-tert-Butyl-4-[[2-(2-hydroxyphenyl)acetyl]amino]pyridine-2-carboxamide

[0291] A solution of 4-[[2-(2-hydroxyphenyl)acetyl]amino]pyridine-2-carboxylic acid (step 2) (138 mg, 0.43 mmol) in DMF (1.5 mL) was treated with EDCI (107 mg, 0.56 mmol), HOAt (59 mg, 0.43 mmol), DIPEA (113 μL, 0.65 mmol) and 2-methylpropan-2-amine (45 μL, 0.43 mmol). The reaction mixture was stirred for 21 hours at room temperature and then concentrated *in vacuo*. The crude residue was purified by preparative HPLC (acidic pH, early elution method) and the product containing fractions freeze-dried to afford the titled compound as a white solid.

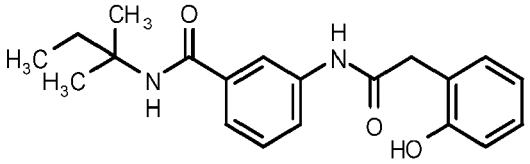
[0292] 1H NMR (500 MHz, DMSO-d6) δ 10.65 (s, 1H), 9.49 (s, 1H), 8.43 (d, J = 5.5 Hz, 1H), 8.18 (d, J = 2.0 Hz, 1H), 8.03 (s, 1H), 7.82 (dd, J = 5.5, 2.2 Hz, 1H), 7.13 (dd, J = 7.5, 1.5 Hz, 1H), 7.07 (td, J = 7.8, 1.7 Hz, 1H), 6.79 (dd, J = 8.0, 0.9 Hz, 1H), 6.75 (td, J = 7.4, 1.1 Hz, 1H), 3.65 (s, 2H), 1.39 (s, 9H).

[0293] LC-MS (Method A): Rt 2.86 mins; MS m/z 328.2 = [M+H]+ (100% @ 215nm)

Example 1.1*

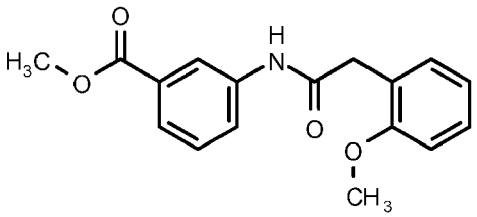
N-(1,1-Dimethylpropyl)-3-[[2-(2-hydroxyphenyl)acetyl]amino]benzamide

[0294]



Step 1: Methyl 3-[[2-(2-methoxyphenyl)acetyl]amino]benzoate

[0295]

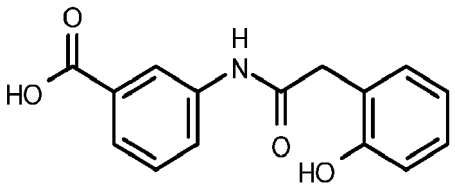


[0296] 2-(2-Methoxyphenyl)acetic acid (1.09 g, 6.62 mmol) in DMF (1.5 mL) was treated with HOAt (900 mg, 6.62 mmol), EDCI (1.65 g, 8.6 mmol), DIPEA (2.89 mL, 16.54 mmol) and methyl 3-aminobenzoate (1.0 g, 6.62 mmol) and the mixture was stirred at room temperature for 3.5 hours. The resulting mixture was partitioned between H_2O (30 mL) and DCM (30 mL) and the two phases separated. The aqueous was further extracted with DCM (30 mL) and the combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by chromatography on silica eluting with EtOAc in heptane to afford the titled compound as a beige crystalline solid.

[0297] 1H NMR (500 MHz, DMSO-d6) δ 10.28 (s, 1H), 8.30 (t, J = 1.8 Hz, 1H), 7.86 - 7.80 (m, 1H), 7.62 (dt, J = 7.7, 1.2 Hz, 1H), 7.44 (t, J = 7.9 Hz, 1H), 7.28 - 7.19 (m, 2H), 6.98 (d, J = 7.9 Hz, 1H), 6.90 (td, J = 7.4, 0.9 Hz, 1H), 3.84 (s, 3H), 3.76 (s, 3H), 3.64 (s, 2H). LC-MS (Method E): Rt 1.10 mins; MS m/z 300.0 = [M+H]+ (100% @ 215nm)

Step 2: 3-[[2-(2-Hydroxyphenyl)acetyl]amino]benzoic acid

[0298]



[0299] A solution of methyl 3-[[2-(2-methoxyphenyl)acetyl]amino]benzoate (step 1) (1.21 g, 4.04 mmol) in DCM (15 mL) was cooled to 0°C and treated with 1M BBr_3 in DCM (16.17 mL, 16.17 mmol) over 15 minutes. After completion of addition, the mixture was stirred at 0°C for 1 hour and then stirred at room temperature for 19 hours. Water (50 mL) was slowly added to the mixture and the DCM concentrated *in vacuo.* The aqueous residue was extracted with EtOAc (2 x 50 mL) and the combined organic extracts were washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo.* The recovered material was suspended in DCM (7.5 mL), cooled to 0°C and treated with 1M BBr3 in DCM (7.0 mL, 7.0 mmol) over 10 minutes. The reaction mixture was stirred at 0°C for 1 hour and then at room temperature for 4 hours. Water (100 mL) was slowly added to the reaction mixture and the DCM was concentrated *in vacuo.* The resulting mixture was extracted with EtOAc (2 x 100 mL). The combined organic extracts were washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the titled compound as a straw-coloured solid.

[0300] 1H NMR (500 MHz, DMSO-d6) δ 12.89 (s, 1H), 10.22 (s, 1H), 9.47 (s, 1H), 8.24 (t, J = 1.7 Hz, 1H), 7.86 - 7.80 (m, 1H), 7.60 (dt, J = 7.7, 1.2 Hz, 1H), 7.41 (t, J = 7.9 Hz, 1H), 7.14 (dd, J = 7.5, 1.4 Hz, 1H), 7.07 (td, J = 7.8, 1.7 Hz, 1H), 6.80 (dd, J = 8.0, 0.9 Hz, 1H), 6.75 (td, J = 7.4, 1.1 Hz, 1H), 3.61 (s, 2H).

[0301] LC-MS (Method E): Rt 0.93 mins; MS m/z 272.1 = [M+H]+ (92% @ 215nm)

Step 3: N-(1,1-Dimethylpropyl)-3-[[2-(2-hydroxyphenyl)acetyl]amino]benzamide

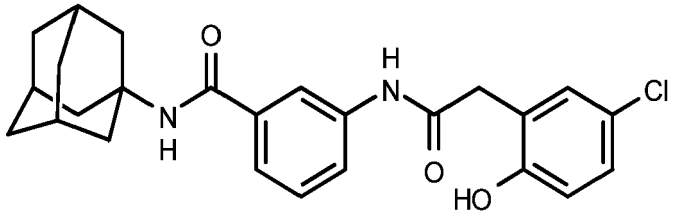
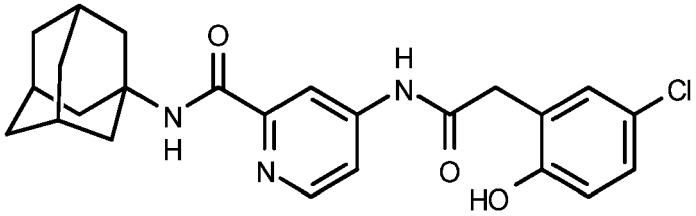
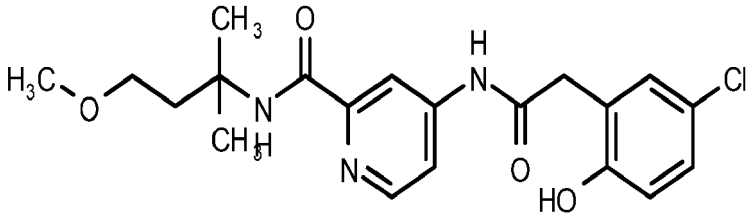
[0302] To a solution of 3-[[2-(2-hydroxyphenyl)acetyl]amino]benzoic acid (step 2) (70 mg, 0.24 mmol) in DMF (1 mL) was added EDCI (59 mg, 0.31 mmol), HOAt (32 mg, 0.24 mmol), DIPEA (62.2 μL, 0.36 mmol) and 2-methylbutan-2-amine (36.1 μL, 0.31 mmol) and the mixture stirred at room temperature for 17 hours. The resulting mixture was partitioned between water (5 mL) and DCM (5 mL). The organic layer was collected using a hydrophobic frit and concentrated *in vacuo.* The residue was purified by preparative HPLC (acidic pH, early elution method) and the product fractions lyophilised overnight to afford the titled compound as an off-white powder.

[0303] 1H NMR (500 MHz, DMSO-d6) δ 10.15 (s, 1H), 9.49 (s, 1H), 7.89 (t, J = 1.8 Hz, 1H), 7.80 - 7.74 (m, 1H), 7.54 (s, 1H), 7.40 (dt, J = 7.7, 1.2 Hz, 1H), 7.33 (t, J = 7.9 Hz, 1H), 7.14 (dd, J = 7.5, 1.6 Hz, 1H), 7.06 (td, J = 7.8, 1.7 Hz, 1H), 6.80 (dd, J = 8.0, 1.0 Hz, 1H), 6.75 (td, J = 7.4, 1.1 Hz, 1H), 3.60 (s, 2H), 1.77 (q, J = 7.5 Hz, 2H), 1.30 (s, 6H), 0.80 (t, J = 7.5 Hz, 3H).LC-MS (Method A): Rt 2.96 mins; MS m/z 341.2 = [M+H]+ (99% @ 215nm).

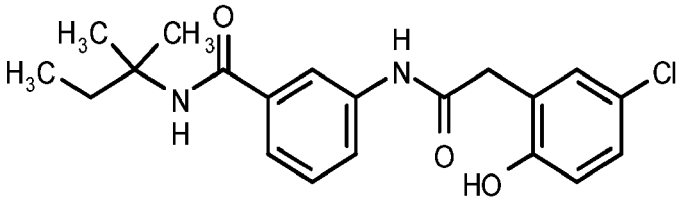
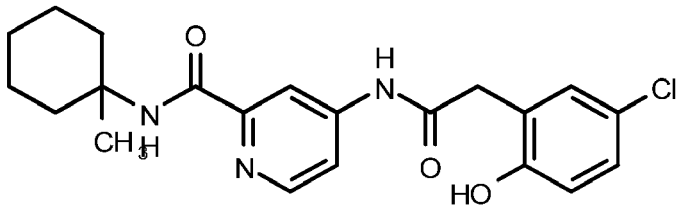
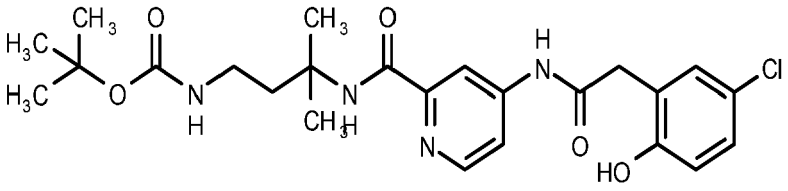
[0304] The compounds of the following tabulated Examples (Table 1) were prepared analogously to Example 1 by replacing 2-(2-methoxyphenyl)acetic acid (step 1) and methyl 4-aminopyridine-2-carboxylate (step 1) with the appropriate commercially available acid and amine and by replacing 2-methylpropan-2-amine (step 3) with the appropriate amine.

Table 1

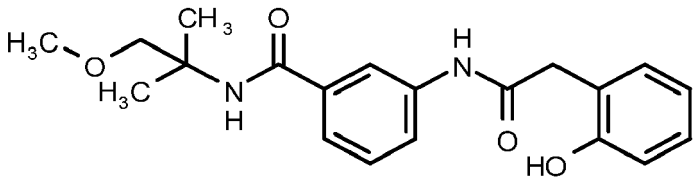
(* denotes a reference compound that is not claimed)

Ex.	Structure and Name	1H NMR, LCMS Retention Time, [M+H]+,
1.2*	 N-(1-Adamantyl)-3-[[2-(5-chloro-2-hydroxyphenyl)acetyl]amino]benzamide	1H NMR (500 MHz, DMSO-d6) δ 10.20 (br. s, 1H), 9.81 (br. s, 1H), 7.87 (t, J = 1.8 Hz, 1H), 7.78 - 7.72 (m, 1H), 7.55 (s, 1H), 7.44 - 7.37 (m, 1H), 7.32 (t, J = 7.9 Hz, 1H), 7.20 (d, J = 2.7 Hz, 1H), 7.11 (dd, J = 8.6, 2.7 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 3.61 (s, 2H), 2.05 (s, 9H), 1.65 (s, 6H). LC-MS (Method A): Rt 3.86 mins; MS m/z 439.3/441.3 = [M+H]+ (100% @ 215nm)
1.3	 N-(1-Adamantyl)-4-[[2-(5-chloro-2-hydroxyphenyl)acetyl]amino] pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.70 (br. s, 1H), 9.83 (br. s, 1H), 8.44 (d, J = 5.5 Hz, 1H), 8.15 (d, J = 2.0 Hz, 1H), 7.91 (s, 1H), 7.82 (dd, J = 5.5, 2.2 Hz, 1H), 7.21 (d, J = 2.7 Hz, 1H), 7.12 (dd, J = 8.6, 2.7 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 3.67 (s, 2H), 2.06 (s, 9H), 1.67 (s, 6H). LC-MS (Method A): Rt 4.12 mins; MS m/z 440.3/442.3 = [M+H]+ (100% @ 215nm)
1.4	 4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(3-methoxy-1,1-dimethyl-propyl)pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.63 (br. s, 1H), 9.82 (br. s, 1H), 8.47 - 8.41 (m, 2H), 8.18 - 8.13 (m, 1H), 7.80 (dd, J = 5.5, 2.0 Hz, 1H), 7.24 - 7.18 (m, 1H), 7.14 - 7.08 (m, 1H), 6.82 - 6.77 (m, 1H), 3.66 (s, 2H), 3.44 (t, J = 6.3 Hz, 2H), 3.23 (s, 3H), 1.95 (t, J = 6.3 Hz, 2H), 1.40 (s, 6H).LC-MS (Method A): Rt 3.15 mins; MS m/z 406.3/408.3 = [M+H]+ (100% @ 215nm)

(continued)

(* denotes a reference compound that is not claimed)		
Ex.	**Structure and Name**	**1H NMR, LCMS Retention Time, [M+H]+,**
1.5*	 3-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1,1-dimethyl propyl) benzamide	1H NMR (500 MHz, DMSO-d6) δ 10.19 (s, 1H), 9.78 (br. s, 1H), 7.88 (t, J = 1.8 Hz, 1H), 7.82 - 7.70 (m, 1H), 7.54 (s, 1H), 7.43 - 7.39 (m, 1H), 7.33 (t, J = 7.9 Hz, 1H), 7.20 (d, J = 2.7 Hz, 1H), 7.11 (dd, J = 8.6, 2.7 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 3.61 (s, 2H), 1.77 (q, J = 7.5 Hz, 2H), 1.30 (s, 6H), 0.80 (t, J = 7.5 Hz, 3H). LC-MS (Method A): Rt 3.31 mins; MS m/z 375.2/377.2 = [M+H]+ (100% @ 215nm)
1.6	Synthesis details given at the end of the table	
1.7	 4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1-methylcyclohexyl) pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.74 (s, 1H), 9.84 (s, 1H), 8.45 (d, J = 5.5 Hz, 1H), 8.17 (d, J = 2.1 Hz, 1H), 7.97 (s, 1H), 7.82 (dd, J = 5.5, 2.2 Hz, 1H), 7.21 (d, J = 2.6 Hz, 1H), 7.12 (dd, J = 8.6, 2.7 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 3.67 (s, 2H), 2.18 - 2.08 (m, 2H), 1.55 - 1.32 (m, 10H), 1.32 - 1.20 (m, 1H). LC-MS (Method A): Rt 3.78 mins; MS m/z 402.3/404.3= [M+H]+ (100% @ 215nm)
1.8	 tert-Butyl N-[3-[[4-[[2-(5-chloro-2-hydroxyphenyl)acetyl]amino]pyridine-2-carbonyl]am i no]-3-m ethylbutyl]carbamate	1H NMR (500 MHz, Methanol-d4) δ 8.43 (d, J = 5.5 Hz, 1H), 8.13 - 8.11 (m, 1H), 7.90 (dd, J = 5.5, 2.2 Hz, 1H), 7.19 (d, J = 2.6 Hz, 1H), 7.09 (dd, J = 8.6, 2.6 Hz, 1H), 6.78 (d, J = 8.6 Hz, 1H), 3.71 (s, 2H), 3.15 - 3.09 (m, 2H), 2.06 - 2.01 (m, 2H), 1.46 (s, 6H), 1.37 (s, 9H). LC-MS (Method A): Rt 3.44 mins; MS m/z 491.3/493.3 = [M+H] + (100% @ 215nm)

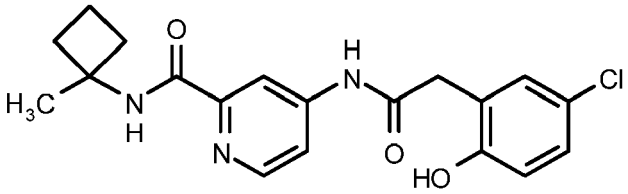
(continued)

(* denotes a reference compound that is not claimed)		
Ex.	**Structure and Name**	**1H NMR, LCMS Retention Time, [M+H]+,**
1.9*	 3-[[2-(2-Hydroxyphenyl)acetyl]amino]-N-(2-methoxy-1,1-dimethyl-ethyl) benzam ide	1H NMR (500 MHz, DMSO-d6) δ 10.15 (s, 1H), 9.48 (s, 1H), 7.90 (t, J = 1.8 Hz, 1H), 7.81 - 7.73 (m, 1H), 7.56 (s, 1H), 7.43 - 7.38 (m, 1H), 7.33 (t, J = 7.9 Hz, 1H), 7.14 (dd, J = 7.5, 1.5 Hz, 1H), 7.06 (td, J = 7.8, 1.7 Hz, 1H), 6.80 (dd, J = 8.0, 1.0 Hz, 1H), 6.75 (td, J = 7.4, 1.1 Hz, 1H), 3.60 (s, 2H), 3.51 (s, 2H), 3.27 (s, 3H), 1.32 (s, 6H). LC-MS (Method A): Rt 2.70 mins; MS m/z 357.2 = [M+H]+ (99% @ 215nm)

Example 1.6

4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1-methylcyclobutyl)pyridine-2-carboxamide

[0305]



[0306] To a solution of 4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxylic acid (Example 31 step 1)(800 mg, 2.61 mmol), 1-methylcyclobutanamine hydrochloride (381 mg, 3.13 mmol) and TEA (800 μL, 5.74 mmol) in DMF (15 mL) was added HATU (1.19 g, 3.13 mmol) and the mixture was stirred at room temperature overnight. The resulting mixture was concentrated *in vacuo* and the residue was dissolved in EtOAc and washed sequentially with aqueous 1M HCl, sat. aqueous $NaHCO_3$, brine and 1M NaOH solution. The organic extracts were dried over Na_2SO_4 and concentrated *in vacuo.* Purifciation of the crude product by chromatography on silica eluting with 50-100% ethyl acetate in heptanes afforded a paleyellow foam. The isolated material was recrystallised by dissolving in methanol (15 mL) and heating to reflux until all solids had dissolved. The mixture was allowed to cool slowly to room temperature. The resulting crystals were filtered to afford the titled compound as a pale yellow solid.

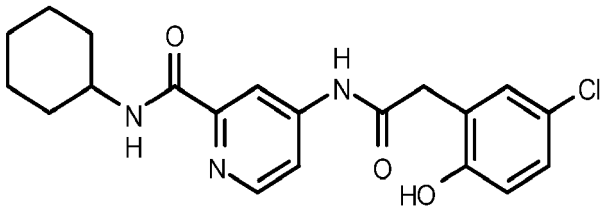
[0307] 1H NMR (500 MHz, DMSO-d6) δ 10.67 (s, 1H), 9.81 (s, 1H), 8.47 (s, 1H), 8.45 (d, J = 5.5 Hz, 1H), 8.15 (d, J = 1.9 Hz, 1H), 7.82 (dd, J = 5.5, 2.2 Hz, 1H), 7.22 (d, J = 2.7 Hz, 1H), 7.12 (dd, J = 8.6, 2.7 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 3.67 (s, 2H), 2.42 - 2.36 (m, 2H), 2.02 - 1.96 (m, 2H), 1.84 - 1.77 (m, 2H), 1.47 (s, 3H).

[0308] LC-MS (Method A): Rt 3.24 mins; MS m/z 374.3/376.3= [M+H]+ (100% @ 215nm)

Example 1.10

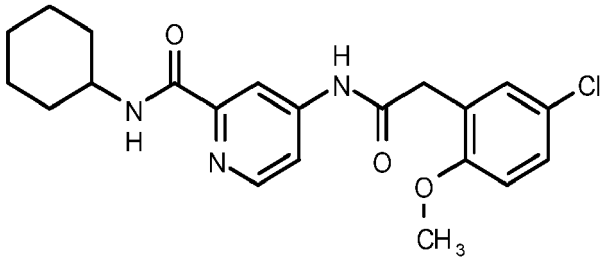
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-cyclohexyl-pyridine-2-carboxamide

[0309]



Step 1: 4-[[2-(5-Chloro-2-methoxy-phenyl)acetyl]amino]-N-cyclohexyl-pyridine-2-carboxamide

[0310]



[0311] A solution of 4-[[2-(5-chloro-2-methoxy-phenyl)acetyl]amino]pyridine-2-carboxylic acid (Example 8.1 step 2) (3.0 g, 9.07 mmol), cyclohexanamine (1.25 mL, 10.89 mmol), EDCI (2.09 g, 10.89 mmol), HOAt (1.48 g, 10.89 mmol) and DIPEA (3.17 mL, 18.15 mmol) in DMF (30 mL) was stirred at room temperature for 19.5 hours. The resulting mixture was concentrated *in vacuo* and the residue partitioned between EtOAc (200 mL) and water (200 mL). The organic portion was separated and the aqueous layer re-extracted with EtOAc (2 x 100 mL). The combined organic extracts were washed with water (2 x 100 mL), brine (2 x 100 mL), dried over Na_2SO_4 and concentrated *in vacuo* to afford the titled compound as red/brown solid.

[0312] 1H NMR (500 MHz, DMSO-d6) δ 10.69 (s, 1H), 8.47 (d, J = 5.5 Hz, 1H), 8.38 (d, J = 8.6 Hz, 1H), 8.18 (d, J = 2.1 Hz, 1H), 7.81 (dd, J = 5.5, 2.2 Hz, 1H), 7.35 - 7.27 (m, 2H), 7.05 - 6.98 (m, 1H), 3.76 (s, 3H), 3.71 (s, 2H), 1.85 - 1.67 (m, 4H), 1.64 - 1.53 (m, 1H), 1.45 - 1.27 (m, 4H), 1.25 - 1.03 (m, 2H).

[0313] LC-MS (Method E): Rt 1.26 mins; MS m/z 402.0/404.1 = [M+H]+ (89% @ 215nm)

Step 2: 4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-cyclohexyl-pyridine-2-carboxamide

[0314] 1M BBr_3 in DCM (21.26 mL, 21.26 mmol) was added to a stirred suspension of 4-[[2-(5-chloro-2-methoxy-phenyl)acetyl]amino]-N-cyclohexyl-pyridine-2-carboxamide (step 1) (3.2 g, 7.09 mmol) in DCM (50 mL) at 0°C. After addition the ice bath was removed and the reaction was stirred at room temperature for 2 hours. The reaction was quenched by slow addition of water (~70 mL) and the mixture was partially concentrated *in vacuo* to remove volatile solvent. EtOAc (200 mL) was added followed by water (100 mL). The organic portion was separated and the aqueous layer extracted with EtOAc (100 mL). The combined organics were washed with sat. $NaHCO_3$ (2 x 150 mL), brine (100 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was purified by C18 reverse phase chromatography eluting with 10-100% MeCN in water with 0.1% formic acid to afford a dark brown/orange solid. The solid was dissolved in a minimum volume of boiling MeCN (~100 mL) and allowed to stand overnight. The resulting crystals were collected by vacuum filtration and dried in a vacuum oven at 40°C for 5 hours to afford the titled compound as pale beige needles.

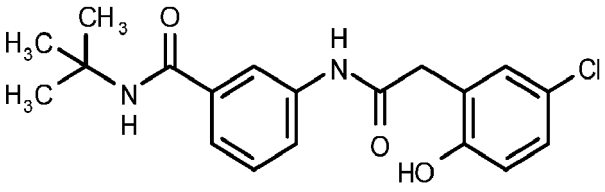
[0315] 1H NMR (500 MHz, DMSO-d6) δ 10.68 (br s, 1H), 9.81 (br s, 1H), 8.46 (d, J = 5.5 Hz, 1H), 8.38 (d, J = 8.6 Hz, 1H), 8.18 (d, J = 2.1 Hz, 1H), 7.82 (dd, J = 5.5, 2.2 Hz, 1H), 7.21 (d, J = 2.7 Hz, 1H), 7.12 (dd, J = 8.6, 2.7 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 3.83 - 3.70 (m, 1H), 3.66 (s, 2H), 1.85 - 1.75 (m, 2H), 1.75 - 1.65 (m, 2H), 1.63 - 1.54 (m, 1H), 1.45 - 1.25 (m, 4H), 1.21 - 1.07 (m, 1H).

[0316] LC-MS (Method A): Rt 3.46 mins; MS m/z 388.2/390.1 = [M+H]+ (100% @ 215nm)

Example 2*

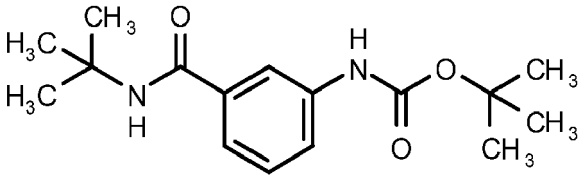
N-tert-Butyl-3-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]benzamide

[0317]



Step 1a: tert-Butyl N-[3-(tert-butylcarbamoyl)phenyl]carbamate

[0318]



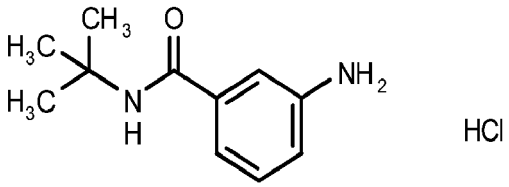
[0319] Commercially available 3-(tert-butoxycarbonylamino)benzoic acid (2.5 g, 10.54 mmol) in DMF (40 mL) was treated with HOAt (1.43 g, 10.54 mmol), EDCI (2.63 g, 13.7 mmol), TEA (1.9 mL, 13.7 mmol) and 2-methylpropan-2-amine (1.44 mL, 13.7 mmol) and stirred at room temperature for 2 hours. The resulting mixture was diluted with water (100 mL) with stirring and the resulting white suspension collected by filtration. The filter cake was washed with water (3 x 15 mL) and oven-dried to afford the titled compound as an off-white solid.

[0320] 1H NMR (500 MHz, Methanol-d4) δ 7.78 - 7.70 (m, 1H), 7.52 - 7.46 (m, 1H), 7.38 - 7.28 (m, 2H), 1.53 (s, 9H), 1.45 (s, 9H).

[0321] LC-MS (Method E): Rt 1.17 mins; MS m/z 293.0 = [M+H]+ (100% @ 215nm)

Step 1b: 3-Amino-N-tert-butyl-benzamide hydrochloride

[0322]



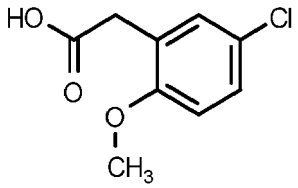
[0323] tert-butyl N-[3-(tert-butylcarbamoyl)phenyl]carbamate (step 1a) (5.3 g, 18.13 mmol) was suspended in 1,4-dioxane (20mL) and then 4M HCl in dioxane (9.59 mL, 271.92 mmol) was added. After stirring at room temperature for 24 hours, the resulting mixture was concentrated in *vacuo* and azeotroped with methanol. The resulting foam was dried in the vacuum oven at 40 °C for a further 3 hours to afford the titled compound as a light orange foam.

[0324] 1H NMR (500 MHz, DMSO-d6) δ 10.25 (br s, 2H), 7.91 (s, 1H), 7.76 (d, J = 7.1 Hz, 1H), 7.71 - 7.68 (m, 1H), 7.50 (t, J = 7.8 Hz, 1H), 7.47 - 7.43 (m, 1H), 1.37 (s, 9H).

[0325] LC-MS (Method E): Rt 0.73 mins; MS m/z 193.1 = [M+H]+ (99% @ 215nm)

Step 2: 2-(5-Chloro-2-methoxy-phenyl)acetic acid

[0326]



[0327] To a cooled (-10 °C), stirred solution of 2-(2-methoxyphenyl)acetic acid (2.0 g, 12.04 mmol) in THF (34.8 mL)

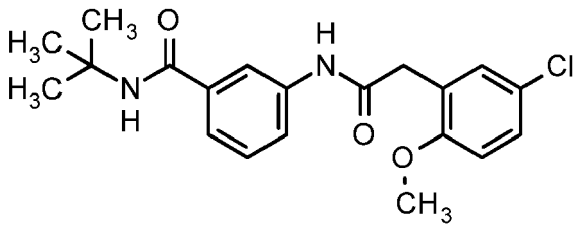
was added dropwise sulfuryl chloride (1.37 mL, 16.85 mmol) over 15 mins and stirring continued for 1 hour. The reaction was quenched with ice cold water (34.8 mL) and extracted into EtOAc (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford the titled compound as a pink solid.

[0328] 1H NMR (250 MHz, DMSO-d6) δ 12.24 (s, 1H), 7.30 (d, J = 2.7 Hz, 2H), 6.99 (d, J = 8.8 Hz, 1H), 3.76 (s, 3H), 3.51 (s, 2H).

[0329] LC-MS (Method E): Rt 1.01 mins; MS m/z no characteristic mass ion observed

Step 3: N-tert-Butyl-3-[[2-(5-chloro-2-methoxy-phenyl)acetyl]amino]benzamide

[0330]



[0331] To 2-(5-chloro-2-methoxy-phenyl)acetic acid (step 2) (114 mg, 0.57 mmol) in DMF (3 mL) was added HOAt (77 mg, 0.57 mmol), EDCI (142 mg, 0.74 mmol), DIPEA (248 μL, 1.42 mmol) and 3-amino-N-tert-butyl-benzamide hydrochloride (step 1b) (130 mg, 0.57 mmol). The reaction mixture was stirred at room temperature for 1 hour. The resulting mixture was partitioned between water (8 mL) and (DCM (8 mL) and the phases separated using a PTFE-fritted phase separator. The organic layer was concentrated *in vacuo* and the crude product purified by chromatography on silica eluting with EtOAc in heptane. The product fractions were *in vacuo* to afford the titled compound as a white solid.

[0332] 1H NMR (500 MHz, Chloroform-d) δ 7.76 - 7.64 (m, 3H), 7.41 - 7.37 (m, 1H), 7.36 - 7.31 (m, 1H), 7.30 - 7.26 (m, 2H), 6.88 (d, J= 8.6 Hz, 1H), 5.97 (br. s, 1H), 3.92 (s, 3H), 3.68 (s, 2H), 1.45 (s, 9H).

[0333] LC-MS (Method E): Rt 1.20 mins; MS m/z 375.0/377.0 = [M+H]+ (94% @ 215nm)

Step 4: N-tert-Butyl-3-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]benzamide

[0334] A solution of N-tert-butyl-3-[[2-(5-chloro-2-methoxy-phenyl)acetyl]amino]benzamide (step 3) (3.83 g, 10.2 mmol) in DCM (80 mL) was cooled to 0 °C and 1M BBr_3 in DCM (20.4 mL, 20.4 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 4 hours. The resulting mixture was diluted with water (10 mL) and the volatile solvent was removed *in vacuo* to afford a gummy residue. The residue was dissolved in EtOAc (60 mL) and saturated sodium bicarbonate (60 mL) and stirred for 1 hour to ensure full dissolution. The biphasic mixture was separated and the organic portion was washed with saturated sodium bicarbonate solution (80 mL), brine (80 mL), dried over Na_2SO_4 and concentrated in *vacuo* to afford a thick beige oil. Purification of the crude product by chromatography on silica eluting with 0-100% EtOAc in heptane yielded a white foam. The material was azeotroped with MeCN (2 x 80 mL) then dissolved in boiling MeCN (~30 mL) and allowed to cool to room temperature. After 3 hours, the resulting crystalline solid was collected by filtration and recrystallized again from boiling MeCN (40 mL) to afford the titled compound as a white crystalline solid.

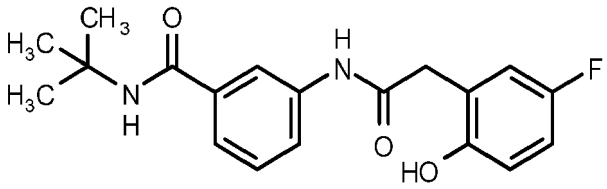
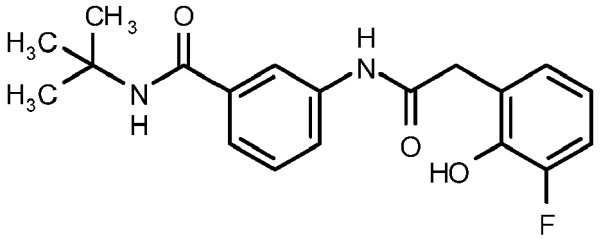
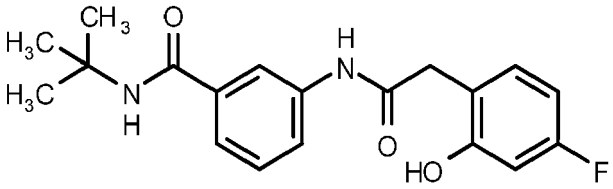
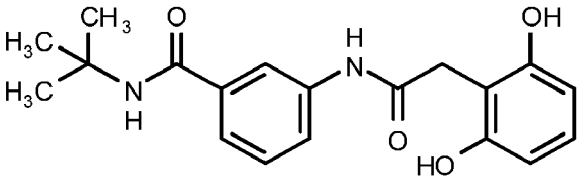
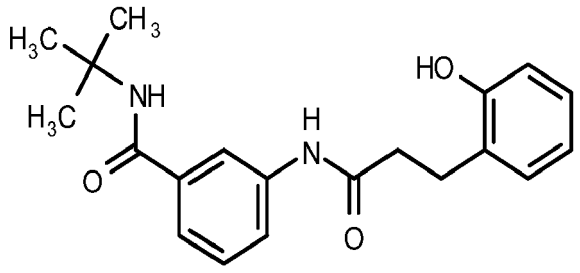
[0335] 1H NMR (500 MHz, DMSO-d6) δ 10.22 (s, 1H), 9.81 (s, 1H), 7.90 (t, J = 1.7 Hz, 1H), 7.78 - 7.72 (m, 1H), 7.69 (s, 1H), 7.42 (dt, J = 7.8, 1.1 Hz, 1H), 7.33 (t, J = 7.9 Hz, 1H), 7.20 (d, J = 2.7 Hz, 1H), 7.10 (dd, J = 8.6, 2.7 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 3.61 (s, 2H), 1.36 (s, 9H).

[0336] LC-MS (Method A): Rt 3.19 mins; MS m/z 361.1/363.2 = [M+H]+ (100% @ 215nm)

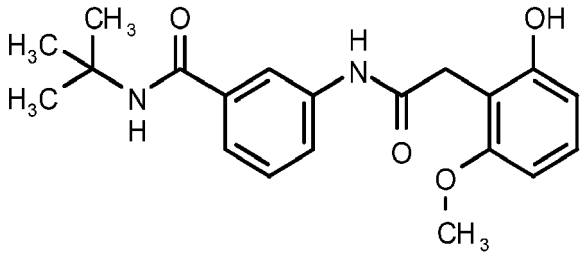
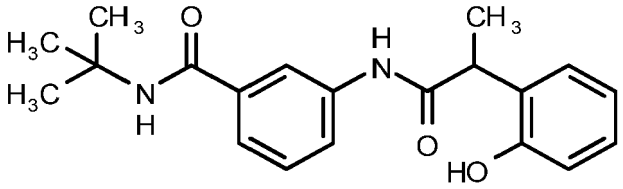
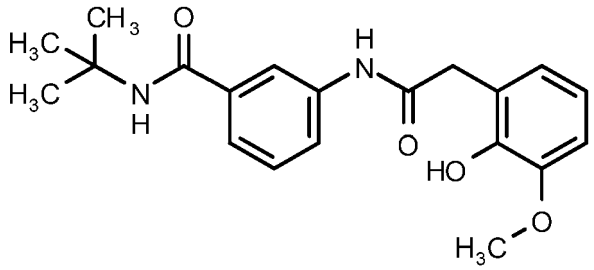
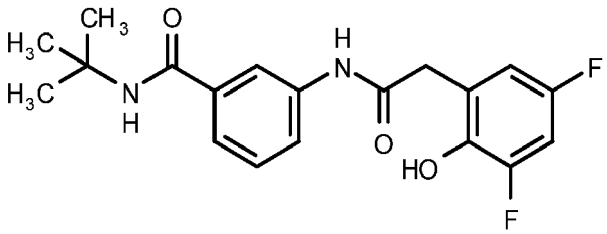
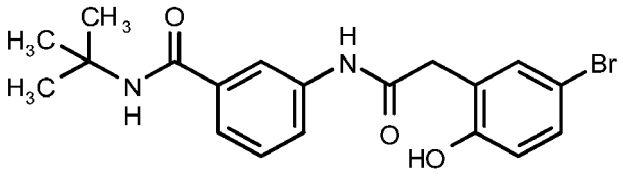
[0337] The compounds of the following tabulated Examples (Table 2) were prepared analogously to Example 2 by replacing 2-(5-chloro-2-methoxy-phenyl)acetic acid (step 2) with the appropriate commercially available acid.

Table 2

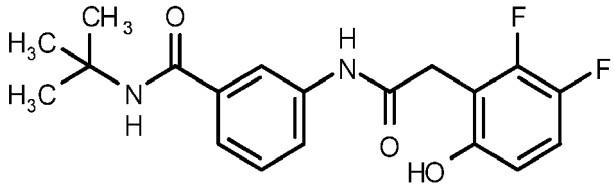
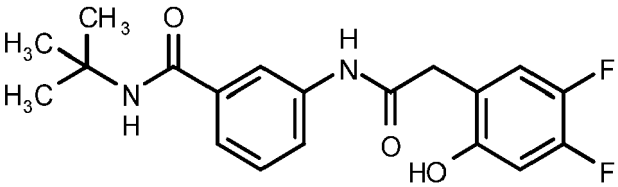
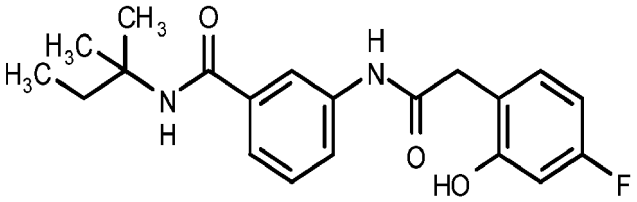
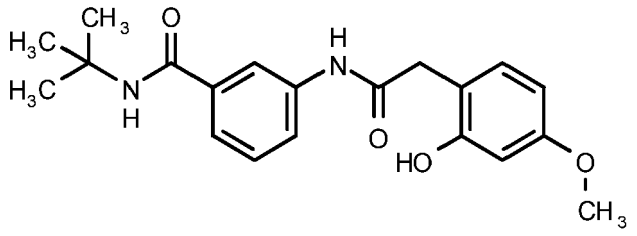
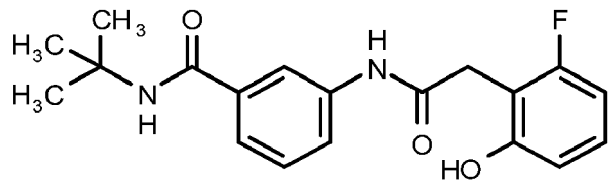
(* denotes a reference compound that is not claimed)

Ex.	Structure and Name	1H NMR, LCMS Retention Time, [M+H]+,
2.1*	 N-tert-Butyl-3-[[2-(5-fluoro-2-hydroxyphenyl)acetyl]am ino] benzamide	1H NMR (500 MHz, DMSO-d6) δ 10.17 (br. s, 1H), 9.49 (br. s, 1H), 7.94 - 7.86 (m, 1H), 7.79 - 7.73 (m, 1H), 7.69 (s, 1H), 7.44 - 7.37 (m, 1H), 7.33 (t, J = 7.9 Hz, 1H), 7.00 (dd, J = 9.4, 3.2 Hz, 1H), 6.89 (td, J = 8.6, 3.2 Hz, 1H), 6.77 (dd, J = 8.8, 4.9 Hz, 1H), 3.61 (s, 2H), 1.36 (s, 9H). LC-MS (Method A): Rt 2.83 mins; MS m/z 345.2 = [M+H]+ (99% @ 215nm)
2.2*	 N-tert-Butyl-3-[[2-(3-fluoro-2-hydroxyphenyl)acetyl]amino] benzamide	1H NMR (500 MHz, DMSO-d6) δ 10.25 (br. s, 1H), 9.65 (br. s, 1H), 7.90 (t, J = 1.7 Hz, 1H), 7.79 - 7.73 (m, 1H), 7.69 (s, 1H), 7.47 - 7.39 (m, 1H), 7.33 (t, J = 7.9 Hz, 1H), 7.09 - 7.01 (m, 1H), 7.01 -6.94 (m, 1H), 6.81 - 6.69 (m, 1H), 3.68 (s, 2H), 1.36 (s, 9H). LC-MS (Method A): Rt 2.80 mins; MS m/z 345.2 = [M+H]+ (99% @ 215nm)
2.3*	 N-tert-Butyl-3-[[2-(4-fluoro-2-hydroxyphenyl)acetyl]am ino] benzamide	1H NMR (500 MHz, DMSO-d6) δ 10.15 (s, 1H), 10.03 (br. s, 1H), 7.90 (t, J = 1.8 Hz, 1H), 7.4-3679 - 7.73 (m, 1H), 7.70 (s, 1H), 7.47 - 7.38 (m, 1H), 7.32 (t, J = 7.9 Hz, 1H), 7.20 - 7.11 (m, 1H), 6.62 - 6.52 (m, 2H), 3.57 (s, 2H), 1.36 (s, 9H). LC-MS (Method A): Rt 2.87 mins; MS m/z 345.2 = [M+H]+ (100% @ 215nm)
2.4*	 N-tert-Butyl-3-[[2-(2,6-dihydroxy phenyl)acetyl]amino] benzamide	1H NMR (500 MHz, DMSO-d6) δ 9.98 (s, 1H), 9.29 (br. s, 2H), 7.88 (t, J = 1.8 Hz, 1H), 7.77 - 7.71 (m, 1H), 7.69 (s, 1H), 7.42 - 7.36 (m, 1H), 7.31 (t, J = 7.9 Hz, 1H), 6.84 (t, J = 8.1 Hz, 1H), 6.30 (d, J = 8.1 Hz, 2H), 3.59 (s, 2H), 1.36 (s, 9H). LC-MS (Method A): Rt 2.36 mins; MS m/z 343.2 = [M+H]+ (99% @ 215nm)
2.5*	 N-tert-Butyl-3-[3-(2-hydroxyphenyl)propanamido]benzamide	1H NMR (500 MHz, DMSO-d6) δ 9.99 (br. s, 1H), 9.35 (br. s, 1H), 7.92 - 7.85 (m, 1H), 7.80 - 7.73 (m, 1H), 7.70 (s, 1H), 7.44 - 7.38 (m, 1H), 7.32 (t, J = 7.9 Hz, 1H), 7.09 (dd, J = 7.4, 1.3 Hz, 1H), 7.00 (td, J = 7.8, 1.6 Hz, 1H), 6.81 - 6.77 (m, 1H), 6.70 (td, J = 7.4, 0.9 Hz, 1H), 2.87 - 2.79 (m, 2H), 2.61 - 2.55 (m, 2H), 1.37 (s, 9H). LC-MS (Method A): Rt 2.83 mins; MS m/z 341.2 = [M+H]+ (100% @ 215nm)

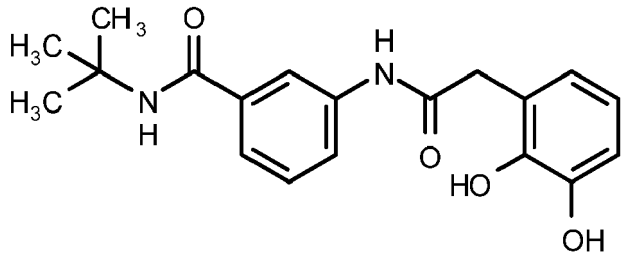
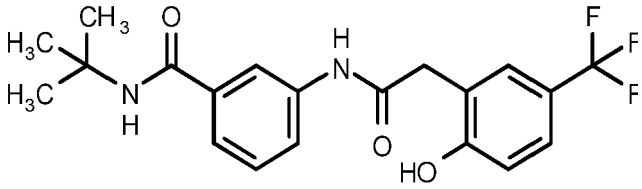
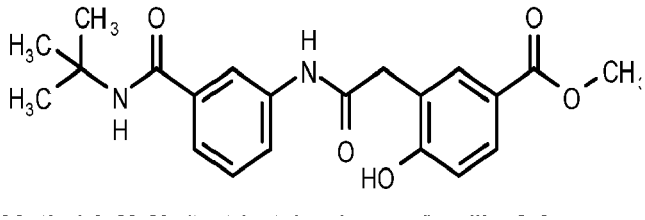
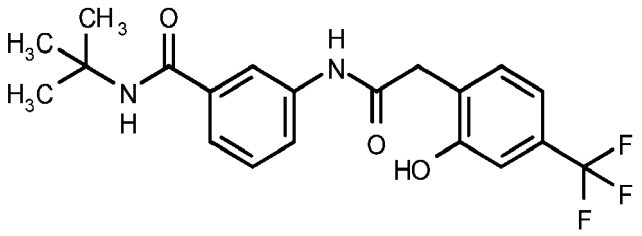
(continued)

(* denotes a reference compound that is not claimed)		
Ex.	**Structure and Name**	**1H NMR, LCMS Retention Time, [M+H]+,**
2.6*	 N-tert-Butyl-3-[[2-(2-hydroxy-6-methoxyphenyl)acetyl]amino] benzamide	1H NMR (500 MHz, DMSO-d6) δ 10.00 (s, 1H), 9.44 (br. s, 1H), 7.89 (t, J = 1.8 Hz, 1H), 7.76 - 7.70 (m, 1H), 7.68 (s, 1H), 7.43 - 7.36 (m, 1H), 7.31 (t, J = 7.9 Hz, 1H), 7.02 (t, J = 8.2 Hz, 1H), 6.49 - 6.43 (m, 2H), 3.71 (s, 3H), 3.61 (s, 2H), 1.36 (s, 9H). LC-MS (Method A): Rt 2.76 mins; MS m/z 357.2 = [M+H]+ (100% @ 215nm)
2.7*	 N-tert-Butyl-3-[2-(2-hydroxyphenyl)propanamido]benzamide	1H NMR (500 MHz, DMSO-d6) δ 10.03 (s, 1H), 9.67 (br. s, 1H), 7.97-7.86 (m, 1H), 7.80 - 7.74 (m, 1H), 7.69 (s, 1H), 7.43 - 7.38 (m, 1H), 7.31 (t, J = 7.9 Hz, 1H), 7.21 (dd, J = 7.6, 1.3 Hz, 1H), 7.05 (td, J = 8.0, 1.4 Hz, 1H), 6.84 - 6.79 (m, 1H), 6.79 - 6.72 (m, 1H), 4.10 (q, J = 7.0 Hz, 1H), 1.49 - 1.21 (m, 12H).LC-MS (Method A): Rt 2.96 mins; MS m/z 341.2 = [M+H]+ (100% @ 215nm)
2.8*	 N-tert-Butyl-3-[[2-(2-hydroxy-3-methoxyphenyl)acetyl]amino] benzamide	1H NMR (500 MHz, DMSO-d6) δ 10.15 (s, 1H), 8.72 (br. s, 1H), 7.94-7.86 (m, 1H), 7.80 - 7.73 (m, 1H), 7.70 (s, 1H), 7.44 - 7.38 (m, 1H), 7.32 (t, J = 7.9 Hz, 1H), 6.86 (dd, J = 7.9, 1.5 Hz, 1H), 6.80 - 6.75 (m, 1H), 6.75 - 6.68 (m, 1H), 3.78 (s, 3H), 3.61 (s, 2H), 1.36 (s, 9H). LC-MS (Method A): Rt 2.79 mins; MS m/z 357.3 = [M+H]+ (98% @ 215nm)
2.9*	 N-tert-Butyl-3-[[2-(3,5-difluoro-2-hydroxyphenyl)acetyl]amino] benzamide	1H NMR (500 MHz, DMSO-d6) δ 10.26 (s, 1H), 9.60 (br. s, 1H), 7.90 (t, J = 1.8 Hz, 1H), 7.78 - 7.73 (m, 1H), 7.71 (s, 1H), 7.45 - 7.40 (m, 1H), 7.33 (t, J = 7.9 Hz, 1H), 7.14 - 7.06 (m, 1H), 6.95 - 6.88 (m, 1H), 3.70 (s, 2H), 1.36 (s, 9H). LC-MS (Method A): Rt 2.91 mins; MS m/z 363.2 = [M+H]+ (98% @ 215nm)
2.10 *	 3-[[2-(5-Bromo-2-hydroxy-phenyl) acetyl]amino]-N-tert-butyl-benzamide	1H NMR (500 MHz, DMSO-d6) δ 10.18 (s, 1H), 9.83 (s, 1H), 7.90 (t, J = 1.8 Hz, 1H), 7.80 - 7.73 (m, 1H), 7.70 (s, 1H), 7.45-7.39 (m, 1H), 7.37 - 7.29 (m, 2H), 7.23 (dd, J = 8.6, 2.6 Hz, 1H), 6.76 (d, J = 8.6 Hz, 1H), 3.61 (s, 2H), 1.36 (s, 9H). LC-MS (Method A): Rt 3.14 mins; MS m/z 405.2/407.2 = [M+H]+ (100% @ 215nm)

(continued)

(* denotes a reference compound that is not claimed)		
Ex.	**Structure and Name**	**1H NMR, LCMS Retention Time, [M+H]+,**
2.11 *	 N-tert-Butyl-3-[[2-(2,3-difluoro-6-hydroxyphenyl)acetyl]amino] benzamide	1H NMR (500 MHz, DMSO-d6) δ 10.29 (s, 1H), 10.01 (s, 1H), 7.89 (t, J = 1.8 Hz, 1H), 7.76 - 7.68 (m, 2H), 7.42 (d, J = 7.8 Hz, 1H), 7.33 (t, J = 7.9 Hz, 1H), 7.12 (q, J = 9.4 Hz, 1H), 6.61 (ddd, J = 8.9, 3.9, 1.6 Hz, 1H), 3.69 (s, 2H), 1.36 (s, 9H). LC-MS (Method A): Rt 2.91 mins; MS m/z 363.2 = [M+H]+ (100% @ 215nm)
2.12 *	 N-tert-Butyl-3-[[2-(4,5-difluoro-2-hydroxyphenyl)acetyl]amino] benzamide	1H NMR (500 MHz, DMSO-d6) δ 10.20 (s, 1H), 7.89 (t, J = 1.7 Hz, 1H), 7.78 - 7.73 (m, 1H), 7.70 (s, 1H), 7.44 - 7.39 (m, 1H), 7.33 (t, J = 7.9 Hz, 1H), 7.22 (dd, J = 11.4, 9.5 Hz, 1H), 6.75 (dd, J = 12.3, 7.2 Hz, 1H), 3.59 (s, 2H), 1.36 (s, 9H). LC-MS (Method A): Rt 2.99 mins; MS m/z 363.2 = [M+H]+ (100% @ 215nm)
2.13 *	 N-(1,1-Dimethylpropyl)-3-[[2-(4-fluoro-2-hydroxyphenyl)acetyl] amino] benzamide	1H NMR (500 MHz, Methanol-d4) δ 7.88 (t, J = 1.8 Hz, 1H), 7.67 (ddd, J = 8.0, 2.1, 1.1 Hz, 1H), 7.53 (s, 1H), 7.47 - 7.41 (m, 1H), 7.36 (t, J = 7.9 Hz, 1H), 7.16 (dd, J = 8.1, 6.9 Hz, 1H), 6.59 - 6.50 (m, 2H), 3.66 (s, 2H), 1.86 (q, J = 7.5 Hz, 2H), 1.38 (s, 6H), 0.90 (t, J = 7.5 Hz, 3H). LC-MS (Method A): Rt 3.08 mins; MS m/z 359.2 = [M+H]+ (100% @ 215nm)
2.14 *	 N-tert-Butyl-3-[[2-(2-hydroxy-4-methoxyphenyl)acetyl]amino] benzamide	1H NMR (500 MHz, DMSO-d6) δ 10.08 (s, 1H), 9.58 (br. s, 1H), 7.90 (t, J = 1.6 Hz, 1H), 7.80 - 7.73 (m, 1H), 7.70 (s, 1H), 7.46 - 7.38 (m, 1H), 7.32 (t, J = 7.9 Hz, 1H), 7.04 (d, J = 8.3 Hz, 1H), 6.39 (d, J = 2.5 Hz, 1H), 6.35 (dd, J = 8.3, 2.5 Hz, 1H), 3.68 (s, 3H), 3.52 (s, 2H), 1.36 (s, 9H). LC-MS (Method A): Rt 2.78 mins; MS m/z 357.3= [M+H]+ (100% @ 215nm)
2.15 *	 N-tert-Butyl-3-[[2-(2-fluoro-6-hydroxyphenyl)acetyl]amino] benzamide	1H NMR (500 MHz, DMSO-d6) δ 10.25 (s, 1H) , 10.15 (br. s, 1H), 7.94 - 7.86 (m, 1H), 7.76 - 7.72 (m, 1H), 7.71 (s, 1H), 7.44 - 7.38 (m, 1H), 7.33 (t, J = 7.9 Hz, 1H), 7.12-7.05 (m, 1H), 6.66 (d, J = 8.2 Hz, 1H), 6.60 (t, J = 8.8 Hz, 1H), 3.64 (s, 2H), 1.36 (s, 9H). LC-MS (Method A): Rt 2.82 mins; MS m/z 345.2 = [M+H]+ (97% @ 215nm)

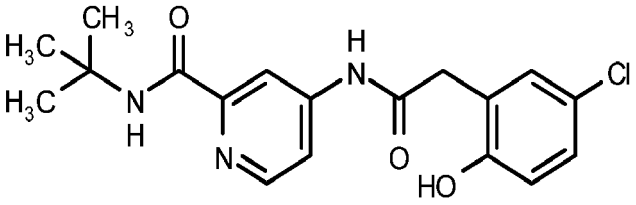
(continued)

(* denotes a reference compound that is not claimed)		
Ex.	**Structure and Name**	**1H NMR, LCMS Retention Time, [M+H]+,**
2.16 *	 N-tert-Butyl-3-[[2-(2,3-dihydroxyphenyl) acetyl]amino] benzamide	1H NMR (500 MHz, DMSO-d6) δ 10.14 (s, 1H), 9.21 (br. s, 1H), 8.50 (br. s, 1H), 7.89 (t, J = 1.8 Hz, 1H), 7.79 - 7.73 (m, 1H), 7.70 (s, 1H), 7.41 (dt, J = 7.6, 1.1 Hz, 1H), 7.33 (t, J = 7.9 Hz, 1H), 6.68 (dd, J = 7.6, 1.8 Hz, 1H), 6.61 (dd, J = 7.6, 1.8 Hz, 1H), 6.57 (t, J = 7.6 Hz, 1H), 3.59 (s, 2H), 1.36 (s, 9H). LC-MS (Method A): Rt 2.48 mins; MS m/z 343.2 = [M+H]+ (100% @ 215nm)
2.17 *	 N-tert-Butyl-3-[[2-[2-hydroxy-5-(trifluoro methyl)phenyl]acetyl] amino]benzamide	1H NMR (500 MHz, DMSO-d6) δ 11.12 - 9.35 (m, 2H), 7.90 (t, J = 1.8 Hz, 1H), 7.77 - 7.72 (m, 1H), 7.70 (s, 1H), 7.52 (d, J = 2.1 Hz, 1H), 7.46 - 7.38 (m, 2H), 7.33 (t, J = 7.9 Hz, 1H), 6.95 (d, J = 8.4 Hz, 1H), 3.69 (s, 2H), 1.36 (s, 9H). LC-MS (Method A): Rt 3.27 mins; MS m/z 395.2 = [M+H] + (100% @ 215nm)
2.18 *	 Methyl 3-[2-[3-(tert-butylcarbamoyl)anilino]-2-oxoethyl]-4-hydroxy- benzoate	1H NMR (500 MHz, DMSO-d6) δ 10.48 (br s, 1H), 10.22 (s, 1H), 7.90 (t, J = 1.8 Hz, 1H), 7.82 (d, J = 2.2 Hz, 1H), 7.79 - 7.74 (m, 1H), 7.73 (dd, J = 8.5, 2.2 Hz, 1H), 7.71 (s, 1H), 7.46 - 7.39 (m, 1H), 7.33 (t, J = 7.9 Hz, 1H), 6.89 (d, J = 8.5 Hz, 1H), 3.78 (s, 3H), 3.66 (s, 2H), 1.36 (s, 9H). LC-MS (Method A): Rt 2.78 mins; MS m/z 385.2 = [M+H]+ (98% @ 215nm)
2.19 *	 N-tert-Butyl-3-[[2-[2-hydroxy-4-(trifluoro methyl)phenyl]acetyl] amino]benzamide	1H NMR (500 MHz, DMSO-d6) δ 10.27 (s, 2H), 7.90 (t, J = 1.8 Hz, 1H), 7.80 - 7.73 (m, 1H), 7.70 (s, 1H), 7.47 - 7.40 (m, 1H), 7.37 (d, J = 7.8 Hz, 1H), 7.33 (t, J = 7.9 Hz, 1H), 7.12 - 7.08 (m, 1H), 7.08 - 7.05 (m, 1H), 3.69 (s, 2H), 1.36 (s, 9H). LC-MS (Method A): Rt 3.30 mins; MS m/z 395.2 = [M+H]+ (100% @ 215nm)

Example 3

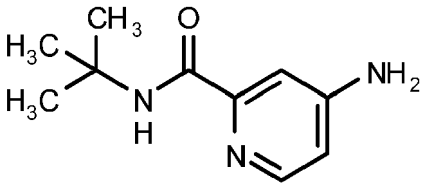
N-tert-Butyl-4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide

[0338]



Step 1: 4-Amino-N-tert-butyl-pyridine-2-carboxamide

[0339]



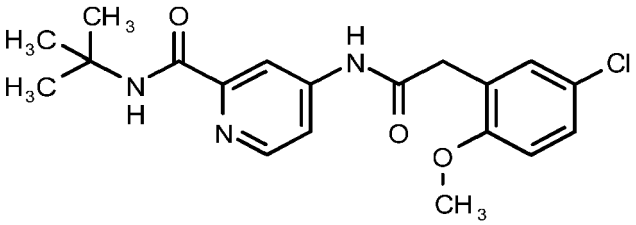
[0340] To a mixture of 4-aminopyridine-2-carboxylic acid (8.0 g, 57.92 mmol), TBTU (22.32 g, 69.5 mmol) and TEA (24.22 mL, 173.76 mmol) in DMF (100 mL) was added 2-methylpropan-2-amine (7.30 mL, 69.5 mmol). The resulting mixture was stirred at room temperature for 22 hours and then concentrated *in vacuo.* The crude material was purified by chromatography on silica eluting with 3.5M methanolic ammonia in DCM and product fractions combined and concentrated *in vacuo* to yield the titled compound as a light yellow solid.

[0341] 1H NMR (500 MHz, Methanol-d4) δ 7.99 (d, J = 5.6 Hz, 1H), 7.23 (d, J = 2.2 Hz, 1H), 6.62 (dd, J = 5.6, 2.4 Hz, 1H), 1.45 (s, 9H).

[0342] LC-MS (Method F): Rt 1.47 mins; MS m/z 194.3 = [M+H]+ (100% @ 215nm)

Step 2: N-tert-Butyl-4-[[2-(5-chloro-2-methoxy-phenyl)acetyl]amino]pyridine-2-carboxamide

[0343]



[0344] A solution of 2-(5-chloro-2-methoxy-phenyl)acetic acid (2.26 g, 11.27 mmol) in thionyl chloride (8.13 mL, 92.21 mmol) was heated at 70 °C for 30 minutes. After cooling to room temperature, excess thionyl chloride was removed *in vacuo,* azeotroping with toluene. The resulting residue was dissolved in DCM (5 mL) and added to a solution of 4-amino-N-tert-butyl-pyridine-2-carboxamide (step 1) (2.0 g, 10.25 mmol) and DIPEA (2.15 mL, 12.29 mmol) in DCM (25 mL). The mixture stirred at room temperature for 1 hour and then diluted with water (50 mL) and extracted with DCM. The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo.* The crude residue was purified by chromatography on silica eluting with 0-50% EtOAc in heptane to afford the titled compound as a pale orange powder.

[0345] 1H NMR (500 MHz, Chloroform-d) δ 8.39 (d, J = 5.6 Hz, 1H), 8.20 (dd, J = 5.6, 2.2 Hz, 1H), 8.10 (br s, 1H), 7.98 (br s, 1H), 7.56 (d, J = 2.1 Hz, 1H), 7.29 - 7.26 (m, 2H), 6.89 (d, J = 9.5 Hz, 1H), 3.94 (s, 3H), 3.70 (s, 2H), 1.47 (s, 9H).

[0346] LC-MS (Method E): Rt 1.21 mins; MS m/z 376.1/ 378.1 = [M+H]+ (92% @ 215nm)

Step 3: N-tert-Butyl-4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide

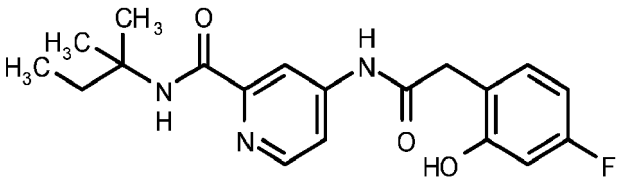
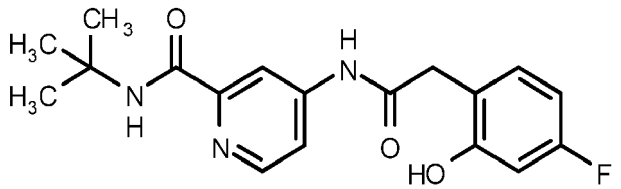
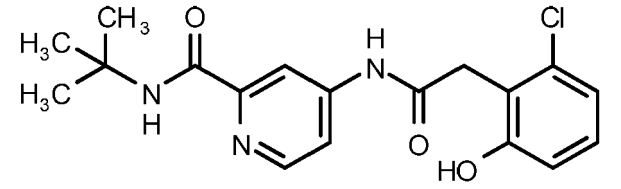
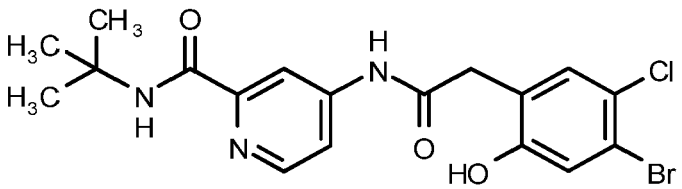
[0347] To a solution of N-tert-butyl-4-[[2-(5-chloro-2-methoxy-phenyl)acetyl]amino]pyridine-2-carboxamide (step 2) (2.7 g, 6.82 mmol, 95%) in DCM (10 mL) at 0 °C was added dropwise 1M BBr3 in DCM (27.3 mL, 27.3 mmol). Once addition was complete the mixture was allowed to warm to room temperature and stirred for 1 hour. The reaction was

quenched by slow addition of water (10 mL) and the DCM removed *in vacuo*. The resulting residue was dissolved in EtOAc and washed with sat. $NaHCO_3$ solution (50 mL) and brine (50 mL). The organic portion was separated, dried Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by chromatography on silica eluting with 0-70% EtOAc in heptane to afford the product as an orange powder. This was further purified by reverse phase chromatography eluting with 0-100% MeCN in water with 0.1% formic acid to give the product as a colourless powder. The product was recrystallised from MeCN to afford the titled compound. A second crop was isolated by dropwise addition of water to the MeCN filtrate followed by heating and cooling of the mixture.

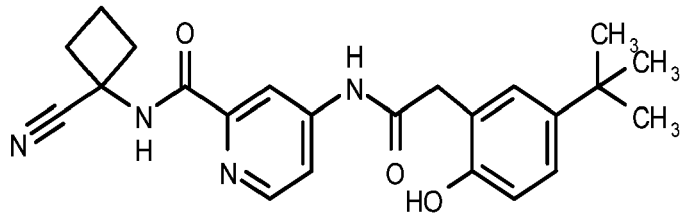
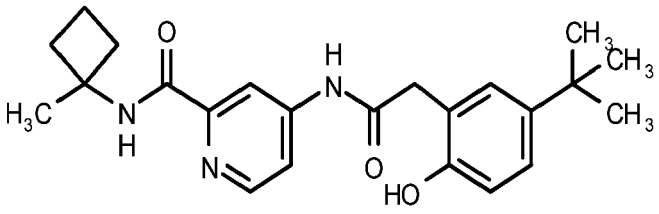
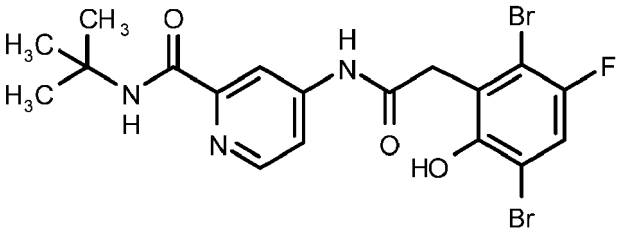
[0348] 1H NMR (500 MHz, DMSO-d6) δ 10.69 (br s, 1H), 9.82 (br s, 1H), 8.44 (d, J = 5.5 Hz, 1H), 8.17 (d, J = 1.9 Hz, 1H), 8.03 (s, 1H), 7.82 (dd, J = 5.5, 2.2 Hz, 1H), 7.22 (d, J = 2.7 Hz, 1H), 7.12 (dd, J = 8.6, 2.7 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 3.67 (s, 2H), 1.40 (s, 9H). LC-MS (Method A): Rt 3.28 mins; MS m/z 362.1/ 364.1 = [M+H]+ (99% @ 215nm)

[0349] Compounds of the following tabulated Examples (Table 3a) were prepared analogously to Example 3 by replacing 2-methylpropan-2-amine (step 1) with the appropriate amine and by replacing 2-(5-chloro-2-methoxy-phenyl)acetic acid (step 2) with the appropriate commercially available acid.

Table 3a

Ex.	Structure and Name	1H NMR, LCMS Retention Time, [M+H]+,
3.1a	 N-(1,1 -Dimethylpropyl)-4-[[2-(4-fluoro-2-hydroxyphenyl)acetyl] amino]pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.69 (s, 1H), 10.05 (br. s, 1H), 8.49 - 8.40 (m, 1H), 8.20 - 8.14 (m, 1H), 7.94 (s, 1H), 7.81 (dd, J = 5.5, 2.2 Hz, 1H), 7.21 - 7.09 (m, 1H), 6.65 - 6.49 (m, 2H), 3.63 (s, 2H), 1.77 (q, J = 7.5 Hz, 2H), 1.34 (s, 6H), 0.81 (t, J = 7.5 Hz, 3H). LC-MS (Method A): Rt 3.25 mins; MS m/z 360.3 = [M+H]+ (100% @ 215nm)
3.2a	 N-tert-Butyl-4-[[2-(4-fluoro-2-hydroxyphenyl)acetyl]amino]pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 12.34 - 9.82 (m, 2H), 9.28-9.21 (m, 1H), 9.00 - 8.96 (m, 1H), 8.84 (s, 1H), 8.62 (dd, J = 5.5, 2.2 Hz, 1H), 8.01 - 7.92 (m, 1H), 7.43 - 7.35 (m, 2H), 4.44 (s, 2H), 2.20 (s, 9H). LC-MS (Method A): Rt 3.00 mins; MS m/z 346.2 = [M+H]+ (100% @ 215nm)
3.3a	 N-tert-Butyl-4-[[2-(2-chloro-6-hydroxyphenyl)acetyl]amino] pyridine-2-carboxamide	1H NMR (500 MHz, Methanol-d4) δ 8.44 - 8.39 (m, 1H), 8.11 - 8.07 (m, 1H), 7.91 (dd, J = 5.6, 2.2 Hz, 1H), 7.09 (t, J = 8.1 Hz, 1H), 6.91 (dd, J = 8.1, 1.0 Hz, 1H), 6.77 (dd, J = 8.2, 1.0 Hz, 1H), 3.96 (s, 2H), 1.47 (s, 9H). LC-MS (Method A): Rt 3.17 mins; MS m/z 362.2/364.2 = [M+H]+ (98%@ 215nm)
3.4a	 4-[[2-(4-Bromo-5-chloro-2-hydroxyphenyl)acetyl]amino]-N-tert-butyl-pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.70 (s, 1H), 10.27 (s, 1H), 8.44 (d, J = 5.5 Hz, 1H), 8.16 (d, J = 2.0 Hz, 1H), 8.03 (s, 1H), 7.80 (dd, J = 5.5, 2.2 Hz, 1H), 7.43 (s, 1H), 7.12 (s, 1H), 3.67 (s, 2H), 1.40 (s, 9H). LC-MS (Method A): Rt 3.59 mins; MS m/z 440.0/441.9/443.9 = [M+H]+ (95% @ 215nm)

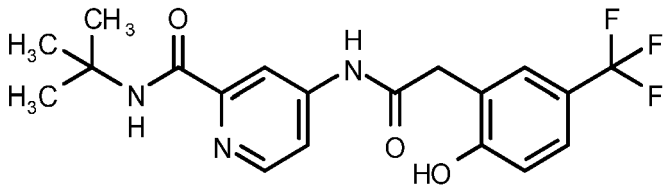
(continued)

Ex.	Structure and Name	1H NMR, LCMS Retention Time, [M+H]+,
3.5a	 4-[[2-(5-tert-Butyl-2-hydroxy-phenyl)acetyl]amino]-N-(1-cyanocyclobutyl)pyridine-2-carboxamide	1H NMR (500 MHz, Methanol-d4) δ 8.48 (d, J = 5.5 Hz, 1H), 8.14 (d, J = 2.0 Hz, 1H), 7.93 (dd, J = 5.5, 2.2 Hz, 1H), 7.21 (d, J = 2.4 Hz, 1H), 7.15 (dd, J = 8.4, 2.5 Hz, 1H), 6.75 (d, J = 8.4 Hz, 1H), 3.72 (s, 2H), 2.84 - 2.75 (m, 2H), 2.63 - 2.53 (m, 2H), 2.28 - 2.16 (m, 1H), 2.18 - 2.06 (m, 1H), 1.28 (s, 9H). LC-MS (Method A): Rt 3.40 mins; MS m/z 407.4 = [M+H]+ (98% @ 215nm)
3.6a	 4-[[2-(5-tert-Butyl-2-hydroxy-phenyl)acetyl]amino]-N-(1-methyl cyclobutyl)pyridine-2-carboxamide	1H NMR (500 MHz, Methanol-d4) δ 8.43 (d, J = 5.4 Hz, 1H), 8.09 (d, J = 1.7 Hz, 1H), 7.90 (dd, J = 5.5, 2.0 Hz, 1H), 7.21 (d, J = 2.4 Hz, 1H), 7.15 (dd, J = 8.4, 2.5 Hz, 1H), 6.75 (d, J = 8.4 Hz, 1H), 3.72 (s, 2H), 2.50 - 2.39 (m, 2H), 2.17 - 2.07 (m, 2H), 1.97 - 1.85 (m, 2H), 1.55 (s, 3H), 1.28 (s, 9H). LC-MS (Method A): Rt 3.77 mins; MS m/z 396.4 = [M+H]+ (100% @ 215nm)
3.7a	 N-tert-butyl-4-[2-(2,5-dibromo-3-fluoro-6-hydroxyphenyl) acetamido]pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.87 (s, 1H), 9.74 (s, 1H), 8.45 (d, J = 5.5 Hz, 1H), 8.15 (d, J = 2.0 Hz, 1H), 8.03 (s, 1H), 7.80 (dd, J = 5.5, 2.2 Hz, 1H), 7.65 (d, J = 8.1 Hz, 1H), 4.03 (s, 2H), 1.40 (s, 9H). LC-MS (Method A): Rt 3.61 mins; MS m/z 502.1/504.1/506.1 = [M+H]+ (99% @ 215nm)

Example 3.5b

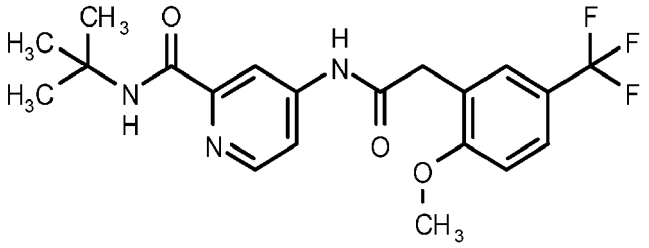
N-tert-Butyl-4-[[2-[2-hydroxy-5-(trifluoromethyl)phenyl]acetyl]amino]pyridine-2-carboxamide

[0350]



Step 1: N-tert-butyl-4-[[2-[2-methoxy-5-(trifluoromethyl)phenyl]acetyl]amino]pyridine-2-carboxamide

[0351]



[0352] To a solution of 4-amino-N-tert-butyl-pyridine-2-carboxamide (Example 3 step 1) (70 mg, 0.36 mmol), TEA (127 μL, 0.72 mmol) and 2-[2-methoxy-5-(trifluoromethyl)phenyl]acetic acid (102 mg, 0.43 mmol) in 1,4-dioxane (1 mL) was added T3P® 50% solution in EtOAc (948 μL, 0.8 mmol) and the reaction mixture was stirred at room temperature for 1 hour. The resulting mixture was partitioned between water (25 mL) and EtOAc (25 mL). The organic layer was separated, washed with water (20 mL), dried over Na_2SO_4 and concentrated *in vacuo.* The crude residue was purified by chromatography on silica eluting with EtOAc in heptane to afford the titled compound as a pale yellow solid.

[0353] 1H NMR (500 MHz, DMSO-d6) δ 10.75 (s, 1H), 8.44 (d, J = 5.5 Hz, 1H), 8.17 (d, J = 2.1 Hz, 1H), 8.03 (s, 1H), 7.80 (dd, J = 5.5, 2.2 Hz, 1H), 7.69 - 7.61 (m, 2H), 7.18 (d, J = 8.5 Hz, 1H), 3.83 (s, 3H), 3.81 (s, 2H), 1.40 (s, 9H).

[0354] LC-MS (Method E): Rt 1.23 mins; MS m/z 410.0 = [M+H]+ (93% @ 215nm)

Step 2: N-tert-Butyl-4-[[2-[2-hydroxy-5-(trifluoromethyl)phenyl]acetyl]amino]pyridine-2-carboxamide

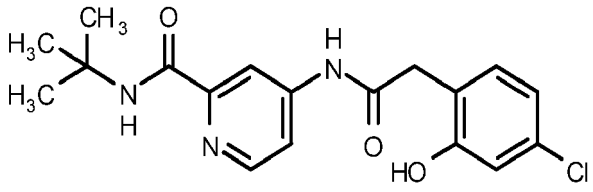
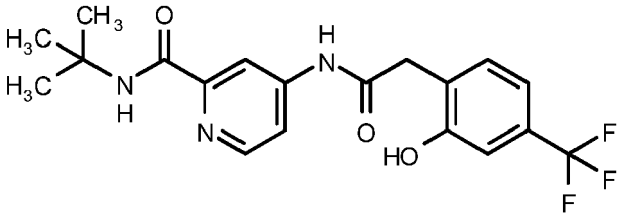
[0355] The titled compound was prepared from N-tert-butyl-4-[[2-[2-methoxy-5-(trifluoromethyl)phenyl]acetyl]amino]pyridine-2-carboxamide (step 2) analogously to Example 3 step 3.

[0356] 1H NMR (500 MHz, DMSO-d6) δ 11.32 - 9.82 (m, 2H), 8.44 (d, J = 5.5 Hz, 1H), 8.17 (d, J = 2.0 Hz, 1H), 8.03 (s, 1H), 7.82 (dd, J = 5.5, 2.2 Hz, 1H), 7.54 (d, J = 2.0 Hz, 1H), 7.45 (dd, J = 8.5, 2.1 Hz, 1H), 6.95 (d,J = 8.4 Hz, 1H), 3.76 (s, 2H), 1.40 (s, 9H).

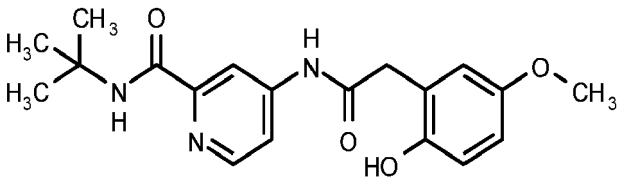
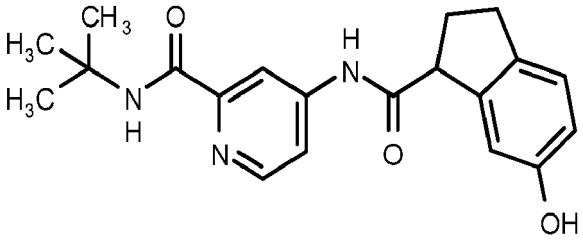
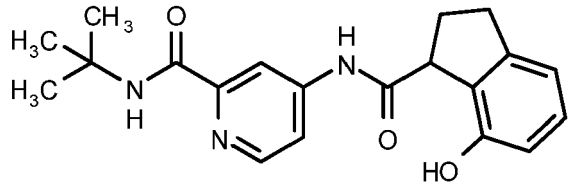
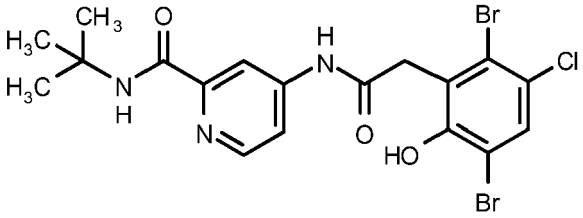
[0357] LC-MS (Method A): Rt 3.41 mins; MS m/z 396.2 = [M+H]+ (100% @ 215nm)

[0358] Compounds of the following tabulated Examples (Table 3b) were prepared analogously Example 3.5b steps 1 and 2 by replacing 2-[2-methoxy-5-(trifluoromethyl)phenyl]acetic acid (step 1) with the appropriate commercially available acid.

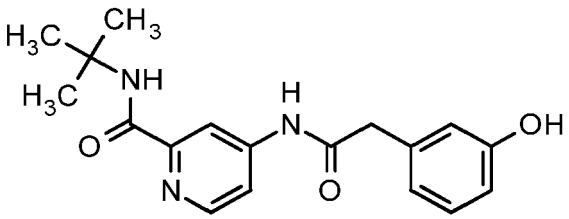
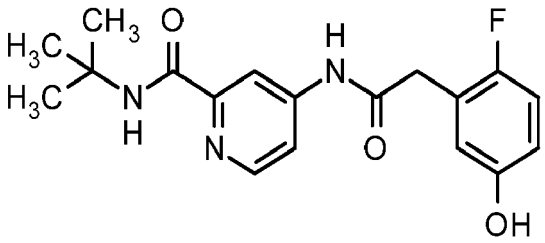
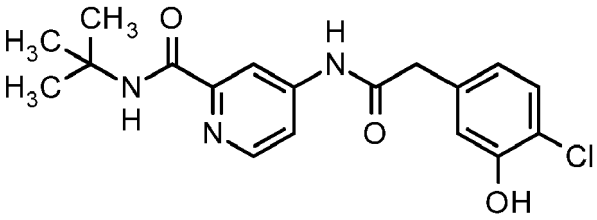
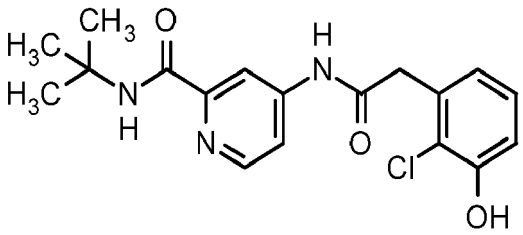
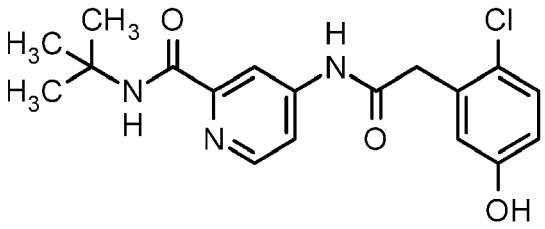
Table 3b

Ex.	Structure and Name	1H NMR LCMS Retention Time, [M+H]+,
3.6b	 N-tert-Butyl-4-[[2-(4-chloro-2-hydroxyphenyl)acetyl]amino] pyridine-2-carboxamide	1H NMR (500 MHz, Methanol-d4) δ 8.42 (d, J = 5.5 Hz, 1H), 8.12 (d, J = 2.0 Hz, 1H), 7.90 (dd, J = 5.5, 2.2 Hz, 1H), 7.14 (d, J = 8.0 Hz, 1H), 6.84 - 6.77 (m, 2H), 3.70 (s, 2H), 1.47 (s, 9H). LC-MS (Method A): Rt 3.33 mins; MS m/z 362.1/364.1 = [M+H]+ (98% @ 215nm)
3.7b	 N-tert-Butyl-4-[[2-[2-hydroxy-4-(trifluoro methyl)phenyl] acetyl]amino]pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.81 (br s, 1H), 10.30 (br s, 1H), 8.44 (d, J = 5.5 Hz, 1H), 8.17 (d, J = 2.0 Hz, 1H), 8.03 (s, 1H), 7.81 (dd, J = 5.5, 2.2 Hz, 1H), 7.38 (d, J = 7.8 Hz, 1H), 7.16 - 7.00 (m, 2H), 3.75 (s, 2H), 1.40 (s, 9H LC-MS (Method A): Rt 3.44 mins; MS m/z 396.2 = [M+H]+ (100% @ 215nm)

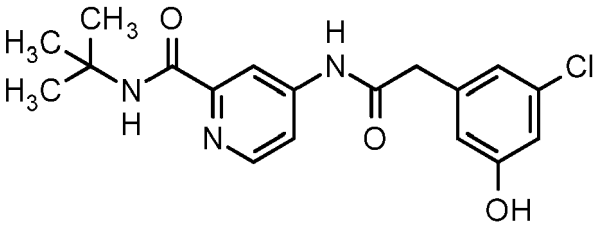
(continued)

Ex.	Structure and Name	1H NMR LCMS Retention Time, [M+H]+,
3.8b	 N-tert-Butyl-4-[[2-(2-hydroxy-5-methoxyphenyl)acetyl]amino] pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.64 (s, 1H), 9.06 (s, 1H), 8.43 (d, J = 5.5 Hz, 1H), 8.18 (d, J = 1.9 Hz, 1H), 8.03 (s, 1H), 7.82 (dd, J = 5.5, 2.2 Hz, 1H), 6.76 (d, J = 3.0 Hz, 1H), 6.71 (d, J = 8.7 Hz, 1H), 6.67 (dd, J = 8.7, 3.0 Hz, 1H), 3.66 (s, 3H), 3.63 (s, 2H), 1.40 (s, 9H). LC-MS (Method A): Rt 2.87 mins; MS m/z 358.2 = [M+H]+ (99% @ 215nm)
3.9b	 N-tert-Butyl-4-[(6-hydroxyindane-1-carbonyl)amino]pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.83 (s, 1H), 9.16 (s, 1H), 8.47 (d, J = 5.5 Hz, 1H), 8.23 (d, J = 2.0 Hz, 1H), 8.05 (s, 1H), 7.90 (dd, J = 5.5, 2.2 Hz, 1H), 7.05 (d, J = 8.1 Hz, 1H), 6.73 (d, J = 1.9 Hz, 1H), 6.60 (dd, J = 8.1, 2.2 Hz, 1H), 4.07 (t, J = 7.4 Hz, 1H), 2.98 - 2.90 (m, 1H), 2.83 - 2.73 (m, 1H), 2.39 - 2.23 (m, 2H), 1.41 (s, 9H). LC-MS (Method A): Rt 3.00 mins; MS m/z354.2 = [M+H]+ (100% @ 215nm)
3.10b	 N-tert-Butyl-4-[(7-hydroxyindane-1-carbonyl)amino]pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.64 (s, 1H), 9.49 (s, 1H), 8.44 (d, J = 5.5 Hz, 1H), 8.20 (d, J = 2.1 Hz, 1H), 8.03 (s, 1H), 7.84 (dd, J = 5.5, 2.2 Hz, 1H), 7.02 (t, J = 7.7 Hz, 1H), 6.72 (d, J = 7.4 Hz, 1H), 6.58 (d, J = 7.9 Hz, 1H), 4.11 (dd, J = 8.6, 5.3 Hz, 1 H), 3.06 - 2.98 (m, 1H), 2.89 - 2.81 (m, 1H), 2.36 - 2.29 (m, 1H), 2.25 - 2.17 (m, 1H), 1.41 (s, 9H). LC-MS (Method A): Rt 3.26 mins; MS m/z 354.2 = [M+H]+ (96% @ 215nm)
3.11b	 N-tert-Butyl-4-[[2-(2,5-dibromo-3-chloro-6-hydroxyphenyl) acetyl]amino]pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.93 (s, 1H), 10.06 (s, 1H), 8.45 (d, J = 5.5 Hz, 1H), 8.14 (d, J = 2.1 Hz, 1H), 8.03 (s, 1H), 7.81 (s, 1H), 7.79 (dd, J = 5.5, 2.2 Hz, 1 H), 4.07 (s, 2H), 1.40 (s, 9H). LC-MS (Method A): Rt 3.84 mins; MS m/z 518.0/520.0/522.1 = [M+H]+ (98% @ 215nm)

(continued)

Ex.	Structure and Name	1H NMR LCMS Retention Time, [M+H]+,
3.12b	 N-tert-Butyl-4-[[2-(3-hydroxyphenyl) acetyl]amino]pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.71 (s, 1H), 9.35 (s, 1H), 8.44 (d, J = 5.5 Hz, 1H), 8.19 (d, J = 2.0 Hz, 1H), 8.02 (s, 1H), 7.81 (dd, J = 5.5, 2.2 Hz, 1H), 7.11 (t, J = 7.9 Hz, 1H), 6.76 - 6.72 (m, 2H), 6.68 - 6.62 (m, 1H), 3.60 (s, 2H), 1.39 (s, 9H). LC-MS (Method A): Rt 2.68 mins; MS m/z 328.2 = [M+H]+ (99% @ 215nm).
3.13b	 N-tert-Butyl-4-[[2-(2-fluoro-5-hydroxy-phenyl) acetyl]amino] pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.77 (s, 1H), 9.33 (s, 1H), 8.45 (d, J = 5.5 Hz, 1H), 8.18 (d, J = 2.0 Hz, 1H), 8.03 (s, 1H), 7.81 (dd, J = 5.5, 2.2 Hz, 1H), 6.97 (t, J = 9.2 Hz, 1H), 6.75 (dd, J = 6.2, 3.0 Hz, 1H), 6.65 (ddd, J = 8.8, 4.0, 3.2 Hz, 1H), 3.70 (s, 2H), 1.40 (s, 9H). LC-MS (Method A): Rt 2.74 mins; MS m/z 346.2 = [M+H]+ (100% @ 215nm)
3.14b	 N-tert-Butyl-4-[[2-(4-chloro-3-hydroxyphenyl)acetyl]amino] pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.74 (s, 1H), 10.14 (s, 1H), 8.45 (d, J = 5.5 Hz, 1H), 8.18 (d, J = 2.1 Hz, 1H), 8.02 (s, 1H), 7.80 (dd, J = 5.5, 2.2 Hz, 1H), 7.26 (d, J = 8.1 Hz, 1H), 6.95 (d, J = 2.0 Hz, 1H), 6.76 (dd, J = 8.1, 2.0 Hz, 1H), 3.62 (s, 2H), 1.40 (s, 9H). LC-MS (Method A): Rt 3.01 mins; MS m/z 362.2/364.2 = [M+H]+ (100% @ 215nm)
3.15b	 N-tert-Butyl-4-[[2-(2-chloro-3-hydroxyphenyl)acetyl]amino] pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.77 (s, 1H), 10.10 (br s, 1H), 8.44 (d, J = 5.5 Hz, 1H), 8.17 (d, J = 2.1 Hz, 1H), 8.03 (s, 1H), 7.80 (dd, J = 5.5, 2.2 Hz, 1H), 7.09 (t, J = 7.8 Hz, 1H), 6.90 (dd, J = 8.2, 1.4 Hz, 1H), 6.84 (dd, J = 7.6, 1.4 Hz, 1H), 3.85 (s, 2H), 1.39 (s, 9H). LC-MS (Method A): Rt 2.97 mins; MS m/z 362.2/364.2= [M+H]+ (100% @ 215nm)
3.16b	 N-tert-Butyl-4-[[2-(2-chloro-5-hydroxy-phenyl) acetyl]amino] pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.78 (s, 1H), 9.64 (s, 1H), 8.45 (d, J = 5.5 Hz, 1H), 8.19 (d, J = 2.0 Hz, 1H), 8.03 (s, 1H), 7.80 (dd, J = 5.5, 2.2 Hz, 1H), 7.21 (d, J = 8.7 Hz, 1H), 6.83 (d, J = 2.9 Hz, 1H),

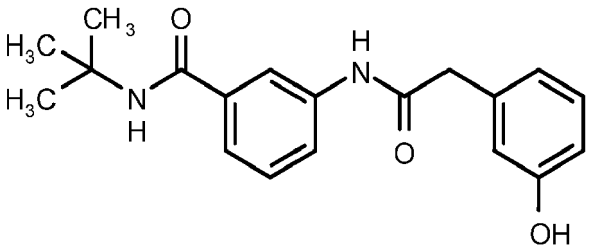
(continued)

Ex.	Structure and Name	1H NMR LCMS Retention Time, [M+H]+,
		6.70 (dd, J = 8.7, 2.9 Hz, 1H), 3.79 (s, 2H), 1.40 (s, 9H). LC-MS (Method A): Rt 2.98 mins; MS m/z 362.2/364.2= [M+H]+ (100% @ 215nm)
3.17b	 N-tert-Butyl-4-[[2-(3-chloro-5-hydroxyphenyl)acetyl]amino] pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.75 (s, 1H), 9.96 (br. s, 1H), 8.46 (d, J = 5.5 Hz, 1H), 8.18 (d, J = 2.1 Hz, 1H), 8.03 (s, 1H), 7.81 (dd, J = 5.5, 2.2 Hz, 1H), 6.83 (t, J = 1.6 Hz, 1H), 6.73 - 6.68 (m, 2H), 3.64 (s, 2H), 1.40 (s, 9H). LC-MS (Method A): Rt 3.12 mins; MS m/z 362.2/364.2= [M+H]+ (100% @ 215nm)

Example 4*

N-tert-Butyl-3-[[2-(3-hydroxyphenyl)acetyl]amino]benzamide

[0359]



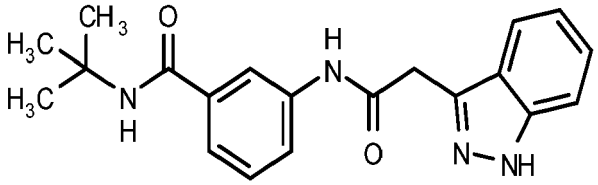
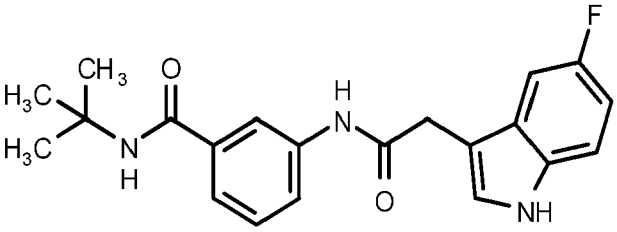
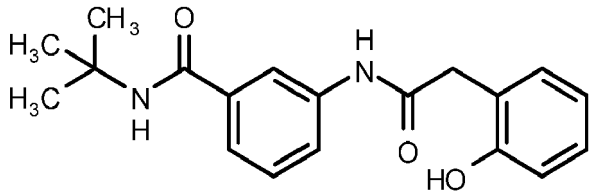
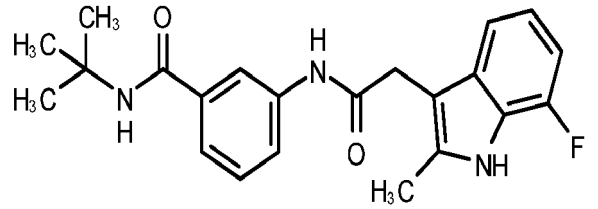
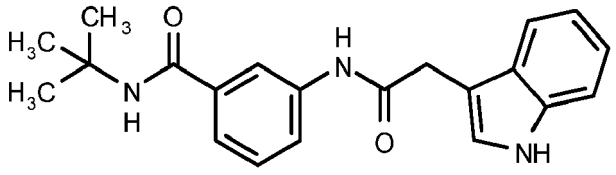
[0360] A mixture comprising 3-amino-N-tert-butyl-benzamide hydrochloride (Example 2 step 1b) (50 mg, 0.22 mmol), EDCI (50 mg, 0.26 mmol), HOAt (36 mg, 0.26 mmol), DIPEA (0.09 mL, 0.52 mmol) in DCM (1.25mL) was treated with 2-(3-hydroxyphenyl)acetic acid (33 mg, 0.22 mmol) and stirred at room temperature for 1 hour. The resulting mixture was diluted with water (5 mL) and extracted with DCM (3 × 5 mL). The combined organics were passed through a PTFE phase separator and concentrated *in vacuo.* The crude product was purified by preparative HPLC (acidic pH, early elution method) and the product fractions were concentrated and dried *in vacuo* to afford the titled compound as a white solid. 1H NMR (500 MHz, Methanol-d4) δ 7.90 (t, J = 1.8 Hz, 1H), 7.72 (s, 1H), 7.69 (ddd, J = 8.0, 2.1, 1.1 Hz, 1H), 7.49 - 7.45 (m, 1H), 7.39 (t, J = 7.9 Hz, 1H), 7.19-7.13 (m, 1H), 6.87 -6.81 (m, 2H), 6.73-6.68 (m, 1H), 3.63 (s, 2H), 1.46 (s, 9H).

[0361] LC-MS (Method B): Rt 2.56 mins; MS m/z 344.3 = $[M+NH_3]+$ (99% @ 215nm)

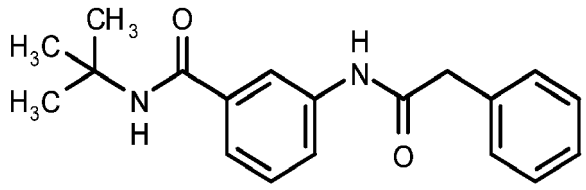
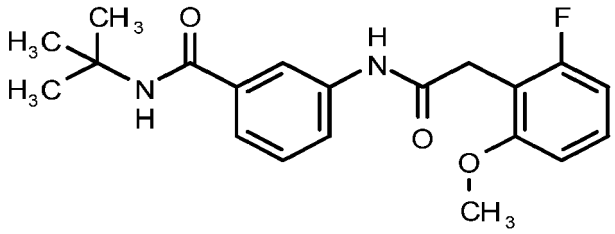
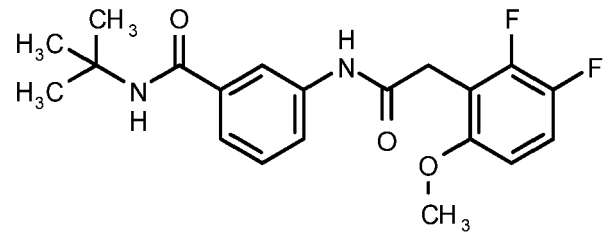
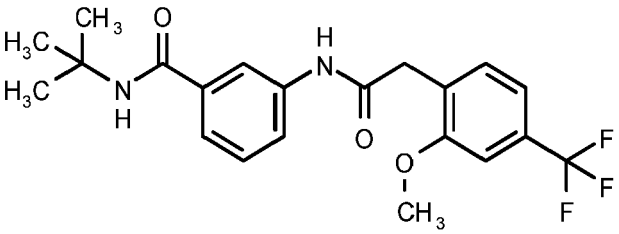
[0362] The compounds of the following tabulated Examples (Table 4) were prepared analogously to Example 4 by replacing 2-(3-hydroxyphenyl)acetic acid with the appropriate commercially available acid.

Table 4

(* denotes a reference compound that is not claimed)

Ex.	Structure and Name	1H NMR LCMS Retention Time, [M+H]+,
4.1*	 N-tert-Butyl-3-[[2-(1H-indazol-3-yl)acetyl]amino] benzam ide	1H NMR (500 MHz, Chloroform-d) δ 10.12 (s, 1H), 8.93 (s, 1H), 7.83 - 7.75 (m, 3H), 7.52 (d, J = 8.4 Hz, 1H), 7.47 - 7.43 (m, 1H), 7.40 (d, J = 7.7 Hz, 1H), 7.34 (t, J = 7.8 Hz, 1H), 7.23 (t, J = 7.5 Hz, 1H), 5.96 (s, 1H), 4.14 (s, 2H), 1.46 (s, 9H). LC-MS (Method A): Rt 2.64 mins; MS m/z 351.2 = [M+H]+ (100% @ 215nm)
4.2*	 N-tert-Butyl-3-[[2-(5-fluoro-1H-indol-3-yl)acetyl] amino] benzamide	1H NMR (500 MHz, Chloroform-d) δ 8.67 (s, 1H), 7.71 (d, J = 8.2 Hz, 1H), 7.61 - 7.57 (m, 2H), 7.35 (d, J = 7.8 Hz, 1H), 7.34 - 7.27 (m, 2H), 7.22 (dd, J = 9.5, 2.1 Hz, 2H), 6.98 (td, J = 9.0, 2.4 Hz, 1H), 5.97 (s, 1H), 3.82 (s, 2H), 1.44 (s, 9H). LC-MS (Method A): Rt 2.97 mins; MS m/z 368.2 = [M+H]+ (100% @ 215nm)
4.3*	 N-tert-Butyl-3-[[2-(2-hydroxyphenyl)acetyl]amino] benzamide	1H NMR (500 MHz, Methanol-d4) δ 7.86 (t, J = 1.7 Hz, 1H), 7.70-7.63 (m, 1H), 7.44 (d, J = 7.8 Hz, 1H), 7.36 (t, J = 7.9 Hz, 1H), 7.19 (d, J = 7.5 Hz, 1H), 7.11 (td, J = 8.0, 1.6 Hz, 1H), 6.89 - 6.75 (m, 2H), 3.70 (s, 2H), 1.44 (s, 9H). LC-MS (Method A): Rt 2.72 mins; MS m/z 327.3 = [M+H]+ (100% @ 215nm)
4.4*	 N-tert-Butyl-3-[[2-(7-fluoro-2-methyl-1H-indol-3-yl)acetyl] amino]benzamide	1H NMR (500 MHz, Chloroform-d) δ 8.35 (s, 1H), 7.71 (ddd, J = 8.0, 2.0, 1.1 Hz, 1H), 7.54 (t, J = 1.9 Hz, 1H), 7.40 (s, 1H), 7.35 (dt, J = 7.7, 1.3 Hz, 1H), 7.30 (t, J = 7.8 Hz, 1H), 7.24 (d, J = 7.9 Hz, 1H), 7.04 (td, J = 7.9, 4.7 Hz, 1H), 6.90 (ddd, J = 11.0, 7.9, 0.6 Hz, 1H), 5.93 (s, 1H), 3.81 (s, 2H), 2.47 (s, 3H), 1.43 (s, 9H). LC-MS (Method A): Rt 3.15 mins; MS m/z 382.2 = [M+H]+ (100% @ 215nm)
4.5*	 N-tert-Butyl-3-[[2-(1H-indol-3-yl)acetyl]amino] benzam ide	1H NMR (500 MHz, DMSO-d6) δ 10.91 (s, 1H), 10.19 (s, 1H), 7.89 (t, J = 1.8 Hz, 1H), 7.81 - 7.75 (m, 1H), 7.70 (s, 1H), 7.61 (d, J = 7.9 Hz, 1H), 7.41 (dt, J = 7.9, 1.3 Hz, 1H), 7.35 (d, J = 8.1 Hz, 1H), 7.32 (t, J = 7.9 Hz, 1H), 7.26 (d, J = 2.3 Hz, 1H), 7.07 (td, J = 8.0, 7.0, 1.1 Hz, 1H), 6.98 (td, J = 7.5, 7.1, 0.9 Hz, 1H), 3.73 (s, 2H), 1.36 (s, 9H). LC-MS (Method A): Rt 2.91 mins; MS m/z 350.2 = [M+H]+ (100% @ 215nm)

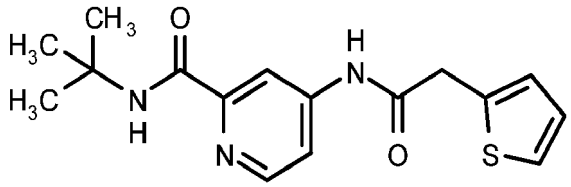
(continued)

(* denotes a reference compound that is not claimed)		
Ex.	**Structure and Name**	**1H NMR LCMS Retention Time, [M+H]+,**
4.6*	 N-tert-Butyl-3-[(2-phenylacetyl) amino]benzamide	1H NMR (500 MHz, Chloroform-d) δ 7.72 (d, J = 7.9 Hz, 1H), 7.65 (d, J = 1.8 Hz, 1H), 7.44 - 7.38 (m, 3H), 7.38 - 7.31 (m, 4H), 7.13 (s, 1H), 5.95 (s, 1H), 3.76 (s, 2H), 1.45 (s, 9H). LC-MS (Method A): Rt 2.96 mins; MS m/z 311.2 = [M+H]+ (99% @ 215nm)
4.7*	 N-tert-Butyl-3-[[2-(2-fluoro-6-methoxyphenyl)acetyl]amino] benzamide	1H NMR (500 MHz, DMSO-d6) δ 10.24 (s, 1H), 7.92 - 7.87 (m, 1H), 7.75 - 7.67 (m, 2H), 7.41 (d, J = 7.8 Hz, 1H), 7.35 - 7.25 (m, 2H), 6.86 (d, J = 8.4 Hz, 1H), 6.80 (t, J = 8.7 Hz, 1H), 3.79 (s, 3H), 3.68 (s, 2H), 1.36 (s, 9H). LC-MS (Method A): Rt 3.01 mins; MS m/z 359.1 = [M+H]+ (100% @ 215nm)
4.8*	 N-tert-Butyl-3-[[2-(2,3-difluoro-6-methoxyphenyl)acetyl] amino]benzamide	1H NMR (500 MHz, Chloroform-d) δ 7.75 (t, J = 1.8 Hz, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.61 (s, 1H), 7.40 (d, J = 7.8 Hz, 1H), 7.34 (t, J = 7.9 Hz, 1H), 7.10 (q, J = 9.2 Hz, 1H), 6.65 (ddd, J = 9.2, 3.4, 2.0 Hz, 1H), 5.97 (s, 1H), 3.90 (s, 3H), 3.79 (d, J = 1.6 Hz, 2H), 1.45 (s, 9H). LC-MS (Method A): Rt 3.19 mins; MS m/z 377.3 = [M+H]+ (98% @ 215nm)
4.9*	 N-tert-Butyl-3-[[2-[2-methoxy-4-(trifluoromethyl) phenyl] acetyl]amino]benzamide	1H NMR (500 MHz, DMSO-d6) δ 10.24 (s, 1H), 7.90 (t, J = 1.8 Hz, 1H), 7.79 - 7.68 (m, 2H), 7.44 (dd, J = 14.6, 7.8 Hz, 2H), 7.33 (t, J = 7.9 Hz, 1H), 7.28 (d, J = 7.8 Hz, 1H), 7.25 (s, 1H), 3.85 (s, 3H), 3.73 (s, 2H), 1.36 (s, 9H). LC-MS (Method A): Rt 3.45 mins; MS m/z 409.2 = [M+H]+ (100% @ 215nm)

Example 5

N-tert-Butyl-4-[[2-(2-thienyl)acetyl]amino]pyridine-2-carboxamide

[0363]



[0364] A solution of 4-amino-N-tert-butyl-pyridine-2-carboxamide (Example 3 step 1) (50 mg, 0.26 mmol), 2-(2-thienyl)acetic acid (37 mg, 0.26 mmol) and TEA (0.09 mL, 0.52 mmol) in 1,4-dioxane (2 mL) was treated with 50% T3P® solution in EtOAc (617 μL, 0.97 mmol) and stirred at room temperature under an inert atmosphere for 1 hour. The resulting mixture was diluted with EtOAc (10 mL) and washed with water (10 mL). The organic portion was separated and concentrated *in vacuo*. Purification by preparative HPLC (acidic pH, standard elution method) and freeze drying of the product fractions afforded the titled compound as a white solid.

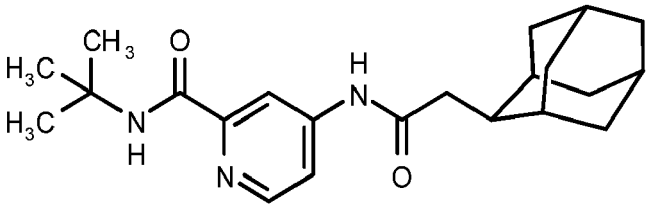
[0365] 1H NMR (500 MHz, DMSO-d6) δ 10.80 (s, 1H), 8.46 (d, *J*= 5.5 Hz, 1H), 8.19 (d, *J* = 2.0 Hz, 1H), 8.03 (s, 1H), 7.80 (dd, J = 5.5, 2.2 Hz, 1H), 7.41 (dd, J = 5.0, 1.4 Hz, 1H), 7.03 - 6.94 (m, 2H), 3.95 (s, 2H), 1.40 (s, 9H)

[0366] LC-MS (Method A): Rt 3.19 mins; MS m/z 318.2 = [M+H]+ (99% @ 215nm).

Example 5.1

4-[[2-(2-Adamantyl)acetyl]amino]-N-tert-butyl-pyridine-2-carboxamide

[0367]



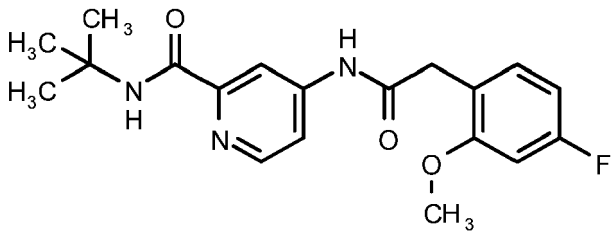
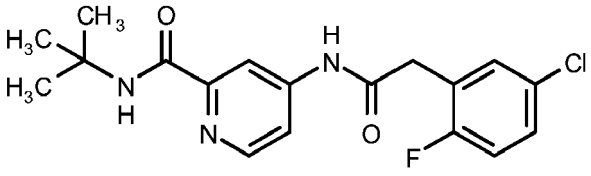
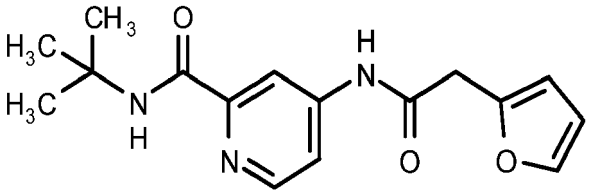
[0368] A solution of 2-(2-adamantyl)acetic acid (40 mg, 0.21 mmol) in thionyl chloride (160 μL, 1.82 mmol) was heated at 70°C for 30 minutes. Excess thionyl chloride was removed in *vacuo* (azeotropic drying with DCM) and the residue was treated with a mixture of 4-amino-N-tert-butyl-pyridine-2-carboxamide (Example 3 step 1) (40 mg, 0.21 mmol) and DIPEA (43 μL, 0.25 mmol) in DCM (1.5 mL) and stirred at room temperature for 1 hour. The resulting mixture was partitioned with water (5 mL) and DCM (5 mL). The phases were separated through a PTFE-fritted separator and the organic layer concentrated *in vacuo*. The crude product was purified by preparative HPLC (acidic pH, standard elution method) and the product fractions concentrated *in vacuo* to afford the titled compound as a white crystalline solid.

[0369] 1H NMR (500 MHz, DMSO-d6) δ 10.50 (s, 1H), 8.42 (d, J = 5.5 Hz, 1H), 8.19 (d, J = 2.0 Hz, 1H), 8.02 (s, 1H), 7.79 (dd, J = 5.5, 2.2 Hz, 1H), 2.54 - 2.51 (m, 2H), 2.27 - 2.19 (m, 1H), 1.94 - 1.87 (m, 2H), 1.87 - 1.83 (m, 1H), 1.83 - 1.77 (m, 3H), 1.77 - 1.71 (m, 2H), 1.71 - 1.65 (m, 4H), 1.54-1.49 (m, 2H), 1.39 (s, 9H).

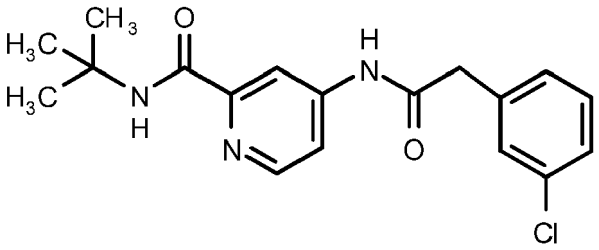
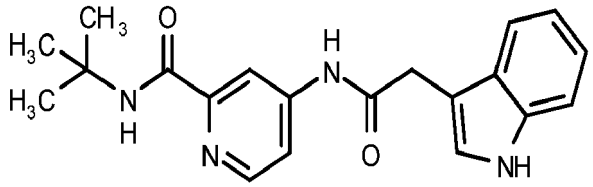
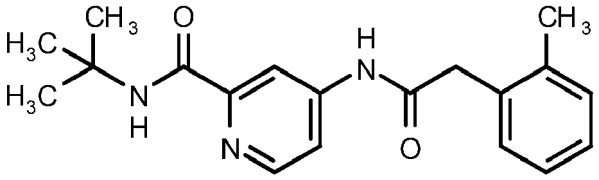
[0370] LC-MS (Method A): Rt 4.29 mins; MS m/z 370.3 = [M+H]+ (100% @ 215nm)

[0371] The compounds of the following tabulated Examples (Table 5) were prepared analogously to either Example 5 (using T3P®) or Example 5.1 (using thionyl chloride) from 4-amino-N-tert-butyl-pyridine-2-carboxamide (Example 3 step 1) and the appropriate commercially available acid.

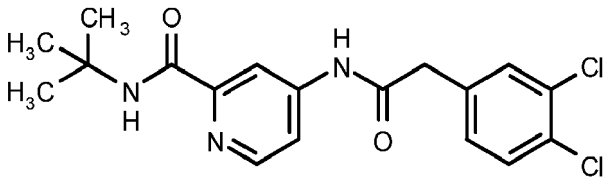
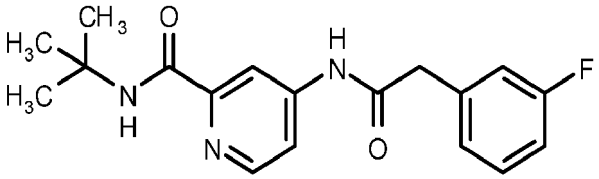
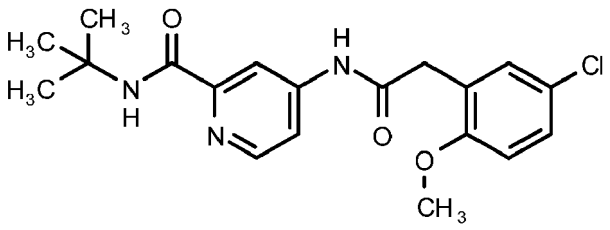
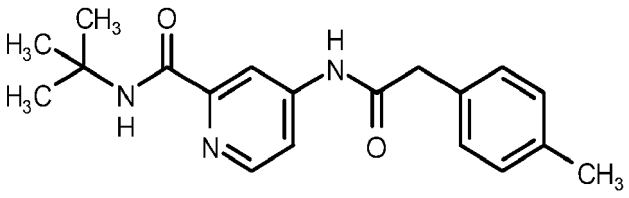
Table 5

Ex.	Structure and Name	Activating Reagent	1H NMR LCMS Retention Time, [M+H]+,
5.2	 N-tert-Butyl-4-[[2-(4-fluoro-2-methoxyphenyl)acetyl]amino] pyridine-2-carboxamide	Thionyl Chloride	1H NMR (500 MHz, Chloroform-d) δ 8.39 (d, J = 5.6 Hz, 1H), 8.21 (dd, J = 5.6, 2.2 Hz, 1H), 8.01-7.93 (m, 2H), 7.55 (d, J = 2.1 Hz, 1H), 7.23 (dd, J = 8.9, 6.5 Hz, 1H), 6.74 - 6.67 (m, 2H), 3.93 (s, 3H), 3.69 (s, 2H), 1.47 (s, 9H). LC-MS (Method A): Rt 3.31 mins; MS m/z 360.2 = [M+H]+ (97% @ 215nm)
5.3	 N-tert-Butyl-4-[[2-(5-chloro-2-fluorophenyl)acetyl]amino] pyridine-2-carboxamide	Thionyl Chloride	1H NMR (500 MHz, DMSO-d6) δ 10.84 (s, 1H), 8.46 (d, J = 5.5 Hz, 1H), 8.16 (d, J = 1.9 Hz, 1H), 8.03 (s, 1H), 7.80 (dd, J = 5.5, 2.2 Hz, 1H), 7.51 (dd, J = 6.4, 2.7 Hz, 1H), 7.40 (ddd, J = 8.7, 4.4, 2.8 Hz, 1H), 7.26 (t, J = 9.1 Hz, 1H), 3.83 (s, 2H), 1.40 (s, 9H). LC-MS (Method A): Rt 3.61 mins; MS m/z 364.2/366.2 = [M+H]+ (97% @ 215nm)
5.4	 N-tert-Butyl-4-[[2-(2-furyl)acetyl]amino] pyridine-2-carboxamide	T3P®	1H NMR (500 MHz, DMSO-d6) δ 10.77 (s, 1H), 8.46 (d, *J* = 5.5 Hz, 1H), 8.18 (d, *J* = 2.0 Hz, 1H), 8.03 (s, 1H), 7.80 (dd, J= 5.5, 2.2 Hz, 1H), 7.58 (dd, *J* = 1.8, 0.7 Hz, 1H), 6.41 (dd, J= 3.1, 1.9 Hz, 1H), 6.36 - 6.24 (m, 1H), 3.81 (s, 2H), 1.40 (s, 9H). LC-MS (Method A): Rt 2.97 mins; MS m/z 302.2 = [M+H]+ (100% @ 215nm)

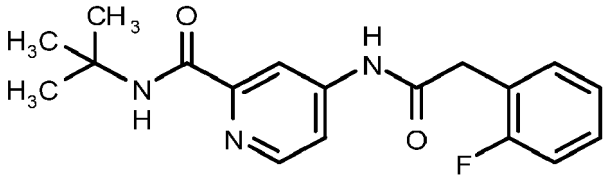
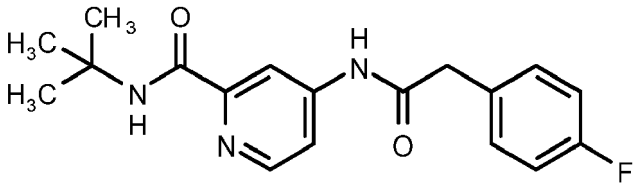
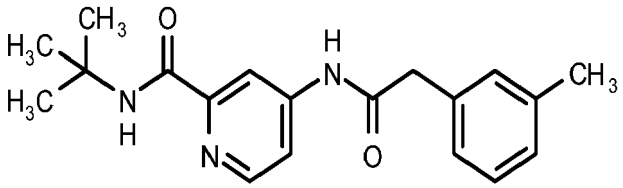
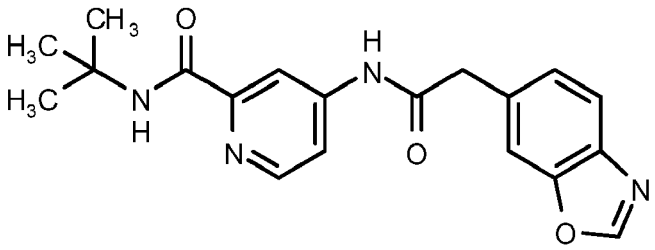
(continued)

Ex.	Structure and Name	Activating Reagent	1H NMR LCMS Retention Time, [M+H]+,
5.5	 N-tert-Butyl-4-[[2-(3-chlorophenyl) acetyl]amino]pyridine-2-carboxamide	T3P®	1H NMR (500 MHz, DMSO-d6) δ 10.78 (s, 1H), 8.45 (d, *J* = 5.5 Hz, 1H), 8.18 (d, *J* = 2.0 Hz, 1H), 8.03 (s, 1H), 7.81 (dd, J = 5.5, 2.2 Hz, 1H), 7.43-7.41 (m, 1H), 7.39 - 7.31 (m, 2H), 7.31-7.27 (m, 1H), 3.75 (s, 2H), 1.39 (s, 9H) LC-MS (Method A): Rt 3.60 mins; MS m/z 346.2, 348.2 = [M+H]+ (100% @ 215nm)
5.6	 N-tert-Butyl-4-[[2-(1H-indol-3-yl)acetyl] amino]pyridine-2-carboxamide	T3P®	1H NMR (500 MHz, DMSO-d6) δ 10.95 (s, 1H), 10.71 (s, 1H), 8.43 (d, J = 5.5 Hz, 1H), 8.20 (d, J = 2.1 Hz, 1H), 8.02 (s, 1H), 7.82 (dd, J = 5.5, 2.2 Hz, 1H), 7.58 (d, J = 7.9 Hz, 1H), 7.36 (d, J = 8.1 Hz, 1H), 7.28 (d, J = 2.1 Hz, 1H), 7.10 - 7.05 (m, 1H), 7.01 - 6.96 (m, 1H), 3.80 (s, 2H), 1.39 (s, 9H). LC-MS (Method A): Rt 3.19 mins; MS m/z 351.2 = [M+H]+ (97% @ 215nm)
5.7	 N-tert- Butyl-4-[[2- (o-tolyl) acetyl]am i no] pyrid i ne-2-carboxamide	T3P®	1H NMR (500 MHz, DMSO-d6) δ 10.76 (s, 1H), 8.45 (d, J = 5.5 Hz, 1H), 8.19 (d, J = 2.0 Hz, 1H), 8.03 (s, 1H), 7.81 (dd, J = 5.5, 2.2 Hz, 1H), 7.27 - 7.22 (m, 1H), 7.20 - 7.12 (m, 3H), 3.75 (s, 2H), 2.28 (s, 3H), 1.39 (s, 9H). LC-MS (Method A): Rt 3.46 mins; MS m/z 326.2 = [M+H]+ (98% @ 215nm)

(continued)

Ex.	Structure and Name	Activating Reagent	1H NMR LCMS Retention Time, [M+H]+,
5.8	 N-tert-Butyl-4-[[2-(3,4-dichlorophenyl) acetyl]amino]pyridine-2-carboxamide	T3P®	1H NMR (500 MHz, DMSO-d6) δ 11.62 (s, 1H), 9.26 (d, J = 5.5 Hz, 1H), 8.98 (d, J = 2.0 Hz, 1H), 8.84 (s, 1H), 8.61 (dd, J = 5.5, 2.2 Hz, 1H), 8.42 (d, J = 2.0 Hz, 1H), 8.41 (d, J = 8.3 Hz, 1H), 8.13 (dd, J = 8.3, 2.0 Hz, 1H), 4.59 (s, 2H), 2.20 (s, 9H). LC-MS (Method A): Rt 3.86 mins; MS m/z 380.1/ 382.1/ 384.1 = [M+H]+ (100% @ 215nm)
5.9	 N-tert-Butyl-4-[[2-(3-fluorophenyl)acetyl] amino]pyridine-2-carboxamide	T3P®	1H NMR (500 MHz, DMSO-d6) δ 10.79 (s, 1H), 8.45 (d, J = 5.5 Hz, 1H), 8.18 (d, J = 2.0 Hz, 1H), 8.02 (s, 1H), 7.81 (dd, J = 5.5, 2.1 Hz, 1H), 7.42 - 7.33 (m, 1H), 7.21 - 7.14 (m, 2H), 7.12 - 7.05 (m, 1H), 3.76 (s, 2H), 1.39 (s, 9H). LC-MS (Method A): Rt 3.39 mins; MS m/z 330.2 = [M+H]+ (99% @ 215nm)
5.10	 N-tert-Butyl-4-[[2-(5-chloro-2-methoxyphenyl)acetyl]amino] pyridine-2-carboxamide	Thionyl Chloride	1H NMR (500 MHz, DMSO-d6) δ 10.70 (s, 1H), 8.44 (d, J = 5.5 Hz, 1H), 8.17 (d, J = 1.9 Hz, 1H), 8.03 (s, 1H), 7.80 (dd, J = 5.5, 2.2 Hz, 1H), 7.33 - 7.28 (m, 2H), 7.03 - 6.99 (m, 1H), 3.75 (s, 3H), 3.71 (s, 2H), 1.40 (s, 9H). LC-MS (Method A): Rt 3.61 mins; MS m/z 376.2/378.2 = [M+H]+ (98% @ 215nm)
5.11	 N-tert- Butyl-4-[[2- (p-tolyl) acetyl]am i no] pyrid i ne-2-carboxamide	T3P®	1H NMR (500 MHz, Methanol-d4) δ 8.42 (d, J = 5.5 Hz, 1H), 8.13 (d, J = 2.0 Hz, 1H), 7.89 (dd, J = 5.5, 2.2 Hz, 1H), 7.22 (d, J = 8.0 Hz, 2H), 7.14 (d, J = 7.9 Hz, 2H), 3.68 (s, 2H), 2.31 (s, 3H), 1.47 (s, 9H). LC-MS (Method A):Rt 3.52 mins; MS m/z 326.2 = [M+H]+ (98% @ 215nm)

(continued)

Ex.	Structure and Name	Activating Reagent	1H NMR LCMS Retention Time, [M+H]+,
5.12	 N-tert-Butyl-4-[[2-(2-fluorophenyl) acetyl]amino]pyridine-2-carboxamide	T3P®	1H NMR (500 MHz, Methanol-d4) δ 8.43 (d, J = 5.3 Hz, 1H), 8.13 (d, J = 1.8 Hz, 1H), 7.90 (dd, J = 5.5, 2.2 Hz, 1H), 7.36 (td, J = 7.6, 1.6 Hz, 1H), 7.31 (tdd, J = 7.4, 5.3, 1.8 Hz, 1H), 7.16 (td, J = 7.5, 1.1 Hz, 1H), 7.10 (ddd, J = 9.5, 8.3, 1.0 Hz, 1H), 3.82 (s, 2H), 1.47 (s, 9H). LC-MS (Method A): Rt 3.30 mins; MS m/z 330.2 = [M+H]+ (98% @ 215nm)
5.13	 N-tert-Butyl-4-[[2-(4-fluorophenyl) acetyl]amino]pyridine-2-carboxamide	T3P®	1H NMR (500 MHz, Methanol-d4) δ 8.43 (d, J = 5.5 Hz, 1H), 8.13 (d, J = 1.9 Hz, 1H), 7.90 (dd, J = 5.5, 2.2 Hz, 1H), 7.36 (dd, J = 8.7, 5.4 Hz, 2H), 7.10 - 7.01 (m, 2H), 3.72 (s, 2H), 1.47 (s, 9H). LC-MS (Method A): Rt 3.34 mins; MS m/z 330.2 = [M+H]+ (98% @ 215nm)
5.14	 N-tert-Butyl-4-[[2-(m-tolyl)acetyl] amino]pyridine-2-carboxamide	T3P®	1H NMR (500 MHz, DMSO-d6) δ 10.74 (s, 1H), 8.44 (d, J = 5.5 Hz, 1H), 8.18 (d, J = 2.1 Hz, 1H), 8.02 (s, 1H), 7.81 (dd, J = 5.5, 2.1 Hz, 1H), 7.21 (t, J = 7.5 Hz, 1H), 7.14 (s, 1H), 7.12 (d, J = 7.6 Hz, 1H), 7.07 (d, J = 7.6 Hz, 1H), 3.66 (s, 2H), 2.29 (s, 3H), 1.39 (s, 9H). LC-MS (Method A): Rt 3.58 mins; MS m/z 326.2 = [M+H]+ (98% @ 215nm)
5.15	 4-[[2-(1,3-Benzoxazol-6-yl)acetyl]amino]-N-tert-butyl-pyridine-2-carboxamide	T3P®	1H NMR (500 MHz, Methanol-d4) δ 8.46 (s, 1H), 8.42 (d, J = 5.5 Hz, 1H), 8.14 (d, J = 1.9 Hz, 1H), 7.90 (dd, J = 5.6, 2.2 Hz, 1H), 7.79 - 7.73 (m, 1H), 7.64 (d, J = 8.4 Hz, 1H), 7.45 (dd, J = 8.5, 1.6 Hz, 1H), 3.88 (s, 2H), 1.47 (s, 9H). LC-MS (Method A): Rt 2.82 mins; MS m/z 353.1 = [M+H]+ (98% @ 215nm)

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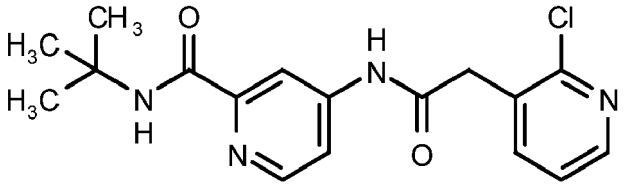
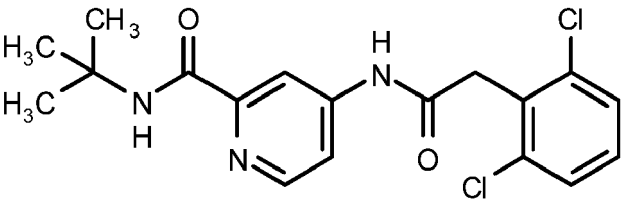
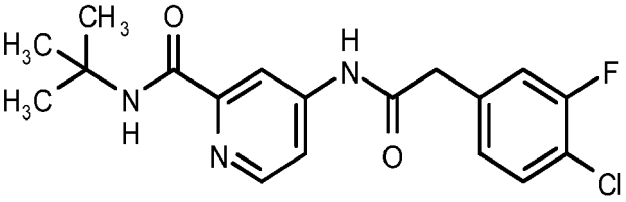
Ex.	Structure and Name	Activating Reagent	1H NMR LCMS Retention Time, [M+H]+,
5.16	 N-tert-Butyl-4-[[2-(2-chloro-3-pyridyl) acetyl]amino]pyridine-2-carboxamide	T3P®	1H NMR (500 MHz, DMSO-d6) δ 10.89 (s, 1H), 8.46 (d, J = 5.5 Hz, 1H), 8.35 (dd, J = 4.8, 1.8 Hz, 1H), 8.18 (d, J = 2.1 Hz, 1H), 8.03 (s, 1H), 7.90 (dd, J = 7.5, 1.8 Hz, 1H), 7.80 (dd, J = 5.5, 2.2 Hz, 1H), 7.44 (dd, J = 7.5, 4.8 Hz, 1H), 3.95 (s, 2H), 1.40 (s, 9H). LC-MS (Method A): Rt 2.76 mins; MS m/z 347.1, 349.1 = [M+H]+ (97% @ 215nm)
5.17	 N-tert-Butyl-4-[[2-(2,6-dichlorophenyl) acetyl]amino]pyridine-2-carboxamide	T3P®	1H NMR (500 MHz, DMSO-d6) δ 10.95 (s, 1H), 8.46 (d, J = 5.5 Hz, 1H), 8.16 (d, J = 2.1 Hz, 1H), 8.03 (s, 1H), 7.78 (dd, J = 5.5, 2.2 Hz, 1H), 7.51 (d, J = 8.1 Hz, 2H), 7.40 - 7.32 (m, 1H), 4.11 (s, 2H), 1.40 (s, 9H). LC-MS (Method A): Rt 3.66 mins; MS m/z 380.1/ 382.1/ 384.1 = [M+H]+ (98% @ 215nm)
5.18	 N-tert-Butyl-4-[[2-(4-chloro-3-fluorophenyl)acetyl]amino] pyridine-2-carboxamide	T3P®	1H NMR (500 MHz, DMSO-d6) δ 10.78 (s, 1H), 8.46 (d, J = 5.5 Hz, 1H), 8.17 (d, J = 2.1 Hz, 1H), 8.03 (s, 1H), 7.80 (dd, J = 5.5, 2.2 Hz, 1H), 7.55 (t, J = 8.1 Hz, 1H), 7.39 (dd, J = 10.5, 1.8 Hz, 1H), 7.20 (dd, J = 8.2, 1.6 Hz, 1H), 3.78 (s, 2H), 1.40 (s, 9H). LC-MS (Method A): Rt 3.67 mins; MS m/z 364.1/ 366.1 = [M+H]+ (97% @ 215nm)

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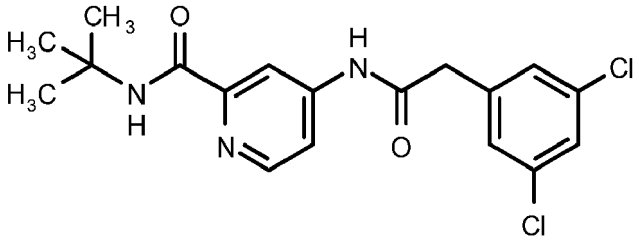
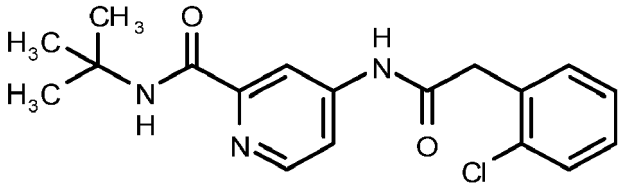
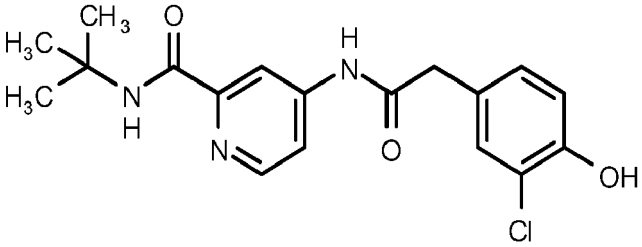
Ex.	Structure and Name	Activating Reagent	1H NMR LCMS Retention Time, [M+H]+,
5.19	 N-tert-Butyl-4-[[2-(3,5-dichloro phenyl)acetyl]amino]pyridine-2-carboxamide	T3P®	1H NMR (250 MHz, DMSO-d6) δ 10.78 (s, 1H), 8.46 (d, J = 5.5 Hz, 1H), 8.16 (d, J = 1.9 Hz, 1H), 8.03 (s, 1H), 7.81 (dd, J = 5.5, 2.2 Hz, 1H), 7.52 (t, J = 1.9 Hz, 1H), 7.41 (d, J = 1.9 Hz, 2H), 3.80 (s, 2H), 1.40 (s, 9H). LC-MS (Method A): Rt 3.99 mins; MS m/z 380.1 /382.1 /384.1 = [M+H]+ (94% @ 215nm)
5.20	 N-tert-Butyl-4-[[2-(2-chlorophenyl) acetyl]amino]pyridine-2-carboxamide	T3P®	1H NMR (500 MHz, DMSO-d6) δ 10.84 (s, 1H), 8.45 (d, J = 5.5 Hz, 1H), 8.19 (d, J = 2.0 Hz, 1H), 8.03 (s, 1H), 7.81 (dd, J = 5.5, 2.1 Hz, 1H), 7.50 - 7.40 (m, 2H), 7.36 - 7.28 (m, 2H), 3.92 (s, 2H), 1.40 (s, 9H). LC-MS (Method A): Rt 3.44 mins; MS m/z 346.1/348.1 = [M+H]+ (100% @ 215nm)
5.21	 N-tert-Butyl-4-[[2-(3-chloro-4-hydroxyphenyl)acetyl]amino] pyridine-2-carboxamide	T3P®	1H NMR (500 MHz, Methanol-d4) δ 8.42 (d, J = 5.5 Hz, 1H), 8.12 (d, J = 2.0 Hz, 1H), 7.90 (dd, J = 5.5, 2.2 Hz, 1H), 7.29 (d, J = 2.1 Hz, 1H), 7.09 (dd, J = 8.3, 2.2 Hz, 1H), 6.87 (d, J = 8.3 Hz, 1H), 3.62 (s, 2H), 1.47 (s, 9H). LC-MS (Method A): Rt 3.03 mins; MS m/z 362.1/ 364.1 = [M+H]+ (99% @ 215nm)

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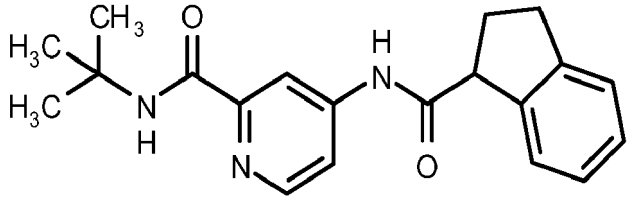
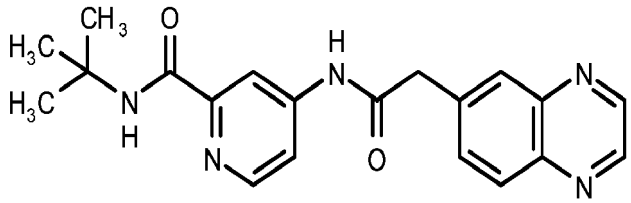
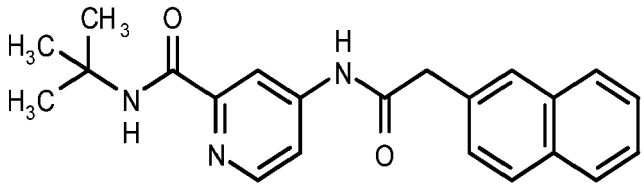
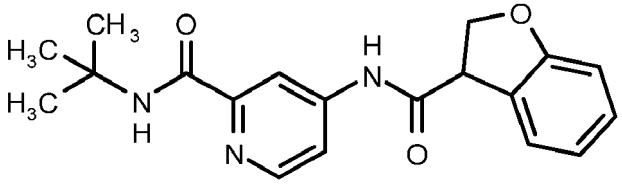
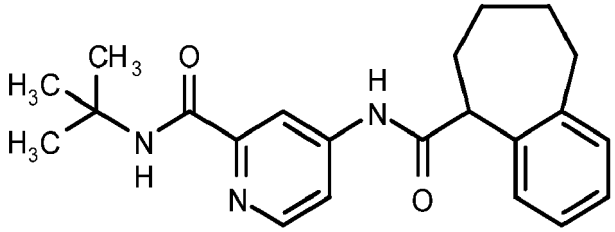
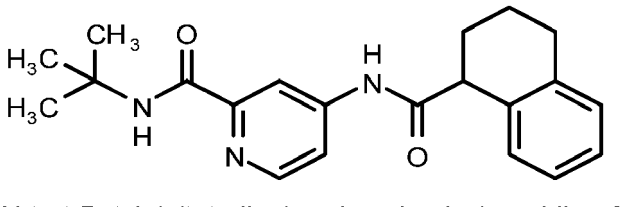
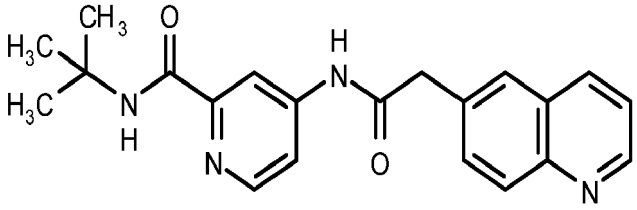
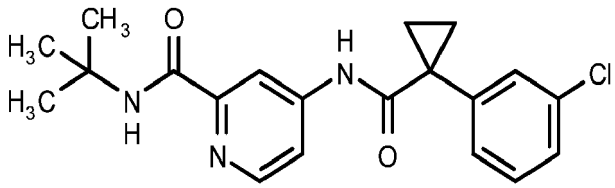
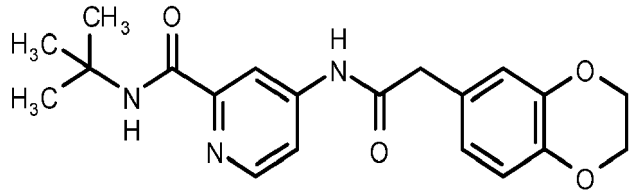
Ex.	Structure and Name	Activating Reagent	1H NMR LCMS Retention Time, [M+H]+,
5.22	 N-tert-Butyl-4-(indane-1-carbonyl amino)pyridine-2-carboxamide	Thionyl Chloride	1H NMR (500 MHz, DMSO-d6) δ 10.86 (s, 1H), 8.46 (d, J = 5.5 Hz, 1H), 8.23 (d, J = 2.1 Hz, 1H), 8.03 (s, 1H), 7.87 (dd, J = 5.5, 2.2 Hz, 1H), 7.30 (dd, J = 19.3, 7.3 Hz, 2H), 7.20 (t, J = 7.0 Hz, 1H), 7.16 (t, J = 7.0 Hz, 1H), 4.16 (t, J = 7.3 Hz, 1H), 3.10-3.03 (m, 1H), 2.94-2.86 (m, 1H), 2.39 - 2.27 (m, 2H), 1.40 (s, 9H). LC-MS (Method A): Rt 3.58 mins; MS m/z 338.2 = [M+H]+ (100% @ 215nm)
5.23	 N-tert-Butyl-4-[(2-quinoxalin-6-ylacetyl) amino]pyridine-2-carboxamide	T3P®	1H NMR (500 MHz, DMSO-d6) δ 10.89 (s, 1H), 8.96 - 8.91 (m, 2H), 8.45 (d, J = 5.5 Hz, 1H), 8.20 (d, J = 2.1 Hz, 1H), 8.09-8.06 (m, 2H), 8.02 (s, 1H), 7.87 - 7.81 (m, 2H), 4.04 (s, 2H), 1.39 (s, 9H). LC-MS (Method A): Rt 2.66 mins; MS m/z 364.2 = [M+H]+ (100% @ 215nm)
5.24	 N-tert-Butyl-4-[[2-(2-naphthyl) acetyl]amino]pyridine-2-carboxamide	T3P®	1H NMR (500 MHz, DMSO-d6) δ 10.86 (s, 1H), 8.45 (d, J = 5.5 Hz, 1H), 8.21 (d, J = 2.1 Hz, 1H), 8.02 (s, 1H), 7.92 - 7.86 (m, 3H), 7.86 - 7.84 (m, 1H), 7.84 - 7.81 (m, 1H), 7.54 - 7.45 (m, 3H), 3.90 (s, 2H), 1.39 (s, 9H). LC-MS (Method A): Rt 3.74 mins; MS m/z 362.2 = [M+H]+ (99% @ 215nm)

(continued)

Ex.	Structure and Name	Activating Reagent	1H NMR LCMS Retention Time, [M+H]+,
5.25	 N-tert-Butyl-4-(2,3-dihydrobenzofuran-3-carbonylamino) pyridine-2-carboxamide	T3P®	1H NMR (500 MHz, DMSO-d6) δ 10.99 (s, 1H), 8.48 (d, J = 5.5 Hz, 1H), 8.21 (d, J = 2.1 Hz, 1H), 8.03 (s, 1H), 7.87 (dd, J = 5.5, 2.1 Hz, 1H), 7.38 (d, J = 7.4 Hz, 1H), 7.17 (t, J = 7.7 Hz, 1H), 6.85 (t, J = 7.5 Hz, 1H), 6.82 (d, J = 8.0 Hz, 1H), 4.85 (dd, J = 9.0, 6.0 Hz, 1H), 4.70 (t, J = 9.2 Hz, 1H), 4.51 (dd, J = 9.3, 6.0 Hz, 1H), 1.40 (s, 9H). LC-MS (Method A): Rt 3.32 mins; MS m/z 340.2 = [M+H]+ (98% @ 215nm)
5.26	 N-tert-Butyl-4-(6,7,8,9-tetrahydro-5H-benzo[7]annulene-5-carbonylam ino) pyridine-2-carboxamide	T3P®	1H NMR (500 MHz, DMSO-d6) δ 10.62 (s, 1H), 8.46 (d, J = 5.5 Hz, 1H), 8.26 (d, J = 2.0 Hz, 1H), 8.03 (s, 1H), 7.82 (dd, J=5.5,2.2Hz, 1H), 7.19 (dd,J=7.2, 1.6Hz, 1H), 7.12 (dtd, J= 14.9, 7.3, 1.6 Hz, 2H), 7.00-6.97 (m, 1H), 4.06-4.01 (m, 1H), 2.93 - 2.80 (m, 2H), 2.06 - 2.00 (m, 1H), 1.91 - 1.63 (m, 4H), 1.43 - 1.32 (m, 10H). LC-MS (Method A): Rt 4.09 mins; MS m/z 366.2 = [M+H]+ (96% @ 215nm)
5.27	 N-tert-Butyl-4-(tetralin-1-carbonylamino) pyridine-2-carboxamide	T3P®	1H NMR (500 MHz, DMSO-d6) δ 10.79 (s, 1H), 8.46 (d, J = 5.5 Hz, 1H), 8.23 (d, J = 2.0 Hz, 1H), 8.03 (s, 1H), 7.85 (dd, J= 5.5, 2.1 Hz, 1H), 7.17-7.06 (m, 4H), 3.92 (t, J = 6.6 Hz, 1H), 2.84-2.69 (m, 2H), 2.11 - 1.95 (m, 3H), 1.73- 1.63 (m, 1H), 1.40 (s, 9H). LC-MS (Method A): Rt 3.73 mins; MS m/z 352.2 = [M+H]+ (99% @ 215nm)

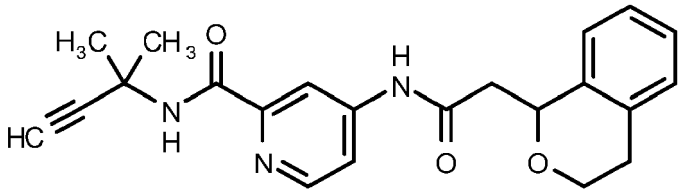
(continued)

Ex.	Structure and Name	Activating Reagent	1H NMR LCMS Retention Time, [M+H]+,
5.29	 N-tert-Butyl-4-[[2-(6-quinolyl)acetyl] amino]pyridine-2-carboxamide	T3P®	1H NMR (500 MHz, DMSO-d6) δ 10.87 (s, 1H), 8.87 (dd, J = 4.2, 1.7 Hz, 1H), 8.45 (d, J = 5.5 Hz, 1H), 8.37 - 8.32 (m, 1H), 8.21 (d, J = 2.0 Hz, 1H), 8.02 (s, 1H), 7.99 (d, J = 8.7 Hz, 1H), 7.90 (d, J = 1.5 Hz, 1H), 7.83 (dd, J = 5.5, 2.2 Hz, 1H), 7.74 (dd, J = 8.7, 2.0 Hz, 1H), 7.52 (dd, J = 8.3, 4.2 Hz, 1H), 3.95 (s, 2H), 1.39 (s, 9H). LC-MS (Method A): Rt 1.98 mins; MS m/z 363.2 = [M+H]+ (97% @ 215nm)
5.31	 N-tert-butyl-4-[[1-(3-chlorophenyl) cyclopropanecarbonyl] amino]pyridine-2-carboxamide	T3P®	1H NMR (500 MHz, Methanol-d4) δ 8.41 (d, J = 5.5 Hz, 1H), 8.12 (d, J = 2.1 Hz, 1H), 7.81 (dd, J = 5.6, 2.2 Hz, 1H), 7.52 - 7.47 (m, 1H), 7.40 (dd, J = 5.2, 2.7 Hz, 2H), 7.37 (ddt, J = 6.7, 4.4, 2.5 Hz, 1H), 1.66 - 1.60 (m, 2H), 1.47 (s, 9H), 1.28 - 1.22 (m, 2H). LC-MS (Method A): Rt 4.01 mins; MS m/z 372.2/374.2 = [M+H]+ (100% @ 215nm)
5.32	 N-tert-Butyl-4-[[2-(2,3-dihydro-1,4-benzodioxin-6-yl)acetyl] amino]pyridine-2-carboxamide	Thionyl Chloride	1H NMR (500 MHz, DMSO-d6) δ 10.67 (s, 1H), 8.44 (d, J = 5.5 Hz, 1H), 8.17 (d, J = 2.0 Hz, 1H), 8.02 (s, 1H), 7.80 (dd, J = 5.5, 2.2 Hz, 1H), 6.83 (d, J = 1.8 Hz, 1H), 6.79 (d, J = 8.2 Hz, 1H), 6.77 (dd, J = 8.3, 1.9 Hz, 1H), 4.21 (s, 4H), 3.57 (s, 2H), 1.39 (s, 9H). LC-MS (Method A): Rt 3.23 mins; MS m/z 370.3/371.3 = [M+H]+ (98% @ 215nm)

Example 5.33

N-(1,1-Dimethylprop-2-ynyl)-4-[(2-isochroman-1-ylacetyl)amino]pyridine-2-carboxamide

[0372]



[0373] The titled compound was prepared from 4-amino-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide (Example 78 step 1) and 2-isochroman-1-ylacetic acid analogously to Example 5.1

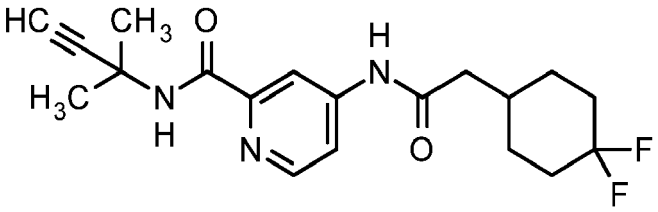
[0374] 1H NMR (500 MHz, DMSO-d6) δ 10.60 (s, 1H), 8.49 (d, J = 5.5 Hz, 1H), 8.33 (s, 1H), 8.22 (d, J = 2.0 Hz, 1H), 7.87 (dd, J = 5.5, 2.2 Hz, 1H), 7.19 (tdd, J = 12.4, 9.2, 5.5 Hz, 4H), 5.19 (dd, J = 10.0, 3.1 Hz, 1H), 4.08-4.01 (m, 1H), 3.72 (ddd, J = 11.4, 9.0, 4.1 Hz, 1H), 3.21 (s, 1H), 3.09 (dd, J = 14.6, 3.4 Hz, 1H), 2.92-2.84 (m, 1H), 2.75-2.67 (m, 2H), 1.65 (s, 6H).

[0375] LC-MS (Method A): Rt 3.22 mins; MS m/z 378.3= [M+H]+ (100% @ 215nm)

Example 5.34

4-[[2-(4,4-Difluorocyclohexyl)acetyl]amino]-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide

[0376]



[0377] The titled compound was prepared from 4-amino-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide (Example 78 step 1) and 2-(4,4-difluorocyclohexyl)acetic acid analogously to Example 5.1

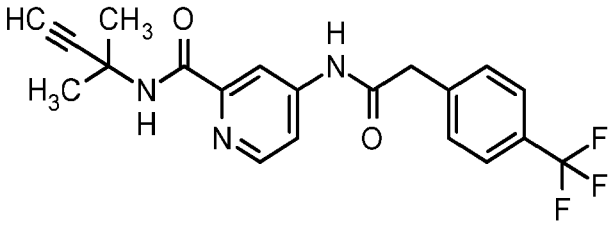
[0378] 1H NMR (500 MHz, DMSO-d6) δ 10.52 (s, 1H), 8.46 (d, J = 5.5 Hz, 1H), 8.30 (s, 1H), 8.20 (d, J = 2.0 Hz, 1H), 7.80 (dd, J = 5.5, 2.2 Hz, 1H), 3.21 (s, 1H), 2.34 (d, J = 7.1 Hz, 2H), 2.05- 1.90 (m, 3H), 1.90- 1.82 (m, 1H), 1.82- 1.75 (m, 3H), 1.64 (s, 6H), 1.32- 1.18 (m, 2H).

[0379] LC-MS (Method A): Rt 3.26 mins; MS m/z 364.3= [M+H]+ (97% @ 215nm)

Example 5.35

N-(1,1-Dimethylprop-2-ynyl)-4-[[2-[4-(trifluoromethyl)phenyl]acetyl]amino]pyridine-2-carboxamide

[0380]



[0381] The titled compound was prepared from 4-amino-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide (Example 78 step 1) and 2-[4-(trifluoromethyl)phenyl]acetic acid analogously to Example 5

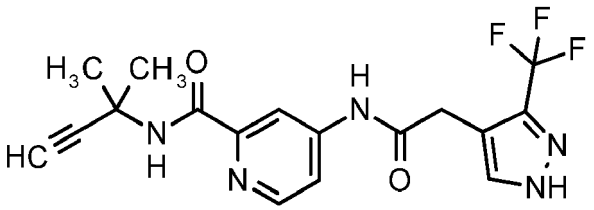
[0382] 1H NMR (500 MHz, DMSO-d6) δ 10.84 (s, 1H), 8.47 (d, J = 5.5 Hz, 1H), 8.31 (s, 1H), 8.19 (d, J = 2.0 Hz, 1H), 7.82 (dd, J = 5.5, 2.2 Hz, 1H), 7.70 (d, J = 8.1 Hz, 2H), 7.56 (d, J = 8.1 Hz, 2H), 3.86 (s, 2H), 3.20 (s, 1H), 1.64 (s, 6H).

[0383] LC-MS (Method A): Rt 3.53 mins; MS m/z 390.2= [M+H]+ (100% @ 215nm)

Example 5.36

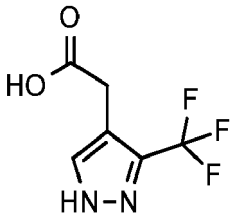
N-(1,1-Dimethylprop-2-ynyl)-4-[[2-[3-(trifluoromethyl)-1H-pyrazol-4-yl]acetyl] amino] pyridine-2-carboxamide

[0384]



Step 1: 2-[3-(Trifluoromethyl)-1H-pyrazol-4-yl]acetic acid

[0385]



[0386] Periodic acid (278 mg, 1.22 mmol) was added to MeCN (4.5 mL) and stirred at room temperature for 20 mins. To this solution was added 2-[3-(trifluoromethyl)-1H-pyrazol-4-yl]ethanol (100 mg, 0.56 mmol) in MeCN (0.93 mL) and the mixture was cooled to 0 °C. Pyridinium chlorochromate (8 mg, 0.04 mmol) was added and the mixture was warmed gradually to room temperature and stirred for 90 hours. The resulting mixture was diluted with excess water, acidified with 3M sulfuric acid and quenched with saturated aqueous sodium thiosulfate. After 3 days, the mixture was filtered and washed with water to afford the titled compound as a pale yellow solid.

[0387] 1H NMR (400 MHz, DMSO-d6) δ 13.44 (s, 1H), 12.38 (s, 1H), 7.85 (s, 1H), 3.53 (s, 2H). LC-MS (Method E): Rt 0.77 mins; MS m/z 195.0= [M+H]+ (95% @ 215nm)

Step 2: N-(1,1-Dimethylprop-2-ynyl)-4-[[2-[3-(trifluoromethyl)-1H-pyrazol-4-yl]acetyl] amino] pyridine-2-carboxamide

[0388] The titled compound was prepared from 4-amino-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide (Example 78 step 1) and 2-[3-(trifluoromethyl)-1H-pyrazol-4-yl]acetic acid (step 1) analogously to Example 5.

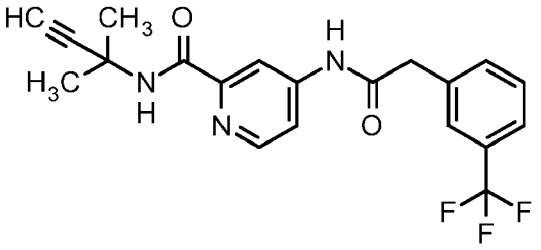
[0389] 1H NMR (400 MHz, DMSO-d6) δ 13.50 (s, 1H), 10.74 (s, 1H), 8.48 (d, J = 5.5 Hz, 1H), 8.32 (s, 1H), 8.20 (d, J = 2.1 Hz, 1H), 7.91 (s, 1H), 7.80 (dd, J = 5.5, 2.1 Hz, 1H), 3.73 (s, 2H), 3.21 (s, 1H), 1.64 (s, 6H).

[0390] LC-MS (Method A): Rt 2.69 mins; MS m/z 380.2= [M+H]+ (100% @ 215nm)

Example 5.37

N-(1,1-Dimethylprop-2-ynyl)-4-[[2-[3-(trifluoromethyl)phenyl]acetyl]amino]pyridine-2-carboxamide

[0391]



[0392] The titled compound was prepared from 4-amino-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide (Example 78 step 1) and 2-[3-(trifluoromethyl)phenyl]acetic acid analogously to Example 5.

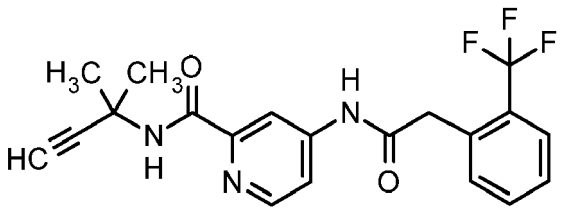
[0393] 1H NMR (500 MHz, DMSO-d6) δ 10.84 (s, 1H), 8.48 (d, J = 5.5 Hz, 1H), 8.31 (s, 1H), 8.19 (d, J = 2.0 Hz, 1H), 7.83 (dd, J = 5.5, 2.2 Hz, 1H), 7.72 - 7.69 (m, 1H), 7.66 - 7.61 (m, 2H), 7.61 - 7.55 (m, 1H), 3.88 (s, 2H), 3.21 (s, 1H), 1.64 (s, 6H).

[0394] LC-MS (Method A): Rt 3.51 mins; MS m/z 390.2= [M+H]+ (100% @ 215nm)

Example 5.38

N-(1,1-Dimethylprop-2-ynyl)-4-[[2-[2-(trifluoromethyl)phenyl]acetyl]amino]pyridine-2-carboxamide

[0395]



[0396] The titled compound was prepared from 4-amino-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide (Example 78 step 1) and 2-[2-(trifluoromethyl)phenyl]acetic acid analogously to Example 5.

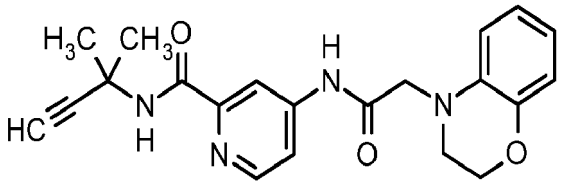
[0397] 1H NMR (500 MHz, DMSO-d6) δ 10.84 (s, 1H), 8.48 (d, J = 5.5 Hz, 1H), 8.32 (s, 1H), 8.18 (d, J = 2.0 Hz, 1H), 7.80 (dd, J = 5.5, 2.2 Hz, 1H), 7.73 (d, J = 7.8 Hz, 1H), 7.67 (t, J = 7.6 Hz, 1H), 7.52 (dd, J = 18.5, 7.7 Hz, 2H), 4.01 (s, 2H), 3.21 (s, 1H), 1.64 (s, 6H).

[0398] LC-MS (Method A): Rt 3.53 mins; MS m/z 390.2= [M+H]+ (100% @ 215nm)

Example 5.39

4-[[2-(2,3-Dihydro-1,4-benzoxazin-4-yl)acetyl]amino]-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide

[0399]



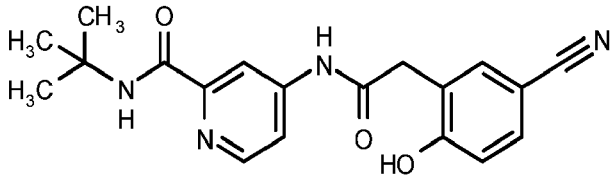
[0400] The titled compound was prepared from 4-amino-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide (Example 78 step 1) and 2-(2,3-dihydro-1,4-benzoxazin-4-yl)acetic acid analogously to Example 5.

[0401] 1H NMR (500 MHz, DMSO-d6) δ 10.65 (s, 1H), 8.48 (d, J = 5.5 Hz, 1H), 8.31 (s, 1H), 8.20 (d, J = 2.1 Hz, 1H), 7.86 (dd, J = 5.5, 2.2 Hz, 1H), 6.74 - 6.67 (m, 2H), 6.59 - 6.52 (m, 2H), 4.26-4.21 (m, 2H), 4.17 (s, 2H), 3.52-3.47 (m, 2H), 3.21 (s, 1H), 1.64 (s, 6H). LC-MS (Method A): Rt 3.32 mins; MS m/z 379.2= [M+H]+ (90% @ 215nm)

Example 6

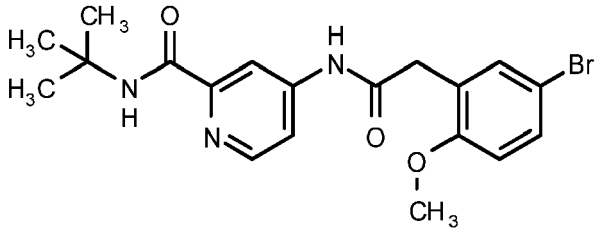
N-tert-Butyl-4-[[2-(5-cyano-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide

[0402]



Step 1: 4-[[2-(5-Bromo-2-methoxy-phenyl)acetyl]amino]-N-tert-butyl-pyridine-2-carboxamide

[0403]



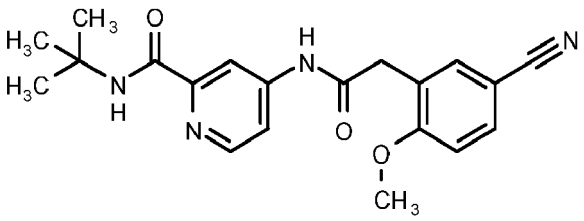
[0404] 2-(5-Bromo-2-methoxy-phenyl)acetic acid (348 mg, 1.42 mmol) in thionyl chloride (1.25 mL, 14.2 mmol) was stirred at 70°C under an inert atmosphere for 1 hour. The resulting solution was cooled to room temperature and concentrated *in vacuo* (azeotroping with toluene and DCM). The dry acid chloride was dissolved in anhydrous DCM (10 mL) and added drop wise to a solution of 4-amino-N-tert-butyl-pyridine-2-carboxamide (Example 3 step 1) (274 mg, 1.42 mmol) and DIPEA (0.5 mL, 2.84 mmol) in anhydrous DCM (10 mL). The reaction mixture was stirred under an inert atmosphere at room temperature. After 1 hour, the mixture was diluted with DCM (25 mL) and washed with water (2 x 25 mL). The organic extracts were dried over Na_2SO_4 and concentrated *in vacuo.* The resulting crude oil was purified by chromatography on silica eluting with EtOAc in heptane. The column was flushed with methanol and the eluent collected and concentrated *in vacuo* to afford a beige solid. The solid was re-purified by chromatography on silica eluting with 0-10% MeOH in DCM and the product fractions concentrated *in vacuo* and dried in a vacuum oven at 40 °C for 2 hours to afford the titled compound.

[0405] 1H NMR (500 MHz, DMSO-d6) δ 10.70 (s, 1H), 8.44 (d, J = 5.5 Hz, 1H), 8.17 (d, J = 2.0 Hz, 1H), 8.03 (s, 1H), 7.80 (dd, J = 5.5, 2.2 Hz, 1H), 7.47-7.38 (m, 2H), 7.01 - 6.92 (m, 1H), 3.74 (s, 3H), 3.71 (s, 2H), 1.40 (s, 9H).

[0406] LC-MS (Method A): Rt 3.62 mins; MS m/z 420.2, 422.2= [M+H]+ (100% @ 215nm)

Step 2: N-tert-Butyl-4-[[2-(5-cyano-2-methoxy-phenyl)acetyl]amino]pyridine-2-carboxamide

[0407]



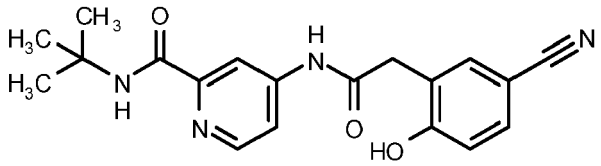
[0408] A solution of 4-[[2-(5-bromo-2-methoxy-phenyl)acetyl]amino]-N-tert-butyl-pyridine-2-carboxamide (step 1) (75 mg, 0.18 mmol) in DMF (2 mL) was de-gassed with nitrogen for 5 minutes before addition of tetrakis(triphenylphosphine)palladium(0) (21 mg, 0.02 mmol). The mixture was purged with nitrogen for a further 5 minutes then treated with zinc cyanide (27 mg, 0.23 mmol). The resulting mixture was stirred at 100 °C for 16 hours. A further portion of zinc cyanide (27 mg, 0.23 mmol) and tetrakis(triphenylphosphine)palladium(0) (21 mg, 0.02 mmol) was added, the mixture purged with nitrogen and stirring continued at 100 °C for a further 24 hours. The mixture was diluted with EtOAc (20 mL) and washed with water (20 mL), aqueous $NaHCO_3$ (sat.) (20 mL) and brine (20 mL). The organics were dried over Na_2SO_4 and concentrated *in vacuo.* The crude material was purified by chromatography on silica eluting with EtOAc in heptane. The product fractions were concentrated *in vacuo* and dried in a vacuum oven to afford the titled compound as a yellow solid.

[0409] 1H NMR (500 MHz, Chloroform-d) δ 8.40 (d, J = 5.6 Hz, 1H), 8.39 (br.s, 1H), 8.20 (dd, J = 5.6, 2.2 Hz, 1H),

8.04 (s, 1H), 7.75-7.69 (m, 1H), 7.63 (dd, J = 8.6, 2.1 Hz, 1H), 7.58 (d, J = 2.0 Hz, 1H), 6.99 (d, J = 8.6 Hz, 1H), 3.95 (s, 3H), 3.77 (s, 2H), 1.47 (s, 9H). LC-MS (Method E): Rt 1.13 mins; MS m/z 367.1 = [M+H]+ (95% @ 215nm)

Step 3: N-tert-Butyl-4-[[2-(5-cyano-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide

[0410]



[0411] To a solution of N-tert-butyl-4-[[2-(5-cyano-2-methoxy-phenyl)acetyl]amino]pyridine-2-carboxamide (step 2) (20 mg, 0.05 mmol) in DCM (2 mL) was added1M BBr3 in DCM (164 μL, 0.16 mmol). The resulting mixture was stirred under an inert atmosphere for 2 hours. Additional 1M BBr_3 in DCM (164 μL, 0.16 mmol) was added and the mixture stirred at room temperature for a further 16 hours. Further 1M BBr_3 in DCM (164 μL, 0.16 mmol) was added and the mixture stirred for 24 hours at room temperature under nitrogen. The mixture was diluted with DCM (20 mL) and washed with water (2 x 20 mL). The organic portion was dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by C18 reverse phase chromatography eluting with 0-100% MeCN in water with 0.1% formic acid. The product fractions were freeze-dried to afford the titled compound as a white solid.

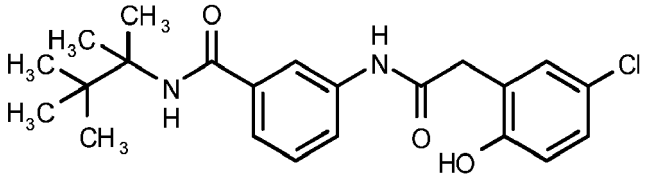
[0412] 1H NMR (500 MHz, DMSO-d6) δ 10.78 (br s, 1H), 10.75 (s, 1H), 10.90-10.60 (m, 2H), 8.44 (d, J = 5.5 Hz, 1H), 8.16 (d, J = 1.9 Hz, 1H), 8.03 (s, 1H), 7.81 (dd, J = 5.5, 2.2 Hz, 1H), 7.63 (d, J = 2.1 Hz, 1H), 7.57 (dd, J = 8.4, 2.2 Hz, 1H), 6.93 (d, J = 8.4 Hz, 1H), 3.72 (s, 2H), 1.40 (s, 9H).

[0413] LC-MS (Method A): Rt 2.84 mins; MS m/z 353.3 = [M+H]+ (94% @ 215nm)

Example 7*

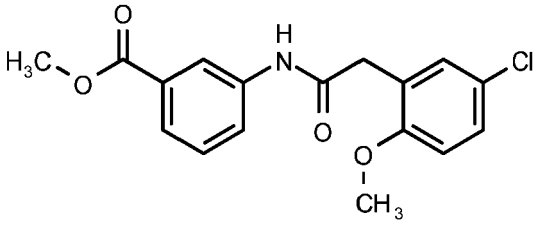
3-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1,1,2,2-tetramethylpropyl) benzamide

[0414]



Step 1: Methyl 3-[[2-(5-chloro-2-methoxy-phenyl)acetyl]amino]benzoate

[0415]



[0416] A solution of 2-(5-chloro-2-methoxy-phenyl)acetic acid (1200 mg, 5.98 mmol), EDCI (1376 mg, 7.18 mmol), HOAt (814 mg, 5.98 mmol), DIPEA (2.61 mL, 14.95 mmol) and methyl 3-aminobenzoate (904 mg, 5.98 mmol) in DMF (5 mL) was stirred at room temperature for 17 hours. The reaction mixture was diluted with water (35 mL) and extracted with EtOAc (2 x 40 mL). The combined organic portions were washed with water (2 x 40 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was purified by chromatograhy on silica eluting with 10-70% EtOAc in heptane.

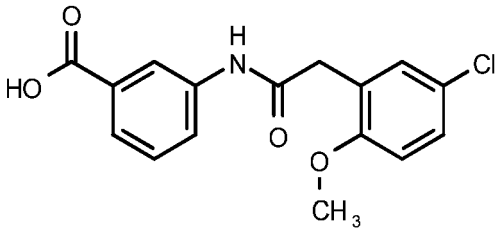
The product fractions were concentrated *in vacuo* to afford the titled compound as an off-white solid.

[0417] 1H NMR (500 MHz, DMSO-d6) δ 10.32 (s, 1H), 8.29 (t, J = 1.8 Hz, 1H), 7.82 (ddd, J = 8.1, 2.1, 1.0 Hz, 1H), 7.63 (dt, J = 7.7, 1.2 Hz, 1H), 7.45 (t, J = 7.9 Hz, 1H), 7.32-7.28 (m, 2H), 7.05-6.95 (m, 1H), 3.84 (s, 3H), 3.76 (s, 3H), 3.66 (s, 2H).

[0418] LC-MS (Method E): Rt 1.21 mins; MS m/z 334.1/ 336.1 = [M+H]+ (96% @ 215nm)

Step 2: 3-[[2-(5-Chloro-2-methoxy-phenyl)acetyl]amino]benzoic acid

[0419]



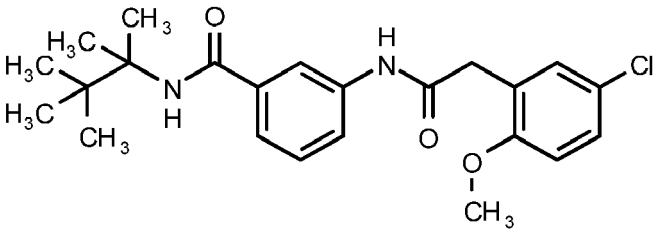
[0420] 2 M LiOH (7.71 mL, 15.42 mmol) was added to a solution of methyl 3-[[2-(5-chloro-2-methoxy-phenyl)acetyl]amino]benzoate (step 1) (1751 mg, 5.14 mmol) in THF (8 mL). The reaction mixture was stirred at room temperature for 7 hours. The resulting mixture was concentrated *in vacuo,* diluted with water (8 mL) and acidified to pH 2 with aqueous 2M HCl. A precipitate formed which was collected by vacuum filtration and washed with Et_2O (2 × 20 mL). The solid was dried in a vacuum oven at 40 °C for 3 hours to afford the titled compound as a pale beige solid.

[0421] 1H NMR (500 MHz, DMSO-d6) δ 10.32 (s, 1H), 8.23 (s, 1H), 7.87 - 7.74 (m, 1H), 7.61 (d, J = 7.7 Hz, 1H), 7.41 (t, J = 7.9 Hz, 1H), 7.31-7.27 (m, 2H), 7.03 - 6.95 (m, 1H), 3.76 (s, 3H), 3.66 (s, 2H).

[0422] LC-MS (Method E): Rt 1.07 mins; MS m/z 320.1/ 322.1 = [M+H]+ (100% @ 215nm)

Step 3: 3-[[2-(5-Chloro-2-methoxy-phenyl)acetyl]amino]-N-(1,1,2,2-tetramethylpropyl) benzamide

[0423]



[0424] A solution of 3-[[2-(5-chloro-2-methoxy-phenyl)acetyl]amino]benzoic acid (step 2) (70 mg, 0.22 mmol), EDCI (50 mg, 0.26 mmol), HOAt (36 mg, 0.26 mmol), DIPEA (0.11 mL, 0.66 mmol) and 2,3,3-trimethylbutan-2-amine hydrochloride (33 mg, 0.22 mmol) in DMF (0.5 mL) was stirred at room temperature for 3 hours. The resulting mixture was diluted with EtOAc (5 mL) and water (5 mL). The aqueous layer was extracted with EtOAc (5 mL) and the combined organic extracts were washed with water (5 mL), brine (5 mL), dried over Na_2SO_4 and concentrated *in vacuo.* The crude residue was purified by preparative HPLC (acidic pH, early elution method) and the product fractions concentrated *in vacuo* to afford the titled compound as an off-white powder.

[0425] 1H NMR (500 MHz, DMSO-d6) δ 10.19 (s, 1H), 7.85 (s, 1H), 7.74 (dt, J = 6.8, 2.1 Hz, 1H), 7.37 - 7.32 (m, 2H), 7.32 - 7.26 (m, 2H), 7.09 (s, 1H), 7.02 - 6.98 (m, 1H), 3.76 (s, 3H), 3.65 (s, 2H), 1.39 (s, 6H), 0.97 (s, 9H).

[0426] LC-MS (Method E): Rt 1.32 mins; MS m/z 417.2/ 419.2 = [M+H]+ (97% @ 215nm)

Step 4: 3-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1,1,2,2-tetramethylpropyl) benzamide

[0427] To a cooled (0 °C) solution of 3-[[2-(5-chloro-2-methoxy-phenyl)acetyl]amino]-N-(1,1,2,2-tetramethylpropyl)benzamide (step 3) (53 mg, 0.13 mmol) in DCM (0.5 mL) was added 1M BBr3 in DCM (0.38 mL, 0.38 mmol) and the mixture was stirred at room temperature for 1 hour. The resulting mixture was diluted with water (5 mL) and extracted with EtOAc (2 x 8 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo.* The crude

residue was purified by preparative HPLC (acidic pH, early elution method) and the product fractions concentrated *in vacuo* to afford the titled compound as an an off-white powder.

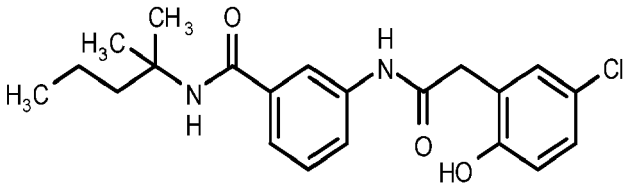
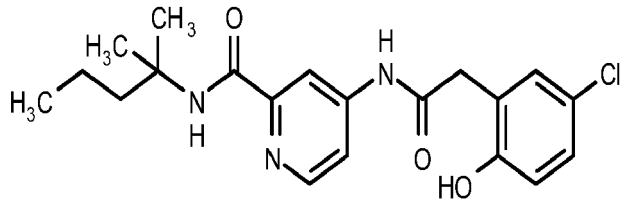
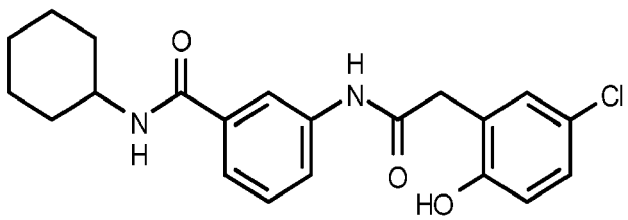
[0428] 1H NMR (500 MHz, DMSO-d6) δ 10.19 (s, 1H), 9.81 (brs, 1H), 7.86 (s, 1H), 7.75 (dt, J = 6.6, 2.2 Hz, 1H), 7.38 - 7.31 (m, 2H), 7.20 (d, J = 2.7 Hz, 1H), 7.13 - 7.05 (m, 2H), 6.80 (d, J = 8.6 Hz, 1H), 3.61 (s, 2H), 1.39 (s, 6H), 0.97 (s, 9H).

[0429] LC-MS (Method D): Rt 4.52 mins; MS m/z 403.2/ 405.2 = [M+H]+ (100% @ 215nm).

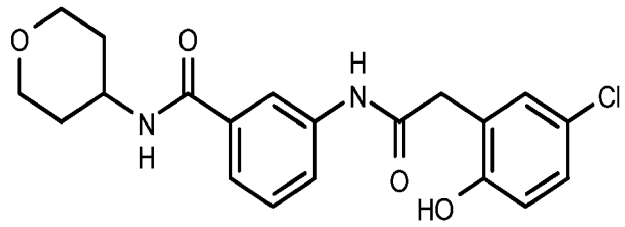
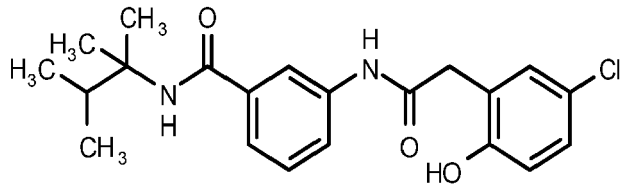
[0430] The compounds of the following tabulated Examples (Table 6) were prepared analogously to Example 7 from the appropriate amino ester and acid (step 1) and by replacing 2,3,3-trimethylbutan-2-amine hydrochloride (step 3) with the appropriate commercially available amine. The amide coupling step was carried out using either (i) EDCI/HOAt/DIPEA or (ii) TBTU/TEA or (iii) T3P®/TEA

Table 6

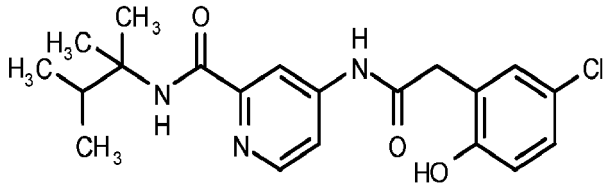
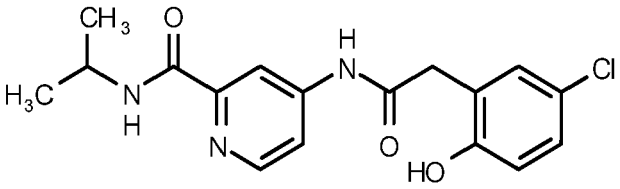
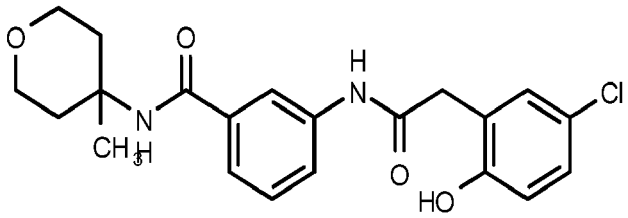
(* denotes a reference compound that is not claimed)

Ex.	Structure and Name	Coupling Reagents	1H NMR LCMS Retention Time, [M+H]+,
7.1*	 3-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(1,1-dimethylbutyl)benzamide	EDCI/HOAt/ DIPEA	1H NMR (500 MHz, DMSO-d6) δ 10.19 (s, 1H), 9.74 (br s, 1H), 7.87 (t, J = 1.8 Hz, 1H), 7.84 - 7.71 (m, 1H), 7.56 (s, 1H), 7.40 (d, J = 7.8 Hz, 1H), 7.33 (t, J = 7.9 Hz, 1H), 7.20 (d, J = 2.7 Hz, 1H), 7.11 (dd, J = 8.6, 2.7 Hz, 1 H), 6.80 (d, J = 8.6 Hz, 1H), 3.61 (s, 2H), 1.78 - 1.64 (m, 2H), 1.37 - 1.20 (m, 8H), 0.86 (t, J = 7.3 Hz, 3H). LC-MS (Method D): Rt 4.40mins; MS m/z 389.2/ 391.2= [M+H]+ (98% @ 215nm)
7.2	 4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(1,1-dimethylbutyl)pyridine-2-carboxamide	EDCI/HOAt/ DIPEA	1H NMR (250 MHz, DMSO-d6) δ 10.69 (br s, 1H), 9.86 (br s, 1H), 8.44 (d, J = 5.8 Hz, 1H), 8.17 (d, J = 1.8 Hz, 1H), 7.95 (s, 1H), 7.80 (dd, J = 5.5, 2.2 Hz, 1H), 7.21 (d, J = 2.7 Hz, 1H), 7.12 (dd, J = 8.6, 2.7 Hz 1H), 6.80 (d, J = 8.6 Hz, 1H), 3.67 (s, 2H), 1.80 - 1.63 (m, 2H), 1.35 (s, 6H), 1.32-1.16 (m, 2H), 0.87 (t, J = 7.3 Hz, 3H). LC-MS (Method A): Rt 3.79 mins; MS m/z 390.2/392 = [M+H] + (100% @ 215nm)
7.3*		EDCI/HOAt/ DIPEA	1H NMR (500 MHz, DMSO-d6) δ 10.23 (s, 1H), 9.79 (s, 1H), 8.16 (d, J = 8.0 Hz, 1H), 7.96 (t, J = 1.8 Hz, 1H), 7.80 - 7.75 (m, 1H), 7.48 (d, J = 7.8 Hz, 1H), 7.35 (t, J = 7.9 Hz, 1H), 7.20 (d, J = 2.7 Hz, 1H), 7.11 (dd, J = 8.6, 2.7 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H),

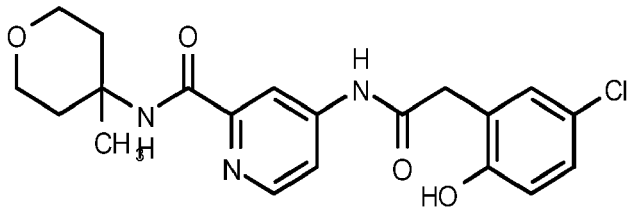
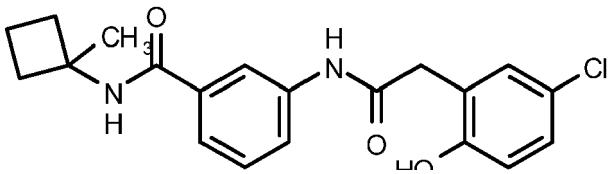
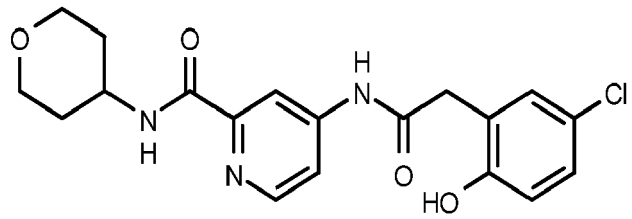
(continued)

(* denotes a reference compound that is not claimed)			
Ex.	**Structure and Name**	**Coupling Reagents**	**1H NMR LCMS Retention Time, [M+H]+,**
	3-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-cyclohexyl-benzamide		3.79 - 3.69 (m, 1H), 3.61 (s, 2H), 1.84 - 1.68 (m, 4H), 1.64 - 1.57 (m, 1H), 1.36 - 1.23 (m, 4H), 1.17 - 1.06 (m, 1H). LC-MS (Method A): Rt 3.31 mins; MS m/z 387.2/ 389.2 = [M+H]+ (100% @ 215nm)
7.4*	 3-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-tetrahydropyran-4-yl-benzamide	EDCI/HOAt/ DIPEA	1H NMR (500 MHz, DMSO-d6) δ 10.22 (s, 1H), 9.80 (br s, 1H), 8.29 (d, J = 7.8 Hz, 1H), 7.99 (t, J = 1.8 Hz, 1H), 7.87 - 7.69 (m, 1H), 7.49 (d, J = 7.9 Hz, 1H), 7.37 (t, J = 7.9 Hz, 1H), 7.21 (d, J = 2.7 Hz, 1H), 7.11 (dd, J = 8.6, 2.7 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 3.98 (m, 1H), 3.92 - 3.80 (m, 2H), 3.61 (s, 2H), 3.41 - 3.36 (m, 2H), 1.80 - 1.65 (m, 2H), 1.63 - 1.51 (m, 2H). LC-MS (Method A): Rt 2.57 mins; MS m/z 389.2/ 391.2 = [M+H]+ (100% @ 215nm)
7.5*	 3-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(1,1,2-trimethylpropyl)benzamide	EDCI/HOAt/ DIPEA	1H NMR (500 MHz, DMSO-d6) δ 10.19 (s, 1H), 9.80 (br s, 1H), 7.87 (t, J = 1.8 Hz, 1H), 7.81 - 7.71 (m, 1H), 7.52 (s, 1H), 7.39 (dd, J = 6.5, 1.3 Hz, 1H), 7.33 (t, J = 7.8 Hz, 1H), 7.20 (d, J = 2.7 Hz, 1H), 7.11 (dd, J = 8.6, 2.7 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 3.61 (s, 2H), 1.27 (s, 6H), 0.85 (d, J = 6.9 Hz, 6H). LC-MS (Method A): Rt 3.52 mins; MS m/z 389.3/ 391.3 = [M+H]+ (100% @ 215nm)

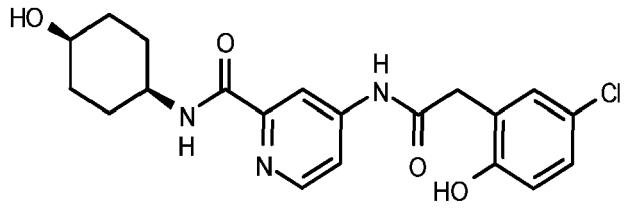
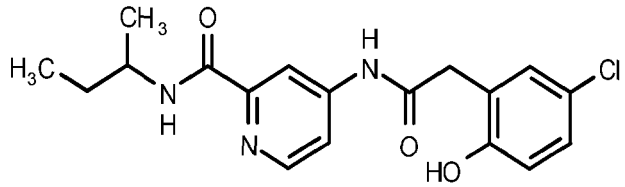
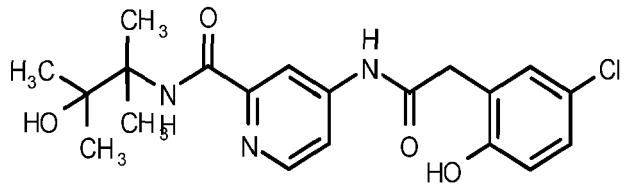
(continued)

(* denotes a reference compound that is not claimed)			
Ex.	**Structure and Name**	**Coupling Reagents**	**1H NMR LCMS Retention Time, [M+H]+,**
7.6	 4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(1,1,2-trimethylpropyl)pyridine-2-carboxamide	EDCI/HOAt/ DIPEA	1H NMR (500 MHz, DMSO-d6) δ 10.71 (br s, 1H), 9.86 (br s, 1H), 8.44 (d, J = 5.6 Hz, 1H), 8.17 (d, J = 2.0 Hz, 1H), 7.99 (s, 1H), 7.81 (dd, J = 5.5, 2.2 Hz, 1H), 7.21 (d, J = 2.7 Hz, 1H), 7.12 (dd, J = 8.6, 2.7 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 3.66 (s, 2H), 2.36 - 2.28 (m, 1H), 1.32 (s, 6H), 0.88 (d, J = 6.9 Hz, 6H). LC-MS (Method A): Rt 3.74 mins; MS m/z 390.2/ 392.2 = [M+H]+ (99% @ 215nm)
7.7	 4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-isopropyl-pyridine-2-carboxamide	TBTU/TEA	1H NMR (500 MHz, DMSO-d6) δ 10.69 (br s, 1H), 9.77 (br s, 1H), 8.46 (d, J = 5.5 Hz, 1H), 8.39 (d, J = 8.4 Hz, 1H), 8.18 (d, J = 2.1 Hz, 1H), 7.81 (dd, J = 5.5, 2.2 Hz, 1H), 7.21 (d, J = 2.7 Hz, 1H), 7.12 (dd, J = 8.6, 2.7 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 4.16-4.03 (m, 1H), 3.66 (s, 2H), 1.18 (d, J = 6.6 Hz, 6H). LC-MS (Method A): Rt 2.89 mins; MS m/z 348.1/ 350.1 = [M+H]+ (99% @ 215nm)
7.8*	 3-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(4-methyltetrahydropyran-4-yl)benzamide	EDCI/HOAt/ DIPEA	1H NMR (500 MHz, DMSO-d6) δ 10.21 (s, 1H), 9.80 (s, 1H), 7.99 - 7.84 (m, 1H), 7.80 - 7.60 (m, 1H), 7.72 (s, 1H), 7.44 (d, J = 7.7 Hz, 1H), 7.35 (t, J = 7.9 Hz, 1H), 7.20 (d, J = 2.7 Hz, 1H), 7.11 (dd, J = 8.6, 2.7 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 3.67 - 3.52 (m, 6H), 2.26-2.19 (m, 2H), 1.58- 1.49 (m, 2H), 1.38 (s, 3H). LC-MS (Method A): Rt 2.79 mins; MS m/z 403.2/ 405.2 = [M+H]+ (100% @ 215nm)

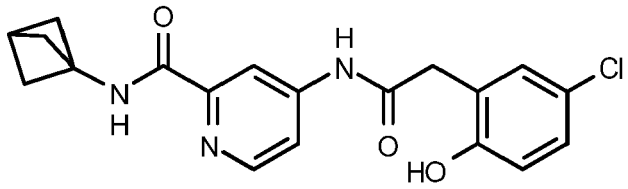
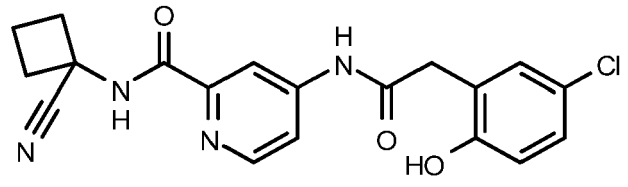
(continued)

(* denotes a reference compound that is not claimed)			
Ex.	**Structure and Name**	**Coupling Reagents**	**1H NMR LCMS Retention Time, [M+H]+,**
7.9	 4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(4-methyltetrahydropyran-4-yl)pyridine-2-carboxamide	T3P®/TEA	1H NMR (500 MHz, DMSO-d6) δ 10.72 (br s, 1H), 9.74 (br s, 1H), 8.47 (d, J = 5.5 Hz, 1H), 8.18 (d, J = 2.1 Hz, 1H), 8.11 (s, 1H), 7.82 (dd, J = 5.5, 2.2 Hz, 1H), 7.21 (d, J = 2.7 Hz, 1H), 7.12 (dd, J = 8.6, 2.7 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 3.70 - 3.60 (m, 4H), 3.55 - 3.46 (m, 2H), 2.23-2.14 (m, 2H), 1.67-1.58 (m, 2H), 1.42 (s, 3H). LC-MS (Method A): Rt 2.90 mins; MS m/z 404.2/ 406.2 = [M+H]+ (96% @ 215nm)
7.10 *	 3-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(1-methylcyclobutyl)benzamide	EDCI/HOAt/ DIPEA	1H NMR (500 MHz, DMSO-d6) δ 10.20 (s, 1H), 9.80 (s, 1H), 8.32 (s, 1H), 7.95 (t, J = 1.8 Hz, 1H), 7.77-7.42 (m, 1H), 7.49-7.44 (m, 1H), 7.34 (t, J = 7.9 Hz, 1H), 7.20 (d, J = 2.7 Hz, 1H), 7.11 (dd, J = 8.6, 2.7 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 3.61 (s, 2H), 2.34 - 2.28 (m, 2H), 2.00 - 1.92 (m, 2H), 1.84 - 1.75 (m, 2H), 1.45 (s, 3H). LC-MS (Method A): Rt 3.15 mins; MS m/z 373.2/ 375.1 = [M+H]+ (99% @ 215nm)
7.11	 4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-tetrahydropyran-4-yl-pyridine-2-carboxamide	TBTU/TEA	1H NMR (500 MHz, DMSO-d6) δ 10.69 (br s, 1H), 9.86 (br s, 1H), 8.58 (d, J = 8.5 Hz, 1H), 8.48 (d, J = 5.5 Hz, 1H), 8.20 (d, J = 2.0 Hz, 1H), 7.82 (dd, J = 5.5, 2.2 Hz, 1H), 7.21 (d, J = 2.7 Hz, 1H), 7.12 (dd, J = 8.6, 2.7 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 4.06-3.95 (m, 1H), 3.89 - 3.83 (m, 2H), 3.66 (s, 2H), 1.75 - 1.61 (m, 4H). LC-MS (Method A): Rt 2.57 mins; MS m/z 390.2/ 392.2 = [M+H]+ (98% @ 215nm)

(continued)

(* denotes a reference compound that is not claimed)			
Ex.	**Structure and Name**	**Coupling Reagents**	**1H NMR LCMS Retention Time, [M+H]+,**
7.12	 4-[2-(5-Chloro-2-nyaroxypnenyl)acetamido]-N-[(1s,4s)-4-hydroxycyclohexyl]pyridine-2-carboxamide	EDCI/HOAt/ DIPEA	1H NMR (500 MHz, DMSO-d6) δ 10.68 (s, 1H), 9.82 (br s, 1H), 8.47 (d, J = 5.5 Hz, 1H), 8.30 (d, J = 8.2 Hz, 1H), 8.19 (d, J = 2.0 Hz, 1H), 7.81 (dd, J = 5.5, 2.2 Hz, 1H), 7.22 (d, J = 2.7 Hz, 1H), 7.12 (dd, J = 8.6, 2.7 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 4.41 (d, J = 3.4 Hz, 1H), 3.87 - 3.76 (m, 1H), 3.74 - 3.68 (m, 1H), 3.66 (s, 2H), 1.83 - 1.66 (m, 2H), 1.65 - 1.47 (m, 6H). LC-MS (Method A): Rt 2.45mins; MS m/z 404.2/ 406.2 = [M+H]+ (100% @ 215nm)
7.13	 4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-sec-butyl-pyridine-2-carboxamide	T3P@/TEA	1H NMR (500 MHz, DMSO-d6) δ 10.69 (br s, 1H), 9.82 (br s, 1H), 8.47 (d, J = 5.5 Hz, 1H), 8.34 (d, J = 8.9 Hz, 1H), 8.18 (d, J = 2.0 Hz, 1H), 7.82 (dd, J = 5.5, 2.2 Hz, 1H), 7.22 (d, J = 2.7 Hz, 1H), 7.12 (dd, J = 8.6, 2.7 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 3.96-3.85 (m, 1H), 3.66 (s, 2H), 1.64 - 1.44 (m, 2H), 1.15 (d, J = 6.6 Hz, 3H), 0.84 (t, J = 7.4 Hz, 3H). LC-MS (Method A): Rt 3.16 mins; MS m/z 362.1/ 364.1 = [M+H]+ (98% @ 215nm)
7.14	 4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(2-hydroxy-1,1,2-trimethyl-propyl)pyridine-2-carboxamide	T3P®/TEA	1H NMR (500 MHz, DMSO-d6) δ 10.67 (s, 1H), 9.81 (br s, 1H), 8.71 (s, 1H), 8.44 (d, J = 5.5 Hz, 1H), 8.18 (d, J = 2.0 Hz, 1H), 7.80 (dd, J = 5.5, 2.2 Hz, 1H), 7.22 (d, J = 2.7 Hz, 1H), 7.12 (dd, J = 8.6, 2.7 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 4.99 (s, 1H), 3.67 (s, 2H), 1.39 (s, 6H), 1.16 (s, 6H). LC-MS (Method A): Rt 3.01 mins; MS m/z 406.2/ 408.2 = [M+H]+ (99% @ 215nm)

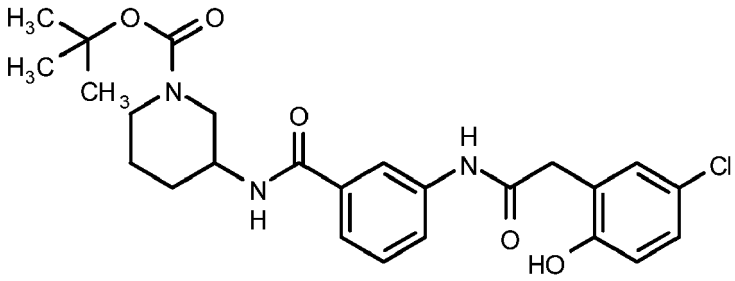
(continued)

(* denotes a reference compound that is not claimed)			
Ex.	**Structure and Name**	**Coupling Reagents**	**1H NMR LCMS Retention Time, [M+H]+,**
7.15	 N-(3-Bicyclo[1.1.1]pentanyl)-4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide	T3P®/TEA	1H NMR (500 MHz, DMSO-d6) δ 10.71 (br s, 1H), 9.82 (br s, 1H), 9.09 (s, 1H), 8.46 (d, J = 5.5 Hz, 1H), 8.14 (d, J = 2.0 Hz, 1H), 7.84 (dd, J = 5.5, 2.2 Hz, 1H), 7.22 (d, J = 2.7 Hz, 1H), 7.13 (dd, J = 8.6, 2.7 Hz, 1H), 6.81 (d, J = 8.6 Hz, 1H), 3.67 (s, 2H), 2.45 (s, 1H), 2.10 (s, 6H). LC-MS (Method A): Rt 3.21 mins; MS m/z 372.1/ 374.1 = [M+H]+ (98% @ 215nm)
7.16	 4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(1-cyanocyclobutyl)pyridine-2-carboxamide	T3P®/TEA	1H NMR (500 MHz, DMSO-d6) δ 10.73 (s, 1H), 9.82 (br s, 1H), 9.59 (s, 1H), 8.52 (d, J = 5.5 Hz, 1H), 8.19 (d, J = 2.0 Hz, 1H), 7.88 (dd, J = 5.5, 2.2 Hz, 1H), 7.22 (d, J = 2.7 Hz, 1H), 7.12 (dd, J = 8.6, 2.7 Hz, 1H),6.81 (d, J = 8.6 Hz, 1H), 3.68 (s, 2H), 2.69 - 2.62 (m, 2H), 2.59 - 2.53 (m, 2H), 2.11 - 1.93 (m, 2H). LC-MS (Method A): Rt 2.89 mins; MS m/z 385.1/ 387.1= [M+H]+ (95% @ 215nm)

Example 8*

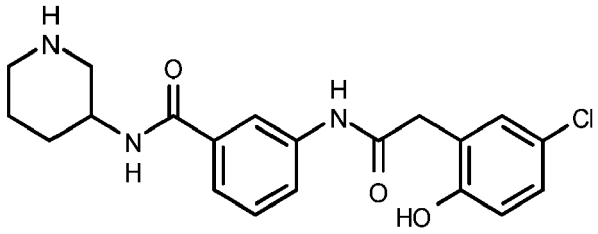
tert-Butyl-3-[[3-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]benzoyl]amino] piperidine-1-carboxylate

[0431]



Step 1: 3-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(3-piperidyl)benzamide

[0432]



[0433] The titled compound was prepared analogously to Example 7 by replacing 2,3,3-trimethylbutan-2-amine hydrochloride (step 3) with tert-butyl 3-aminopiperidine-1-carboxylate.

[0434] 1H NMR (500 MHz, DMSO-d6) δ 10.22 (s, 1H), 8.15 (d, J = 7.9 Hz, 1H), 7.98 (s, 1H), 7.82 -7.70 (m, 1H), 7.50-7.46 (m, 1H), 7.36 (t, J = 7.9 Hz, 1H), 7.20 (d, J = 2.7 Hz, 1H), 7.11 (dd, J = 8.6, 2.7 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 3.88-3.80 (m, 1H), 3.61 (s, 2H), 3.02-2.95 (m, 1H), 2.88 - 2.80 (m, 1H), 2.48 - 2.42 (m, 2H), 1.90 - 1.77 (m, 1H), 1.74 - 1.59 (m, 1H), 1.54- 1.37 (m, 2H).

[0435] LC-MS (Method A): Rt 1.66 mins; MS m/z 388.2/ 390.2 = [M+H]+ (96% @ 215nm)

Step 2: tert-Butyl-3-[[3-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]benzoyl]amino] piperidine-1-carboxylate

[0436] To a solution of 3-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]-N-(3-piperidyl)benzamide (step 1)(19 mg, 0.05 mmol) in THF (0.5 mL) was added BOC anhydride (12 mg, 0.06 mmol). The resulting mixture was stirred at room temperature for 3 hr. Additional BOC anhydride (12 mg, 0.06 mmol) was added and stirring continued for a further hour. The reaction mixture was concentrated *in vacuo* and purification of the crude product by chromatography on silica eluting with EtOAc in heptane afforded the titled compound as an off-white powder.

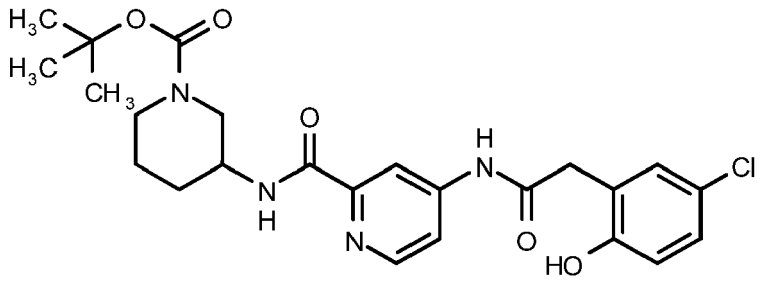
[0437] 1H NMR (500 MHz, DMSO-d6) δ 10.26 (br s, 1H), 9.81 (br s, 1H), 8.24 (d, J = 7.0 Hz, 1H), 7.99 (s, 1H), 7.83 - 7.74 (m, 1H), 7.49 (d, J = 7.8 Hz, 1H), 7.37 (m, 1H), 7.20 (d, J = 2.7 Hz, 1H), 7.11 (dd, J = 8.6, 2.7 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 4.05-3.67 (m, 3H), 3.61 (s, 2H), 3.03-2.70 (m, 2H), 1.91 - 1.81 (m, 1H), 1.76-1.67 (m, 1H), 1.60-1.46 (m, 1H), 1.45-1.31 (m, 10H).

[0438] LC-MS (Method A): Rt 3.41 mins; MS m/z 488.3/ 490.4 = [M+H]+ (99% @ 215nm)

Example 8.1

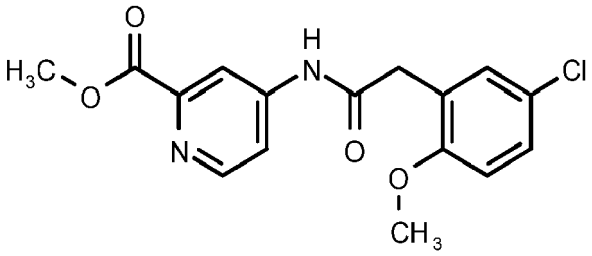
tert-Butyl-3-[[4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carbonyl]amino]piperidine-1-carboxylate

[0439]



Step 1: Methyl 4-[[2-(5-chloro-2-methoxy-phenyl)acetyl]amino]pyridine-2-carboxylate

[0440]



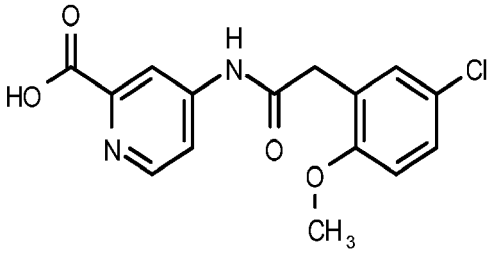
[0441] 2-(5-Chloro-2-methoxy-phenyl)acetic acid (24.19 g, 120.59 mmol) was suspended in thionyl chloride (103.68 mL, 1427.48 mmol) and heated at 70 °C for 1.5 hours. After cooling to room temperature the mixture was concentrated *in vacuo.* The residue was then dissolved in DCM (135 mL) and re-concentrated. The resulting brown viscous oil was dissolved in DCM (135 mL) and added dropwise to a cooled (ice bath) suspension of methyl 4-aminopyridine-2-carboxylate (17.9 g, 117.65 mmol) and DIPEA (30.82 mL, 176.47 mmol) in DCM (225 mL). The reaction mixture was allowed to warm to room temperature and stirred overnight. The resulting mixture was diluted with water (180 mL) and stirred for 10 mins. The organic portion was separated, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo.* The residue was purified by chromatography on silica eluting with EtOAc to afford the titled compound as an orange glassy solid.

[0442] 1H NMR (500 MHz, DMSO-d6) δ 10.72 (s, 1H), 8.54 (d, J = 5.5 Hz, 1H), 8.30 (d, J = 1.9 Hz, 1H), 7.77 (dd, J = 5.5, 2.2 Hz, 1H), 7.32 - 7.29 (m, 2H), 7.02 - 6.99 (m, 1H), 3.86 (s, 3H), 3.75 (s, 3H), 3.71 (s, 2H).

[0443] LC-MS (Method E): Rt 1.04 mins; MS m/z 335.0/337.0 = [M+H]+ (98% @ 215nm)

Step 2: 4-[[2-(5-Chloro-2-methoxy-phenyl)acetyl]amino]pyridine-2-carboxylic acid

[0444]



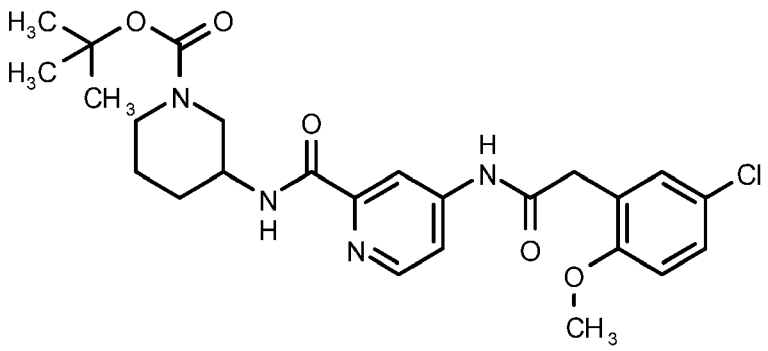
[0445] To a solution of methyl 4-[[2-(5-chloro-2-methoxy-phenyl)acetyl]amino]pyridine-2-carboxylate (step 1) (95%, 38.09 g, 108.1 mmol) in THF (200 mL) was added a 2M aqueous solution of lithium hydroxide hydrate (162.15 mL, 324.29 mmol) and the resulting mixture was stirred at room temperature for 1 hour. The volatile organics were removed in *vacuo* and the aqueous residue cooled (ice-bath) and treated with the gradual addition of 3M aqueous HCl (150 mL). The resulting suspension was filtered, washed with water (3 x 200 mL), diethyl ether (2 x 250 mL), dried under suction and then further dried in a high vacuum oven at 40 °C to afford the titled compound as a beige solid.

[0446] 1H NMR (500 MHz, DMSO-d6) δ 10.78 (s, 1H), 8.53 (d, J = 5.6 Hz, 1H), 8.27 (d, J = 2.0 Hz, 1H), 7.81 (dd, J = 5.6, 2.2 Hz, 1H), 7.34 - 7.28 (m, 2H), 7.04 - 6.98 (m, 1H), 3.75 (s, 3H), 3.72 (s, 2H).

[0447] LC-MS (Method E): Rt 0.88 mins; MS m/z 320.9/ 323.0 = [M+H]+ (97% @ 215nm)

Step 3: tert-Butyl 3-[[4-[[2-(5-chloro-2-methoxy-phenyl)acetyl]amino]pyridine-2-carbonyl]am ino]piperidine-1-carboxylate

[0448]



[0449] A solution of 4-[[2-(5-chloro-2-methoxy-phenyl)acetyl]amino]pyridine-2-carboxylic acid (step 2) (70 mg, 0.22 mmol), EDCI (50 mg, 0.26 mmol), HOAt (36 mg, 0.26 mmol), DIPEA (0.08 mL, 0.44 mmol) and tert-butyl 3-aminopiperidine-1-carboxylate (27.2 μL, 0.26 mmol) in DMF (0.5 mL) was stirred at room temperature for 20 hours. The resulting mixture was diluted with EtOAc (5 mL) and water (5 mL). The aqueous layer was extracted with EtOAc (5 mL) and the combined organic extracts washed with water (5 mL), brine (5 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by preparative HPLC (acidic pH, early elution method) to afford the titled compound as an off-white solid.

[0450] 1H NMR (500 MHz, DMSO-d6) δ 10.71 (br s, 1H), 8.52 (br s, 1H), 8.46 (m, 1H), 8.19 (br s,1H), 7.87-7.79 (m, 1H), 7.35-7.26 (m, 2H), 7.08-6.93 (m, 1H), 3.87 - 3.78 (m, 1H), 3.75 (s, 3H), 3.71 (s, 2H), 3.17-2.83 (m, 2H), 1.87 - 1.77 (m, 1H), 1.77- 1.58 (m, 2H), 1.57-1.20 (m, 10H).

[0451] LC-MS (Method E): Rt 1.28 mins; MS m/z 503.3/505.2 = [M+H]+ (93% @ 215nm)

Step 4 and 5: tert-Butyl-3-[[4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carbonyl]am ino]piperidine-1-carboxylate

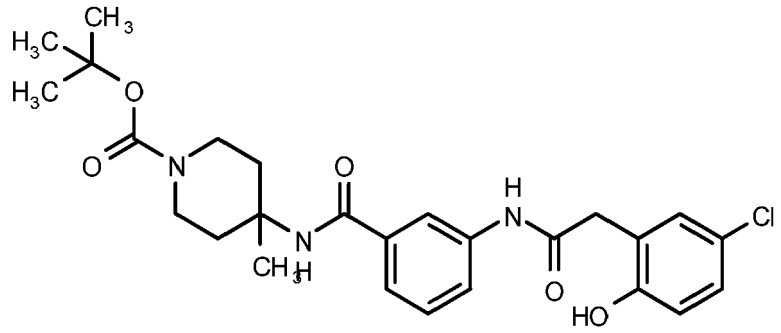
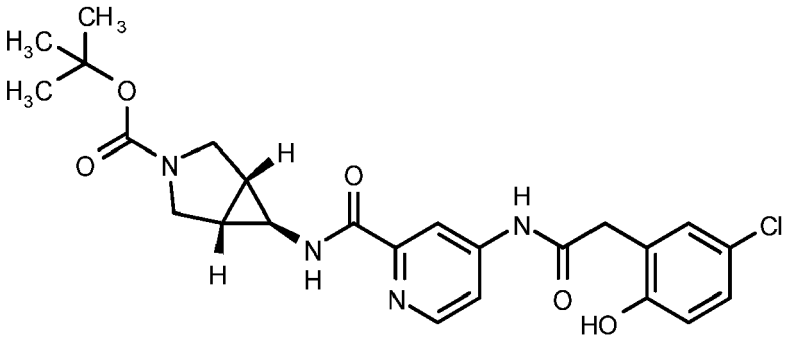
[0452] The titled compound was prepared analogously to Example 8 from tert-butyl 3-[[4-[[2-(5-chloro-2-methoxyphenyl)acetyl]amino]pyridine-2-carbonyl]amino]piperidine-1-carboxylate (step 3).

[0453] 1H NMR (500 MHz, DMSO-d6) δ 10.71 (br s, 1H), 9.83 (br s, 1H), 8.61 - 8.40 (m, 2H), 8.20 (s, 1H), 7.83 (dd, J = 5.5, 2.0 Hz, 1H), 7.21 (d, J = 2.7 Hz, 1H), 7.12 (dd, J = 8.6, 2.7 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 3.90 - 3.76 (m, 2H), 3.66 (s, 2H), 3.57 - 3.49 (m, 1H), 3.11 - 2.80 (m, 1H), 1.87- 1.76 (m, 1H), 1.75-1.57 (m, 2H), 1.45- 1.27 (m, 10H).

[0454] LC-MS (Method A): Rt 3.51 mins; MS m/z 489.3/ 491.3 = [M+H]+ (99% @ 215nm)

[0455] The compounds of the following tabulated Examples (Table 7) were prepared analogously to Example 8 from the appropriate aryl acid and by replacing tert-butyl 3-aminopiperidine-1-carboxylate (Example 8, step 1) with the appropriate commercially available amine.

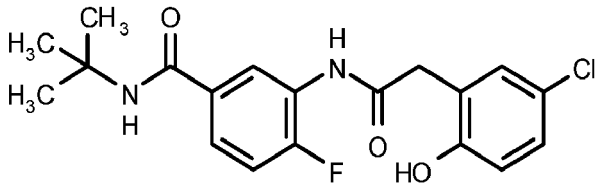
Table 7

(* denotes a reference compound that is not claimed)		
Ex.	**Structure and Name**	**1H NMR; LCMS Retention Time, [M+H]+,**
8.2*	 tert-Butyl 4-[[3-[[2-(5-chloro-2-hydroxy-phenyl) acetyl]amino]benzoyl]amino]-4-methyl-piperidine-1-carboxylate	1H NMR (500 MHz, DMSO-d6) δ 10.20 (s, 1H), 9.81 (br s, 1H), 7.92-7.85 (m, 1H), 7.81-7.77 (m, 1H), 7.70 (s, 1 H), 7.42 (d, J = 7.8 Hz, 1H), 7.34 (t, J = 7.9 Hz, 1H), 7.20 (d, J = 2.7 Hz, 1H), 7.10 (dd, J = 8.6, 2.7 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 3.66 - 3.54 (m, 4H), 3.08 (m, 2H), 2.29-2.21 (m, 2H), 1.45-1.36 (m, 11H), 1.35 (s, 3H). LC-MS (Method A): Rt 3.61 mins; MS m/z 524.2/ 526.2 = [M+Na]+ (99% @ 215nm)
8.3	 tert-Butyl (1 r,5s,6s)-6-{4-[2-(5-chloro-2-hydroxyphenyl)acetamido]pyridine-2-amido}-3-azabicyclo[3.1.0]hexane-3-carboxylate	1H NMR (500 MHz, DMSO-d6) δ 10.74 (br s, 1H), 9.86 (br s, 1H), 8.85 (d, J = 4.9 Hz, 1H), 8.46 (d, J = 5.5 Hz, 1H), 8.16 (d, J = 2.1 Hz, 1H), 7.84 (dd, J = 5.5, 2.2 Hz, 1H), 7.21 (d, J = 2.7 Hz, 1H), 7.12 (dd, J = 8.6, 2.7 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 3.66 (s, 2H), 3.52 (m, 2H), 2.54 - 2.52 (m, 1H), 1.95 - 1.82 (m, 2H), 1.40 (s, 9H). LC-MS (Method A): Rt 3.44 mins; MS m/z 487.2/ 489.2 = [M+H]+ (99% @ 215nm)

Example 9*

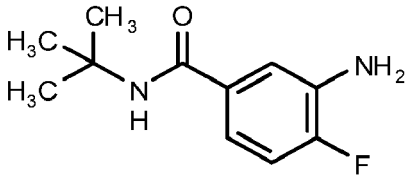
N-tert-Butyl-3-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]-4-fluoro-benzamide

[0456]



Step 1: 3-Amino-N-tert-butyl-4-fluoro-benzamide

[0457]



[0458] To a solution of 3-amino-4-fluoro-benzoic acid (205 mg, 1.32 mmol) in DCM (5 mL) was added sequentially 2-methylpropan-2-amine (306 μL, 2.91 mmol), DIPEA (0.92 mL, 5.29 mmol) and HATU (553 mg, 1.46 mmol) and the mixture was shaken at room temperature overnight. The resulting mixture washed with 2M HCl (5 mL) and sat. NaHCO3 solution (5 mL). The organic phase was separated by passing through a hydrophobic frit and concentrated *in vacuo.* Purification by flash chromatography on silica eluting with 0-100% EtOAc in heptane afforded the titled compound as an off-white solid.

[0459] 1H NMR (500 MHz, Chloroform-d) δ 7.25-7.19 (m, 1H), 6.99-6.95 (m, 2H), 5.82 (s, 1H), 3.82 (s, 2H), 1.45 (s, 9H).

[0460] LC-MS (Method E): Rt 0.95 mins; MS m/z 211.1 = [M+H]+ (97% @ 215nm)

Step 2: N-tert-Butyl-3-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]-4-fluoro-benzamide

[0461] A suspension of 3-amino-N-tert-butyl-4-fluoro-benzamide (step 1) (105 mg, 0.5 mmol) and 5-chloro-3H-benzofuran-2-one (84 mg, 0.5 mmol) in toluene (3 mL) was heated to 110°C in a sealed tube for 4 days. After cooling to room temperature, the mixture was concentrated *in vacuo* and crude residue was purified by preparative HPLC (acidic pH, early elution method) to afford the titled compound as an off-white powder.

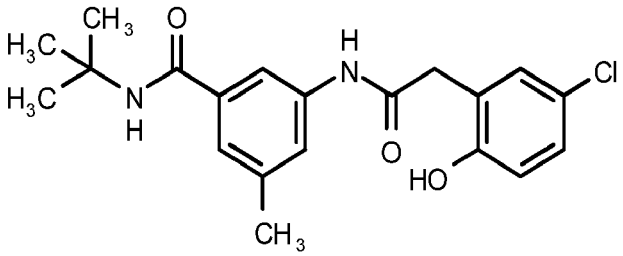
[0462] 1H NMR (500 MHz, MeOD) δ 8.28 (dd, J = 7.4, 2.1 Hz, 1H), 7.56 - 7.49 (m, 1H), 7.24 - 7.18 (m, 2H), 7.10 (dd, J = 8.6, 2.6 Hz, 1H), 6.81 (d, J = 8.6 Hz, 1H), 3.74 (s, 2H), 1.43 (s, 9H).

[0463] LC-MS (Method A): Rt 3.18 mins; MS m/z 379.1/ 381.1 = [M+H]+ (97% @ 215nm)

Example 9.1*

N-tert-Butyl-3-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]-5-methyl-benzamide

[0464]



[0465] The titled compound was prepared analogously to Example 9 by replacing 3-amino-4-fluoro-benzoic acid (step 1) with 3-amino-5-methyl-benzoic acid.

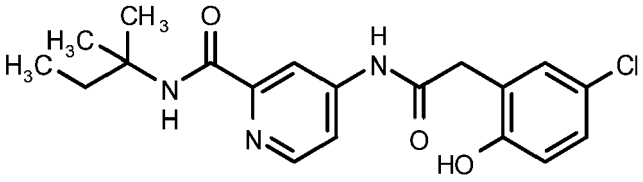
[0466] 1H NMR (500 MHz, Methanol-d4) δ 7.67 (s, 1H), 7.50 (s, 1H), 7.28 (s, 1H), 7.19 (d, J = 2.6 Hz, 1H), 7.08 (dd, J = 8.6, 2.6 Hz, 1H), 6.78 (d, J = 8.6 Hz, 1H), 3.67 (s, 2H), 2.36 (s, 3H), 1.44 (s, 9H).

[0467] LC-MS (Method A): Rt 3.32 mins; MS m/z 375.2/ 377.2 = [M+H]+ (99% @ 215nm).

Example 9.2

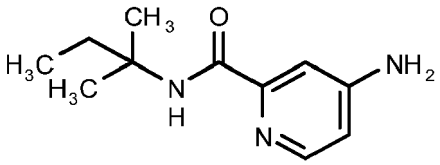
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1,1-dimethylpropyl)pyridine-2-carboxamide

[0468]



Step 1: 4-Amino-N-(1,1-dimethylpropyl)pyridine-2-carboxamide

[0469]



[0470] To a mixture of 2-methylbutan-2-amine (1.69 mL, 14.48 mmol), TBTU (1023 mg, 3.19 mmol) and TEA (0.81 mL, 5.79 mmol) was added 4-aminopyridine-2-carboxylic acid (400 mg, 2.9 mmol) and the mixture was stirred at room temperature for 5 hours.

[0471] The resulting mixture was partitioned between water (40 mL) and DCM (40 mL). The phases were separated and the organic portion concentrated *in vacuo.* The crude product was purified by C18 reverse phase chromatography eluting with MeCN in H_2O with 0.1% ammonium hydroxide to afford the titled compound as a white solid.

[0472] 1H NMR (500 MHz, DMSO-d6) δ 7.97 (d, J = 5.6 Hz, 1H), 7.92 (s, 1H), 7.17 (d, J = 2.3 Hz, 1H), 6.56 (dd, J = 5.6, 2.4 Hz, 1H), 6.32 (s, 2H), 1.74 (q, J = 7.5 Hz, 2H), 1.31 (s, 6H), 0.80 (t, J = 7.5 Hz, 3H).

[0473] LC-MS (Method F): Rt 1.55 mins; MS m/z 208.3 = [M+H]+ (100% @ 215nm)

Step 2: 4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1, 1-dimethylpropyl)pyridine-2-carboxamide

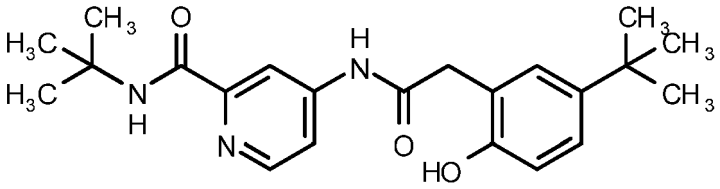
[0474] The titled compound was prepared analogously to Example 9 (step 2) from 4-amino-N-(1,1-dimethylpropyl)pyridine-2-carboxamide and 5-chloro-3H-benzofuran-2-one.

[0475] 1H NMR (500 MHz, Methanol-d_4) δ 8.42 (d, J= 5.6 Hz, 1H), 8.13-8.08 (m, 1H), 7.91 (dd, *J* = 5.5, 2.2 Hz, 1H), 7.19 (d, *J* = 2.6 Hz, 1H), 7.09 (dd, J = 8.6, 2.6 Hz, 1H), 6.77 (d, *J* = 8.6 Hz, 1H), 3.71 (s, 2H), 1.86 (q, *J* = 7.5 Hz, 2H), 1.42 (s, 6H), 0.91 (t, *J* = 7.5 Hz, 3H). LC-MS (Method A): Rt 3.50 mins; MS m/z 376.0/ 378.0 = [M+H]+ (98% @ 215nm).

Example 10

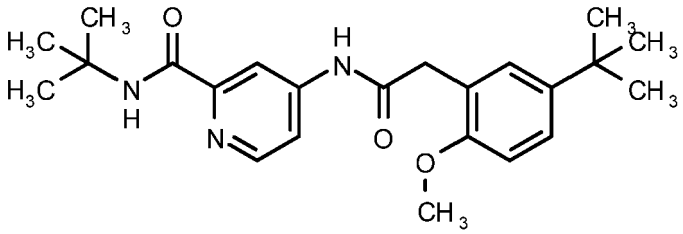
N-tert-Butyl-4-[[2-(5-tert-butyl-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide

[0476]



Step 1: N-tert-Butyl-4-[[2-(5-tert-butyl-2-methoxy-phenyl)acetyl]amino]pyridine-2-carboxamide

[0477]



[0478] The titled compound was prepared from 4-amino-N-tert-butyl-pyridine-2-carboxamide (Example 3 step 1) and commercially available 2-(5-tert-butyl-2-methoxy-phenyl)acetic acid analogously to Example 4.

[0479] 1H NMR (500 MHz, Chloroform-d) δ 8.45 (br s, 1H), 8.38 (d, J = 5.7 Hz, 1H), 8.29 (d, J = 5.3 Hz, 1H), 8.16 (br s, 1H), 7.57 (s, 1H), 7.34 (dd, J = 8.6, 2.5 Hz, 1H), 7.28 (d, J = 2.5 Hz, 1H), 6.92 (d, J = 8.6 Hz, 1H), 3.98 (s, 3H), 3.75 (s, 2H), 1.48 (s, 9H), 1.30 (s, 9H). LC-MS (Method E): Rt 1.31 mins; MS m/z 398.2 = [M+H]+ (85% @ 215nm)

Step 2: N-tert-Butyl-4-[[2-(5-tert-butyl-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide

[0480] The titled compound was prepared analogously to Example 3 (step 3) from N-tert-Butyl-4-[[2-(5-tert-butyl-2-methoxy-phenyl)acetyl]amino]pyridine-2-carboxamide.

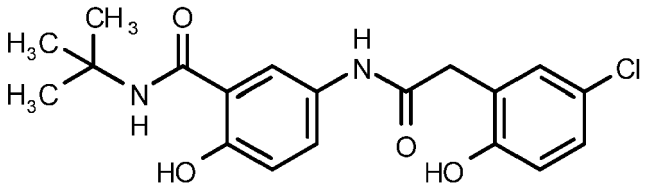
[0481] 1H NMR (500 MHz, Methanol-d_4) δ 8.42 (d, J = 5.5 Hz, 1H), 8.09 (d, J = 1.8 Hz, 1H), 7.91 (dd, J = 5.5, 2.2 Hz, 1H), 7.21 (d, J = 2.5 Hz, 1H), 7.15 (dd, J = 8.4, 2.5 Hz, 1H), 6.75 (d, J = 8.4 Hz, 1H), 3.72 (s, 2H), 1.47 (s, 9H), 1.28 (s, 9H).

[0482] LC-MS (Method A): Rt 3.81 mins; MS m/z 384.3 = [M+H]+ (97% @ 215nm)

Example 11*

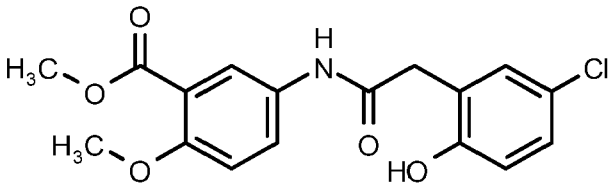
N-tert-Butyl-5-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]-2-hydroxy-benzamide

[0483]



Step 1: Methyl 5-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]-2-methoxy-benzoate

[0484]



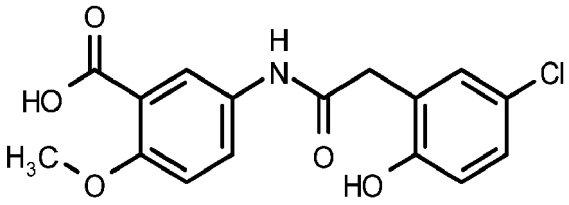
[0485] A mixture of 5-chloro-3H-benzofuran-2-one (75 mg, 0.44 mmol) and methyl 5-amino-2-methoxy-benzoate (81 mg, 0.44 mmol) in toluene (2 mL) was stirred at 100 °C in a sealed tube for 2 hours. The resulting mixture was allowed to cool to room temperature, toluene was added and the suspension was filtered, washing with toluene. The solid was dried *in vacuo* to afford the titled compound as an off-white solid.

[0486] 1H NMR (500 MHz, Chloroform-d) δ 7.79 (s, 1H), 7.77 (d, J = 2.8 Hz, 1H), 7.72 (dd, J = 9.0, 2.8 Hz, 1H), 7.14 (dd, J = 8.6, 2.6 Hz, 1H), 7.08 (d, J = 2.6 Hz, 1H), 6.93 (d, J = 9.0 Hz, 1H), 6.90 (d, J = 8.6 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.67 (s, 2H).

[0487] LC-MS (Method E): Rt 1.05 mins; MS m/z 350.0 / 351.9 = [M+H]+ (98% @ 215nm)

Step 2: 5-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-2-methoxy-benzoic acid

[0488]

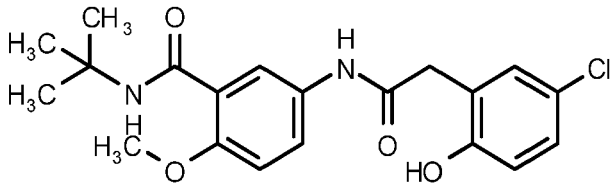


[0489] To a solution of methyl 5-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]-2-methoxybenzoate (step 1) (105 mg, 0.29 mmol) in 1,4-dioxane (2 mL) was added aqueous 2M LiOH (0.29 mL, 0.59 mmol) and the mixture was shaken at room temperature for 5 hours. A further equivalence of aqueous 2M LiOH (0.15 mL, 0.29 mmol) was added and shaking continued for an hour. Dioxane was removed *in vacuo* and the resulting mixture acidified to pH 1 with 1M HCl (1 mL). The mixture was extracted with EtOAc (2x5 mL) and the combined extracts were dried over Na_2SO_4 and concentrated *in vacuo* to afford the titled compound as an off-white solid.

[0490] 1H NMR (500 MHz, DMSO-d6) δ 12.60 (br s, 1H), 10.05 (s, 1H), 9.79 (s, 1H), 7.89 (d, J = 2.7 Hz, 1H), 7.70 (dd, J = 9.0, 2.8 Hz, 1H), 7.19 (d, J = 2.7 Hz, 1H), 7.10 (dd, J = 8.6, 2.7 Hz, 1H), 7.07 (d, J = 9.1 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 3.77 (s, 3H), 3.57 (s, 2H). LC-MS (Method E): Rt 0.99 mins; MS m/z 336.0/ 338.0 = [M+H]+ (99% @ 215nm)

Step 3: N-tert-Butyl-5-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-2-methoxybenzamide

[0491]



[0492] The titled compound was prepared from 5-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]-2-methoxy-benzoic acid (step 2) analogously to Example 1 step 3.

[0493] 1H NMR (500 MHz, DMSO-d6) δ 10.13 (s, 1H), 9.80 (s, 1H), 7.90 (d, J = 2.8 Hz, 1H), 7.85 (s, 1H), 7.74 (dd, J = 8.9, 2.8 Hz, 1H), 7.18 (d, J = 2.7 Hz, 1H), 7.09 (dd, J = 8.6, 2.7 Hz, 1H), 7.07 (d, J = 9.0 Hz, 1H), 6.79 (d, J = 8.6 Hz, 1H), 3.86 (s, 3H), 3.56 (s, 2H), 1.36 (s, 9H).

[0494] LC-MS (Method A): Rt 3.34 mins; MS m/z 391.2/ 393.2 = [M+H]+ (99% @ 215nm)

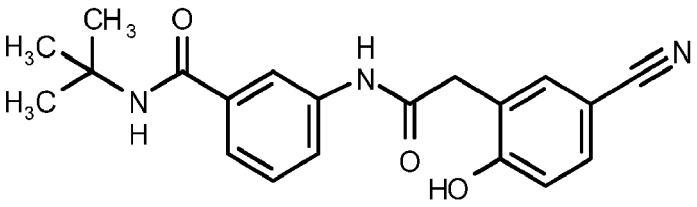
Step 4: N-tert-Butyl-5-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]-2-hydroxy-benzamide

[0495] The titled compound was prepared from N-tert-butyl-5-[[2-(5-chloro-2-hydroxyphenyl)acetyl]amino]-2-methoxy-benzamide (step 3) analogously to Example 3 step 3. 1H NMR (500 MHz, DMSO-d6) δ 11.50 (br.s, 1H), 9.94 (s, 1H), 9.82 (s, 1H), 8.24 (s, 1H), 7.98 - 7.88 (m, 1H), 7.60 - 7.53 (m, 1H), 7.19 (d, J = 2.6 Hz, 1H), 7.10 (dd, J = 8.6, 2.7 Hz, 1H), 6.83 (d, J = 8.7 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 3.56 (s, 2H), 1.38 (s, 9H). LC-MS (Method A): Rt 3.29 mins; MS m/z 377.2/ 379.2 = [M+H]+ (95% @ 215nm)

Example 12*

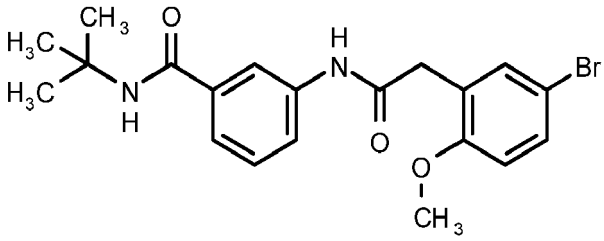
N-tert-Butyl-3-[[2-(5-cyano-2-hydroxy-phenyl)acetyl]amino]benzamide

[0496]



Step 1: 3-[[2-(5-Bromo-2-methoxy-phenyl)acetyl]amino]-N-tert-butyl-benzamide

[0497]



[0498] The titled compound was prepared analogously to Example 4 from 3-amino-N-tert-butyl-benzamide hydrochloride (Example 2 step 1b) and 2-(5-bromo-2-methoxy-phenyl)acetic acid.

[0499] 1H NMR (500 MHz, DMSO-d6) δ 10.19 (s, 1H), 7.89 (s, 1H), 7.74 (d, 1H), 7.70 (s, 1H), 7.44-7.40 (m, 3H), 7.33 (t, J = 7.9 Hz, 1H), 6.99 - 6.92 (m, 1H), 3.76 (s, 3H), 3.65 (s, 2H), 1.36 (s, 9H).

[0500] LC-MS (Method A): Rt 3.41 mins; MS m/z 419.2, 421.2 = [M+H]+ (100% @ 215nm)

Steps 2-3: N-tert-Butyl-3-[[2-(5-cyano-2-hydroxy-phenyl)acetyl]amino]benzamide

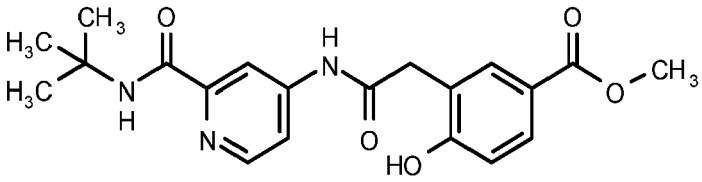
[0501] The titled compound was prepared analogously to Example 6 steps 2 and 3 from 3-[[2-(5-bromo-2-methoxy-phenyl)acetyl]amino]-N-tert-butyl-benzamide (step 1).

[0502] 1H NMR (500 MHz, DMSO-d6) δ 10.76 (br. S, 1H), 10.23 (s, 1H), 7.89 (t, J= 1.8 Hz, 1H), 7.80-7.72 (m, 1H), 7.70 (s, 1H), 7.61 (d, *J* = 2.1 Hz, 1H), 7.56 (dd, J= 8.4, 2.2 Hz, 1H), 7.42 (d, *J* = 7.8 Hz, 1H), 7.33 (m, 1H), 6.93 (d, *J* = 8.4 Hz, 1H), 3.66 (s, 2H), 1.36 (s, 9H). LC-MS (Method A): Rt 2.66 mins; MS m/z 352.2 = [M+H]+ (98% @ 215nm)

Example 13

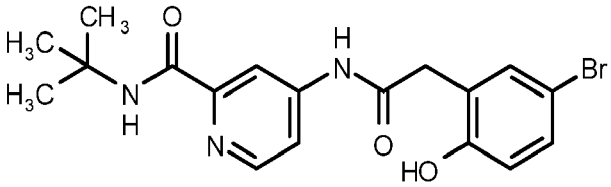
Methyl 3-[2-[[2-(tert-butylcarbamoyl)-4-pyridyl]amino]-2-oxo-ethyl]-4-hydroxybenzoate

[0503]



Step 1: 4-[[2-(5-Bromo-2-hydroxy-phenyl)acetyl]amino]-N-tert-butyl-pyridine-2-carboxamide

[0504]



[0505] A solution of 4-[[2-(5-bromo-2-methoxy-phenyl)acetyl]amino]-N-tert-butyl-pyridine-2-carboxamide (Example 6, step 1) (500 mg, 1.19 mmol) in DCM (25 mL) was treated with 1M BBr3 in DCM (3.57 mL, 3.57 mmol) and stirred at room temperature under nitrogen overnight. The resulting mixture was diluted with DCM (50 mL) and washed with water (25 mL x 2). The organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude solid by C18 reverse phase chromatography eluting with 0-100% MeCN in water with 0.1 % formic acid afforded the titled compound as a light yellow solid. 1H NMR (500 MHz, DMSO-d6) δ 10.69 (s, 1H), 9.86 (s, 1H), 8.44 (d, J = 5.5 Hz, 1H), 8.17 (d, J = 2.0 Hz, 1H), 8.03 (s, 1H), 7.81 (dd, J = 5.5, 2.2 Hz, 1H), 7.34 (d, J = 2.5 Hz, 1H), 7.24 (dd, J = 8.6, 2.6 Hz, 1H), 6.76 (d, J = 8.6 Hz, 1H), 3.67 (s, 2H), 1.40 (s, 9H).

[0506] LC-MS (Method A): Rt 3.34 mins; MS m/z 406.1/ 408.1 = [M+H]+ (90% @ 215nm)

Step 2: Methyl 3-[2-[[2-(tert-butylcarbamoyl)-4-pyridyl]amino]-2-oxo-ethyl]-4-hydroxybenzoate

[0507] All reagents charged to Coware equipment (carbon monoxide generating system) according to the following procedure; To chamber A was added sodium carbonate (53 mg, 0.50 mmol), 4-[[2-(5-bromo-2-hydroxy-phenyl)acetyl]amino]-N-tert-butyl-pyridine-2-carboxamide (step 1) (75 mg, 0.16 mmol), XantPhos Pd-G3 (third generation (G3) Buchwald precatalyst) (8 mg, 0.01 mmol) and toluene (2 mL). The reaction mixture was de-gassed for 5 minutes and MeOH (0.25 mL) was added. To chamber B was added formic acid (19 μL, 0.50 mmol) in toluene (2 mL) followed by mesyl chloride (39 μL, 0.50 mmol). Both chambers were sealed and TEA (139 μL, 0.99 mmol) added to chamber B to generate carbon monoxide. The Coware equipment was heated at 75 °C for 7 hours. The resulting mixture was concentrated *in vacuo,* dissolved in EtOAc (20 mL) and washed with water (2 x 20 mL). The organic portion was concentrated *in vacuo* and purified by preparative HPLC (acidic pH, early elution method). The product fractions were isolated and freeze-dried to afford the titled compound as an off-white solid.

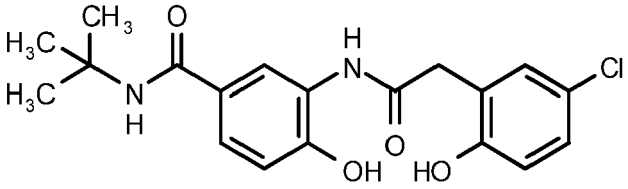
[0508] 1H NMR (500 MHz, DMSO-d6) δ 10.78 (br s , 1H), 10.55 (br s, 1H), 8.44 (d, J = 5.5 Hz, 1H), 8.17 (d, J = 2.0 Hz, 1H), 8.03 (s, 1H), 7.83-7.80 (m, 2H), 7.74 (dd, J = 8.5, 2.2 Hz, 1H), 6.88 (d, J = 8.5 Hz, 1H), 3.79 (s, 3H), 3.72 (s, 2H), 1.40 (s, 9H).

[0509] LC-MS (Method A): Rt 2.94 mins; MS m/z 386.3= [M+H]+ (95% @ 215nm)

Example 14*

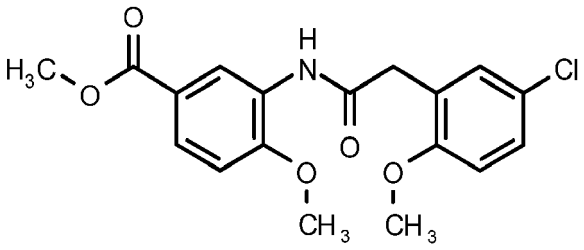
N-tert-Butyl-3-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]-4-hydroxy-benzamide

[0510]



Step 1: Methyl 3-[[2-(5-chloro-2-methoxy-phenyl)acetyl]amino]-4-methoxy-benzoate

[0511]



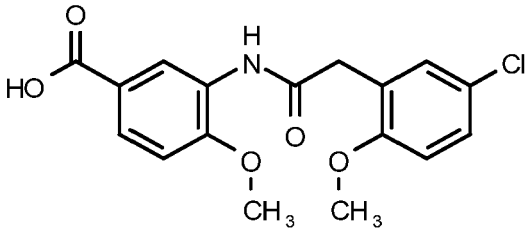
[0512] The titled compound was prepared analogously to Example 6 (step1) from methyl 3-amino-4-methoxy-benzoate and 2-(5-chloro-2-methoxy-phenyl)acetic acid.

[0513] 1H NMR (500 MHz, Chloroform-d) δ 8.98 (m, 1H), 8.28 (s, 1H), 7.77 (dd, J = 8.6, 2.1 Hz, 1H), 7.31 (d, J = 2.6 Hz, 1H), 7.24 (dd, J = 8.7, 2.6 Hz, 1H), 6.86 (dd, J = 8.7, 6.1 Hz, 2H), 3.90 (s, 3H), 3.90 (s, 3H), 3.86 (s, 3H), 3.71 (s, 2H).

[0514] LC-MS (Method E): Rt 1.20 mins; MS m/z 364.1/366.1= [M+H]+ (72% @ 215nm)

Step 2: 3-[[2-(5-Chloro-2-methoxy-phenyl)acetyl]amino]-4-methoxy-benzoic acid

[0515]



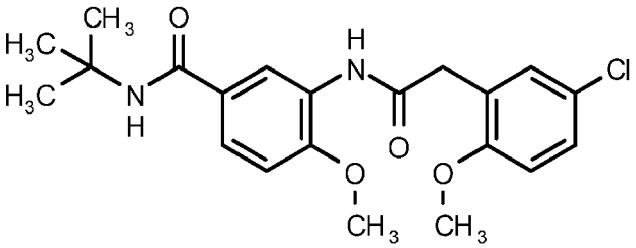
[0516] To a solution of methyl 3-[[2-(5-chloro-2-methoxy-phenyl)acetyl]amino]-4-methoxybenzoate (step 1)(301 mg, 0.83 mmol) in 1,4-dioxane (4 mL) was added aqueous 2M LiOH (1.24 mL, 2.48 mmol) and the mixture was shaken at room temperature overnight. The dioxane was removed *in vacuo* and the resulting mixture acidified to pH 1 with 1M HCl. The mixture was washed with EtOAc (2x5 mL). The aqueous phase was concentrated in *vacuo* and the resultant solid sonicated with MeOH (20 mL). The suspension was filtered, washed with further MeOH (5 mL) and the combined filtrate concentrated *in vacuo* to give an off-white solid.

[0517] 1H NMR (500 MHz, DMSO-d6) δ 9.26 (s, 1H), 8.56 (s, 1H), 7.68 (dd, J = 8.5, 2.1 Hz, 1H), 7.35 - 7.20 (m, 3H), 7.13 (d, J = 8.6 Hz, 1H), 7.03 (d, J = 8.5 Hz, 1H), 3.92 (s, 3H), 3.82 (s, 2H), 3.80 (s, 3H).

[0518] LC-MS (Method E): Rt 1.08 mins; MS m/z 350.1/ 352.1 = [M+H]+ (85% @ 215nm)

Step 3: N-tert-Butyl-3-[[2-(5-chloro-2-methoxy-phenyl)acetyl]amino]-4-methoxybenzamide

[0519]



[0520] To a solution of 3-[[2-(5-chloro-2-methoxy-phenyl)acetyl]amino]-4-methoxy-benzoic acid (step 2)(201 mg, 0.57 mmol) in DMF (2 mL) was added EDCI (110 mg, 0.57 mmol), HOAt (78 mg, 0.57 mmol), DIPEA (251 μL, 1.44 mmol) and 2-methylpropan-2-amine (79 μL, 0.75 mmol). The reaction mixture was shaken at room temperature overnight and then partitioned between DCM (6 mL) and water (6 mL). The organic layer collected using a hydrophobic frit and concentrated *in vacuo*. Chromatography on silica eluting with EtOAc in heptane afforded the titled compound as a colourless glass.

[0521] 1H NMR (500 MHz, Chloroform-d) δ 8.63 (d, J = 2.2 Hz, 1H), 8.36 (s, 1H), 7.64 (dd, J = 8.6, 2.3 Hz, 1H), 7.30 (d, J = 2.6 Hz, 1H), 7.25 (dd, J = 8.8, 2.6 Hz, 1H), 6.87 (dd, J = 10.9, 8.7 Hz, 2H), 5.99 (s, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.70 (s, 2H), 1.43 (s, 9H).

[0522] LC-MS (Method E): Rt 1.20 mins; MS m/z 405.1/407.1 = [M+H]+ (62% @ 215nm)

Step 4: N-tert-Butyl-3-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]-4-hydroxy-benzamide

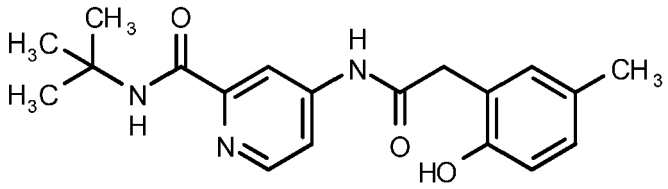
[0523] The titled compound was prepared from N-tert-butyl-3-[[2-(5-chloro-2-methoxyphenyl)acetyl]amino]-4-methoxy-benzamide (step 3) analogously to Example 3 step 3. 1H NMR (500 MHz, Methanol-d4) δ 8.23 (d, J = 2.2 Hz, 1H), 7.48 (s, 1H), 7.39 (dd, J = 8.4, 2.2 Hz, 1H), 7.24 (d, J = 2.6 Hz, 1H), 7.11 (dd, J = 8.6, 2.6 Hz, 1H), 6.86 (d, J = 8.4 Hz, 1H), 6.82 (d, J = 8.6 Hz, 1H), 3.72 (s, 2H), 1.43 (s, 9H).

[0524] LC-MS (Method A): Rt 2.93 mins; MS m/z 377.3/ 379.2= [M+H]+ (99% @ 215nm).

Example 15

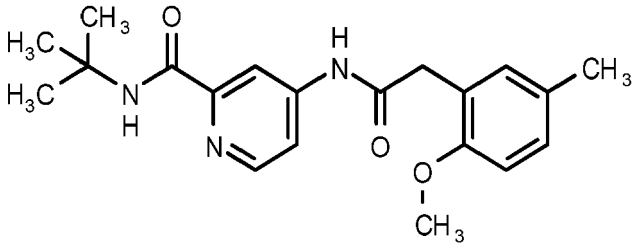
N-tert-Butyl-4-[[2-(2-hydroxy-5-methyl-phenyl)acetyl]amino]pyridine-2-carboxamide

[0525]



Step 1: N-tert-Butyl-4-[[2-(2-methoxy-5-methyl-phenyl)acetyl]amino]pyridine-2-carboxamide

[0526]



[0527] To a solution of 4-[[2-(5-bromo-2-methoxy-phenyl)acetyl]amino]-N-tert-butyl-pyridine-2-carboxamide (Example 6 step 1) (200 mg, 0.48 mmol) and potassium carbonate (132 mg, 0.95 mmol) in diglyme (5 mL) was added $Pd(dppf)_2Cl_2$ (17 mg, 0.02 mmol) followed by 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane in THF (50%, 0.16 mL, 0.57 mmol). The resulting mixture was degassed with nitrogen for 5 minutes and then stirred in a pressure tube at 100 °C for 16 hours. The resulting mixture was diluted with EtOAc (25 mL) and washed with water (2 x 25 mL) and brine (2 x 25 mL). The organic portion was dried over Na_2SO_4, concentrated *in vacuo* and purified by chromatography on silica eluting with EtOAc in heptane. The product fractions were concentrated *in vacuo* to afford the titled compound as a beige solid.
[0528] 1H NMR (500 MHz, DMSO-d6) δ 10.65 (s, 1H), 8.43 (d, J = 5.5 Hz, 1H), 8.18 (d, J = 2.0 Hz, 1H), 8.03 (s, 1H), 7.81 (dd, J = 5.5, 2.2 Hz, 1H), 7.06 - 7.01 (m, 2H), 6.86 (d, J = 8.2 Hz, 1H), 3.71 (s, 3H), 3.65 (s, 2H), 2.23 (s, 3H), 1.40 (s, 9H).
[0529] LC-MS (Method E): Rt 1.22 mins; MS m/z 356.2 = [M+H]+ (97% @ 215nm)

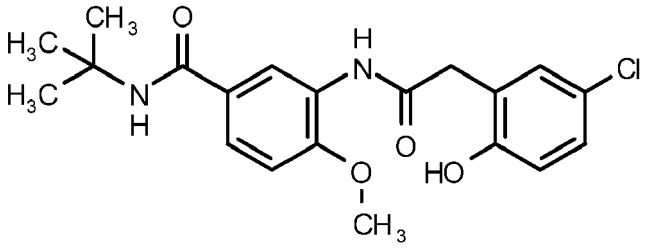
Step 2: N-tert-Butyl-4-[[2-(2-hydroxy-5-methyl-phenyl)acetyl]amino]pyridine-2-carboxamide

[0530] The titled compound was prepared from N-tert-Butyl-4-[[2-(2-methoxy-5-methylphenyl)acetyl]amino]pyridine-2-carboxamide (step 1) analogously to Example 3 (step 3). 1H NMR (500 MHz, DMSO-d6) δ 10.63 (s, 1H), 9.25 (s, 1H), 8.43 (d, *J* = 5.5 Hz, 1H), 8.18 (d, *J* = 2.0 Hz, 1H), 8.03 (s, 1H), 7.82 (dd, J = 5.5, 2.2 Hz, 1H), 6.94 (d, *J* = 1.9 Hz, 1H), 6.87 (dd, J= 8.1, 1.9 Hz, 1H), 6.68 (d, *J* = 8.1 Hz, 1H), 3.61 (s, 2H), 2.18 (s, 3H), 1.40 (s, 9H).
[0531] LC-MS (Method A): Rt 3.19 mins; MS m/z 342.3 = [M+H]+ (100% @ 215nm)

Example 16*

N-tert-Butyl-3-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]-4-methoxy-benzamide

[0532]



[0533] The titled compound was prepared from methyl 3-amino-4-methoxy-benzoate and 5-chloro-3H-benzofuran-2-one analogously to Example 11 steps 1-3.

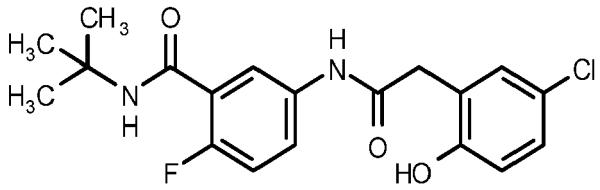
[0534] 1H NMR (500 MHz, Methanol-d_4) δ 8.36 (d, J = 2.1 Hz, 1H), 7.51 (dd, J = 8.6, 2.2 Hz, 1H), 7.24 (d, J = 2.6 Hz, 1H), 7.12 (dd, J = 8.6, 2.6 Hz, 1H), 7.03 (d, J = 8.6 Hz, 1H), 6.83 (d, J = 8.6 Hz, 1H), 3.91 (s, 3H), 3.72 (s, 2H), 1.43 (s, 9H).

[0535] LC-MS (Method A): Rt 3.18 mins; MS m/z 391.2/393.2 = [M+H]+ (95% @ 215nm)

Example 17*

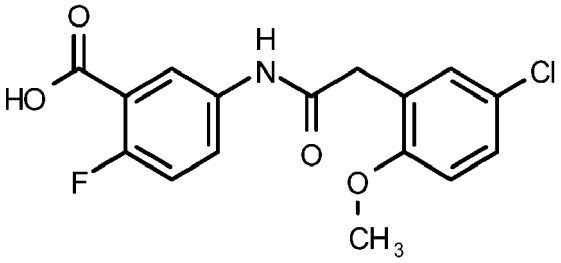
N-tert-Butyl-5-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]-2-fluoro-benzamide

[0536]



Steps 1-2: 5-[[2-(5-Chloro-2-methoxy-phenyl)acetyl]amino]-2-fluoro-benzoic acid

[0537]



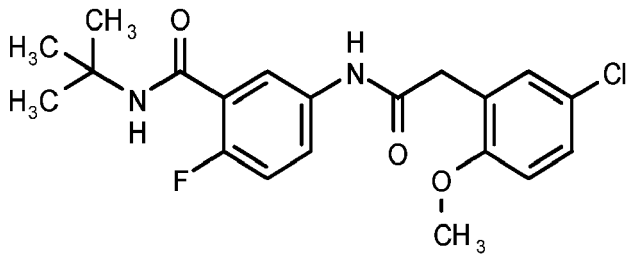
[0538] The titled compound was prepared from methyl 5-amino-2-fluoro-benzoate and 2-(5-chloro-2-methoxy-phenyl)acetic acid analogously to Example 7 steps 1 and 2.

[0539] 1H NMR (500 MHz, DMSO-d6) δ 13.25 (br s, 1H), 10.29 (s, 1H), 8.14 (dd, J = 6.6, 2.8 Hz, 1H), 7.83-7.76 (m, 1H), 7.32-7.28 (m, 2H), 7.25 (dd, J = 10.5, 9.0 Hz, 1H), 7.03-6.98 (m, 1H), 3.77 (s, 3H), 3.65 (s, 2H).

[0540] LC-MS (Method E): Rt 1.04 mins; MS m/z 338.0, 340.1 = [M+H]+ (95% @ 215nm)

Step 3: N-tert-Butyl-5-[[2-(5-chloro-2-methoxy-phenyl)acetyl]amino]-2-fluoro-benzamide

[0541]



[0542] To a mixture of 5-[[2-(5-chloro-2-methoxy-phenyl)acetyl]amino]-2-fluoro-benzoic acid (step 2) (100 mg, 0.28 mmol), TBTU (108 mg, 0.34 mmol) and TEA (0.08 mL, 0.56 mmol) in DMF (1.5 mL) was added 2-methylpropan-2-amine (35 μL, 0.34 mmol) and the mixture was stirred at room temperature for 3 hours. The resulting mixture was concentrated in *vacuo* and the residue was partitioned between water (10 mL) and DCM (10 mL). The organic phase was separated and concentrated *in vacuo.* Purification of the crude product by chromatography on silica eluting with EtOAc in heptane afforded the titled compound as a white solid.

[0543] 1H NMR (500 MHz, DMSO-d6) δ 10.21 (s, 1H), 7.83 (s, 1H), 7.73 (dd, J = 6.3, 2.7 Hz, 1H), 7.65 (ddd, J = 8.8, 4.4, 2.8 Hz, 1H), 7.32 - 7.29 (m, 1H), 7.29-7.27 (m, 1H), 7.17 (t, J = 9.4 Hz, 1H), 7.02 - 6.98 (m, 1H), 3.76 (s, 3H), 3.63 (s, 2H), 1.34 (s, 9H).

[0544] LC-MS (Method E): Rt 1.22 mins; MS m/z 393.2, 395.1 = [M+H]+ (99% @ 215nm)

Step 4: N-tert-Butyl-5-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]-2-fluoro-benzamide

[0545] The titled compound was prepared from N-tert-butyl-5-[[2-(5-chloro-2-methoxyphenyl)acetyl]amino]-2-fluoro-benzamide (step 3) analogously to Example 7, step 4.

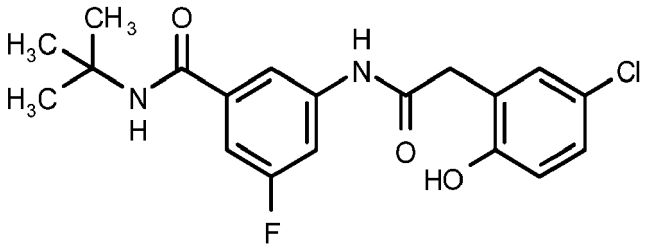
[0546] 1H NMR (500 MHz, DMSO-d6) δ 10.21 (s, 1H), 9.84 (s, 1H), 7.83 (s, 1H), 7.73 (dd, J = 6.3, 2.7 Hz, 1H), 7.66 (ddd, J = 8.9, 4.4, 2.8 Hz, 1H), 7.24 - 7.13 (m, 2H), 7.11 (dd, J = 8.6, 2.7 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 3.59 (s, 2H), 1.34 (s, 9H).

[0547] LC-MS (Method A): Rt 3.30 mins; MS m/z 379.2/381.1 = [M+H]+ (99% @ 215nm)

Example 18*

N-tert-Butyl-3-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]-5-fluoro-benzamide

[0548]



Step 1: 3-Amino-N-tert-butyl-5-fluoro-benzamide

[0549] The titled compound was prepared from 3-amino-5-fluoro-benzoic acid analogously to Example 9 step 1.

[0550] 1H NMR (500 MHz, Chloroform-d) δ 6.85-6.80 (m, 1H), 6.69 (dt, J = 9.1, 1.8 Hz, 1H), 6.45 (dt, J = 10.2, 2.2 Hz, 1H), 5.81 (s, 1H), 3.89 (s, 2H), 1.45 (s, 9H).

[0551] LC-MS (Method E): Rt 0.96 mins; MS m/z 211.1 = [M+H]+ (100% @ 215nm)

Steps 2-3: N-tert-Butyl-3-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]-5-fluoro-benzamide

[0552] The titled compound was prepared from 3-amino-N-tert-butyl-5-fluoro-benzamide (step 1) analogously to Example 3 steps 2 and 3.

[0553] 1H NMR (500 MHz, DMSO-d6) δ 10.41 (s, 1H), 9.81 (s, 1H), 7.81 (s, 1H), 7.75 (dt, J = 11.2, 2.0 Hz, 1H), 7.66 (s, 1H), 7.32-7.24 (m, 1H), 7.20 (d, J = 2.7 Hz, 1H), 7.11 (dd, J = 8.6, 2.7 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 3.62 (s, 2H),

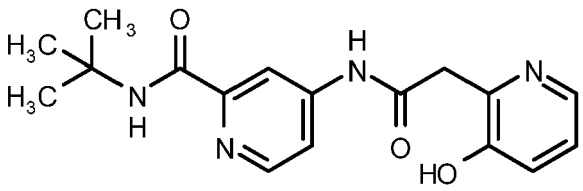
1.36 (s, 9H).

[0554] LC-MS (Method A): Rt 3.34 mins; MS m/z 379.1/381.1 = [M+H]+ (97% @ 215nm)

Example 19

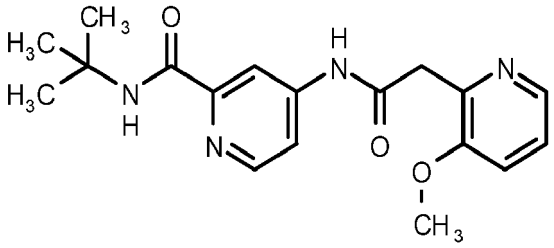
N-tert-Butyl-4-[[2-(3-hydroxy-2-pyridyl)acetyl]amino]pyridine-2-carboxamide

[0555]



Step 1 : N-tert-Butyl-4-[[2-(3-methoxy-2-pyridyl)acetyl]amino]pyridine-2-carboxamide

[0556]



[0557] The titled compound was prepared from 4-amino-N-tert-butyl-pyridine-2-carboxamide (Example 3 step 1) and 2-(3-methoxy-2-pyridyl)acetic acid analogously to Example 5.

[0558] 1H NMR (500 MHz, DMSO-d6) δ 10.75 (s, 1H), 8.44 (d, J = 5.5 Hz, 1H), 8.18 (d, J = 2.1 Hz, 1H), 8.07 (dd, J = 4.7, 1.3 Hz, 1H), 8.03 (s, 1H), 7.80 (dd, J = 5.5, 2.2 Hz, 1H), 7.42 (dd, J = 8.3, 1.2 Hz, 1H), 7.30 (dd,J = 8.3, 4.7 Hz, 1H), 3.88 (s, 2H), 3.81 (s, 3H), 1.40 (s, 9H).

[0559] LC-MS (Method A): Rt 2.11 mins; MS m/z 343.2 = [M+H]+ (100% @ 215nm)

Step 2: N-tert-Butyl-4-[[2-(3-hydroxy-2-pyridyl)acetyl]amino]pyridine-2-carboxamide

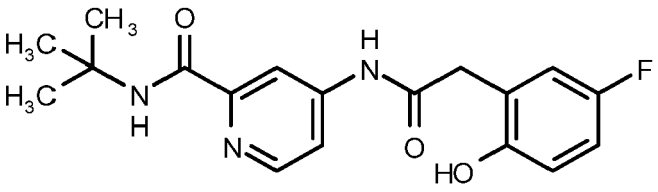
[0560] The titled compound was prepared from N-tert-Butyl-4-[[2-(3-methoxy-2-pyridyl)acetyl]amino]pyridine-2-carboxamide (step 1) analogously to Example 7, step 4. 1H NMR (500 MHz, DMSO-d6) δ 10.73 (s, 1H), 10.01 (br s, 1H), 8.44 (d, J = 5.5 Hz, 1H), 8.18 (d, J = 2.1 Hz, 1H), 8.03 (s, 1H), 7.95 (dd, J = 4.4, 1.6 Hz, 1H), 7.81 (dd, J = 5.5, 2.2 Hz, 1H), 7.20 - 7.09 (m, 2H), 3.84 (s, 2H), 1.40 (s, 9H).

[0561] LC-MS (Method A): Rt 1.60 mins; MS m/z 329.1 = [M+H]+ (98% @ 215nm)

Example 20

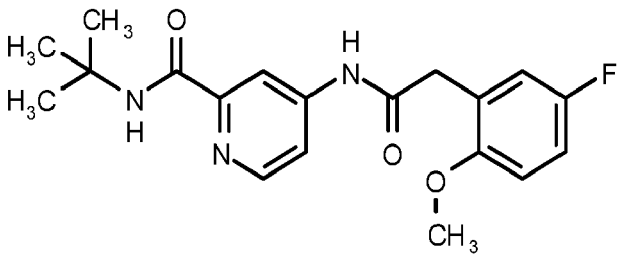
N-tert-Butyl-4-[[2-(5-fluoro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide

[0562]



Step 1: N-tert-Butyl-4-[[2-(5-fluoro-2-methoxy-phenyl)acetyl]amino]pyridine-2-carboxamide

[0563]



[0564] A solution of 2-(5-fluoro-2-methoxy-phenyl)acetic acid (57 mg, 0.31 mmol) in thionyl chloride (246 μL, 2.79 mmol) was heated at 70 °C for 1 hr. Excess thionyl chloride was removed *in vacuo,* azeotroping with DCM. The residue was added to a mixture of 4-amino-N-tert-butyl-pyridine-2-carboxamide (Example 3 step 1) (60 mg, 0.31 mmol) and DIPEA (65 μL, 0.37 mmol) in DCM (30 mL) and the mixture was stirred at room temperature. After 1 hour, the mixture was partitioned between water (25 mL) and DCM (25 mL). The organic layer was separated, dried over Na_2SO_4, filtered and concentrated *in vacuo.* Purification of the crude residue by chromatography on silica eluting with EtOAc in heptane followed by freeze drying of the product fractions afforded the titled compound as a white solid.

[0565] 1H NMR (500 MHz, DMSO-d6) δ 10.68 (s, 1H), 8.44 (d, J = 5.5 Hz, 1H), 8.17 (d, J = 2.0 Hz, 1H), 8.03 (s, 1H), 7.81 (dd, J = 5.5, 2.2 Hz, 1H), 7.12 (dd, J = 9.2, 3.2 Hz, 1H), 7.08 (td, J = 8.6, 3.2 Hz, 1H), 6.98 (dd, J = 9.0, 4.6 Hz, 1H), 3.74 (s, 3H), 3.71 (s, 2H), 1.40 (s, 9H).

[0566] LC-MS (Method E): Rt 1.16 mins; MS m/z 360.1 = [M+H]+ (98% @ 215nm)

Step 2: N-tert-Butyl-4-[[2-(5-fluoro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide

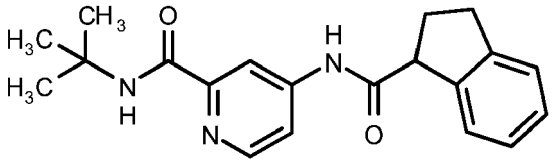
[0567] To a solution of N-tert-butyl-4-[[2-(5-fluoro-2-methoxy-phenyl)acetyl]amino]pyridine-2-carboxamide (step 1) (54.1 mg, 0.15 mmol) in DCM (1.3 mL) was added 1M BBr3 in DCM (452 μL, 0.45 mmol) slowly at room temperature. The reaction was stirred at room temperature for 2.5 hours and then concentrated *in vacuo.* The residue was partitioned between H_2O (10 mL) and EtOAc (10 mL) and the organic portion separated and concentrated *in vacuo.* The crude product was purified by preparative HPLC (acidic pH, early elution method) to afford the titled compound as a white solid.

[0568] 1H NMR (500 MHz, DMSO-d6) δ 10.67 (s, 1H), 9.52 (s, 1H), 8.44 (d, J = 5.5 Hz, 1H), 8.18 (d, J = 2.1 Hz, 1H), 8.03 (s, 1H), 7.82 (dd, J = 5.5, 2.2 Hz, 1H), 7.01 (dd, J = 9.4, 3.2 Hz, 1H), 6.91 (td, J = 8.6, 3.2 Hz, 1H), 6.77 (dd, J = 8.8, 4.9 Hz, 1H), 3.67 (s, 2H), 1.40 (s, 9H). LC-MS (Method A): Rt 3.01 mins; MS m/z 346.1 = [M+H]+ (98% @ 215nm)

Example 21

Racemic N-tert-butyl-4-[[-indane-1-carbonyl]amino]pyridine-2-carboxamide

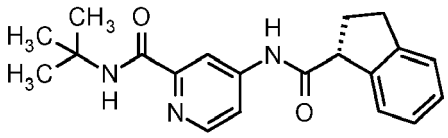
[0569]



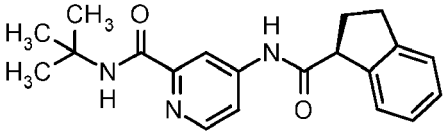
[0570] A mixture of 4-amino-N-tert-butyl-pyridine-2-carboxamide (Example 3 step 1) (100 mg, 0.52 mmol) and indane-1-carboxylic acid (84 mg, 0.52 mmol) in 1,4-dioxane (1 mL) was treated with 50% T3P® solution in EtOAc (616 μL, 1.03 mmol) and TEA (181 μL, 1.03 mmol) and stirred at room temperature for 1.5 hours. The resulting mixture was diluted with EtOAc (20 mL) and water (20 mL). The organic portion was separated, dried over Na_2SO_4, filtered and concentrated *in vacuo.* The crude product was purified by chromatography on silica eluting with EtOAc in heptane to afford racemic N-tert-butyl-4-[[-indane-1-carbonyl]amino]pyridine-2-carboxamide.

Example 21a: N-tert-Butyl-4-[[(1R) or (1S)-indane-1-carbonyl]amino]pyridine-2-carboxamide and Example 21b: N-tert-Butyl-4-[[(1R) or (1S)-indane-1-carbonyl]amino]pyridine-2-carboxamide

[0571]



(R)-isomer



(S)-isomer

[0572] Chiral separation of racemic N-tert-butyl-4-[[-indane-1-carbonyl]amino]pyridine-2-carboxamide using Supercritical Fluid Chromatography [chiral phase column (25% IPA: 75% CO2 with Chiralcel OD-H 25cm column at 15ml/min)] afforded the individual enantiomers:

Example 21a: First eluted peak: N-tert-Butyl-4-[[(1R)-indane-1-carbonyl]amino]pyridine-2-carboxamide or N-tert-Butyl-4-[[(1S)-indane-1-carbonyl]amino]pyridine-2-carboxamide SFC Retention time: 5.46 min, MS m/z 338.3 = [M+H]+ (100% @ 215nm)

[0573] 1H NMR (500 MHz, DMSO-d6) δ 10.85 (s, 1H), 8.46 (d, J = 5.5 Hz, 1H), 8.23 (d, J = 2.0 Hz, 1H), 8.03 (s, 1H), 7.87 (dd, J = 5.5, 2.2 Hz, 1H), 7.32 (d, J = 7.4 Hz, 1H), 7.28 (d, J = 7.3 Hz, 1H), 7.20 (m, 1H), 7.16 (m, 1H), 4.16 (m, 1H), 3.11 - 3.03 (m, 1H), 2.95 - 2.87 (m, 1H), 2.40 - 2.27 (m, 2H), 1.40 (s, 9H).
e.e 100%

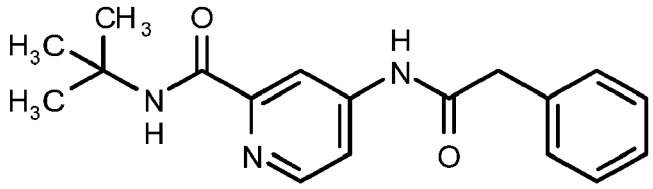
Example 21b: Second eluted peak: N-tert-Butyl-4-[[(1R)-indane-1-carbonyl]amino]pyridine-2-carboxamide or N-tert-Butyl-4-[[(1S)-indane-1-carbonyl]amino]pyridine-2-carboxamide

[0574] SFC Retention time: 8.00 min, MS m/z 338.3 = [M+H]+ (91% @ 215nm)
[0575] 1H NMR (500 MHz, DMSO-d6) δ 10.85 (s, 1H), 8.46 (d, J = 5.5 Hz, 1H), 8.23 (d, J = 2.0 Hz, 1H), 8.03 (s, 1H), 7.87 (dd, J = 5.5, 2.2 Hz, 1H), 7.32 (d, J = 7.3 Hz, 1H), 7.28 (d, J = 7.3 Hz, 1H), 7.20 (m, 1H), 7.16 (m, 1H), 4.16 (m, 1H), 3.11 - 3.03 (m, 1H), 2.95 - 2.87 (m, 1H), 2.39 - 2.27 (m, 2H), 1.40 (s, 9H).
e.e 88%

Example 22

N-tert-Butyl-4-[(2-phenylacetyl)amino]pyridine-2-carboxamide

[0576]



[0577] To a mixture of 4-amino-N-tert-butyl-pyridine-2-carboxamide (Example 3 step 1) (50 mg, 0.26 mmol) in DCM (2.59 mL) was added TEA (113 μL, 0.65 mmol) and 2-phenylacetyl chloride (41 μL, 0.31 mmol) and the mixture was stirred for 16 hours. The resulting mixture was diluted with DCM (10 mL) and washed with water (2 $\times$ 10 mL) followed by saturated aqueous $NaHCO_3$ (10 mL). The organic layer was separated and dried over Na_2SO_4, filtered and concentrated *in vacuo.* The crude residue was dissolved in a mixture of DMSO:MeCN (800 μl, 1:1), filtered and purified by preparative HPLC (acidic pH, early elution method). The product fractions were combined, the pH of the mixture adjusted to pH 7 using saturated aqueous $NaHCO_3$ (20 mL) and extracted with DCM (3 $\times$ 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the titled compound as an off-white solid.
[0578] 1H NMR (500 MHz, DMSO-d6) δ 10.75 (s, 1H), 8.44 (d, J = 5.5 Hz, 1H), 8.18 (d, J = 1.9 Hz, 1H), 8.02 (s, 1H),

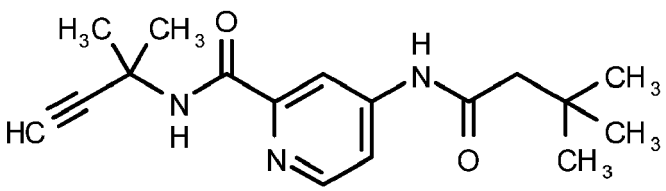
7.81 (dd, J = 5.5, 2.2 Hz, 1H), 7.33 (d, J = 4.4 Hz, 4H), 7.29 - 7.23 (m, 1H), 3.71 (s, 2H), 1.39 (s, 9H).

[0579] LC-MS (Method A): Rt 3.23 mins; MS m/z 312.2 = [M+H]+ (100% @ 215nm)

Example 22.1

4-(3,3-Dimethylbutanoylamino)-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide

[0580]



[0581] The titled compound was prepared from 4-amino-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide (Example 78 step 1) and 3,3-dimethylbutanoyl chloride analogously to Example 22.

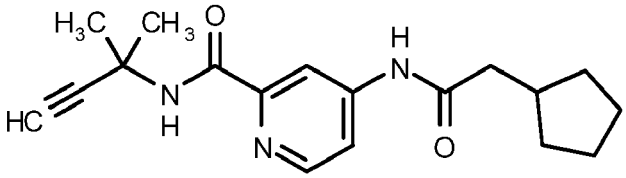
[0582] 1H NMR (500 MHz, DMSO-d6) δ 10.41 (s, 1H), 8.45 (d, J = 5.5 Hz, 1H), 8.31 (s, 1H), 8.22 (d, J = 2.1 Hz, 1H), 7.81 (dd, J = 5.5, 2.2 Hz, 1H), 3.21 (s, 1H), 2.25 (s, 2H), 1.64 (s, 6H), 1.02 (s, 9H).

[0583] LC-MS (Method A): Rt 3.22 mins; MS m/z 302.2 = [M+H]+ (100% @ 215nm)

Example 22.2

4-[(2-Cyclopentylacetyl)amino]-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide

[0584]



[0585] The titled compound was prepared from 4-amino-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide (Example 78 step 1) and 2-cyclopentylacetyl chloride analogously to Example 22.

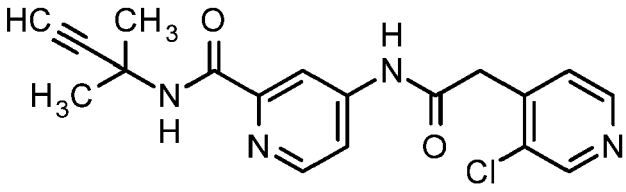
[0586] 1H NMR (500 MHz, DMSO-d6) δ 10.47 (s, 1H), 8.45 (d, J = 5.5 Hz, 1H), 8.31 (s, 1H), 8.21 (d, J = 2.1 Hz, 1H), 7.81 (dd, J = 5.5, 2.2 Hz, 1H), 3.21 (s, 1H), 2.39 - 2.35 (m, 2H), 2.28 - 2.19 (m, 1H), 1.80 - 1.72 (m, 2H), 1.64 (s, 6H), 1.63 - 1.56 (m, 2H), 1.56 - 1.47 (m, 2H), 1.23 - 1.13 (m, 2H).

[0587] LC-MS (Method A): Rt 3.33 mins; MS m/z 314.2 = [M+H]+ (97% @ 215nm)

Example 22.3

4-[[2-(3-Chloro-4-pyridyl)acetyl]amino]-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide

[0588]



[0589] The titled compound was prepared from 4-amino-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide (Example 78 step 1) and 2-(3-chloro-4-pyridyl)acetic acid hydrochloride analogously to Example 22.

[0590] 1H NMR (500 MHz, DMSO-d6) δ 10.95 (s, 1H), 8.63 (s, 1H), 8.49 (t, J = 5.3 Hz, 2H), 8.32 (s, 1H), 8.19 (d, J =

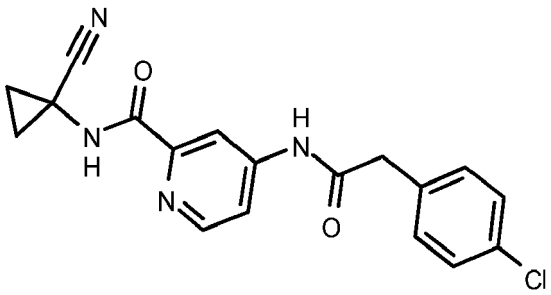
2.0 Hz, 1H), 7.81 (dd, J = 5.5, 2.2 Hz, 1H), 7.51 (d, J = 4.9 Hz, 1H), 3.99 (s, 2H), 3.21 (s, 1H), 1.64 (s, 6H).

[0591] LC-MS (Method A): Rt 2.53 mins; MS m/z 357.1/359.1 = [M+H]+ (100% @ 215nm)

Example 23

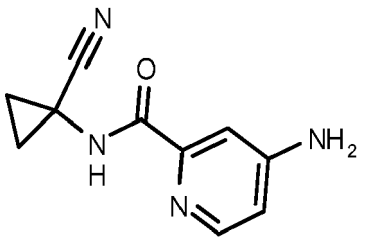
4-[[2-(4-Chlorophenyl)acetyl]amino]-N-(1-cyanocyclopropyl)pyridine-2-carboxamide

[0592]



Step 1 : 4-Amino-N-(1-cyanocyclopropyl)pyridine-2-carboxamide

[0593]



[0594] To a mixture of 4-aminopyridine-2-carboxylic acid (1 g, 7.24 mmol), TBTU (2.79 g, 8.69 mmol) and TEA (1.21 mL, 8.69 mmol) in DMF (8 mL) was added 1-aminocyclopropanecarbonitrile (22.82 mL, 8.69 mmol) and the mixture was stirred at 40°C for 2 days. The resulting mixture was concentrated *in vacuo* and the crude residue dissolved in EtOAc (15 mL). The mixture was washed with water (20 mL), $NaHCO_3$ (15 mL) dried over Na_2SO_4 and concentrated *in vacuo* to afford the titled compound as an orange solid.

[0595] 1H NMR (500 MHz, DMSO-d6) δ 9.41 (s, 1H), 8.01 (d, J = 5.6 Hz, 1H), 7.22 (d, J = 2.3 Hz, 1H), 6.62 (dd, J = 5.6, 2.4 Hz, 1H), 6.37 (s, 2H), 1.51 - 1.47 (m, 2H), 1.31 - 1.27 (m, 2H).

[0596] LC-MS (Method E): Rt 0.25 mins; MS m/z 203.1 = [M+H]+

Step 2: 4-[[2-(4-Chlorophenyl)acetyl]amino]-N-(1-cyanocyclopropyl)pyridine-2-carboxamide

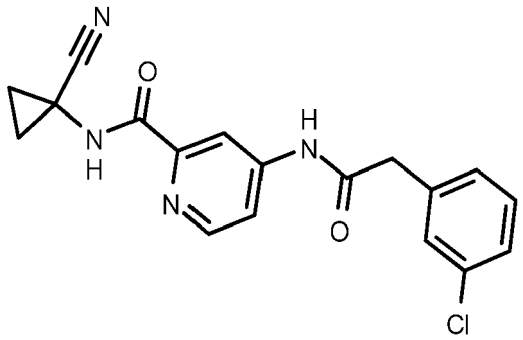
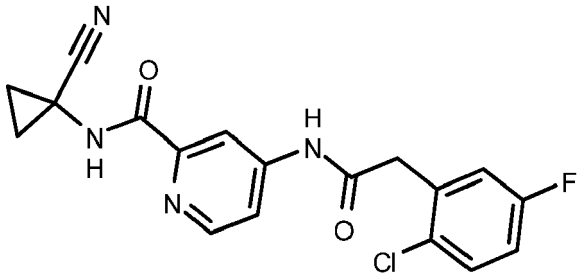
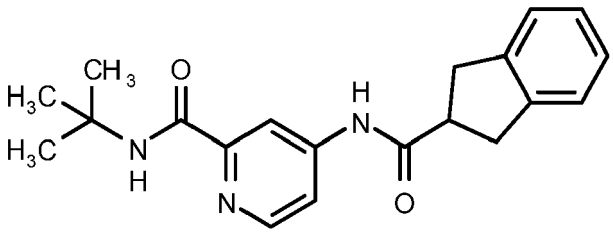
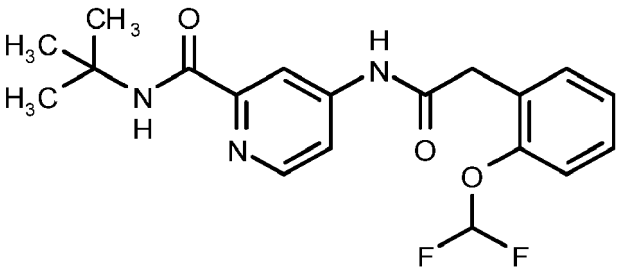
[0597] To a solution of 4-amino-N-(1-cyanocyclopropyl)pyridine-2-carboxamide (step 1) (100 mg, 0.45 mmol), 2-(4-chlorophenyl)acetic acid (83.52 mg, 0.49 mmol) and TEA (155 μL, 0.89 mmol) in 1,4-dioxane (2 mL) was slowly added 50% T3P® solution in EtOAc (529.41 μL, 0.89 mmol). The reaction mixture was stirred at room temperature for 1 hour and concentrated *in vacuo.* The crude residue was dissolved in EtOAc (10 mL) washed with $NaHCO_3$ (15 mL), brine (15 mL) dried over Na_2SO_4 and concentrated *in vacuo.* Purification by preparative HPLC (acidic pH, early elution method) afforded the titled compound as an off-white solid.

[0598] 1H NMR (500 MHz, DMSO-d6) δ = 10.80 (s, 1H), 9.65 (s, 1H), 8.49 (d, J=5.5, 1H), 8.21 (d, J=1.9, 1H), 7.86 (dd, J=5.5, 2.2, 1H), 7.41 - 7.34 (m, 4H), 3.74 (s, 2H), 1.55 - 1.51 (m, 2H), 1.34 - 1.30 (m, 2H).

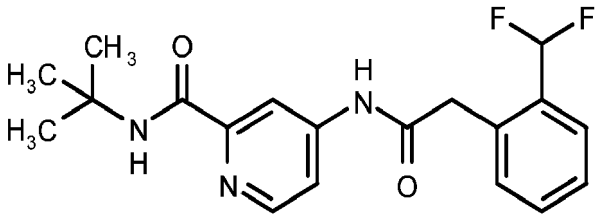
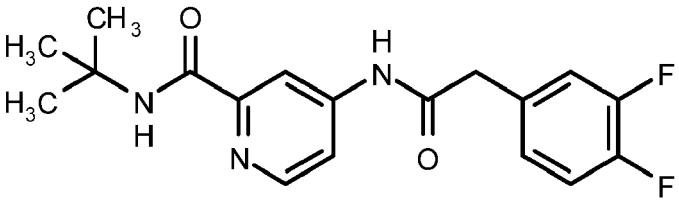
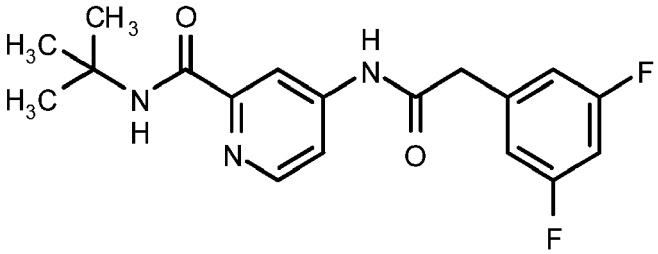
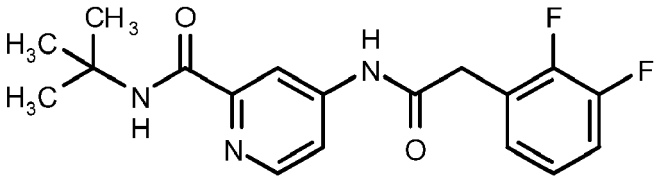
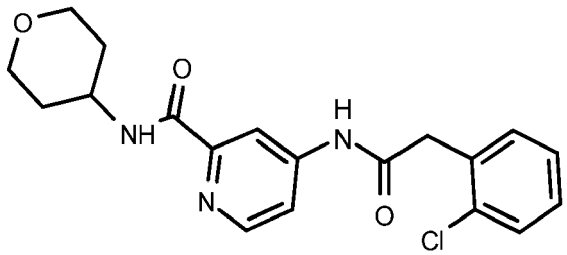
[0599] LC-MS (Method A): Rt 2.92 mins; MS m/z 355.3= [M+H]+ (98% @ 215nm)

[0600] The compounds of the following tabulated Examples (Table 8) were prepared analogously to Example 23 by replacing 1-aminocyclopropanecarbonitrile (step 1) with the appropriate amine and by replacing 2-(4-chlorophenyl)acetic acid (step 2) with the appropriate commercially available acid.

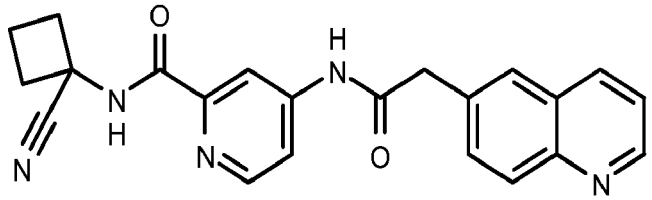
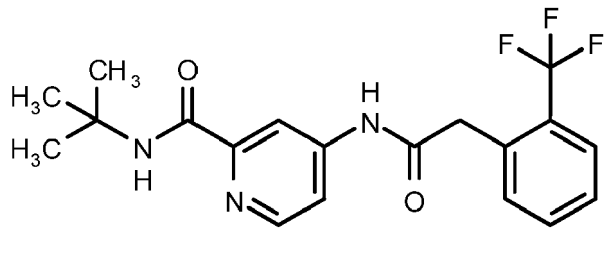
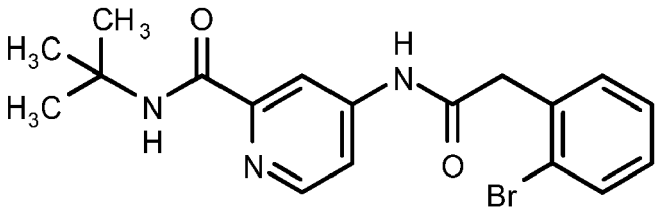
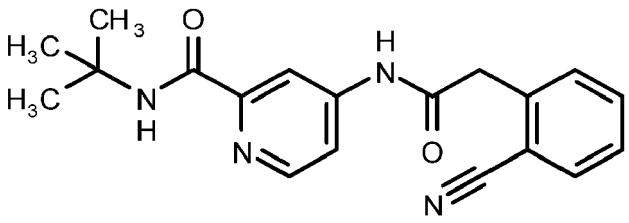
Table 8

Ex.	Structure and Name	1H NMR LCMS Retention Time, [M+H]+,
23.1	 4-[[2-(3-Chlorophenyl)acetyl] amino]-N-(1-cyanocyclo propyl) pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ = 10.81 (s, 1H), 9.66 (s, 1H), 8.50 (d, J=5.5, 1H), 8.21 (d, J=2.0, 1H), 7.86 (dd, J=5.5, 2.2, 1H), 7.42 - 7.41 (m, 1H), 7.39 - 7.28 (m, 3H), 3.76 (s, 2H), 1.55 - 1.51 (m, 2H), 1.34 - 1.31 (m, 2H). LC-MS (Method A): Rt 2.92 mins; MS m/z 355.3/357.3 = [M+H] + (96% @ 215nm)
23.2	 4-[[2-(2-Chloro-5-fluoro-phenyl) acetyl] amino]-N-(1-cyanocyclo propyl)pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ = 10.89 (s, 1H), 9.66 (s, 1H), 8.50 (d, J=5.5, 1H), 8.21 (d, J=2.0, 1H), 7.85 (dd, J=5.5, 2.2, 1H), 7.51 (dd, J=8.8, 5.3, 1H), 7.37 (dd, J=9.4, 3.1, 1H), 7.21 (td, J=8.5, 3.1, 1H), 3.94 LC-MS (Method A): Rt 2.86 mins; MS m/z 373.3/375.3 = [M+H]+ (99% @ 215nm)
23.3	 N-tert-Butyl-4-(indane-2-carbonyl amino)pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.64 (s, 1H), 8.45 (d, J = 5.5 Hz, 1H), 8.22 (d, J = 2.0 Hz, 1H), 8.03 (s, 1H), 7.86 (dd, J = 5.5, 2.2 Hz, 1H), 7.25 - 7.20 (m, 2H), 7.17 - 7.13 (m, 2H), 3.45 (p, J = 8.4 Hz, 1H), 3.25 - 3.13 (m, 4H), 1.40 (s, 9H). LC-MS (MethodA): Rt 3.62 mins; MS m/z 338.2 = [M+H]+ (3.62% @ 215nm)
23.4	 N-tert-Butyl-4-[[2-[2-(difluoromethoxy) phenyl]acetyl]amino]pyridine-2-carboxamide	1H NMR (500 MHz, Methanol-d4) δ 8.44 (d, J = 5.5 Hz, 1H), 8.17 - 8.14 (m, 1H), 7.90 (dd, J = 5.5, 2.2 Hz, 1H), 7.39 (dd, J = 7.5, 1.5 Hz, 1H), 7.36 (td, J = 7.9, 1.7 Hz, 1H), 7.24 (td, J = 7.5, 1.1 Hz, 1H), 7.20 - 7.18 (m, 1H), 6.78 (t, J = 74.2 Hz, 1H), 3.85 (s, 2H). LC-MS (Method A): Rt 3.42 mins; MS m/z 378.3 = [M+H]+ (99% @ 215nm)

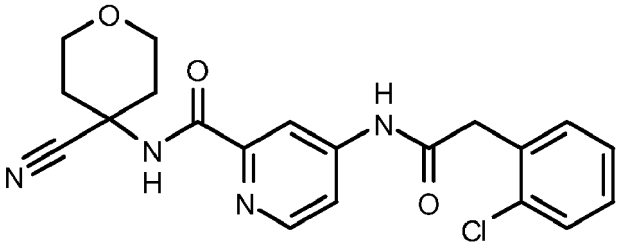
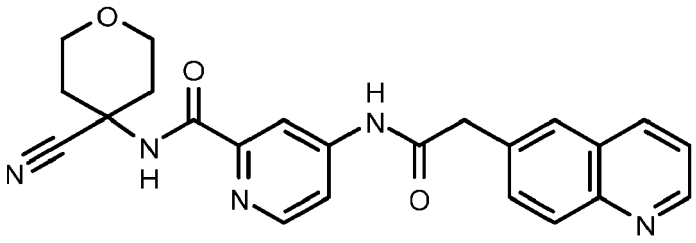
(continued)

Ex.	Structure and Name	1H NMR LCMS Retention Time, [M+H]+,
23.5	 N-tert-Butyl-4-[[2-[2-(difluoromethyl) phenyl]acetyl]amino]pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.80 (s, 1H), 8.46 (d, J = 5.5 Hz, 1H), 8.18 (d, J = 2.0 Hz, 1H), 8.03 (s, 1H), 7.80 (dd, J = 5.5, 2.2 Hz, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.54 - 7.50 (m, 1H), 7.46 - 7.42 (m, 2H), 7.20 (t, J = 54.8 Hz, 1H), 3.96 (s, 2H), 1.40 (s, 9H). LC-MS (Method A): Rt 3.41 mins; MS m/z 362.2 = [M+H]+
23.6	 N-tert-Butyl-4-[[2-(3,4-difluorophenyl) acetyl]amino]pyridine-2-carboxamide	1H NMR (500 MHz, Methanol-d4) δ 8.45 (dd, J = 5.5, 0.5 Hz, 1H), 8.15 (dd, J = 2.2, 0.5 Hz, 1H), 7.91 (dd, J = 5.5, 2.2 Hz, 1H), 7.32 - 7.20 (m, 2H), 7.18 - 7.13 (m, 1H), 3.75 (s, 2H), 1.49 (s, 9H). LC-MS (Method A): Rt 3.43 mins; MS m/z 348.3 = [M+H]+ (99% @ 215nm)
23.7	 N-tert-Butyl-4-[[2-(3,5-difluorophenyl) acetyl]amino]pyridine-2-carboxamide	1H NMR (500 MHz, Methanol-d4) δ 8.45 (dd, J = 5.7, 0.5 Hz, 1H), 8.15 (dd, J = 2.2, 0.5 Hz, 1H), 7.91 (dd, J = 5.5, 2.2 Hz, 1H), 7.03 - 6.95 (m, 2H), 6.88 (tt, J = 9.2, 2.3 Hz, 1H), 3.78 (s, 2H), 1.49 (s, 9H). LC-MS (Method A): Rt 3.46 mins; MS m/z 348.3 = [M+H]+ (97% @ 215nm)
23.8	 N-tert-Butyl-4-[[2-(2,3-difluorophenyl) acetyl]amino]pyridine-2-carboxamide	1H NMR (500 MHz, Methanol-d4) δ 8.45 (dd, J = 5.5, 0.4 Hz, 1H), 8.15 (dd, J = 2.2, 0.5 Hz, 1H), 7.92 (dd, J = 5.5, 2.2 Hz, 1H), 7.25 - 7.12 (m, 3H), 3.89 (d, J = 1.4 Hz, 2H), 1.49 (s, 9H). LC-MS (Method A): Rt 3.36 mins; MS m/z 348.2 = [M+H]+ (98% @ 215nm)
23.9	 4-[[2-(2-Chlorophenyl)acetyl]amino]-N-tetrahydropyran-4-yl-pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.83 (s, 1H), 8.59 (d, J = 8.5 Hz, 1H), 8.50 (d, J = 5.5 Hz, 1H), 8.21 (d, J = 1.9 Hz, 1H), 7.82 (dd, J = 5.5, 2.2 Hz, 1H), 7.48 - 7.42 (m, 2H), 7.35 - 7.31 (m, 2H), 4.06 - 3.97 (m, 1H), 3.92 (s, 2H), 3.89 - 3.84 (m, 2H), 3.43 - 3.36 (m, 2H), 1.72 - 1.63 (m, 4H). LC-MS (Method A): Rt 2.64 mins; MS m/z 374.2/376.2 = [M+H]+ (100% @ 215nm)

(continued)

Ex.	Structure and Name	1H NMR LCMS Retention Time, [M+H]+,
23.11	 N-(1-Cyanocyclobutyl)-4-[[2-(6-quinolyl) acetyl]amino]pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.90 (s, 1H), 9.59 (s, 1H), 8.88 (dd, J = 4.2, 1.7 Hz, 1H), 8.53 (d, J = 5.7 Hz, 1H), 8.39 - 8.32 (m, 1H), 8.22 (d, J = 1.9 Hz, 1H), 7.99 (d, J = 8.6 Hz, 1H), 7.93 - 7.84 (m, 2H), 7.75 (dd, J = 8.7, 2.0 Hz, 1H), 7.52 (dd, J = 8.3, 4.2 Hz, 1H), 3.96 (s, 2H), 2.73 - 2.61 (m, 2H), 2.59 - 2.51 (m, 2H), 2.09 - 1.94 (m, 2H). LC-MS (Method A): Rt 1.65 mins; MS m/z 386.3 = [M+H]+ (98% @ 215nm)
23.12	 N-tert-Butyl-4-[[2-[2-(trifluoromethyl) phenyl]acetyl]amino]pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.81 (s, 1H), 8.45 (d, J = 5.5 Hz, 1H), 8.17 (d, J = 2.1 Hz, 1H), 8.03 (s, 1H), 7.78 (dd, J = 5.5, 2.2 Hz, 1H), 7.72 (d, J = 7.8 Hz, 1H), 7.69 - 7.63 (m, 1H), 7.57 - 7.47 (m, 2H), 4.00 (s, 2H), 1.40 (s, 9H). LC-MS (Method A): Rt 3.58 mins; MS m/z 380.2 = [M+H]+ (100% @ 215nm)
23.13	 4-[[2-(2-Bromophenyl)acetyl]amino]-N-tert-butyl-pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.83 (s, 1H), 8.45 (d, J = 5.5 Hz, 1H), 8.18 (d, J = 2.0 Hz, 1H), 8.03 (s, 1H), 7.81 (dd, J = 5.5, 2.2 Hz, 1H), 7.62 (dd, J = 8.0, 1.1 Hz, 1H), 7.43 (dd, J = 7.6, 1.7 Hz, 1H), 7.41 - 7.30 (m, 1H), 7.27 - 7.20 (m, 1H), 3.92 (s, 2H), 1.40 (s, 9H). LC-MS (Method A): Rt 3.49 mins; MS m/z 390.2/392.2 = [M+H]+ (99% @ 215nm)
23.14	 N-tert-Butyl-4-[[2-(2-cyanophenyl) acetyl]amino]pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.92 (s, 1H), 8.47 (d, J = 5.5 Hz, 1H), 8.18 (d, J = 2.0 Hz, 1H), 8.03 (s, 1H), 7.85 (dd, J = 7.7, 1.1 Hz, 1H), 7.80 (dd, J = 5.5, 2.2 Hz, 1H), 7.72 - 7.66 (m, 1H), 7.57 (d, J = 7.3 Hz, 1H), 7.53 - 7.44 (m, 1H), 4.03 (s, 2H), 1.40 (s, 9H). LC-MS (Method A): Rt 3.06 mins; MS m/z 337.3 = [M+H]+ (100% @ 215nm)

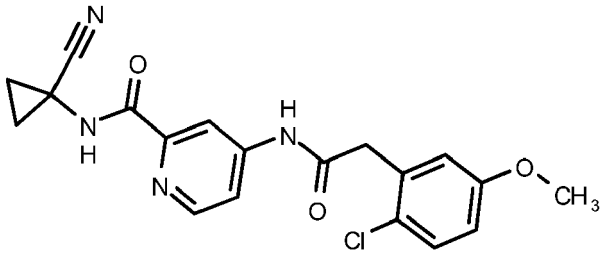
(continued)

Ex.	Structure and Name	1H NMR LCMS Retention Time, [M+H]+,
23.15	 4-[[2-(2-Chlorophenyl)acetyl]amino]-N-(4-cyanotetrahydropyran-4-yl)pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.89 (s, 1H), 9.01 (s, 1H), 8.54 (d, J = 5.5 Hz, 1H), 8.24 (d, J = 2.1 Hz, 1H), 7.86 (dd, J = 5.5, 2.2 Hz, 1H), 7.49 - 7.42 (m, 2H), 7.36 - 7.28 (m, 2H), 3.93 (s, 2H), 3.87 (dt, J = 12.2, 3.8 Hz, 2H), 3.62 - 3.54 (m, 2H), 2.39-2.34 (m, 2H), 2.12-2.03 (m, 2H). LC-MS (Method A): Rt 2.83 mins; MS m/z 399.2/401.3 = [M+H]+ (100% @ 215nm)
23.16	 N-(4-Cyanotetrahydropyran-4-yl)-4-[[2-(6-quinolyl)acetyl]amino] pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.91 (s, 1H), 9.01 (s, 1H), 8.88 (dd, J = 4.2, 1.7 Hz, 1H), 8.54 (d, J = 5.5 Hz, 1H), 8.36 - 8.33 (m, 1H), 8.26 (d, J = 2.1 Hz, 1H), 8.00 (d, J = 8.7 Hz, 1H), 7.91 (d, J = 1.6 Hz, 1H), 7.89 (dd, J = 5.5, 2.2 Hz, 1H), 7.75 (dd, J = 8.7, 2.0 Hz, 1H), 7.52 (dd, J = 8.3, 4.2 Hz, 1H), 3.97 (s, 2H), 3.86 (dt, J = 12.2, 3.8 Hz, 2H), 3.61 - 3.56 (m, 2H), 2.37 (d, J = 13.5 Hz, 2H), 2.07 (td, J = 10.1, 5.2 Hz, 2H) LC-MS (Method A): Rt 1.52 mins; MS m/z 416.3 = [M+H]+ (100% @ 215nm)

Example 24

4-[[2-(2-Chloro-5-methoxy-phenyl)acetyl] amino]-N-(1-cyanocyclopropyl)pyridine-2-carboxamide

[0601]



Steps 1 and 2: N-(1-Cyanocyclopropyl)-4-[[2-(3-methoxyphenyl)acetyl]amino]pyridine-2-carboxamide

[0602] The titled compound was prepared analogously to Example 23 by replacing 2-(4-chlorophenyl)acetic acid (step 2) with 2-(3-methoxyphenyl)acetic acid.

[0603] 1H NMR (500 MHz, DMSO-d6) δ = 10.77 (s, 1H), 9.65 (s, 1H), 8.49 (d, J=5.5, 1H), 8.21 (d, J=2.1, 1H), 7.86 (dd, J=5.5, 2.2, 1H), 7.24 (t, J=7.8, 1H), 6.92-6.88 (m, 2H), 6.83 (dd, J=8.0, 2.1, 1H), 3.74 (s, 3H), 3.68, (s, 2H), 1.55 - 1.51 (m, 2H), 1.34 - 1.30 (m, 2H). LC-MS (Method E): Rt 1.03 mins; MS m/z 351.0 = [M+H]+ (97% @ 215nm)

Step 2: 4-[[2-(2-Chloro-5-methoxy-phenyl)acetyl] amino]-N-(1-cyanocyclopropyl)pyridine-2-carboxam ide

[0604] To a solution of N-(1-cyanocyclopropyl)-4-[[2-(3-methoxyphenyl)acetyl]amino]pyridine-2-carboxamide (step 1) (81 mg, 0.23 mmol) in MeCN (33.7 mL) was added NCS (77 mg, 0.58 mmol) and the mixture was stirred at 60°C for 16 hours. The resulting mixture was concentrated *in vacuo* to yield a crude dry residue. The dry residue was dissolved in EtOAc (10 mL), washed with water (10 mL), $NaHCO_3$ (10 ml) and concentrated *in vacuo.* Purification by preparative HPLC (acidic pH, standard elution method) afforded the titled compound as an off-white solid.

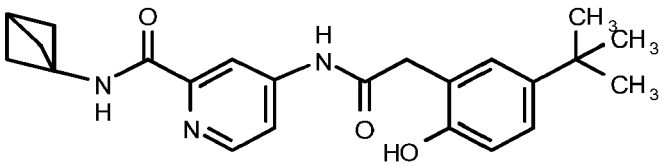
[0605] 1H NMR (500 MHz, DMSO-d6) δ 10.84 (s, 1H), 9.66 (s, 1H), 8.50 (d, J = 5.5 Hz, 1H), 8.21 (d, J = 2.0 Hz, 1H), 7.86 (dd, J = 5.5, 2.2 Hz, 1H), 7.35 (d, J = 8.8 Hz, 1H), 7.04 (d, J = 3.1 Hz, 1H), 6.90 (dd, J = 8.8, 3.1) Hz, 1H), 3.87 (s, 2H), 3.76 (s, 3H), 1.55 - 1.51 (m, 2H), 1.35 - 1.30 (m, 2H).

[0606] LC-MS (Method A): Rt 2.84 mins; MS m/z 385.2/387.2 = [M+H]+ (100% @ 215nm)

Example 25

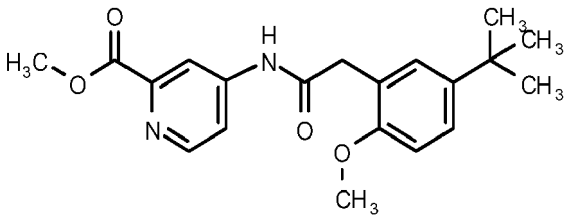
N-(3-Bicyclo[1.1.1]pentanyl)-4-[[2-(5-tert-butyl-2-hydroxy-phenyl)acetyl]amino] pyridine-2-carboxamide

[0607]



Step 1: Methyl 4-[[2-(5-tert-butyl-2-methoxy-phenyl)acetyl]amino]pyridine-2-carboxylate

[0608]



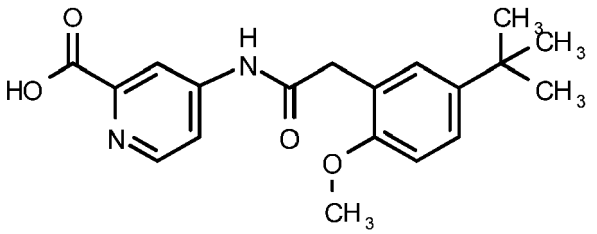
[0609] 2-(5-tert-Butyl-2-methoxy-phenyl)acetic acid (700 mg, 3.15 mmol) was dissolved in thionyl chloride (2.5 mL, 28.37 mmol) and stirred at 70°C for 30 mins. The resulting mixture was concentrated *in vacuo* and azeotroped with toluene (3 $\times$ 5 mL). The residue was dissolved in DCM (15 mL) to form a solution of acid chloride and added to a stirred solution of methyl 4-aminopyridine-2-carboxylate (527 mg, 3.46 mmol) in DCM (15 mL). After stirring for 10 mins, the mixture was concentrated *in vacuo* to yield a brown gum. The gum was purified by chromatography on silica eluting with 25-100% EtOAc in heptane to afford the titled compound as a dark yellow glass.

[0610] 1H NMR (250 MHz, DMSO-d6) δ 10.68 (s, 1H), 8.54 (d, J = 5.5 Hz, 1H), 8.31 (d, J = 2.0 Hz, 1H), 7.77 (dd, J = 5.5, 2.1 Hz, 1H), 7.29 - 7.20 (m, 2H), 6.89 (d, J = 9.3 Hz, 1H), 3.86 (s, 3H), 3.72 (s, 3H), 3.68 (s, 2H), 1.26 (s, 9H).

[0611] LC-MS (Method E): Rt 1.17 mins; MS m/z 357 = [M+H]+

Step 2: 4-[[2-(5-tert-Butyl-2-methoxy-phenyl)acetyl]amino]pyridine-2-carboxylic acid

[0612]

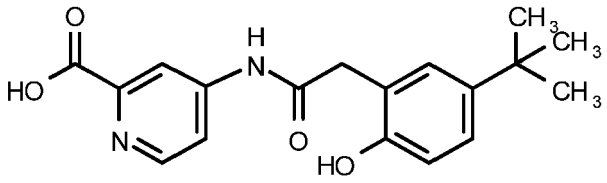


[0613] To a solution of methyl 4-[[2-(5-tert-butyl-2-methoxy-phenyl)acetyl]amino]pyridine-2-carboxylate (step 1) (594 mg, 1.55 mmol) in THF (12 mL) was added 1M sodium hydroxide solution (1.86 mL, 1.86 mmol) and the mixture stirred for 30 mins. The pH of resulting mixture was adjusted to pH 4 by addition of hydrochloric acid. The mixture was partitioned between EtOAc (20 mL) and water (20 mL) at which point a precipitate formed in the organic layer. The organic suspension was washed with water (20 mL), brine (20 mL), filtered through a phase separator and dried to afford the titled compound as a fine powder. 1H NMR (250 MHz, DMSO-d6) δ 10.70 (s, 1H), 8.52 (d, J = 5.6 Hz, 1H), 8.28 (d, J = 1.9 Hz, 1H), 7.80 (dd, J = 5.6, 2.2 Hz, 1H), 7.29 - 7.20 (m, 2H), 6.89 (d, J = 9.4 Hz, 1H), 3.72 (s, 3H), 3.69 (s, 2H), 1.26 (s, 9H).

[0614] LC-MS (Method E): Rt 0.98 mins; MS m/z 343= [M+H]+

Step 3: 4-[[2-(5-tert-Butyl-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxylic acid

[0615]



[0616] An ice-cooled suspension of 4-[[2-(5-tert-butyl-2-methoxy-phenyl)acetyl]amino]pyridine-2-carboxylic acid (step 2) (330 mg, 0.93 mmol) in DCM (9 mL) was treated with 1M BBr3 in DCM (1.85 mL, 1.85 mmol) and stirred for 70 mins. The reaction was quenched with methanol (1 mL) and the mixture was partitioned between EtOAc (20 mL) and water (20 mL) resulting in the formation of a fine white precipitate. The precipitate was filtered and dried to afford the titled compound as a solid.

[0617] 1H NMR (250 MHz, DMSO-d6) δ 11.51 (s, 1H), 8.65 (d, J = 6.4 Hz, 1H), 8.51 (d, J = 2.2 Hz, 1H), 8.14 (dd, J = 6.4, 2.3 Hz, 1H), 7.18 (d, J = 2.4 Hz, 1H), 7.10 (dd, J = 8.4, 2.5 Hz, 1H), 6.74 (d, J = 8.4 Hz, 1H), 3.75 (s, 2H), 1.23 (s, 9H).

[0618] LC-MS (Method E): Rt 0.97 mins; MS m/z 329 = [M+H]+ (91% @ 215nm)

Step 4: N-(3-Bicyclo[1.1.1]pentanyl)-4-[[2-(5-tert-butyl-2-hydroxy-phenyl)acetyl]amino] pyridine-2-carboxam ide

[0619] To a suspension of 4-[[2-(5-tert-butyl-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxylic acid (step 3) (25 mg, 0.08 mmol) in DMF (0.5 mL) was added bicyclo[1.1.1]pentan-3-amine hydrochloride (11 mg, 0.09 mmol), DIPEA (0.05 mL, 0.3 mmol) and HATU (43 mg, 0.11 mmol). After stirring at room temperature for 18 hours, the mixture was partitioned between EtOAc (10 mL) and water (10 mL) and the aqueous portion extracted with EtOAc (2 $\times$ 20 mL). The combined organic extracts were washed with water (20 mL), brine (20 mL), dried over Na_2SO_4 and concentrated *in vacuo.* The crude residue was purified by C18 reverse phase chromatography eluting with 45-65% MeCN in water with 0.1% formic acid to afford the titled compound as a white powder.

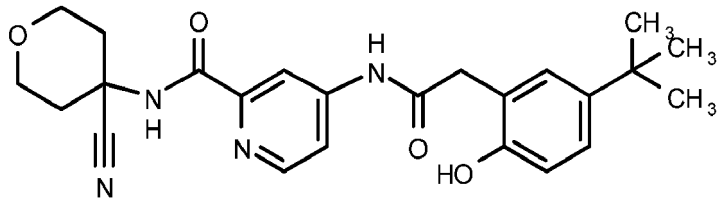
[0620] 1H NMR (500 MHz, DMSO-d6) δ 10.70 (s, 1H), 9.28 (s, 1H), 9.07 (s, 1H), 8.44 (d, J = 5.5 Hz, 1H), 8.16 (d, J = 2.1 Hz, 1H), 7.84 (dd, J = 5.5, 2.2 Hz, 1H), 7.16 (d, J = 2.5 Hz, 1H), 7.08 (dd, J = 8.4, 2.5 Hz, 1H), 6.72 (d, J = 8.4 Hz, 1H), 3.65 (s, 2H), 2.44 (s, 1H), 2.09 (s, 6H), 1.23 (s, 9H).

[0621] LC-MS (Method A): Rt 3.71 mins; MS m/z 394 = [M+H]+

Example 25.1

4-[[2-(5-tert-Butyl-2-hydroxy-phenyl)acetyl]amino]-N-(4-cyanotetrahydropyran-4-yl)pyridine-2-carboxamide

[0622]



[0623] The titled compound was prepared from 4-[[2-(5-tert-butyl-2-hydroxyphenyl)acetyl]amino]pyridine-2-carboxylic acid (Example 25, step 3) and 4-aminotetrahydropyran-4-carbonitrile analogously to Example 25 step 4.

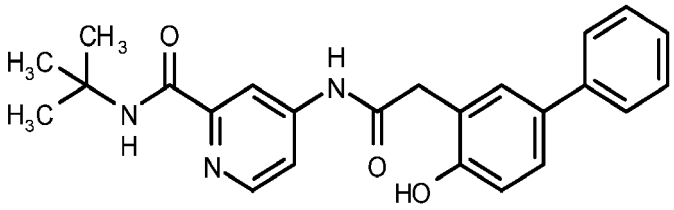
[0624] 1H NMR (500 MHz, Methanol-d4) δ 8.47 (d, J = 5.5 Hz, 1H), 8.17 (d, J = 1.8 Hz, 1H), 7.94 (dd, J = 5.5, 2.2 Hz, 1H), 7.22 (d, J = 2.4 Hz, 1H), 7.15 (dd, J = 8.4, 2.5 Hz, 1H), 6.75 (d, J = 8.4 Hz, 1H), 3.96 (dt, J = 12.5, 4.0 Hz, 2H), 3.80 - 3.74 (m, 2H), 3.72 (s, 2H), 2.49 - 2.43 (m, 2H), 2.14 - 2.07 (m, 2H), 1.28 (s, 9H).

[0625] LC-MS (Method A): Rt 3.22 mins; MS m/z 437 = [M+H]+ (100% @ 215nm)

Example 26

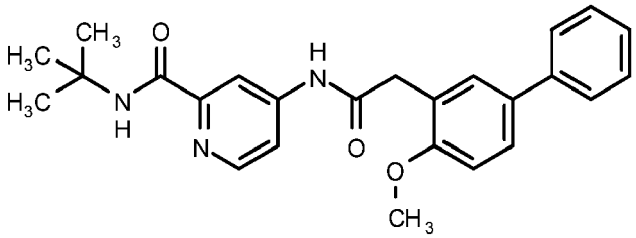
N-tert-Butyl-4-[[2-(2-hydroxy-5-phenyl-phenyl)acetyl]amino]pyridine-2-carboxamide

[0626]



Step 1: N-tert-butyl-4-[[2-(2-methoxy-5-phenyl-phenyl)acetyl]amino]pyridine-2-carboxamide

[0627]



[0628] A pressure tube was charged with 4-[[2-(5-bromo-2-methoxy-phenyl)acetyl]amino]-N-tert-butyl-pyridine-2-carboxamide (Example 6, step 1) (250 mg, 0.59 mmol), tripotassium phosphate (379 mg, 1.78 mmol), phenylboronic acid (80 mg, 0.65 mmol) in 1,4-dioxane (4 mL) and the suspension was degassed with nitrogen. Bis[3-(diphenylphosphanyl)cyclopenta-2,4-dien-1-yl]iron; dichloromethane; dichloropalladium (24 mg, 0.03 mmol) was added under an atmosphere of nitrogen and the sealed tube was heated to 80°C for 23 hours. The reaction mixture was concentrated *in vacuo* and the crude residue re-dissolved in EtOAc. The mixture was filtered through Celite® (filter material) and the filtrate concentrated *in vacuo* to afford a brown oil. The oil was purified by chromatography on silica eluting 25-100% EtOAc in heptane to afford the titled compound as a white solid.

[0629] 1H NMR (250 MHz, Chloroform-d) δ 8.38 (d, J = 5.6 Hz, 1H), 8.26 - 8.14 (m, 2H), 7.97 (s, 1H), 7.59 - 7.50 (m, 5H), 7.46 - 7.37 (m, 2H), 7.37 - 7.28 (m, 1H), 7.05 (d, J = 8.3 Hz, 1H), 4.01 (s, 3H), 3.80 (s, 2H), 1.47 (s, 9H).

[0630] LC-MS (Method E): Rt 1.29 mins; MS m/z 418 = [M+H]+

Step 2: N-tert-Butyl-4-[[2-(2-hydroxy-5-phenyl-phenyl)acetyl]amino]pyridine-2-carboxamide

[0631] To an ice-cooled solution of N-tert-butyl-4-[[2-(2-methoxy-5-phenyl-phenyl)acetyl]amino]pyridine-2-carboxamide (step 1) (160 mg, 0.38 mmol) in DCM (2.5 mL) was added dropwise 1M BBr_3 in DCM (1.92 mL, 1.92 mmol). After

stirring for 10 mins, the reaction was quenched by addition of methanol (1 mL). The resulting mixture was concentrated *in vacuo* and the residue partitioned between EtOAc (20 mL) and water (20 mL). The organic layer was separated and the aqueous portion re-extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with water (20 mL), brine (20 mL), dried over Na_2SO_4 and concentrated *in vacuo* to afford the titled compound as an amber-coloured glass.

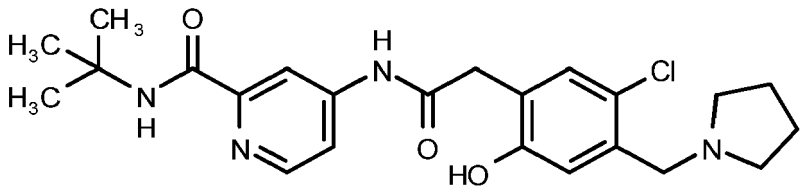
[0632] ^{1}H NMR (500 MHz, Chloroform-d) δ 10.14 - 9.39 (m, 2H), 8.32 (d, *J* = 5.6 Hz, 1H), 8.16 (s, 1H), 8.04 (dd, *J* = 5.6, 1.9 Hz, 1H), 7.94 (s, 1H), 7.42 (d, *J* = 7.3 Hz, 2H), 7.39 (d, *J* = 2.1 Hz, 1H), 7.36 - 7.29 (m, 3H), 7.25 (t, *J* = 7.3 Hz, 1H), 7.00 (d, *J* = 8.3 Hz, 1H), 3.83 (s, 2H), 1.49 (s, 9H).

[0633] LC-MS (Method A): Rt 3.64 mins; MS m/z 404 = [M+H]+

Example 27

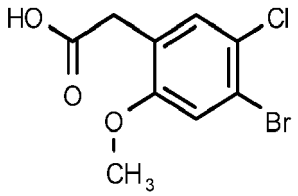
N-tert-Butyl-4-[[2-[5-chloro-2-hydroxy-4-(pyrrolidin-1-ylmethyl)phenyl]acetyl] amino]pyridine-2-carboxamide

[0634]



Step 1: 2-(4-Bromo-5-chloro-2-methoxy-phenyl)acetic acid

[0635]



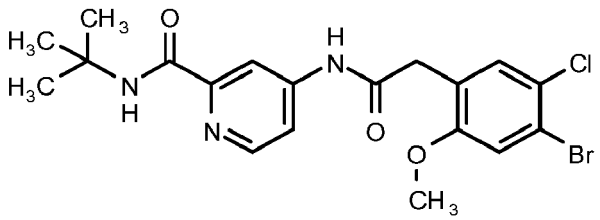
[0636] 2-(4-Bromo-2-methoxy-phenyl)acetic acid (2 g, 8.16 mmol) and NCS (1.14 g, 8.57 mmol) were dissolved in MeCN (40.8 mL) and stirred at 50 °C for 22 hours. The resulting mixture was concentrated *in vacuo* and the residue purified by chromatography on silica eluting with 20-100% EtOAc in heptane. The product was further purified by dissolving in EtOAc (100 mL) and extracting into saturated aqueous $NaHCO_3$ (3 × 100 mL). The combined aqueous extracts were acidified with 1M HCl and extracted with EtOAc (3 × 150 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the titled compound as a colourless solid.

[0637] 1H NMR (250 MHz, DMSO-d6) δ 11.97 (s, 1H), 7.46 (s, 1H), 7.34 (s, 1H), 3.79 (s, 3H), 3.50 (s, 2H).

[0638] LC-MS (Method E): Rt 1.07 mins; MS m/z not observed = [M+H]+

Step 2: 4-[[2-(4-Bromo-5-chloro-2-methoxy-phenyl)acetyl]amino]-N-tert-butyl-pyridine-2-carboxamide

[0639]

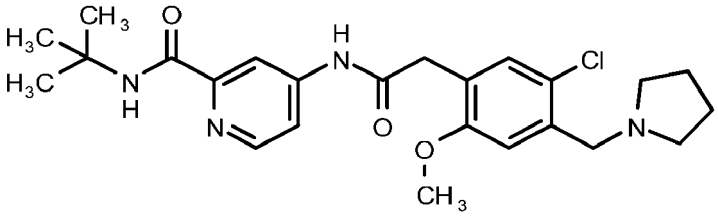


[0640] The titled compound was prepared from 4-amino-N-tert-butyl-pyridine-2-carboxamide and 2-(4-bromo-5-chloro-2-methoxy-phenyl)acetic acid (step1) analogously to Example 3.5b step 1

[0641] 1H NMR (250 MHz, DMSO-d6) δ 10.70 (s, 1H), 8.44 (d, J = 5.6 Hz, 1H), 8.16 (d, J = 1.9 Hz, 1H), 8.03 (s, 1H), 7.79 (dd, J = 5.5, 2.2 Hz, 1H), 7.51 (s, 1H), 7.36 (s, 1H), 3.78 (s, 3H), 3.71 (s, 2H), 1.40 (s, 9H).
[0642] LC-MS (Method E): Rt 1.28mins; MS m/z 454 = [M+H]+ 97% @ 215nm)

Step 3: N-tert-Butyl-4-[[2-[5-chloro-2-methoxy-4-(pyrrolidin-1-ylmethyl)phenyl]acetyl] amino]pyridine-2-carboxamide

[0643]

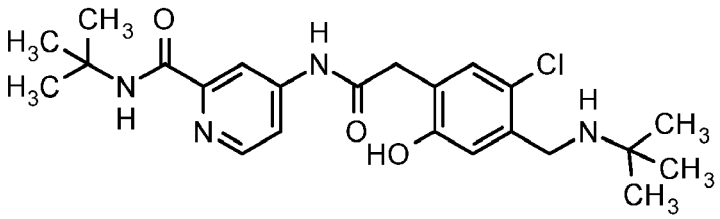


[0644] A vessel was charged with 4-[[2-(4-bromo-5-chloro-2-methoxy-phenyl)acetyl]amino]-N-tert-butyl-pyridine-2-carboxamide (step 2)(100 mg, 0.21 mmol), potassium trifluoropyrrolin-1-ylmethyl)boranuide (45 mg, 0.23 mmol), Xphos (6 mg, 0.01 mmol), $Pd(Oac)_2$ (1.4 mg, 0.01 mmol) and Cs_2CO_3 (209 mg, 0.64 mmol) and placed under an atmosphere of nitrogen. THF:water (1 mL of a 10:1 mixture) was added and the mixture was heated at 80 °C for 20 hours. The resulting mixture was diluted with water (2 mL) and extracted with DCM (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo.* The residue was purified by chromatography on silica eluting with 0-100% EtOAc in heptane to afford the titled compound as a colourless solid. 1H NMR (500 MHz, DMSO-d6) δ 10.68 (s, 1H), 8.44 (d, J = 5.5 Hz, 1H), 8.16 (dd, J = 6.4, 2.0 Hz, 1H), 8.03 (s, 1H), 7.80 (dd, J = 5.5, 2.2 Hz, 1H), 7.29 (s, 1H), 7.07 (s, 1H), 3.75 (s, 3H), 3.69 (s, 2H), 3.65 (s, 2H), 2.51-2.49 (obscured m, 4H), 1.73-1.71 (m, 4H), 1.40 (s, 9H).
[0645] LC-MS (Method E): Rt 1.04mins; MS m/z 459/461 = [M+H]+ (78% @ 215nm)

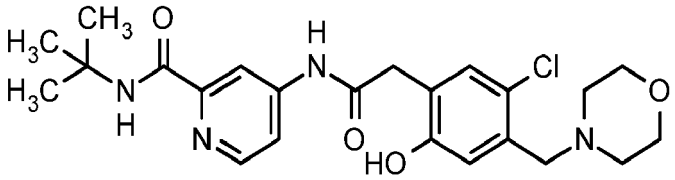
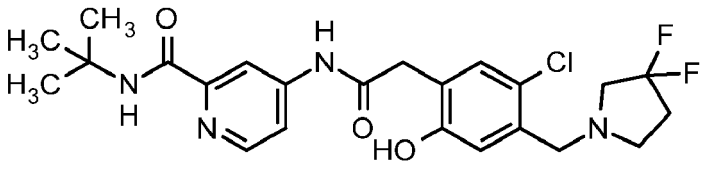
Step 4: N-tert-Butyl-4-[[2-[5-chloro-2-hydroxy-4-(pyrrolidin-1-ylmethyl)phenyl]acetyl] amino]pyridine-2-carboxamide

[0646] The titled compound was prepared from N-tert-Butyl-4-[[2-[5-chloro-2-methoxy-4-(pyrrolidin-1-ylmethyl)phenyl]acetyl] amino]pyridine-2-carboxamide N-tert-butyl-4-[[2-[5-(step 3) analogously to Example 26 step 2.
[0647] 1H NMR (500 MHz, DMSO-d6) δ 10.72 (s, 1H), 9.70 (s, 1H), 8.44 (d, J = 5.5 Hz, 1H), 8.17 (d, J = 2.0 Hz, 1H), 8.03 (s, 1H), 7.81 (dd, J = 5.5, 2.2 Hz, 1H), 7.18 (s, 1H), 6.97 (s, 1H), 3.64 (s, 2H), 3.57 (s, 2H), 2.51-2.49 (obscured m, 4H), 1.72-1.70 (m, 4H), 1.40 (s, 9H). LC-MS (Method A): Rt 2.08 mins; MS m/z 445.3/447.3 = [M+H]+ (99% @ 215nm)
[0648] The compounds of the following tabulated Examples (Table 9) were prepared analogously to Example 27 by replacing potassium trifluoropyrrolin-1-ylmethyl)boranuide (step 3) with the appropriate boranuide

Table 9

Ex.	Structure and Name	1H NMR LCMS Retention Time, [M+H]+,
27.1	 N-tert-Butyl-4-[[2-[4-[(tert-butylamino)methyl]-5-chloro-2-hydroxy-phenyl]acetyl]amino]pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.67 (s, 1H), 9.66 (s, 1H), 8.43 (d, J = 5.5 Hz, 1H), 8.17 (d, J = 2.1 Hz, 1H), 8.03 (s, 1H), 7.81 (dd, J = 5.5, 2.2 Hz, 1H), 7.16 (s, 1H), 7.06 (s, 1H), 3.63-3.61 (m, 4H), 1.40 (s, 9H), 1.09 (s, 9H). LC-MS (Method A): Rt 2.08 mins; MS m/z 445.4/447.4 = [M+H]+ (99% @ 215nm)

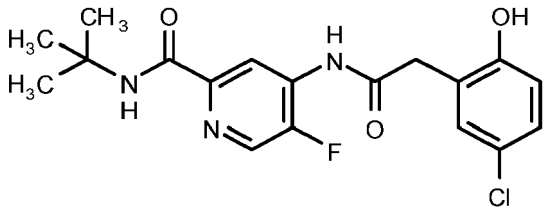
(continued)

Ex.	Structure and Name	1H NMR LCMS Retention Time, [M+H]+,
27.2	 N-tert-Butyl-4-[[2-[5-chloro-2-hydroxy-4-(morpholinomethyl)phenyl] acetyl]amino]pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.68 (s, 1H), 9.74 (s, 1H), 8.44 (d, J = 5.5 Hz, 1H), 8.17 (d, J = 2.0 Hz, 1H), 8.03 (s, 1H), 7.81 (dd, J = 5.5, 2.2 Hz, 1H), 7.21 (s, 1H), 6.98 (s, 1H), 3.65 (s, 2H), 3.62 - 3.56 (m, 4H), 3.46 (s, 2H), 2.42-2.40 (m, 4H), 1.40 (s, 9H). LC-MS (Method A): Rt 1.91 mins; MS m/z 459.3/460.3 = [M+H]+ (100% @ 215nm)
27.3	 N-tert-Butyl-4-[[2-[5-chloro-4-[(3,3-difluoropyrrolidin-1-yl)methyl]-2-hydroxy-phenyl]acetyl]amino]pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.70 (s, 1H), 9.78 (s, 1H), 8.44 (d, J = 5.5 Hz, 1H), 8.17 (d, J = 2.1 Hz, 1H), 8.03 (s, 1H), 7.81 (dd, J = 5.5, 2.2 Hz, 1H), 7.22 (s, 1H), 6.95 (s, 1H), 3.64 (s, 2H), 2.93 (t, J = 13.3 Hz, 2H), 2.76 (t, J = 7.0 Hz, 2H), 2.31-2.22 (m, 2H), 1.40 (s, 9H). LC-MS (Method A): Rt 2.6 mins; MS m/z 481.3/483.3 = [M+H]+ (98% @ 215nm)

Example 28

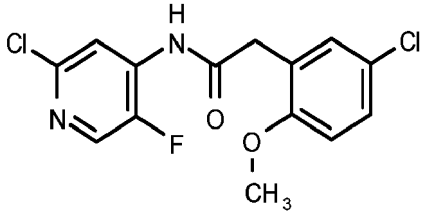
N-tert-butyl-4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]-5-fluoro-pyridine-2-carboxamide

[0649]



Step 1: N-(2-Chloro-5-fluoro-4-pyridyl)-2-(5-chloro-2-methoxy-phenyl)acetamide

[0650]



[0651] A solution of 2-(5-chloro-2-methoxy-phenyl)acetic acid (753 mg, 3.75 mmol) in thionyl chloride (6.01 mL, 68.24 mmol) was stirred at 70 °C for 1 hour. The resulting mixture was concentrated to dryness and azeotroped with toluene (2 × 10 mL). The crude residue was dissolved in DMF (10 mL) and treated dropwise with a solution of 2-chloro-5-fluoro-

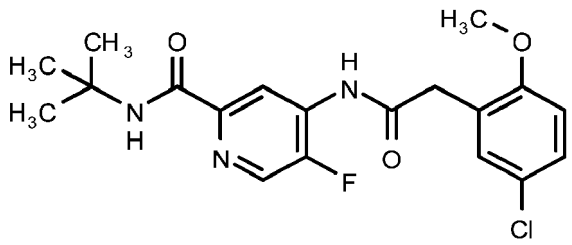
pyridin-4-amine (500 mg, 3.41 mmol) in DMF (3 mL) followed by DIPEA (1.49 mL, 8.53 mmol). After stirring at room temperature under an inert atmosphere for 16 hours, the mixture was diluted with EtOAc (100 mL) and washed with water (2 × 50 mL) and brine (2 x50 mL). The organic portion was dried over Na_2SO_4 and concentrated *in vacuo.* The crude material was purified by C18 reverse phase chromatography eluting with 0-100% MeCN in water with 0.1% formic acid modifier to afford the titled compound as a light yellow solid.

[0652] 1H NMR (250 MHz, DMSO-d6) δ 10.58 (s, 1H), 8.41 (d, J = 2.7 Hz, 1H), 8.24 (d, J = 5.6 Hz, 1H), 7.33-7.28 (m, 2H), 7.01 (d, J = 9.5 Hz, 1H), 3.83 (s, 2H), 3.75 (s, 3H).

[0653] LC-MS (Method E): Rt 1.25 mins; MS m/z 328.9, 330.9= [M+H]+

Step 2: N-tert-Butyl-4-[[2-(5-chloro-2-methoxy-phenyl)acetyl]amino]-5-fluoro-pyridine-2-carboxamide

[0654]



[0655] All reagents charged to Coware equipment (carbon monoxide generating system) according to the following procedure; To chamber A was added N-(2-chloro-5-fluoro-4-pyridyl)-2-(5-chloro-2-methoxy-phenyl)acetamide (step 1) (170 mg, 0.52 mmol), sodium carbonate (164 mg, 1.55 mmol), XantPhos Pd-G3 (third generation (G3) Buchwald pre-catalyst) (49 mg, 0.05 mmol) and toluene (5 mL) followed by 2-methylpropan-2-amine (64 mg, 0.88 mmol). The resulting solution was de-gassed with nitrogen for 5 minutes. To chamber B was added formic acid (49 μL, 1.29 mmol) in toluene (5 mL) followed by mesyl chloride (100 μL, 1.29 mmol). The vessel was sealed and TEA (288 μL, 2.07 mmol) added to chamber B to generate carbon monoxide. The Coware equipment was heated at 100°C overnight and allowed to cool to room temperature. The resulting mixture was concentrated *in vacuo,* dissolved in EtOAc (30 mL) and washed with water (2 × 25 mL). The organic portion was dried over $Na_2SO_4$and concentrated *in vacuo.* Purification of the crude residue by preparative HPLC (acidic pH, early elution method) afforded the titled compound as a beige solid.

[0656] 1H NMR (250 MHz, Methanol-d4) δ 8.91 (d, J = 6.5 Hz, 1H), 8.41 (d, J = 2.6 Hz, 1H), 7.29-7.23 (m, 2H), 7.00 - 6.94 (m, 1H), 3.84 (s, 3H), 3.79 (s, 2H), 1.45 (s, 9H).

[0657] LC-MS (Method E): Rt 1.25 mins; MS m/z 394.1, 396.1= [M+H]+ (97% @ 215nm)

Step 3: N-tert-Butyl-4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]-5-fluoro-pyridine-2-carboxamide

[0658] To a cooled (0°C) solution of N-tert-butyl-4-[[2-(5-chloro-2-methoxy-phenyl)acetyl]amino]-5-fluoro-pyridine-2-carboxamide (step 2) (30 mg, 0.08 mmol) in DCM (2 mL) was added 1M BBr_3 in DCM (190 μL, 0.19 mmol). The reaction mixture was allowed to warm to room temperature and stirring continued for a further 1 hour. The reaction was quenched by addition of water (0.5 mL) and concentrated *in vacuo.* The crude material was re-dissolved in EtOAc (2 mL) and washed with sat. $NaHCO_3$ (2 mL). The organic portion was concentrated *in vacuo* and purification of the crude residue was carried out by C18 reverse phase chromatography (0-100% MeCN in water with 0.1% formic acid modifier). The product fractions were concentrated *in vacuo* and freeze-dried to afford the titled compound as a white solid.

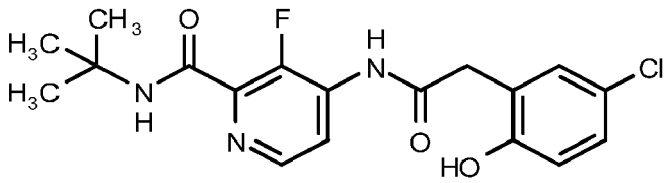
[0659] 1H NMR (500 MHz, DMSO-d6) δ 10.02 (br. S, 1H), 8.82 (d, J = 6.6 Hz, 1H), 8.54 (d, J = 2.5 Hz, 1H), 7.91 (s, 1H), 7.22 (d, J = 2.7 Hz, 1H), 7.12 (dd, J = 8.6, 2.7 Hz, 1H), 6.81 (d, J = 8.6 Hz, 1H), 3.79-3.74 (m, 2H), 1.38 (s, 9H).

[0660] LC-MS (Method A): Rt 3.37 mins; MS m/z 380.3/381.3/382.3 = [M+H]+ (99% @ 215nm)

Example 28.1

N-tert-Butyl-4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]-3-fluoro-pyridine-2-carboxamide

[0661]



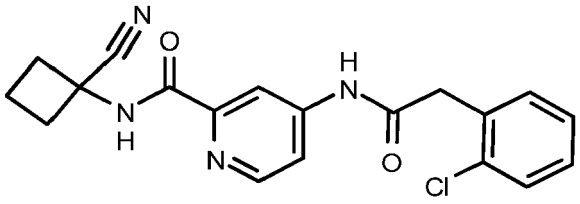
[0662] The titled compound was prepared from 2-chloro-3-fluoro-pyridin-4-amine and 2-(5-chloro-2-methoxy-phenyl)acetic acid analogously to Example 28 steps 1-3.

[0663] 1H NMR (500 MHz, DMSO-d6) δ 8.29 - 8.25 (m, 2H), 8.02 (s, 1H), 7.21 (d, J = 2.7 Hz, 1H), 7.12 (dd, J = 8.6, 2.7 Hz, 1H), 6.81 (d, J = 8.6 Hz, 1H), 3.78 (s, 2H), 1.38 (s, 9H). LC-MS (Method A): Rt 3.30 mins; MS m/z 380.2/382.2= [M+H]+

Example 30

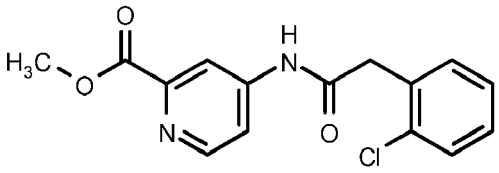
4-[[2-(2-Chlorophenyl)acetyl]amino]-N-(1-cyanocyclobutyl)pyridine-2-carboxamide

[0664]



Step 1: Methyl 4-[[2-(2-chlorophenyl)acetyl]amino]pyridine-2-carboxylate

[0665]



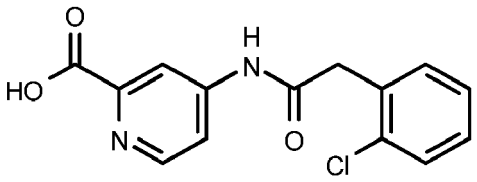
[0666] To a stirred solution of 2-(2-chlorophenyl)acetic acid (3.08 g, 18.07 mmol), methyl 4-aminopyridine-2-carboxylate (2.5 g, 16.43 mmol) and TEA (4.3 mL, 24.65 mmol) in 1,4-dioxane (40 mL) was added 50% T3P® solution in EtOAc (14.68 mL, 24.65 mmol). The resulting mixture was stirred at room temperature for 2 hour and then diluted with EtOAc (100 mL) and water (100 mL). The organic layer was separated, dried over Na_2SO_4 and concentrated *in vacuo.* The crude residue was purified by chromatography on silica eluting with 10-100% EtOAc in heptane to afford the titled compound as a pale orange solid.

[0667] 1H NMR (500 MHz, DMSO-d6) δ 10.85 (s, 1H), 8.55 (d, J = 5.5 Hz, 1H), 8.31 (d, J = 1.9 Hz, 1H), 7.77 (dd, J = 5.5, 2.2 Hz, 1H), 7.48 - 7.40 (m, 2H), 7.36 - 7.28 (m, 2H), 3.91 (s, 2H), 3.86 (s, 3H).

[0668] LC-MS (Method E): Rt 1.00 mins; MS m/z 305.0/307.0 = [M+H]+ (96% @ 215nm)

Step 2: 4-[[2-(2-Chlorophenyl)acetyl]amino]pyridine-2-carboxylic acid

[0669]



[0670] 2M LiOH (16.07 mL, 32.13 mmol) was added to a stirred solution of methyl 4-[[2-(2-chlorophenyl)acetyl]amino]pyridine-2-carboxylate (step 2) (3.4 g, 10.71 mmol) in THF (40 mL) and stirred at room temperature for 20 minutes. The resulting mixture was partially concentrated *in vacuo* to remove the volatile solvent and acidified to pH 2 with 2M aq HCl. The resulting suspension was filtered and dried in a vacuum oven at 40°C to afford the titled compound as an off-white solid.

[0671] 1H NMR (500 MHz, DMSO-d6) δ 10.89 (s, 1H), 8.53 (d, J = 5.5 Hz, 1H), 8.27 (d, J = 2.1 Hz, 1H), 7.79 (dd, J = 5.5, 2.2 Hz, 1H), 7.49 - 7.41 (m, 2H), 7.35 - 7.29 (m, 2H), 3.92 (s, 2H).

[0672] LC-MS (Method E): Rt 0.89 mins; MS m/z 290.9/292.9 = [M+H]+ (100% @ 215nm)

Step 3 : 4-[[2-(2-Chlorophenyl)acetyl]amino]-N-(1-cyanocyclobutyl)pyridine-2-carboxamide

[0673] A solution of 1-aminocyclobutanecarbonitrile (33 mg, 0.34 mmol), DIPEA (0.07 mL, 0.41 mmol), HATU (131 mg, 0.34 mmol) and 4-[[2-(2-chlorophenyl)acetyl]amino]pyridine-2-carboxylic acid (step 2) (100 mg, 0.34 mmol) in DMF (2 mL) was stirred at room temperature for 2 hours. The resulting mixture was concentrated *in vacuo* and the residue partitioned between EtOAc (10 mL) and water (10 mL). The organic layer was separated, dried over Na_2SO_4 and concentrated *in vacuo.* The residue was purified by preparative HPLC (acidic pH, early elution method) and the product fractions lyophilised overnight to afford the titled compound as an off-white powder.

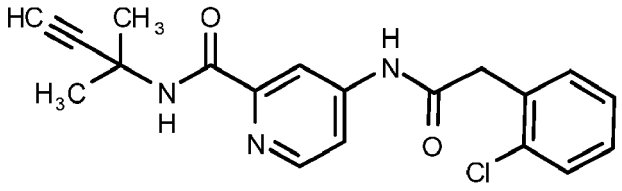
[0674] 1H NMR (500 MHz, DMSO-d6) δ 10.87 (s, 1H), 9.60 (s, 1H), 8.53 (d, J = 5.5 Hz, 1H), 8.20 (d, J = 1.9 Hz, 1H), 7.87 (dd, J = 5.5, 2.2 Hz, 1H), 7.52 - 7.38 (m, 2H), 7.38 - 7.24 (m, 2H), 3.92 (s, 2H), 2.70 - 2.62 (m, 2H), 2.59 - 2.52 (m, 2H), 2.09 - 1.93 (m, 2H).

[0675] LC-MS (Method A): Rt 3.02 mins; MS m/z 369.2= [M+H]+ (100% @ 215nm)

Example 30.1

4-[[2-(2-Chlorophenyl)acetyl]amino]-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide

[0676]



[0677] A solution of 2-methylbut-3-yn-2-amine (14mg, 0.17 mmol), DIPEA (0.08 mL, 0.43 mmol), HATU (65 mg, 0.17 mmol) and 4-[[2-(2-chlorophenyl)acetyl]amino]pyridine-2-carboxylic acid (Example 30, step 2)(50 mg, 0.17 mmol) in DMF (1 mL) was stirred at room temperature for 2 hours. The resulting mixture was concentrated *in vacuo* then the residue partitioned between EtOAc (10 mL) and water (10 mL). The organic layer was separated, dried over Na_2SO_4 and concentrated *in vacuo.* The residue was purified by preparative HPLC (acidic pH, early elution method) and the product fractions were combined and lyophilised overnight to afford the titled compound as an off-white powder.

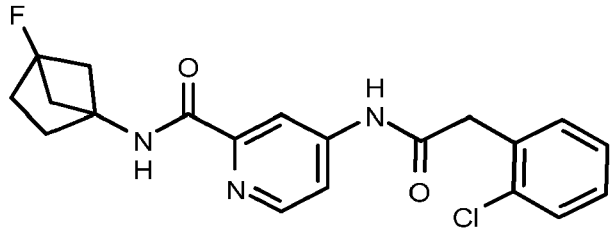
[0678] 1H NMR (500 MHz, DMSO-d6) δ 10.85 (s, 1H), 8.48 (d, J = 5.5 Hz, 1H), 8.32 (s, 1H), 8.19 (d, J = 2.0 Hz, 1H), 7.83 (dd, J = 5.5, 2.2 Hz, 1H), 7.49 - 7.39 (m, 2H), 7.37 - 7.29 (m, 2H), 3.92 (s, 2H), 3.21 (s, 1H), 1.64 (s, 6H).

[0679] LC-MS (Method A): Rt 3.25 mins; MS m/z 356.3/358.2 = [M+H]+ (100% @ 215nm)

Example 30.2

4-[[2-(2-Chlorophenyl)acetyl]amino]-N-(4-fluoro-1-bicyclo[2.1.1]hexanyl)pyridine-2-carboxamide

[0680]

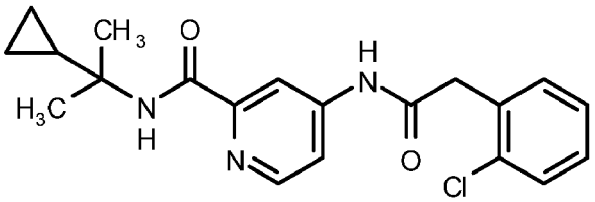


[0681] A solution of 4-fluorobicyclo[2.1.1]hexan-1-amine hydrochloride (26 mg, 0.17 mmol), DIPEA (0.08 mL, 0.43 mmol), HATU (65 mg, 0.17 mmol) and 4-[[2-(2-chlorophenyl) acetyl]amino]pyridine-2-carboxylic acid (Example 30, step 2) (50 mg, 0.17 mmol) in DMF (1 mL) was stirred at room temperature for 2 hours. The resulting mixture was concentrated *in vacuo* and the residue partitioned between EtOAc (10 mL) and water (10 mL). The organic layer was separated, dried over Na_2SO_4 and concentrated *in vacuo.* The residue was purified by preparative HPLC (acidic pH, early elution method) and the product fractions were combined and lyophilised overnight to afford the titled compound as an off-white powder.
[0682] 1H NMR (500 MHz, DMSO-d6) δ 10.83 (s, 1H), 9.05 (s, 1H), 8.48 (d, J = 5.5 Hz, 1H), 8.16 (d, J = 2.0 Hz, 1H), 7.83 (dd, J = 5.5, 2.2 Hz, 1H), 7.54 - 7.40 (m, 2H), 7.40 - 7.25 (m, 2H), 3.91 (s, 2H), 2.14 - 2.08 (m, 2H), 2.08 - 2.04 (m, 2H), 2.00 - 1.94 (m, 2H), 1.87 - 1.81 (m, 2H).
[0683] LC-MS (Method A): Rt 3.39 mins; MS m/z 388.3/390.3 = [M+H]+ (99% @ 215nm)

Example 30.3

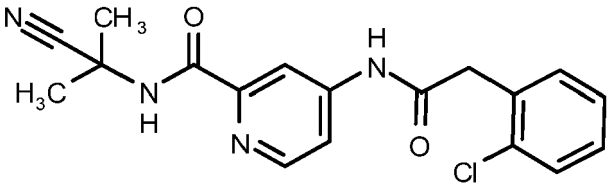
4-[[2-(2-Chlorophenyl)acetyl]amino]-N-(1-cyclopropyl-1-methyl-ethyl)pyridine-2-carboxamide

[0684]

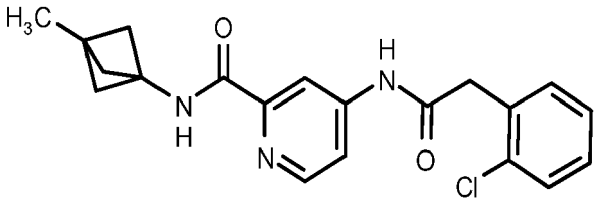
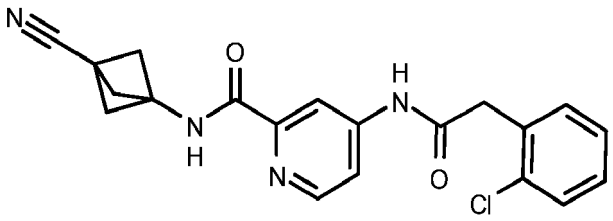
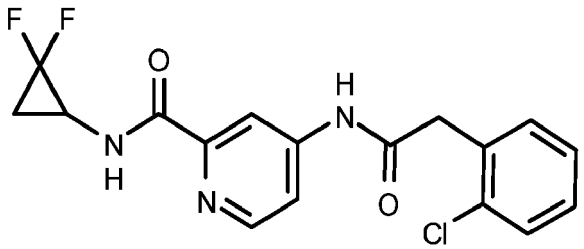
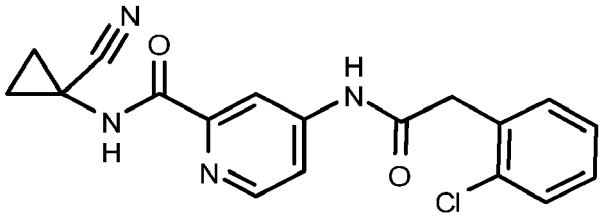
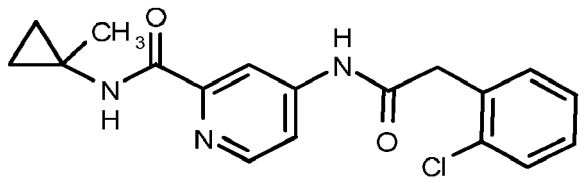


[0685] The titled compound was prepared from 4-[[2-(2-chlorophenyl)acetyl]amino]pyridine-2-carboxylic acid (Example 30 step 2) and 2-cyclopropylpropan-2-amine analogously to Example 30 step 3.
[0686] 1H NMR (500 MHz, DMSO-d6) δ 10.84 (s, 1H), 8.47 (d, J = 5.5 Hz, 1H), 8.20 (d, J = 2.1 Hz, 1H), 8.03 (s, 1H), 7.81 (dd, J = 5.5, 2.2 Hz, 1H), 7.49 - 7.42 (m, 2H), 7.35 - 7.31 (m, 2H), 3.92 (s, 2H), 1.41 - 1.34 (m, 1H), 1.31 (s, 6H), 0.43 - 0.36 (m, 4H).
[0687] LC-MS (Method A): Rt 3.73 mins; MS m/z 372.2/374.2 = [M+H]+ (100% @ 215nm)
[0688] The compounds of the following tabulated Examples (Table 9a) were prepared analogously to Example 30 by replacing 1-aminocyclobutanecarbonitrile (step 3) with the appropriate commercially available amine.

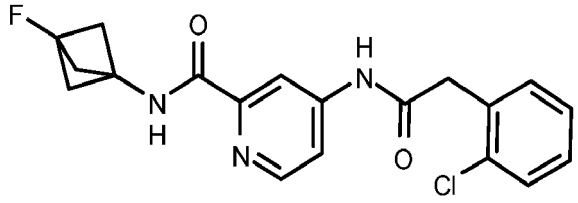
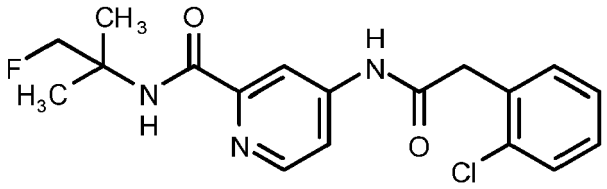
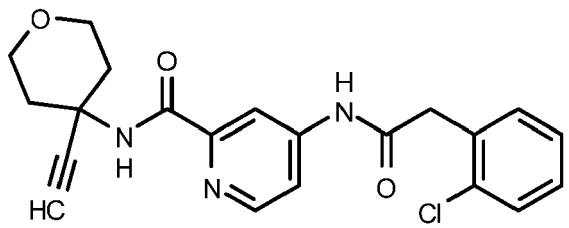
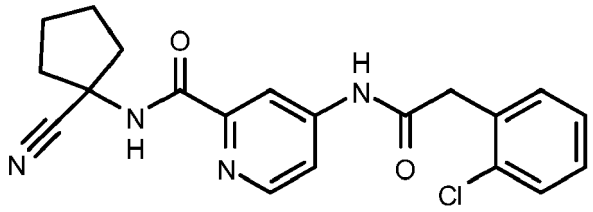
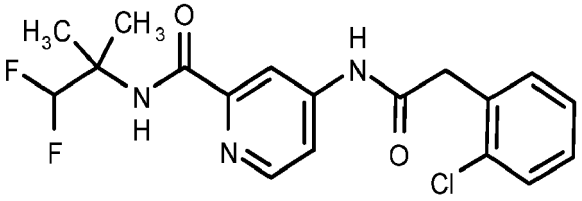
Table 9a

Ex.	Structure and Name	1H NMR LCMS Retention Time, [M+H]+,
30.3a	 4-[[2-(2-Chlorophenyl)acetyl]amino]-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.89 (s, 1H), 8.84 (s, 1H), 8.53 (d, J = 5.5 Hz, 1H), 8.23 (d, J = 2.0 Hz, 1H), 7.87 (dd, J = 5.5, 2.2 Hz, 1H), 7.50 - 7.42 (m, 2H), 7.38 - 7.29 (m, 2H), 3.93 (s, 2H), 1.73 (s, 6H). LC-MS (Method A): Rt 2.96 mins; MS m/z 357.2/359.3 = [M+H]+ (99% @ 215nm)

(continued)

Ex.	Structure and Name	1H NMR LCMS Retention Time, [M+H]+,
30.4	 4-[[2-(2-Chlorophenyl)acetyl]amino]-N-(1-methyl-3-bicyclo [1.1.1] pentanyl)pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.82 (s, 1H), 8.99 (s, 1H), 8.45 (d, J = 5.5 Hz, 1H), 8.13 (d, J = 2.0 Hz, 1H), 7.82 (dd, J = 5.5, 2.2 Hz, 1H), 7.49 - 7.40 (m, 2H), 7.36 - 7.29 (m, 2H), 3.91 (s, 2H), 1.96 (s, 6H), 1.22(s, 3H). LC-MS (Method A): Rt 3.65 mins; MS m/z 370.3/372.3 = [M+H]+ (97% @ 215nm)
30.5	 4-[[2-(2-Chlorophenyl)acetyl]amino]-N-(1-cyano-3-bicyclo [1.1.1]pentanyl) pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.84 (s, 1H), 9.49 (s, 1H), 8.47 (d, J = 5.5 Hz, 1H), 8.14 (d, J = 2.0 Hz, 1H), 7.84 (dd, J = 5.5, 2.2 Hz, 1H), 7.49 - 7.38 (m, 2H), 7.36 - 7.28 (m, 2H), 3.91 (s, 2H), 2.57 (s, 6H). LC-MS (Method A): Rt 3.08 mins; MS m/z 381.2/383.2 = [M+H]+ (100% @ 215nm)
30.6	 4-[[2-(2-Chlorophenyl)acetyl]amino]-N-(2,2-difluorocyclopropyl)pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.85 (s, 1H), 9.07 (t, J = 3.3 Hz, 1H), 8.50 (d, J = 5.5 Hz, 1H), 8.21 (d, J = 2.0 Hz, 1H), 7.84 (dd, J = 5.5, 2.2 Hz, 1H), 7.56 - 7.40 (m, 2H), 7.40 - 7.25 (m, 2H), 3.92 (s, 2H), 3.57 - 3.42 (m, 1H), 2.03 - 1.80 (m, 2H). LC-MS (Method A): Rt 3.04 mins; MS m/z 366.1/368.2 = [M+H]+ (99% @ 215nm)
30.7	 4-[[2-(2-Chlorophenyl)acetyl]amino]-N-(1-cyanocyclopropyl) pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.87 (s, 1H), 9.66 (s, 1H), 8.50 (d, J = 5.5 Hz, 1H), 8.22 (d, J = 2.1 Hz, 1H), 7.86 (dd, J = 5.5, 2.2 Hz, 1H), 7.50 - 7.40 (m, 2H), 7.36 - 7.27 (m, 2H), 3.92 (s, 2H), 1.59 - 1.46 (m 2H), 1.37- 1.28 (m, 2H). LC-MS (Method A): Rt 2.77 mins; MS m/z 355.2/357.2 = [M+H]+ (98% @ 215nm)
30.8	 4-[[2-(2-Clorophenyl)acetyl]amino]-N-(1-methylcyclopropyl) pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.81 (s, 1H), 8.76 (s, 1H), 8.44 (d, J = 5.5 Hz, 1H), 8.16 (d, J = 2.1 Hz, 1H), 7.80 (dd, J = 5.5, 2.2 Hz, 1H), 7.44 (m, 2H), 7.36 - 7.17 (m, 2H), 3.91 (s, 2H), 1.36 (s, 3H), 0.91 - 0.72 (m, 2H), 0.72 - 0.57 (m, 2H). LC-MS (Method A): Rt 3.02 mins; MS m/z 344.2/346.2 = [M+H]+ (100% @ 215nm)

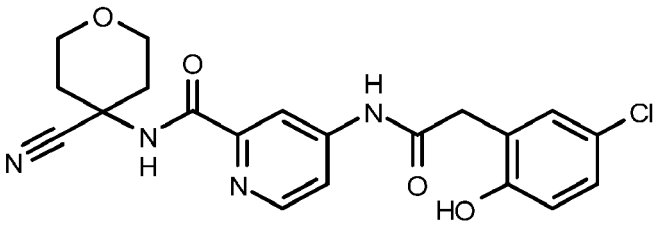
(continued)

Ex.	Structure and Name	1H NMR LCMS Retention Time, [M+H]+,
30.9	 4-[[2-(2-Chlorophenyl)acetyl]amino]-N-(3-fluoro-1-bicyclo [1.1.1]pentanyl)pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.84 (s, 1H), 9.37 (s, 1H), 8.48 (d, J = 5.5 Hz, 1H), 8.15 (d, J = 2.0 Hz, 1H), 7.84 (dd, J = 5.5, 2.2 Hz, 1H), 7.48 - 7.40 (m, 2H), 7.35 - 7.30 (m, 2H), 3.91 (s, 2H), 2.41 (d, J = 2.2 Hz, 6H). LC-MS (Method A): Rt 3.30 mins; MS m/z 374.3/376.2 = [M+H]+ (100% @ 215nm)
30.10	 4-[[2-(2-Chlorophenyl)acetyl]amino]-N-(2-fluoro-1,1-dimethyl-ethyl)pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.85 (s, 1H), 8.47 (d, J = 5.5 Hz, 1H), 8.20 (d, J = 2.0 Hz, 1H), 8.12 (s, 1H), 7.81 (dd, J = 5.5, 2.2 Hz, 1H), 7.44 (d, J = 11.9 Hz, 2H), 7.35 - 7.31 (m, 2H), 4.58 (d, J = 47.5 Hz, 2H), 3.92 (s, 2H), 1.39 (d, J = 1.9 Hz, 6H). LC-MS (Method A): Rt 3.32 mins; MS m/z 364.2/366.2 = [M+H]+ (100% @ 215nm)
30.11†	 4-[[2-(2-Chlorophenyl)acetyl]amino]-N-(4-ethynyltetrahydropyran-4-yl)pyridine-2-carboxamide.	1H NMR (500 MHz, DMSO-d6) δ 10.86 (s, 1H), 8.50 (d, J = 5.5 Hz, 1H), 8.45 (s, 1H), 8.20 (d, J = 2.1 Hz, 1H), 7.83 (dd, J = 5.5, 2.2 Hz, 1H), 7.48 - 7.41 (m, 2H), 7.35 - 7.30 (m, 2H), 3.92 (s, 2H), 3.76 (dt, J = 11.7, 3.9 Hz, 2H), 3.67 - 3.59 (m, 2H), 3.38 (s, 1H), 2.19-2.13 (m, 2H), 2.09-2.01 (m, 2H). LC-MS (Method A): Rt 2.95 mins; MS m/z 398.2/400.2 = [M+H]+ (100% @ 215nm)
30.12	 4-[[2-(2-Chlorophenyl)acetyl]amino]-N-(1-cyanocyclopentyl) pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.88 (s, 1H), 9.05 (s, 1H), 8.52 (d, J = 5.5 Hz, 1H), 8.22 (d, J = 1.9 Hz, 1H), 7.85 (dd, J = 5.5, 2.2 Hz, 1H), 7.48 - 7.42 (m, 2H), 7.35 - 7.30 (m, 2H), 3.92 (s, 2H), 2.33 - 2.27 (m, 4H), 1.79 - 1.72 (m, 4H). LC-MS (Method A): Rt 3.24 mins; MS m/z 383.2/385.2 = [M+H]+ (99% @ 215nm)
30.13	 4-[[2-(2-Chlorophenyl)acetyl]amino]-N-(2,2-difluoro-1,1-dimethyl-ethyl)pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.86 (s, 1H), 8.49 (d, J = 5.5 Hz, 1H), 8.29 (s, 1H), 8.22 (d, J = 2.0 Hz, 1H), 7.82 (dd, J = 5.5, 2.2 Hz, 1H), 7.47 - 7.41 (m, 2H), 7.34 - 7.30 (m, 2H), 6.46 (t, J = 57.0 Hz, 1H), 3.92 (s, 2H), 1.44 (s, 6H) LC-MS (Method A): Rt 3.53 mins; MS m/z 382.2/384.2 = [M+H]+
†Example 30.11: the amine, 4-ethynyltetrahydropyran-4-amine hydrochloride was prepared according to the procedure described in Journal of Organic Chemistry, 71(18), 7110-7112; 2006		

Example 31

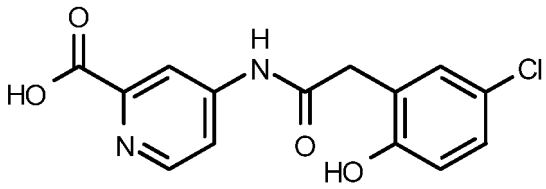
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(4-cyanotetrahydropyran-4-yl)pyridine-2-carboxamide

[0689]



Step 1: 4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxylic acid

[0690]



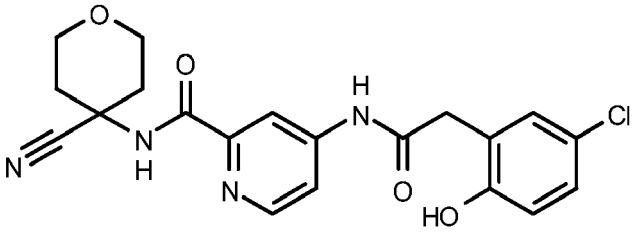
[0691] 1M BBr_3 in DCM (308.67 mL, 308.67 mmol) was added slowly over 1 hour to a suspension of 4-[[2-(5-chloro-2-methoxy-phenyl)acetyl]amino]pyridine-2-carboxylic acid (Example 8.1, step 2) (25.0 g, 77.17 mmol, 99%) in DCM (500 mL) at 0 - 5°C under an inert atmosphere of N_2. The mixture was allowed to warm to room temperature and stirred for a further hour. The reaction mixture was concentrated *in vacuo* and the residue was suspended in EtOAc (500 mL) and water (500 mL) at 0°C. The resulting mixture was allowed to warm to room temperature and the aqueous layer adjusted to pH 4 by portion-wise addition of sat. aq. $NaHCO_3$ (350 mL). The precipitate was collected by filtration, washed with water (2 x100 mL), EtOAc (2 x100 mL), diethyl ether (2 × 150 mL) and dried in a high vacuum oven at 40 °C to afford the titled compound as a beige solid.

[0692] 1H NMR (500 MHz, DMSO-d6) δ 10.72 (s, 1H), 9.82 (br. s, 1H), 8.53 (d, J = 5.5 Hz, 1H), 8.27 (d, J = 2.0 Hz, 1H), 7.80 (dd, J = 5.6, 2.2 Hz, 1H), 7.22 (d, J = 2.7 Hz, 1H), 7.13 (dd, J = 8.6, 2.7 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 3.67 (s, 2H).

[0693] LC-MS (Method E): Rt 0.86 mins; MS m/z 306.9/308.9 = [M+H]+ (97% @ 215nm)

Step 2: 4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(4-cyanotetrahydropyran-4-yl)pyridine-2-carboxamide

[0694]



[0695] HATU (19.34 g, 50.86 mmol) was added to a stirred solution of 4-[[2-(5-chloro-2-hydroxyphenyl)acetyl]amino]pyridine-2-carboxylic acid (Example 31 step 1) (13 g, 42.39 mmol), 4-aminotetrahydropyran-4-carbonitrile (8.02 g, 63.58 mmol) and DIPEA (18.51 mL, 105.97 mmol) in DMF (150 mL) and the reaction mixture was stirred at room temperature for 2 hours. The resulting mixture was diluted with 0.5 M aq. NaOH (100 mL) and stirred at room temperature for 30 mins. Water (500 mL) and EtOAc (500 mL) were added and the resulting precipitate was removed by filtration. The aqueous portion was extracted with EtOAc (250 mL) and the combined organics were washed with water (2 × 750 mL), sat. $NaHCO_3$ (500 mL), brine (700 mL), dried over Na_2SO_4 and concentrated in vacuo to afford a yellow oil. The

material was purified on chromatography on silica eluting with 0-100% EtOAc in heptane then 0-15% MeOH in EtOAc . The product fractions were combined and concentrated *in vacuo.* The residue was subsequently purified on KP-NH silica eluting with 50-100% EtOAc in heptane then 0-15% MeOH in EtOAc. The clean product fractions were combined and concentrated *in vacuo* and azeotroped with MeCN (3 × 500 mL) to afford the titled compound.

[0696] 1H NMR (500 MHz, DMSO-d6) δ 10.74 (br s, 1H), 9.83 (s, 1H), 9.00 (s, 1H), 8.52 (d, J = 5.5 Hz, 1H), 8.23 (d, J = 2.1 Hz, 1H), 7.87 (dd, J = 5.5, 2.2 Hz, 1H), 7.22 (d, J = 2.7 Hz, 1H), 7.13 (dd, J = 8.6, 2.7 Hz, 1H), 6.81 (d, J = 8.6 Hz, 1H), 3.86 (td, J = 12.5 Hz, 3.9 Hz, 2H), 3.68 (s, 2H), 3.64 - 3.53 (m, 2H), 2.41 - 2.32 (m, 2H), 2.12 - 2.00 (m, 2H).

[0697] LC-MS (Method A): Rt 2.67 mins; MS m/z 415.2/417.2 = [M+H]+

Step 3: Recrystallisation 4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(4-cyanotetrahydropyran-4-yl)pyridine-2-carboxamide

[0698] 4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(4-cyanotetrahydropyran-4-yl) pyridine-2-carboxamide (step 2) (1881 mg, 4.44 mmol) was suspended in MeCN (16 mL) and heated at reflux for 10 min. Additional MeCN (2 mL) was added and the mixture was heated at reflux for 30 mins at which point it was observed that all the material had gone into solution. The heat was reduced to 55°C and the mixture was seeded with a crystal of 4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]-N-(4-cyanotetrahydropyran-4-yl) pyridine-2-carboxamide. The temperature of the mixture was maintained at 55°C for 1 hour and then allowed to cool slowly to room temperature overnight. The resulting crystals were collected by filtration, washed with minimum volume of ice cold MeCN (~5 mL) and dried in a vacuum oven at 40 °C for 2 hours to afford the titled compound as an off-white crystalline solid.

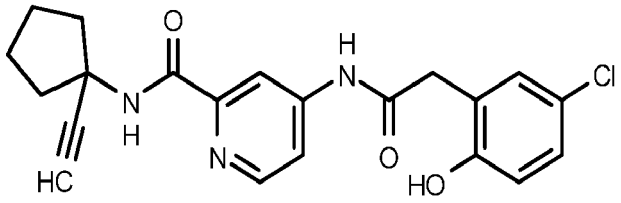
[0699] 1H NMR (500 MHz, DMSO-d6) δ 10.74 (brs, 1H), 9.82 (brs, 1H), 9.00 (s, 1H), 8.53 (d, J = 5.5 Hz, 1H), 8.23 (d, J = 2.0 Hz, 1H), 7.87 (dd, J = 5.5, 2.2 Hz, 1H), 7.22 (d, J = 2.7 Hz, 1H), 7.13 (dd, J = 8.6, 2.7 Hz, 1H), 6.81 (d, J = 8.6 Hz, 1H), 3.86 (td, J = 12.5 Hz, 3.9 Hz, 2H), 3.68 (s, 2H), 3.63 - 3.54 (m, 2H), 2.40 - 2.34 (m, 2H), 2.12 - 2.03 (m, 2H).

[0700] LC-MS (Method A): Rt 2.68 mins; MS m/z 415.3/417.2 = [M+H]+ (99% @ 215nm)

Example 31.2

4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1-ethynylcyclopentyl)pyridine-2-carboxamide

[0701]



[0702] The titled compound was prepared from 4-[[2-(5-chloro-2-hydroxyphenyl)acetyl]amino]pyridine-2-carboxylic acid (Example 31 step 1) and 1-ethynylcyclopentanamine hydrochloride analogously to Example 31 step 2.

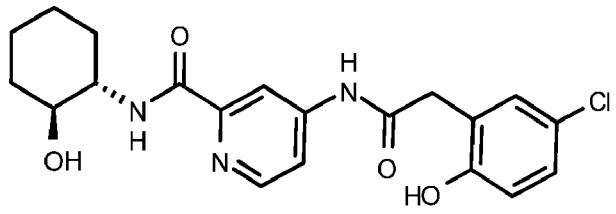
[0703] 1H NMR (500 MHz, DMSO-d6) δ 10.70 (s, 1H), 9.82 (br. s, 1H), 8.48 - 8.45 (m, 2H), 8.17 (d, J = 1.9 Hz, 1H), 7.84 (dd, J = 5.5, 2.2 Hz, 1H), 7.22 (d, J = 2.7 Hz, 1H), 7.12 (dd, J = 8.6, 2.7 Hz, 1H), 6.81 (d, J = 8.6 Hz, 1H), 3.67 (s, 2H), 3.16 (s, 1H), 2.30 - 2.22 (m, 2H), 2.14-2.05 (m, 2H), 1.77 - 1.66 (m, 4H).

[0704] LC-MS (Method A): Rt 3.34 mins; MS m/z 398.2/400.2 = [M+H]+ (100% @ 215nm)

Example 31.3

4-[2-(5-Chloro-2-hydroxyphenyl)acetamido]-N-[(1s,2s)-2-hydroxycyclohexyl] pyridine-2-carboxamide

[0705]



[0706] 4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(2-hydroxycyclohexyl)pyridine-2-carboxamide was prepared from 4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxylic acid (Example 31 step 1) and *trans*-2-aminocyclohexanol analogously to Example 31 step 2.

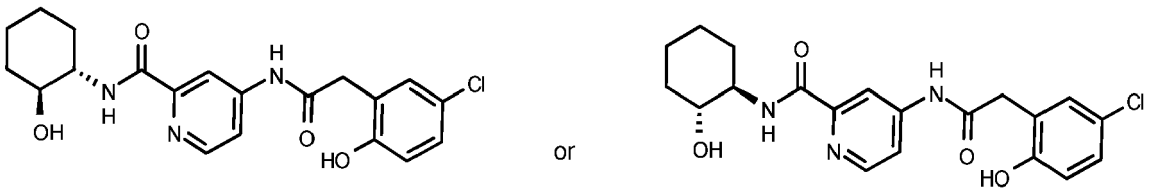
[0707] 1H NMR (500 MHz, DMSO-d6) δ 10.74 (s (br), 1H), 9.82 (s (br), 1H), 8.47 (d, J = 5.5 Hz, 1H), 8.34 (d, J = 8.1 Hz, 1H), 8.19 (d, J = 2.1 Hz, 1H), 7.82 (dd, J = 5.5, 2.2 Hz, 1H), 7.21 (d, J = 2.6 Hz, 1H), 7.11 (dd, J = 8.6, 2.7 Hz, 1H), 6.79 (d, J = 8.6 Hz, 1H), 4.68 (d, J = 5.5 Hz, 1H), 3.66 (s, 2H), 3.60 - 3.53 (m, 1H), 3.45 - 3.41 (m, 1H), 1.94 - 1.85 (m, 2H), 1.67 - 1.57 (m, 2H), 1.30 - 1.18 (m, 4H).

[0708] LC-MS (Method A): Rt 2.64 mins; MS m/z 404.3/406.3 = [M+H]+ (97% @ 215nm)

Example 31.3a

4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[(1S,2S)-2-hydroxycyclo hexyl]pyridine-2-carboxamide or 4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[(1R,2R)-2-hydroxycyclohexyl]pyridine-2-carboxamide

[0709]



(1S,2S)-isomer or (1R,2R)-isomer

[0710] Chiral separation of 4-[2-(5-chloro-2-hydroxyphenyl)acetamido]-N-[(1s,2s)-2-hydroxycyclohexyl]pyridine-2-carboxamide (Example 31.3) using Supercritical Fluid Chromatography SFC (15% Methanol + 0.2% DEA: 85% CO_2 with Chiralcel OJ-H 25cm column at 4ml/min) afforded the titled compound.

[0711] SFC Retention Time (second eluted peak) = 23.32 mins MS (ESIPos): m/z = 404.1 (M+H)+ .

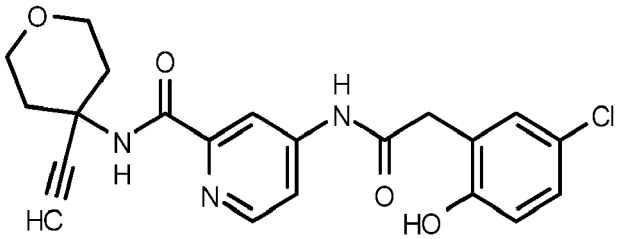
[0712] 1H NMR (500 MHz, DMSO-d6) δ 8.47 (d, J = 5.5 Hz, 1H), 8.34 (d, J = 8.1 Hz, 1H), 8.18 (d, J = 2.1 Hz, 1H), 7.82 (dd, J = 5.5, 2.2 Hz, 1H), 7.20 (d, J = 2.5 Hz, 1H), 7.10 (dd, J = 8.6, 2.6 Hz, 1H), 6.78 (d, J = 8.6 Hz, 1H), 4.69 (d, J = 5.5 Hz, 1H), 3.66 (s, 2H), 3.61 - 3.53 (m, 1H), 3.47 - 3.41 (m, 1H), 1.95 - 1.86 (m, 2H), 1.68 - 1.58 (m, 2H), 1.28 - 1.23 (m, 4H).

[0713] LC-MS (Method A): Rt 2.64 mins; MS m/z 404.2/406.2 = [M+H]+ (100% @ 215nm)

Example 31.4

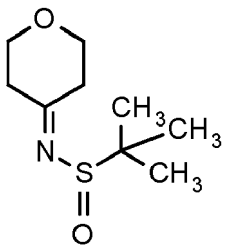
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(4-ethynyltetrahydropyran-4-yl)pyridine-2-carboxamide

[0714]



Step 1: 2-Methyl-N-tetrahydropyran-4-ylidene-propane-2-sulfinamide

[0715]

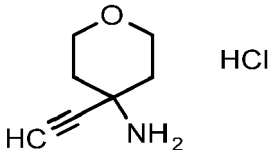


[0716] A solution of tetrahydropyran-4-one (2.4 g, 23.97 mmol) in THF (50 mL) under an inert atmosphere was treated with tetraethoxytitanium (9.57 g, 41.95 mmol) followed by 2-methylpropane-2-sulfinamide (2.91 g, 23.97 mmol) and the reaction mixture was stirred at room temperature overnight. The mixture was poured into sat. aq. $NaHCO_3$ (100 mL) and stirred for 5 minutes. A resulting suspension was filtered and the solid washed further with water (50 mL) and EtOAc (100 mL). The filtrate was separated and the aqueous layer washed once more with EtOAc (50 mL). The combined organic portions were washed with brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo* to afford a crude oil. The oil was purified by chromatography on silica eluting with 0-100% EtOAc in heptane to afford the titled compound as a colourless oil.

[0717] LC-MS (Method E): Rt 0.74 mins; MS m/z 204.0 = [M+H]+ (100% @ 215nm)

Step 2: 4-Ethynyltetrahydropyran-4-amine hydrochloride

[0718]



[0719] A cooled (-78 °C) solution of ethynyl(trimethyl)silane (725 mg, 7.38 mmol) in toluene (10 mL) under nitrogen was treated dropwise with n-BuLi (1.6M in hexanes) (3.38 mL, 5.41 mmol). After stirring at -78 °C for 15 mins, the mixture was treated with a cooled (-78 °C) solution of 2-methyl-N-tetrahydropyran-4-ylidene-propane-2-sulfinamide (500 mg, 2.46 mmol) in toluene (5 mL) and trimethylalumane (1.48 mL, 2.95 mmol) via canula. Stirring was continued at -78 °C for 2 hours and then the solution was allowed to warm to room temperature and stirred overnight. The resulting mixture was cooled to 0 °C and quenched with sat. aq. Na_2SO_4 (~20 mL). The mixture was filtered and washed with EtOAc (~50 mL). The biphasic filtrate was separated and organic portion washed further with water (25 mL). The aqueous layer was back-extracted with EtOAc (50 mL) and the combined organic extracts were washed with brine (25 mL), dried over Na_2SO_4 and concentrated *in vacuo* to afford an off-white solid. The solid was dissolved in anhydrous dioxane (2 mL) and treated with 4M HCl (2 mL). After stirring at room temperature for 4 hours, the resulting precipitate was filtered and washed with cold dioxane to afford the titled compound as a beige solid.

[0720] 1H NMR (500 MHz, DMSO-d6) δ 8.98 (s, 3H), 3.91 (s, 1H), 3.91 - 3.86 (m, 2H), 3.48 (td, J = 11.9, 2.0 Hz, 2H), 1.95 (td, J = 12.4, 4.5 Hz, 2H), 1.89-1.84 (m, 2H).

[0721] LC-MS (Method E): Rt 0.2 mins; MS m/z 126.0 = [M+H]+

Step 3: 4-[[2-(5-Chloro-2-hydroxy-phenyl) acetyl]amino]-N-(4-ethynyltetrahydro pyran-4-yl)pyridine-2-carboxamide

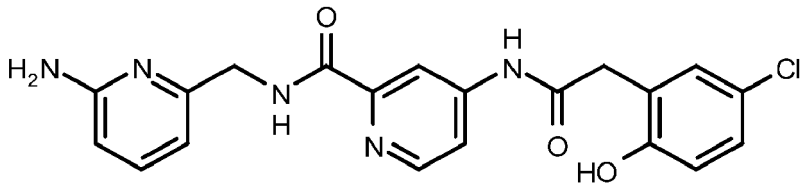
[0722] The titled compound was prepared from 4-[[2-(5-chloro-2-hydroxyphenyl)acetyl]amino]pyridine-2-carboxylic acid (Ex 31 step 1) and 4-ethynyltetrahydropyran-4-amine hydrochloride (step 2) analogously to Example 31 step 2. 1H NMR (500 MHz, DMSO-d6) δ 10.70 (s, 1H), 9.81 (s, 1H), 8.48 (d, J = 5.5 Hz, 1H), 8.45 (s, 1H), 8.19 (d, J = 2.1 Hz, 1H), 7.85 (dd, J = 5.5, 2.2 Hz, 1H), 7.22 (d, J = 2.7 Hz, 1H), 7.12 (dd, J = 8.6, 2.7 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 3.76 (dt, J = 7.7, 4.0 Hz, 2H), 3.68 (s, 2H), 3.66 - 3.60 (m, 2H), 3.38 (s, 1H), 2.18-2.13 (m, 2H), 2.09 - 2.01 (m, 2H).

[0723] LC-MS (Method A): Rt 2.80 mins; MS m/z 414.2/416.2 = [M+H]+ (99% @ 215nm)

Example 32

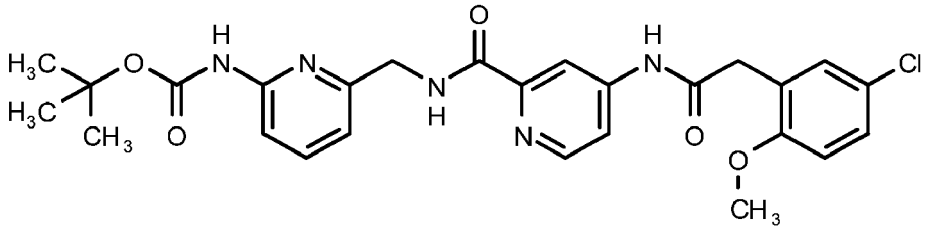
N-[(6-Amino-2-pyridyl)methyl]-4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl] amino]pyridine-2-carboxamide

[0724]



Step 1: tert-butyl N-[6-[[[4-[[2-(5-chloro-2-methoxy-phenyl)acetyl]amino]pyridine-2-carbonyl]amino]methyl]-2-pyridyl]carbamate

[0725]



[0726] To a solution of 4-[[2-(5-chloro-2-methoxy-phenyl)acetyl]amino]pyridine-2-carboxylic acid (Example 8.1 step 2)(100 mg, 0.3 mmol) in DMF (1 mL) was added tert-butyl N-[6-(aminomethyl)-2-pyridyl]carbamate (68 mg, 0.3 mmol) followed by DIPEA (63 μL, 0.36 mmol) and the mixture stirred at room temperature for 15 mins. HATU (126 mg, 0.33 mmol) was added and the stirring continued at room temperature for 1 hour. The resulting mixture was diluted with H_2O (2 mL) and the pH adjusted to pH 6 by addition of sat. aq. NH_4Cl. The mixture was extracted with EtOAc (2 × 5 mL) and the combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo.* The crude residue was triturated with MeCN and water to afford the titled compound as white solid.

[0727] 1H NMR (500 MHz, DMSO-d6) δ 10.71 (s, 1H), 9.70 (s, 1H), 9.23 (t, J = 6.1 Hz, 1H), 8.52 (d, J = 5.5 Hz, 1H), 8.22 (d, J = 2.1 Hz, 1H), 7.84 (dd, J = 5.5, 2.2 Hz, 1H), 7.69 - 7.63 (m, 2H), 7.32 - 7.29 (m, 2H), 7.03 - 7.00 (m, 1H), 6.91 (dd, J = 6.9, 1.2 Hz, 1H), 4.49 (d, J = 6.1 Hz, 2H), 3.75 (s, 3H), 3.72 (s, 2H), 1.46 (s, 9H).

[0728] LC-MS (Method A): Rt 3.78 mins; MS m/z 526.3/528.2 = [M+H]+ (100% @ 215nm)

Step 2: N-[(6-Amino-2-pyridyl)methyl]-4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl] amino] pyridine-2-carboxamide

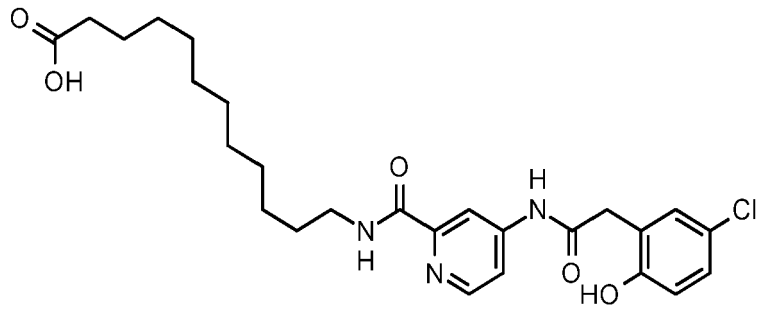
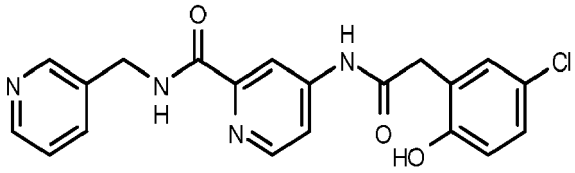
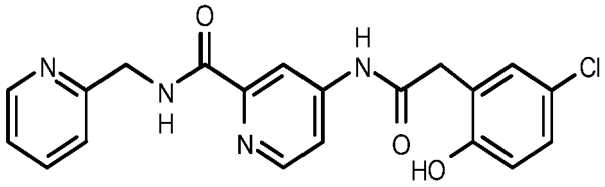
[0729] tert-Butyl N-[6-[[[4-[[2-(5-chloro-2-methoxy-phenyl)acetyl]amino]pyridine-2-carbonyl] amino]methyl]-2-pyridyl]carbamate (step 1)(107 mg, 0.2 mmol) was added to a cooled (0-5°C) suspension of 1M BBr3 in DCM (895 μL, 0.9 mmol) in DCM (1.1 mL). The ice bath was removed and the mixture was stirred at room temperature for 2 hours. The resulting mixture was concentrated *in vacuo* and the residue partitioned between EtOAc (5 mL) and water (4 mL). The pH of the aqueous layer to pH7 by addition of sat. aq. $NaHCO_3$ and the organic layer was separated, dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was triturated in MeCN:H_2O (4:1), filtered, washed with MeCN and dried in a high vacuum oven to afford the titled compound as a light tan solid.

[0730] 1H NMR (500 MHz, DMSO-d6) δ 10.68 (s, 1H), 9.81 (s, 1H), 9.05 (t, J = 5.9 Hz, 1H), 8.50 (d, J = 5.5 Hz, 1H), 8.22 (d, J = 2.0 Hz, 1H), 7.84 (dd, J = 5.5, 2.1 Hz, 1H), 7.31 (t, J = 7.7 Hz, 1H), 7.22 (d, J = 2.6 Hz, 1H), 7.12 (dd, J = 8.6, 2.7 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 6.40 (d, J = 7.2 Hz, 1H), 6.32 (d, J = 8.2 Hz, 1H), 5.93 (br. S, 2H), 4.36 (d, J = 5.9 Hz, 2H), 3.67 (s, 2H).

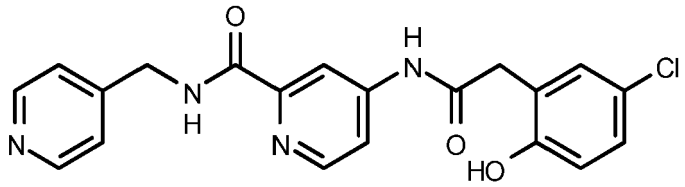
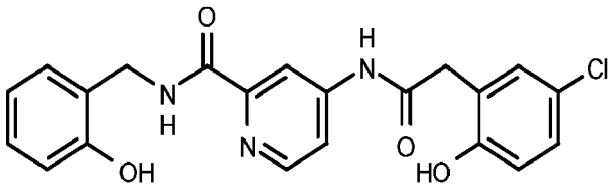
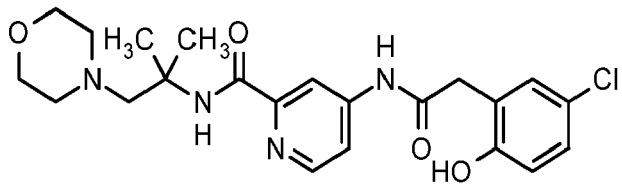
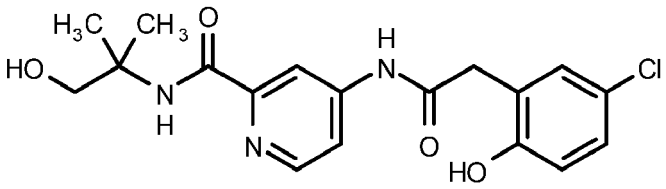
[0731] LC-MS (Method A): Rt 1.70 mins; MS m/z 412.2/414.4 = [M+H]+ (97% @ 215nm)

[0732] The compounds of the following tabulated Examples (Table 10) were prepared analogously to Example 32 by replacing tert-butyl N-[6-(aminomethyl)-2-pyridyl]carbamate (step 1) with the appropriate commercially available amine.

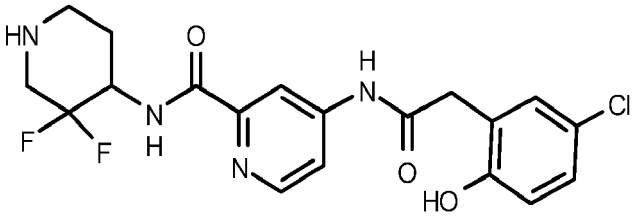
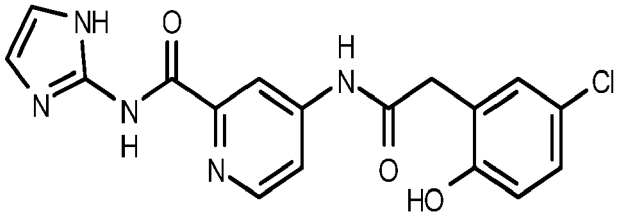
Table 10

Ex.	Structure and Name	1H NMR LCMS Retention Time, [M+H]+,
32.1	 12-[[4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carbonyl] amino]dodecanoic acid	1H NMR (500 MHz, Methanol-d4) δ 8.47 (d, J = 5.6 Hz, 1H), 8.24 - 8.17 (m, 1H), 7.93-7.89 (m, 1H), 7.19 (d, J = 2.4 Hz, 1H), 7.09 (d, J = 8.6, 2.2 Hz, 1H), 6.78 (d, J = 8.6 Hz, 1H), 3.72 (s, 2H), 3.40 (t, J = 7.1 Hz, 2H), 2.27 (t, J = 7.4 Hz, 2H), 1.67-1.55 (m, 4H), 1.42-1.26 (m, 14H). LC-MS (Method A): Rt 3.71 mins; MS m/z 504.4/506.4 = [M+H]+
32.2	 4-[[2-(5-Chloro-2-hydroxy-phenyl) acetyl]amino]-N-(3-pyridylmethyl) pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.84 (s, 1H), 9.89 (s, 1H), 9.40 (t, J = 6.4 Hz, 1H), 8.55 (d, J = 1.8 Hz, 1H), 8.49 (d, J = 5.5 Hz, 1H), 8.45 (dd, J = 4.8, 1.6 Hz, 1H), 8.21 (d, J = 2.0 Hz, 1H), 7.84 (dd, J = 5.5, 2.2 Hz, 1H), 7.73 (dt, J = 7.8, 1.9 Hz, 1H), 7.34 (dd, J = 7.8, 4.8 Hz, 1H), 7.21 (d, J = 2.9 Hz, 1H), 7.11 (dd, J = 8.6, 2.7 Hz, 1H), 6.79 (d, J = 8.6 Hz, 1H), 4.51 (d, J = 6.4 Hz, 2H), 3.67 (s, 2H). LC-MS (Method A): Rt 1.80 mins; MS m/z 397.2/399.2 = [M+H]+ (96% @ 215nm)
32.3	 4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(2-pyridylmethyl) pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.70 (s, 1H), 9.82 (s, 1H), 9.33 (t, J = 5.7 Hz, 1H), 8.56-8.50 (m, 2H), 8.24 (s, 1H), 7.86 (d, J = 3.7 Hz, 1H), 7.76 (t, J = 7.2 Hz, 1H), 7.32 (d, J = 7.9 Hz, 1H), 7.31 - 7.25 (m, 1H), 7.25 - 7.20 (m, 1H), 7.13 (dd, J = 8.5, 2.2 Hz, 1H), 6.81 (d, J = 8.6 Hz, 1H), 4.62 (d, J = 5.8 Hz, 2H), 3.68 (s, 2H). LC-MS (Method A): Rt 1.98 mins; MS m/z 397.2/399.2 = [M+H]+ (97% @ 215nm)

(continued)

Ex.	Structure and Name	1H NMR LCMS Retention Time, [M+H]+,
32.4	 4-[[2-(5-Chloro-2-hydroxy-phenyl) acetyl]amino]-N-(4-pyridylmethyl) pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.74 (s, 1H), 9.82 (s, 1H), 9.43 (t, J = 6.4 Hz, 1H), 8.52 (d, J = 5.5 Hz, 1H), 8.52 - 8.46 (m, 2H), 8.22 (d, J = 2.1 Hz, 1H), 7.86 (dd, J = 5.5, 2.2 Hz, 1H), 7.29 (d, J = 6.0 Hz, 2H), 7.22 (d, J = 2.7 Hz, 1H), 7.13 (dd, J = 8.6, 2.7 Hz, 1H), 6.81 (d, J = 8.6 Hz, 1H), 4.51 (d, J = 6.4 Hz, 2H), 3.68 (s, 2H). LC-MS (Method A): Rt 1.63 mins; MS m/z 397.2/399.2 = [M+H]+ (96% @ 215nm)
32.5	 4-[[2-(5-Chloro-2-hydroxy-phenyl) acetyl]amino]-N-[(2-hydroxyphenyl) methyl]pyridine-2-carboxamide	1H NMR (500 MHz, Methanol-d4) δ 8.35 dd, J = 5.01, 0.52 Hz, 1H), 8.06 (dd, J = 1.71, 0.49, 1H), 7.80 (dd, J = 5.5, 2.2 Hz, 1H), 7.11 (dd, J = 7.5, 1.5 Hz, 1H), 7.08 (d, J = 2.6 Hz, 1H), 7.04 - 6.96 (m, 2H), 6.74 - 6.70 (m, 1H), 6.69 - 6.65 (m, 2H), 4.47 (s, 2H), 3.60 (s, 2H). LC-MS (Method A): Rt 3.01mins; MS m/z 412.2/414.2 = [M+H]+ (97% @ 215nm)
32.6	 4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(1,1-dimethyl-2-morpholino-ethyl)pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.66 (s, 1H), 9.80 (s, 1H), 8.44 (d, J = 5.5 Hz, 1H), 8.33 (s, 1H), 8.17 (d, J = 2.1 Hz, 1H), 7.80 (dd, J = 5.5, 2.2 Hz, 1H), 7.22 (d, J = 2.7 Hz, 1H), 7.12 (dd, J = 8.6, 2.7 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 3.67 (s, 2H), 3.58 - 3.54 (m, 4H), 2.57 (s, 2H), 1.37 (s, 6H), 1.24 (s, 2H). LC-MS (Method A): Rt 1.80 mins; MS m/z 447.3/449.3 = [M+H]+ (100% @ 215nm)
32.7	 4-[[2-(5-Chloro-2-hydroxy-phenyl) acetyl]amino]-N-(2-hydroxy-1,1-dimethyl-ethyl)pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.67 (s, 1H), 9.81 (s, 1H), 8.44 (d, J = 5.5 Hz, 1H), 8.24 (s, 1H), 8.17 (d, J = 2.0 Hz, 1H), 7.81 (dd, J = 5.5, 2.2 Hz, 1H), 7.22 (d, J = 2.7 Hz, 1H), 7.12 (dd, J = 8.6, 2.7 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 5.12 (t, J = 5.5 Hz, 1H), 3.67 (s, 2H), 3.44 (d, J = 5.5 Hz, 2H), 1.33 (s, 6H). LC-MS (Method A): Rt 2.56 mins; MS m/z 378.2/380.2 = [M+H]+ (100% @ 215nm)

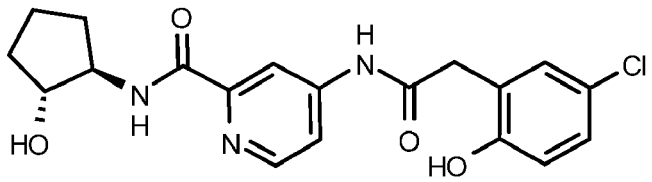
(continued)

Ex.	Structure and Name	1H NMR LCMS Retention Time, [M+H]+,
32.8	 4-[[2-(5-Chloro-2-hydroxy-phenyl) acetyl] amino]-N-(3,3-difluoro-4-piperidyl)pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.71 (s, 1H), 9.82 (s, 1H), 8.51 (d, J = 5.5 Hz, 1H), 8.42 (d, J = 9.6 Hz, 1H), 8.27 (d, J = 1.9 Hz, 1H), 7.84 (dd, J = 5.5, 2.2 Hz, 1H), 7.23 (d, J = 2.7 Hz, 1H), 7.13 (dd, J = 8.6, 2.7 Hz, 1H), 6.81 (d, J = 8.6 Hz, 1H), 4.60 - 4.32 (m, 1H), 3.68 (s, 2H), 3.18 - 3.07 (m, 1H), 2.97 - 2.79 (m, 2H), 2.69 - 2.62 (m, 1H), 1.90-1.79 (m, 1H), 1.78-1.63 (m, 1H). LC-MS (Method A): Rt 1.95 mins; MS m/z 425.2/427.2 = [M+H]+ (99% @ 215nm)
32.9	 4-[[2-(5-Chloro-2-hydroxy-phenyl) acetyl]amino]-N-(1H-imidazol-2-yl) pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 11.88 (s, 1H), 10.89 - 10.63 (m, 2H), 9.86 (s, 1H), 8.56 (d, J = 5.5 Hz, 1H), 8.38 (d, J = 2.0 Hz, 1H), 7.85 (dd, J = 5.5, 2.2 Hz, 1H), 7.23 (d, J = 2.7 Hz, 1H), 7.13 (dd, J = 8.6, 2.7 Hz, 1H), 6.91 (m, 3H), 3.69 (s, 2H). LC-MS (Method A): Rt 1.65 mins; MS m/z 372.2/374.2 = [M+H]+ (97% @ 215nm)

Example 33

4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[(1R,2R)-2-hydroxycyclopentyl] pyridine-2-carboxam ide

[0733]



[0734] To a solution of 4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxylic acid (Example 31 step 1)(100 mg, 0.33 mmol), (1R,2R)-2-aminocyclopentanol hydrochloride (45 mg, 0.33 mmol) and DIPEA (228 μL, 1.3 mmol) in DMF (2 mL) was added HATU (149 mg, 0.39 mmol) and the mixture was stirred at room temperature for 1 hour. The resulting mixture was partitioned between EtOAc (10 mL) and water (15 mL) then washed with sat. aq NaHCO3 (10 mL). The combined aqueous washes were extracted with EtOAc (2x10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo.* Purification of the crude residue by chromatography on silica using a Biotage® Isolera 11g KP-NH system eluting with 0-15% MeOH in EtOAc afforded the titled compound as an off-white solid.

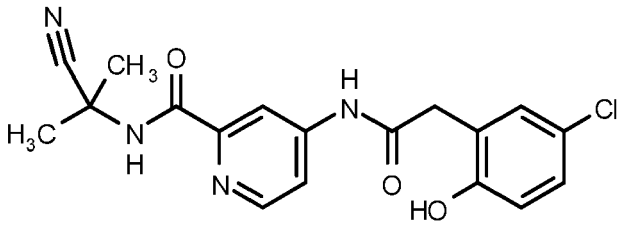
[0735] 1H NMR (500 MHz, DMSO-d6) δ 10.75 (s, 1H), 9.83 (s, 1H), 8.47 (d, J = 5.5 Hz, 1H), 8.43 (d, J = 7.6 Hz, 1H), 8.19 (d, J = 2.1 Hz, 1H), 7.82 (dd, J = 5.5, 2.2 Hz, 1H), 7.21 (d, J = 2.7 Hz, 1H), 7.12 (dd, J = 8.6, 2.7 Hz, 1H), 6.79 (d, J = 8.6 Hz, 1H), 4.80 (s, 1H), 4.03-3.94 (m, 2H), 3.66 (s, 2H), 2.03 - 1.96 (m, 1H), 1.89-1.81 (m, 1H), 1.71 - 1.58 (m, 2H), 1.54 -1.42 (m, 2H).

[0736] LC-MS (Method A): Rt 2.50 mins; MS m/z 390.3/392.3 = [M+H]+ (99% @ 215nm)

Example 34

4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1-cyano-1-methylethyl)pyridine-2-carboxamide

[0737]



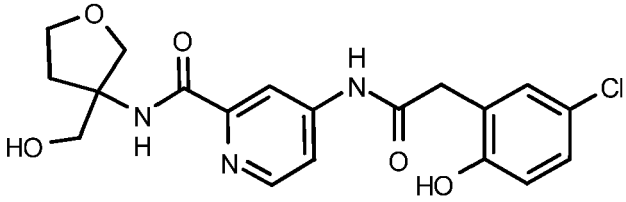
[0738] 4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxylic acid (Example 31 step 1)(4.0 g, 13.04 mmol) and 2-amino-2-methyl-propanenitrile hydrochloride (3.15 g, 26.08 mmol) were suspended in DMF (40 mL) and treated with DIPEA (9.11 mL, 52.17 mmol) and stirred to form a solution. HATU (5.95 g, 15.65 mmol) was added the reaction mixture was stirred at room temperature for 3 hours. The resulting mixture was diluted with water (60 mL) and 4:1 EtOAc/heptane (100 ml). The biphasic suspension was filtered using minimal EtOAc and the organic portion was separated, washed with water, dried over Na_2SO_4 and concentrated *in vacuo.* Purification of the residue by chromatography on silica eluting with 0-100% EtOAc in heptane followed by 0-100% MeOH in EtOAc afforded a yellow glassy solid. TBME (10 mL) was added to the solid and the mixture was heated to reflux (90°C) and further TBME (90 mL) was added gradually. MeCN was added in 0.5 mL aliquots until full dissolution occurred (9 mL).The mixture was cooled to 60°C then to 0 °C for 3 hours. The resulting mixture was allowed to stand at room temperature for 4 days and then filtered and dried in a vacuum oven to afford the titled compound as a white crystalline solid.

[0739] 1H NMR (500 MHz, DMSO-d6) δ 10.88 (s, 1H), 9.87 (s, 1H), 8.82 (s, 1H), 8.50 (d, J = 5.5 Hz, 1H), 8.21 (d, J = 1.9 Hz, 1H), 7.86 (dd, J = 5.5, 2.2 Hz, 1H), 7.21 (d, J = 2.7 Hz, 1H), 7.11 (dd, J = 8.6, 2.7 Hz, 1H), 6.79 (d, J = 8.6 Hz, 1H), 3.67 (s, 2H), 1.72 (s, 6H). LC-MS (Method A): Rt 2.81 mins; MS m/z 373.2/375.2 = [M+H]+ (98% @ 215nm)

Example 35

4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[3-(hydroxymethyl) tetrahydrofuran-3-yl]pyridine-2-carboxamide

[0740]



[0741] 4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxylic acid (Example 31 step 1) (150 mg, 0.49 mmol) and DIPEA (256.27 μL, 1.47 mmol) were suspended in DMF (2 mL) and treated with (3-aminotetrahydrofuran-3-yl)methanol (69 mg, 0.59 mmol) and HATU (223 mg, 0.59 mmol).The reaction mixture was stirred at room temperature for 30 min and then partitioned between EtOAc (15 mL) and water (15 mL). The organic portion was washed with sat. aq. NaHCO3 (10 mL). The combined aqueous washes were extracted with EtOAc (2 x 10 mL) and the combined organic extracts dried over Na_2SO_4 and concentrated *in vacuo.* Purification by chromatography on silica using a Biotage® Isolera 11g KP-NH system, eluting with 0-15% DCM/MeOH afforded the titled compound as an off-white solid.

[0742] 1H NMR (500 MHz, DMSO-d6) δ = 10.73 (s, 1H), 9.82 (s, 1H), 8.46 (d, J = 5.5 Hz, 1H), 8.41 (s, 1H), 8.19 (d, J = 2.0 Hz, 1H), 7.82 (dd, J = 5.5, 2.2 Hz, 1H), 7.21 (d, J = 2.7 Hz, 1H), 7.12 (dd, J = 8.6, 2.7 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 5.17 (s, 1H), 3.88-3.77 (m, 4H), 3.67 (s, 2H), 3.62 - 3.59 (m, 2H), 2.34 - 2.28 (m, 1H), 2.00 - 1.94 (m, 1H).

[0743] LC-MS (Method A): Rt 2.36 mins; MS m/z 406.3/408.3 = [M+H]+ (97% @ 215nm)

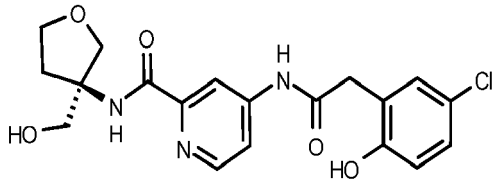
Example 35a and 35b

Enantiomers of 4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]-N-3-(hydroxymethyl)tetrahydrofuran-3-ylpyridine-2-carboxamide

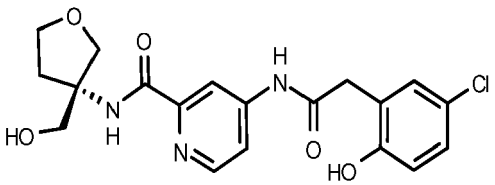
[0744] Chiral separation of racemic 4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]-N-3-(hydroxymethyl)tetrahydrofuran-3-ylpyridine-2-carboxamide (Example 35) using Supercritical Fluid Chromatography [chiral phase column (5μL at 1mg/mL MeOH + 95/5% CO2 / (IPOH) + 0.5% IPAm with Chiralpak IG (300 mm x 4.6) 20μm column at 2.4mL/min)] afforded the individual enantiomers:

Example 35a: 4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[(3R)-3-(hydroxymethyl)tetrahydro furan-3-yl]pyridine-2-carboxamide or 4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]-N-[(3S)-3-(hydroxymethyl)tetrahydrofuran-3-yl]pyridine-2-carboxamide

[0745]



(R)-isomer



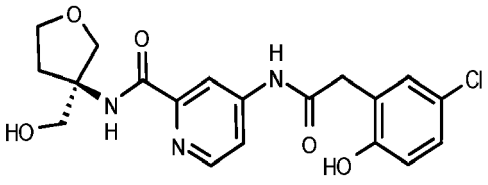
(S)-isomer

First eluted peak: SFC Retention Time =6.10 mins

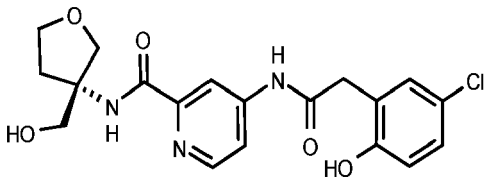
[0746] 1H NMR (500 MHz, DMSO-d6) δ 10.71 (s, 1H), 9.76 (s, 1H), 8.46 (d, J = 5.5 Hz, 1H), 8.41 (s, 1H), 8.19 (d, J = 2.0 Hz, 1H), 7.82 (dd, J = 5.5, 2.2 Hz, 1H), 7.21 (d, J = 2.7 Hz, 1H), 7.12 (dd, J = 8.6, 2.7 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 5.16 (t, J = 5.3 Hz, 1H), 3.88-3.77 (m, 4H), 3.67 (s, 2H), 3.61 (m, 2H), 2.34 - 2.29 (m, 1H), 2.00 - 1.94 (m, 1H).
[0747] LC-MS (Method A): Rt 2.23 mins; MS m/z 406.2/408.2 = [M+H]+ (97% @ 215nm)

Example 35b: 4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[(3R)-3-(hydroxymethyl)tetrahydro furan-3-yl]pyridine-2-carboxamide or 4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]-N-[(3S)-3-(hydroxymethyl)tetrahydrofuran-3-yl]pyridine-2-carboxamide

[0748]



(R)-isomer



(S)-isomer

Second eluted peak: SFC Retention Time =7.70 mins

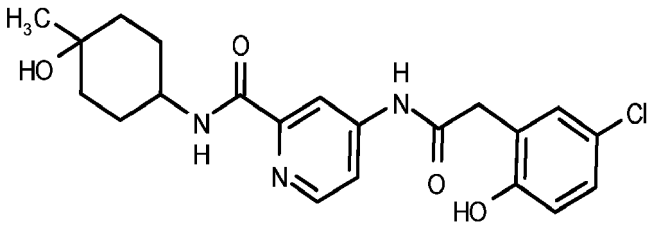
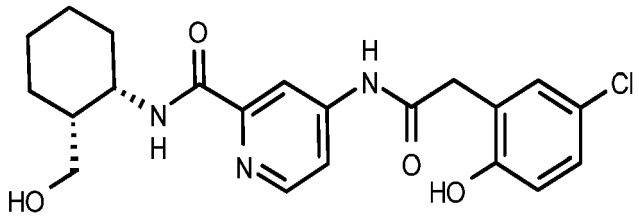
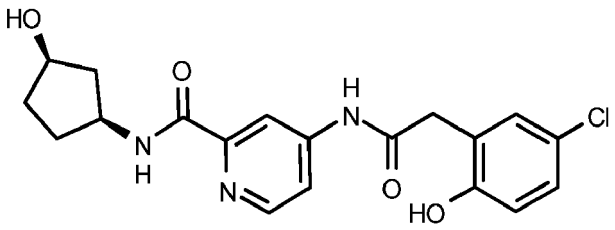
[0749] 1H NMR (500 MHz, DMSO-d6) δ 10.72 (s, 1H), 9.77 (s, 1H), 8.46 (d, J = 5.5 Hz, 1H), 8.41 (s, 1H), 8.19 (d, J = 2.1 Hz, 1H), 7.82 (dd, J = 5.5, 2.2 Hz, 1H), 7.21 (d, J = 2.7 Hz, 1H), 7.12 (dd, J = 8.6, 2.7 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 5.17 (s, 1H), 3.89 - 3.76 (m, 4H), 3.67 (s, 2H), 3.61 (d, J = 3.0 Hz, 2H), 2.35 - 2.28 (m, 1H), 2.01 - 1.93 (m, 1H).

[0750] LC-MS (Method A): Rt 2.23 mins; MS m/z 406.2/408.2 = [M+H]+ (97% @ 215nm)

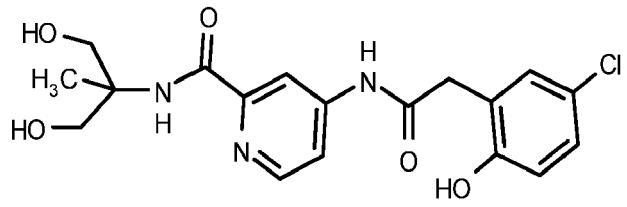
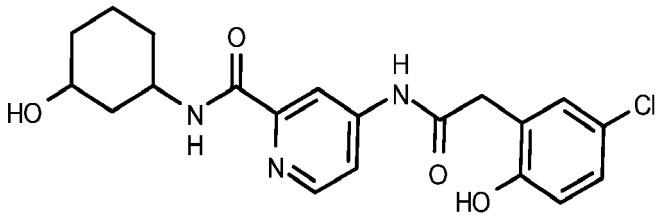
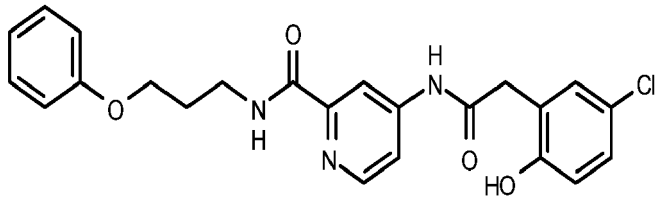
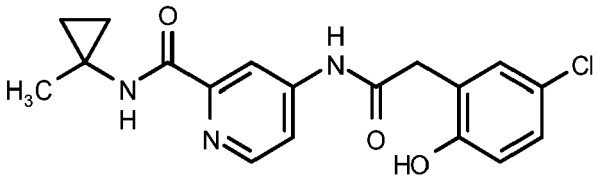
[0751] The compounds of the following tabulated Examples (Table 11) were prepared analogously to Example 35 from either 4-[[2-(5-chloro-2-hydroxyphenyl)acetyl]amino]pyridine-2-carboxylic acid (Example 31 step 1) or 3-[[2-(5-fluoro-2-hydroxy-phenyl)acetyl]amino]benzoic acid (Example 41 step 3) and the appropriate commercially available amine.

Table 11

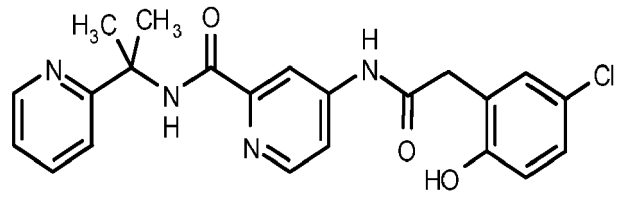
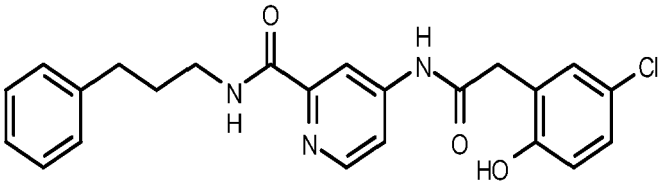
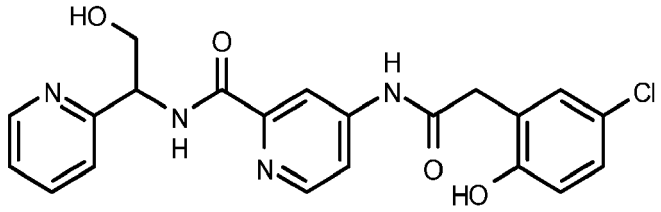
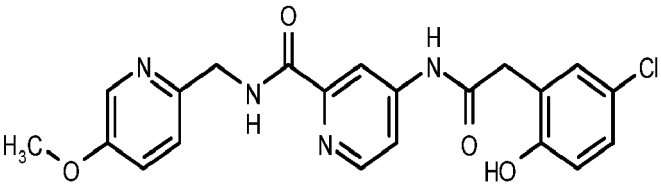
(* denotes a reference compound that is not claimed)

Ex.	Structure and Name	1H NMR LCMS Retention Time, [M+H]+,
35.1	 4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(4-hydroxy-4-methyl-cyclohexyl) pyridine-2-carboxamide as a 6:4 mixture of stereoisomers	1H NMR (500 MHz, DMSO-d6) δ = 8.46 (dd, J = 5.6, 2.1 Hz, 1H), 8.43 - 8.23 (m, 1H), 8.18 (t, J = 2.5 Hz, 1H), 7.83-7.80 (m, 1H), 7.21 (d, J = 2.7 Hz, 1H), 7.12 (dd, J= 8.6, 2.7 Hz, 1 H), 6.80 (d, J = 8.6 Hz, 1H), 4.35 -4.00 (m, 1H), 3.84 - 3.67 (m, 1H), 3.66 (s, 2H), 1.77 -1.67 (m, 2H), 1.61 -1.50 (m, 4H), 1.49-1.34 (m, 2H), 1.17 - 1.10 (m, 3H). LC-MS (Method A): Rt 2.52 mins; MS m/z 418.3/420.3 = [M+H]+ (96% @ 215nm)
35.2	 4-[[2-(5-Chloro-2-hydroxy-phenyl) acetyl]amino]-N-[(1s,2r)-2-(hydroxy methyl)cyclohexyl]pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ = 10.78 (s, 1H), 9.31 (s, 1H), 8.67 (d, J = 8.3 Hz, 1H), 8.47 (d, J = 5.6 Hz, 1H), 8.20 (d, J = 2.1 Hz, 1H), 7.81 (dd, J = 5.5 Hz, 2.2, 1H), 7.21 (d, J = 2.6 Hz, 1H), 7.12 (dd, J = 8.6, 2.7 Hz, 1H), 6.79 (d, J = 8.6 Hz, 1H), 4.63 (t, J = 4.3 Hz, 1H), 4.19-4.13 (m, 1H), 3.66 (s, 2H), 3.51 - 3.45 (m, 2H), 1.84 (s, 1H), 1.76 - 1.69 (m, 1H), 1.61 - 1.53 (m, 3H), 1.51 - 1.44 (m, 2H), 1.36 - 1.28 (m, 2H). LC-MS (Method A): Rt 3.03 mins; MS m/z 418.3/420.3 = [M+H]+ (99% @ 215nm)
35.3	 4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-[(1s,3r)-3-hydroxycyclopentyl] pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ = 10.70 (s, 1H), 9.80 (s, 1H), 8.68 (d, J = 8.8 Hz, 1H), 8.46 (d, J = 5.5 Hz, 1H), 8.20 (d, J= 2.1 Hz, 1H), 7.81 (dd, J= 5.5, 2.2 Hz, 1H), 7.22 (d, J = 2.7 Hz, 1H), 7.12 (dd, J = 8.6 Hz, 2.7, 1H), 6.80 (d, J = 8.6 Hz, 1H), 4.81 (d, J = 2.6 Hz, 1H), 4.40 - 4.33 (m, 1H), 4.23 -4.17 (m, 1H), 3.67 (s, 2H), 2.01 - 1.93 (m, 2H), 1.75 - 1.65 (m, 3H), 1.61 -1.55 (m, 1H). LC-MS (Method A): Rt 2.36 mins; MS m/z 390.3/392.3 = [M+H]+ (98% @ 215nm)

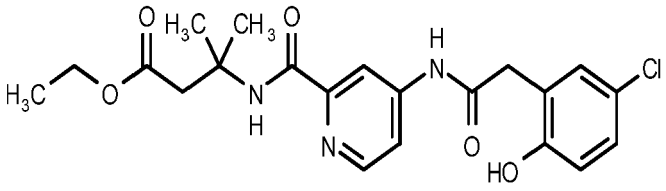
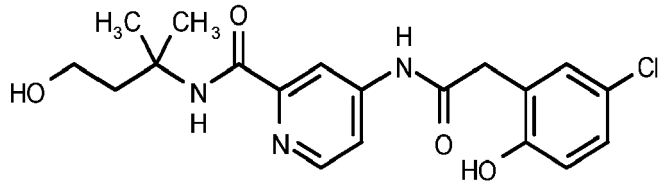
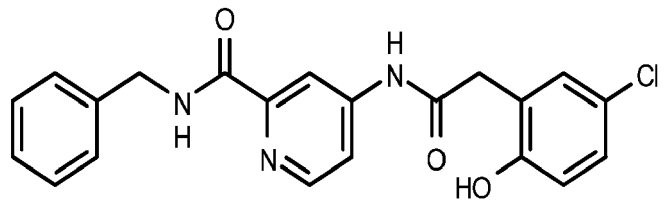
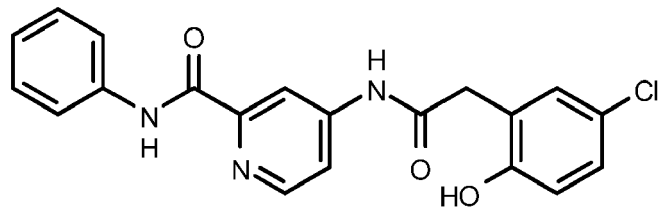
(continued)

(* denotes a reference compound that is not claimed)		
Ex.	**Structure and Name**	**1H NMR LCMS Retention Time, [M+H]+,**
35.4	 4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-[2-hydroxy-1-(hydroxy methyl)-1-methylethyl]pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ = 8.43 (d, J=5.6, 1H), 8.36 (s, 1H), 8.17 (d , J = 2.1 Hz, 1H), 7.78 (dd, J = 5.4, 2.1 Hz, 1H), 7.17 (s, 1H), 7.08 (d, J = 8.2 Hz, 1H), 6.75 (d, J = 8.4 Hz, 1H), 4.96 (t, J = 5.6 Hz, 2H), 3.64 (s, 2H), 3.59 - 3.62 (m, 2H), 3.48 - 3.51 (m, 2H), 1.29 (s, 3H), LC-MS (Method A): Rt 2.21 mins; MS m/z 394.3/337.3 = [M+H]+ (95% @ 215nm)
35.6	 4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(3-hydroxycyclohexyl)pyridine-2-carboxamide as a mixture of stereoisomers	1H NMR (500 MHz, DMSO-d6) δ 8.52 (d, J = 5.5 Hz, 1H), 8.37 (d, J = 8.8 Hz, 1H), 8.24 (d, J = 2.1 Hz, 1H), 7.88 (dd, J = 5.5, 2.2 Hz, 1H), 7.27 (d, J = 2.6 Hz, 1H), 7.18 (dd, J = 8.6, 2.7 Hz, 1H), 6.86 (d, J = 8.6 Hz, 1H), 4.54 (d, J = 3.2 Hz, 1H), 4.31 - 4.21 (m, 1H), 3.99 (s, 1H), 3.72 (s, 2H), 1.82 - 1.74 (m, 3H), 1.75 - 1.64 (m, 1H), 1.62 - 1.55 (m, 1H), 1.55 - 1.49 (m, 1H), 1.49 - 1.39 (m, 2H). LC-MS (Method A): Rt 2.56 mins; MS m/z 404.2/406.2 = [M+H]+ (100% @ 215nm)
35.7	 4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(3-phenoxypropyl)pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.40 (s, 1H), 9.82 (s, 1H), 8.87 (t, J = 6.0 Hz, 1H), 8.48 (d, J = 5.5 Hz, 1H), 8.18 (d, J = 2.1 Hz, 1H), 7.82 (dd, 1H), 7.30 - 7.25 (m, 2H), 7.21 (d, J = 2.6 Hz, 1H), 7.11 (dd, J = 8.6, 2.7 Hz, 1H), 6.96 - 6.89 (m, 3H), 6.79 (d, J = 8.6 Hz, 1H), 4.02 (t, J = 6.2 Hz, 2H), 3.66 (s, 2H), 3.46 (q, J = 6.7 Hz, 2H), 2.02 - 1.94 (m, 2H). LC-MS (Method A): Rt 3.45 mins; MS m/z 440.3/442.3 = [M+H]+ (98% @ 215nm)
35.8	 4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(1-methylcyclo propyl)pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.66 (s, 1H), 9.80 (s, 1H), 8.76 (s, 1H), 8.43 (d, J = 5.5 Hz, 1H), 8.16 (d, J = 1.9 Hz, 1H), 7.82 (dd, J = 5.5, 2.2 Hz, 1H), 7.22 (d, J = 2.7 Hz, 1H), 7.12 (dd, J = 8.6, 2.7 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 3.67 (s, 2H), 1.36 (s, 3H), 0.80 - 0.75 (m, 2H), 0.64 - 0.57 (m, 2H). LC-MS (Method A): Rt 2.85 mins; MS m/z 360.1/362.1 = [M+H]+

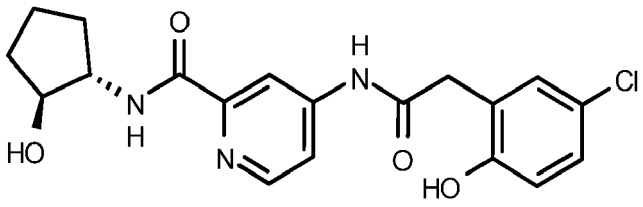
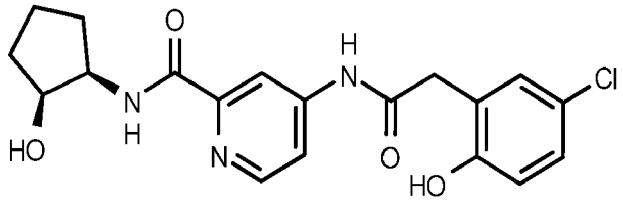
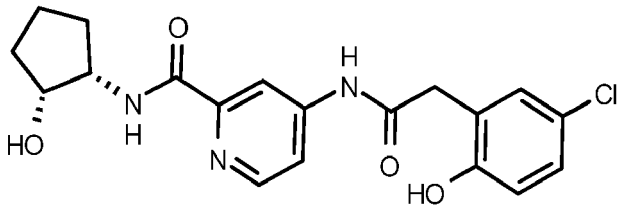
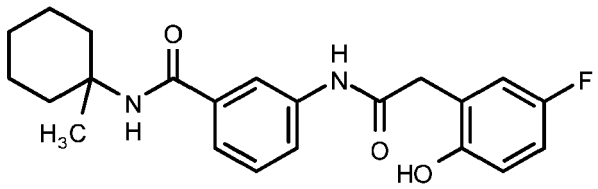
(continued)

(* denotes a reference compound that is not claimed)		
Ex.	**Structure and Name**	**1H NMR LCMS Retention Time, [M+H]+,**
35.9	 4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-[1-methyl-1-(2-pyridyl) ethyl]pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.68 (s, 1H), 9.81 (s, 1H), 9.63 (s, 1H), 8.60 (m,1H), 8.53 (d, J = 5.5 Hz, 1H), 8.18 (d, J = 2.0 Hz, 1H), 7.90-7.80 (m, 2H), 7.60 (d, J = 8.1 Hz, 1H), 7.39-7.27 (m, 1H), 7.22 (d, J = 2.7 Hz, 1H), 7.12 (dd, J = 8.6, 2.7 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 3.67 (s, 2H), 1.76 (s, 6H). LC-MS (Method A): Rt 2.34 mins; MS m/z 425.3/427.2 = [M+H]+ (98% @ 215nm)
35.10	 4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(3-phenylpropyl)pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.81 (s, 1H), 9.83 (s, 1H), 8.78 (t, J = 6.1 Hz, 1H), 8.47 (d, J = 5.5 Hz, 1H), 8.18 (d, J = 2.0 Hz, 1H), 7.82 (dd, J = 5.5, 2.2 Hz, 1H), 7.31 - 7.25 (m, 2H), 7.25-7.20 (m, 3H), 7.20-7.15 (m, 1H), 7.14-7.09 (m, 1H), 6.80 (d, 1H), 3.66 (s, 2H), 2.61 (t, J = 7.8 Hz, 2H), 1.85 (p, J = 7.6 Hz, 2H). LC-MS (Method A): Rt 3.53 mins; MS m/z 424.3/426.3 = [M+H]+ (98% @ 215nm)
35.11	 4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-[2-hydroxy-1-(2-pyridyl)ethyl] pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.72 (br. S, 1H), 9.80 (br. S, 1H), 9.08 (d, J = 8.2 Hz, 1H), 8.60 - 8.55 (m, 1H), 8.53 (d, J = 5.6 Hz, 1H), 8.23 (d, J = 2.0 Hz, 1H), 7.84 (dd, J = 5.5, 2.2 Hz, 1H), 7.76 (td, J = 7.7, 1.8 Hz, 1H), 7.41 - 7.38 (m, 1H), 7.31 - 7.28 (m, 1H), 7.21 (d, J = 2.7 Hz, 1H), 7.12 (dd, J = 8.6, 2.7 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 5.10 (dt, J = 8.2, 5.5 Hz, 1H), 5.03 (t, J = 5.6 Hz, 1H), 3.87-3.80 (m, 1H), 3.76-3.70 (m, 1H), 3.67 (s, 2H). LC-MS (Method A): Rt 2.09 mins; MS m/z 427.2/429.2 = [M+H]+ (98% @ 215nm)
35.12	 4-[[2-(5-Chloro-2-hydroxy-phenyl) acetyl]amino]-N-[(5-methoxy-2-pyridyl)methyl]pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.74 (br. S, 1H), 9.82 (br. S, 1H), 9.23 (t, J = 6.0 Hz, 1H), 8.50 (d, J = 5.5 Hz, 1H), 8.23 (dd, J = 9.5, 2.5 Hz, 2H), 7.84 (dd, J = 5.5, 2.2 Hz, 1H), 7.36 (dd, J = 8.6, 3.0 Hz, 1H), 7.28 (d, J = 8.6 Hz, 1H), 7.21 (d, J = 2.7 Hz, 1H), 7.12 (dd, J = 8.6, 2.7 Hz, 1H), 6.79 (d, J = 8.6 Hz, 1H), 4.54 (d, J = 6.0 Hz, 2H), 3.81 (s, 3H), 3.67 (s, 2H). LC-MS (Method A): Rt 2.39 mins; MS m/z 427.2/429.2 = [M+H]+ (100% @ 215nm)

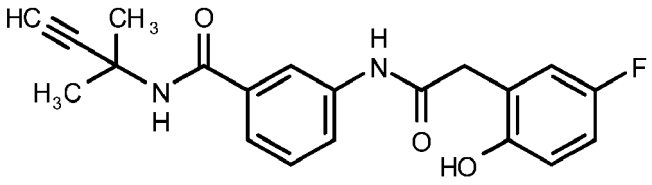
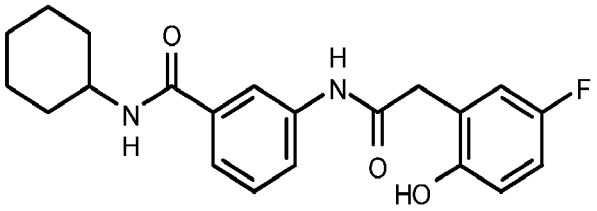
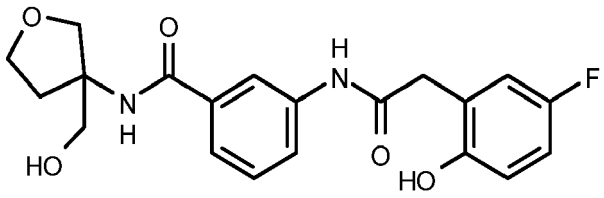
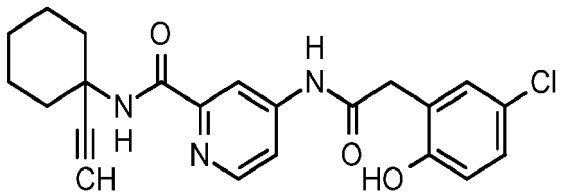
(continued)

(* denotes a reference compound that is not claimed)		
Ex.	**Structure and Name**	**1H NMR LCMS Retention Time, [M+H]+,**
35.13	 Ethyl 3-[[4-[[2-(5-chloro-2-hydroxy-phenyl) acetyl]amino]pyridine-2-carbonyl]amino]-3-methylbutanoate	1H NMR (500 MHz, DMSO-d6) δ 10.74 (s, 1H), 9.80 (s, 1H), 8.45 (d, J = 5.5 Hz, 1H), 8.35 (s, 1H), 8.18 (d, J = 2.1 Hz, 1H), 7.82 (dd, J = 5.5, 2.2 Hz, 1H), 7.22 (d, J = 2.7 Hz, 1H), 7.12 (dd, J = 8.6, 2.7 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 4.03 (q, J = 7.1 Hz, 2H), 3.67 (s, 2H), 2.81 (s, 2H), 1.47 (s, 6H), 1.11 (t, J = 7.1 Hz, 3H). LC-MS (Method A): Rt 3.39 mins; MS m/z 434.3/436.3 = [M+H]+ (92% @ 215nm)
35.14	 4-[[2-(5-Chloro-2-hydroxy-phenyl) acetyl]amino]-N-(3-hydroxy-1,1-dimethyl-propyl)pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.71 (s, 1H), 9.82 (s, 1H), 8.53 (s, 1H), 8.42 (d, J = 5.5 Hz, 1H), 8.16 (d, J = 2.0 Hz, 1H), 7.80 (dd, J = 5.5, 2.2 Hz, 1H), 7.22 (d, J = 2.7 Hz, 1H), 7.12 (dd, J = 8.6, 2.7 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 4.63 (t, J = 4.7 Hz, 1H), 3.67 (s, 2H), 3.56 (q, J = 6.4 Hz, 2H), 1.86 (t, J = 6.5 Hz, 2H), 1.41 (s, 6H). LC-MS (Method A): Rt 2.56 mins; MS m/z 392.2/394.2 = [M+H]+ (100% @ 215nm)
35.15	 N-Benzyl-4-[[2-(5-chloro-2-hydroxy-phenyl) acetyl]amino] pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.70 (s, 1H), 9.81 (s, 1H), 9.25 (t, J = 6.4 Hz, 1H), 8.48 (d, J = 5.5 Hz, 1H), 8.20 (d, J = 2.1 Hz, 1H), 7.83 (dd, J = 5.5, 2.2 Hz, 1H), 7.32 (s, 2H), 7.31 (d, J = 1.2 Hz, 2H), 7.26 - 7.21 (m, 1H), 7.20 (d, J = 2.6 Hz, 1H), 7.11 (dd, J = 8.6, 2.6 Hz, 1H), 6.78 (d, J = 8.6 Hz, 1H), 4.48 (d, J = 6.4 Hz, 2H), 3.66 (s, 2H). LC-MS (Method A): Rt 3.23 mins; MS m/z 396.4/398.4 = [M+H]+ (100% @ 215nm)
35.16	 4-[[2-(5-Chloro-2-hydroxy-phenyl) acetyl] amino]-N-phenyl-pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.78 (s, 1H), 10.56 (s, 1H), 9.83 (s, 1H), 8.58 (d, J = 5.5 Hz, 1H), 8.33 (d, J = 2.0 Hz, 1H), 7.92 - 7.86 (m, 3H), 7.39 - 7.33 (m, 2H), 7.23 (d, J = 2.7 Hz, 1H), 7.16 - 7.08 (m, 2H), 6.81 (d, J = 8.6 Hz, 1H), 3.69 (s, 2H). LC-MS (Method A): Rt 3.41 mins; MS m/z 382.3/384.3 = [M+H]+ (100% @ 215nm)

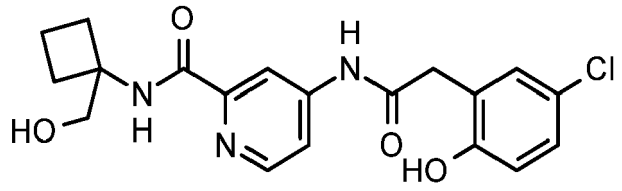
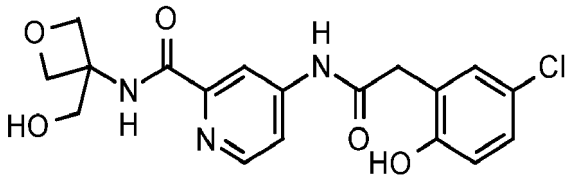
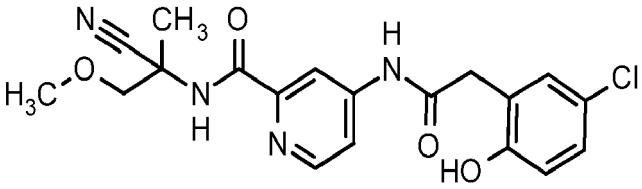
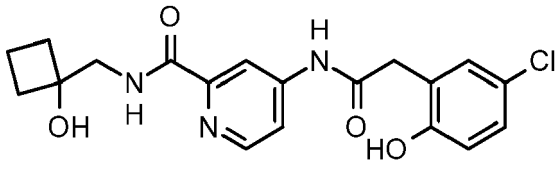
(continued)

(* denotes a reference compound that is not claimed)		
Ex.	**Structure and Name**	**1H NMR LCMS Retention Time, [M+H]+,**
35.17	 4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-[(1S,2S)-2-hydroxycyclopentyl]pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.70 (s, 1H), 9.82 (s, 1H), 8.47 (d, J = 5.5 Hz, 1H), 8.43 (d, J = 7.6 Hz, 1H), 8.19 (d, J = 1.9 Hz, 1H), 7.82 (dd, J = 5.5, 2.2 Hz, 1H), 7.22 (d, J = 2.7 Hz, 1H), 7.12 (dd, J = 8.6, 2.7 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 4.80 (d, J = 4.4 Hz, 1H), 4.02 - 3.94 (m, 2H), 3.67 (s, 2H), 2.03 - 1.95 (m, 1H), 1.90 - 1.81 (m, 1H), 1.71 - 1.59 (m, 2H), 1.54 - 1.42 (m, 2H). LC-MS (Method A): Rt 2.50 mins; MS m/z 390.2/392.2 = [M+H]+ (99% @ 215nm)
35.18	 4-[[2-(5-Chloro-2-hydroxy-phenyl) acetyl] am i no]- N-[(1R,2S)-2-hydroxy cyclopentyl]pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.75 (s, 1H), 9.81 (s, 1H), 8.46 (d, 1H), 8.43 (d, J = 7.8 Hz, 1H), 8.22 (d, J = 1.9 Hz, 1H), 7.81 (dd, J = 5.5, 2.2 Hz, 1H), 7.21 (d, J = 2.7 Hz, 1H), 7.12 (dd, J = 8.6, 2.7 Hz, 1H), 6.79 (d, J = 8.6 Hz, 1H), 5.09 (s, 1H), 4.05 - 3.98 (m, 2H), 3.66 (s, 2H), 1.99 - 1.88 (m, 1H), 1.88 - 1.79 (m, 1H), 1.79 - 1.71 (m, 1H), 1.64 - 1.57 (m, 1H), 1.56 - 1.46 (m, 2H). LC-MS (Method A): Rt 2.58 mins; MS m/z 390.3/392.3 = [M+H]+ (100% @ 215nm)
35.19	 4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-[(1S,2R)-2-hydroxy cyclopentyl]pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.73 (s, 1H), 9.83 (s, 1H), 8.47 (d, J = 5.5 Hz, 1H), 8.44 (d, J = 7.8 Hz, 1H), 8.22 (d, J = 2.0 Hz, 1H), 7.81 (dd, J = 5.5, 2.2 Hz, 1H), 7.22 (d, J = 2.7 Hz, 1H), 7.12 (dd, J = 8.6, 2.7 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 5.09 (s, 1H), 4.06 - 3.97 (m, 2H), 3.67 (s, 2H), 2.01 - 1.90 (m, 1H), 1.89- 1.79 (m, 1H), 1.80 - 1.71 (m, 1H), 1.65 - 1.58 (m, 1H), 1.57 - 1.46 (m, 2H). LC-MS (Method A): Rt 2.63 mins; MS m/z 390.3/392.3 = [M+H]+ (99% @ 215nm)
35.20 *	 3-[[2-(5-Fluoro-2-hydroxy-phenyl)acetyl] amino]-N-(1-methylcyclohexyl)benzamide	1H NMR (500 MHz, DMSO-d6) δ 10.17 (s, 1H), 9.49 (s, 1H), 7.90 (t, J = 1.7 Hz, 1H), 7.77 (d, J = 8.1 Hz, 1H), 7.43-7.40 (m, 2H), 7.34 (t, J = 7.9 Hz, 1H), 7.00 (dd, J = 9.4, 3.2 Hz, 1H), 6.89 (td, J = 8.6, 3.2 Hz, 1H), 6.77 (dd, J = 8.8, 4.9 Hz, 1H), 3.61 (s, 2H), 2.21 (d, J = 13.3 Hz, 2H), 1.54 - 1.41 (m, 5H), 1.38 - 1.29 (m, 2H), 1.32 (s, 3H), 1.28 - 1.22 (m, 1H). LC-MS (Method A): Rt 3.36 mins; MS m/z 385.3 = [M+H]+ (98% @ 215nm)

(continued)

(* denotes a reference compound that is not claimed)		
Ex.	**Structure and Name**	**1H NMR LCMS Retention Time, [M+H]+,**
35.21 *	 N-(1,1-Dimethylprop-2-ynyl)-3-[[2-(5-fluoro-2-hydroxy-phenyl) acetyl]amino]benzamide	1H NMR (500 MHz, DMSO-d6) δ 10.19 (s, 1H), 9.48 (s, 1H), 8.20 (s, 1H), 7.94 (t, J = 1.8 Hz, 1H), 7.79-7.75 (m, 1H), 7.44 (dt, J = 7.8, 1.29 Hz, 1H), 7.35 (t, J = 7.9 Hz, 1H), 7.00 (dd, J = 9.4, 3.2 Hz, 1H), 6.89 (td, J = 8.6, 3.2 Hz, 1H), 6.77 (dd, J = 8.8, 4.9 Hz, 1H), 3.62 (s, 2H), 3.08 (s, 1H), 1.59 (s, 6H). LC-MS (Method A): Rt 2.67 mins; MS m/z 355.3 = [M+H]+ (97% @ 215nm)
35.22 *	 N-Cyclohexyl-3-[[2-(5-fluoro-2-hydroxyphenyl)acetyl]amino] benzamide	1H NMR (500 MHz, DMSO-d6) δ 10.18 (s, 1H), 9.46 (s, 1H), 8.15 (d, J = 7.9 Hz, 1H), 7.96 (t, J = 1.8 Hz, 1H), 7.79-7.75 (m, 1H), 7.47 (d, J = 7.8 Hz, 1H), 7.35 (t, J = 7.9 Hz, 1H), 7.00 (dd, J = 9.4, 3.2 Hz, 1H), 6.89 (td, J = 8.6, 3.2 Hz, 1H), 6.79 - 6.75 (m, 1H), 3.78 - 3.68 (m, 1H), 3.61 (s, 2H), 1.85 - 1.68 (m, 4H), 1.60 (d, J = 12.6 Hz, 1H), 1.31 (q, J = 10.7, 8.8 Hz, 4H), 1.18 - 1.06 (m, 1H). LC-MS (Method A): Rt 3.03 mins; MS m/z 371.3 = [M+H]+ (98% @ 215nm)
35.23 *	 3-[[2-(5-Fluoro-2-hydroxy-phenyl)acetyl] amino]-N-[3-(hydroxymethyl)tetrahydro furan-3-yl]benzamide	1H NMR (500 MHz, DMSO-d6) δ 10.18 (s, 1H), 9.48 (s, 1H), 8.12 (s, 1H), 7.95 (t, J = 1.8 Hz, 1H), 7.81 - 7.75 (m, 1H), 7.50 (d, J = 7.9 Hz, 1H), 7.36 (t, J = 7.9 Hz, 1H), 7.00 (dd, J = 9.4, 3.2 Hz, 1H), 6.89 (td, J = 8.6, 3.2 Hz, 1H), 6.77 (dd, J = 8.8, 4.9 Hz, 1H), 4.97 (s, 1H), 3.89 (d, J = 9.2 Hz, 1H), 3.81 - 3.73 (m, 3H), 3.69 - 3.61 (m, 4H), 2.22 (dt, J = 12.8, 6.4 Hz, 1H), 2.05 (dt, J = 12.9, 7.7 Hz, 1H). LC-MS (Method A): Rt 1.98 mins; MS m/z 389.2 = [M+H]+ (98% @ 215nm)
35.24	 4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1-ethynylcyclohexyl)pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.72 (s, 1H), 9.82 (s, 1H), 8.47 (d, J = 5.5 Hz, 1H), 8.24 (s, 1H), 8.19 (d, J = 1.9 Hz, 1H), 7.84 (dd, J = 5.5, 2.2 Hz, 1H), 7.22 (d, J = 2.7 Hz, 1H), 7.13 (dd, J = 8.6, 2.7 Hz, 1H), 6.81 (d, J = 8.6 Hz, 1H), 3.68 (s, 2H), 3.27 (s, 1H), 2.15-2.08 (m, 2H), 1.95 - 1.86 (m, 2H), 1.62 - 1.50 (m, 5H), 1.34 - 1.23 (m, 1H). LC-MS (Method A): Rt 3.62 mins; MS m/z 412.1/414.1 = [M+H]+ (98% @ 215nm)

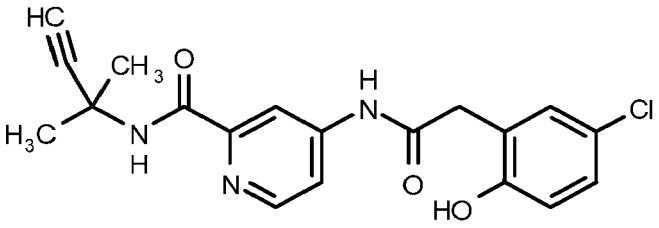
(continued)

(* denotes a reference compound that is not claimed)		
Ex.	**Structure and Name**	**1H NMR LCMS Retention Time, [M+H]+,**
35.25	 4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-[1-(hydroxymethyl)cyclobutyl]pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.68 (s, 1H), 9.82 (br s, 1H), 8.45 (d, J = 5.5 Hz, 1H), 8.40 (s, 1H), 8.21 -8.14 (m, 1H), 7.82 (dd, J = 5.5, 2.2 Hz, 1H), 7.22 (d, J = 2.7 Hz, 1H), 7.12 (dd, J = 8.6, 2.7 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 5.00 (t, J = 5.3 Hz, 1H), 3.67 (s, 2H), 3.61 (d, J = 4.7 Hz, 2H), 2.07-2.01 (m, 2H), 1.89- 1.78 (m, 1H), 1.78-1.66 (m, 1H). LC-MS (Method A): Rt 2.53 mins; MS m/z 390.2/392.2 = [M+H]+ (98% @ 215nm)
35.26	 4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-[3-(hydroxymethyl)oxetan-3-yl]pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.69 (s, 1H), 9.82 (s, 1H), 9.00 (s, 1H), 8.49 (d, J = 5.5 Hz, 1H), 8.17 (d, J = 2.0 Hz, 1H), 7.84 (dd, J = 5.5, 2.2 Hz, 1H), 7.22 (d, J = 2.7 Hz, 1H), 7.12 (dd, J = 8.6, 2.7 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 5.18 (t, J = 5.9 Hz, 1H), 4.73 (d, J = 6.5 Hz, 2H), 4.53 (d, J = 6.6 Hz, 2H), 3.70 (d, J = 5.9 Hz, 2H), 3.67 (s, 2H). LC-MS (Method A): Rt 2.11 mins; MS m/z 392.2/394.2 = [M+H]+ (98% @ 215nm)
35.27	 4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1-cyano-2-methoxy-1-methyl-ethyl)pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.78 (s, 1H), 9.77 (s, 1H), 8.77 (s, 1H), 8.52 (d, J = 5.5 Hz, 1H), 8.24 (d, J = 2.0 Hz, 1H), 7.87 (dd, J = 5.5, 2.2 Hz, 1H), 7.23 (d, J = 2.7 Hz, 1H), 7.13 (dd, J = 8.6, 2.7 Hz, 1H), 6.81 (d, J = 8.6 Hz, 1H), 3.86 (d, J = 9.5 Hz, 1H), 3.69 (s, 2H), 3.67 (d, J = 9.5 Hz, 1H), 3.42 (s, 3H), 1.71 (s, 3H). LC-MS (Method A): Rt 3.02 mins; MS m/z 403.2/405.2 = [M+H]+ (98% @ 215nm)
35.28	 4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[(1-hydroxycyclobutyl)methyl]pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.68 (s, 1H), 9.81 (s, 1H), 8.48 (d, J = 5.5 Hz, 1H), 8.42 (t, J = 5.9 Hz, 1H), 8.23 (d, J = 2.1 Hz, 1H), 7.82 (dd, J = 5.5, 2.2 Hz, 1H), 7.22 (d, J = 2.7 Hz, 1H), 7.12 (dd, J = 8.6, 2.7 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 5.38 (s, 1H), 3.67 (s, 2H), 3.43 (d, J = 5.9 Hz, 2H), 2.00- 1.86 (m, 4H), 1.70- 1.57 (m, 1H), 1.57 - 1.41 (m, 1H). LC-MS (Method A): Rt 2.59 mins; MS m/z 390.1/392.1 = [M+H]+ (95% @ 215nm)

Example 36

4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide

[0752]

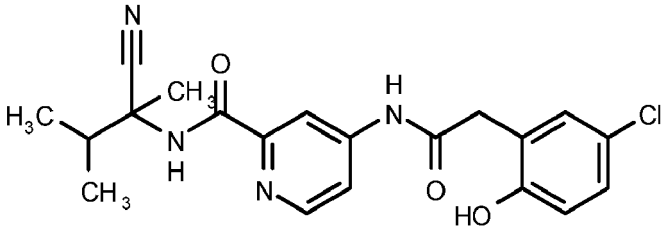


[0753] To a solution of 4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxylic acid (Example 31 step 1) (20 g, 63.25 mmol, 97%), 2-methylbut-3-yn-2-amine (7.99 mL, 75.9 mmol) and DIPEA (16.57 mL, 94.88 mmol) in DMF (315 mL) was addded HATU (28.86 g, 75.9 mmol) and the mixture stirred at room temperature for 1 hour. The resulting mixture was concentrated *in vacuo* and the residue was dissolved in EtOAc and washed sequentially with 1M HCl, 1M NaOH and brine. The acid washing was re-extracted with EtOAc and the combined organic extracts were washed with 1M NaOH, brine, dried over Na_2SO_4 and concentrated *in vacuo* to afford a yellow foam. The foam was absorbed onto silica and purifed by chromatography eluting with 0-100% EtOAc in heptanes. The isolated material was suspended in MeCN (50 mL) and heated to reflux until all solids had dissolved. The resulting solution was allowed to cool to room temperature and stand for 8 hours to yield crystals. The crystals were filtered, washed with ice cooled MeCN and dried in a vacuum oven overnight to afford crop 1 of the the titled compound. The filtrate from was combined with the impure fractions from chromatography and repurified by chromatography on silica eluting with 0-100% EtOAc in heptanes. The isolated material was combined with crop 1 and recrystallised again by heating at reflux in MeCN. The solution was allowed to cool and stand at room temperature to afford crystals which were filtered, washed with ice-cooled MeCN and dried in a vacuum oven to afford the titled compound as a crystalline solid.1H NMR (500 MHz, DMSO-d6) δ 10.71 (br s, 1H), 9.82 (br s, 1H), 8.46 (d, J = 5.5 Hz, 1H), 8.31 (s, 1H), 8.19 (d, J = 1.9 Hz, 1H), 7.84 (dd, J = 5.5, 2.2 Hz, 1H), 7.22 (d, J = 2.7 Hz, 1H), 7.12 (dd, J = 8.6, 2.7 Hz, 1H), 6.81 (d, J = 8.6 Hz, 1H), 3.68 (s, 2H), 3.20 (s, 1H), 1.64 (s, 6H).
[0754] LC-MS (Method A): Rt 3.07 mins; MS m/z 372.1/374.1 = [M+H]+ (99% @ 215 nm)

Example 37

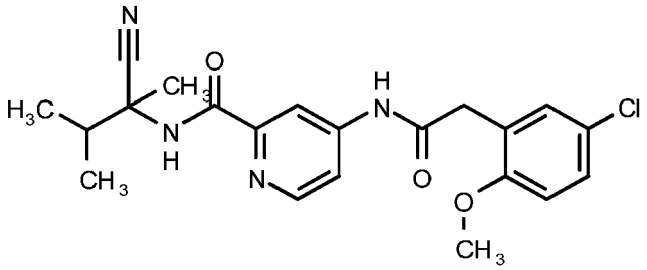
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1-cyano-1,2-dimethylpropyl)pyridine-2-carboxamide

[0755]



Step 1: 4-[[2-(5-Chloro-2-methoxy-phenyl)acetyl]amino]-N-(1-cyano-1,2-dimethylpropyl) pyrid ine-2-carboxam ide

[0756]



[0757] To a solution of 4-[[2-(5-chloro-2-methoxy-phenyl)acetyl]amino]pyridine-2-carboxylic acid (Example 8.1 step 2)(100 mg, 0.31 mmol) in DMF (2 mL) was added DIPEA (0.06 mL, 0.33 mmol) and HATU (124 mg, 0.33 mmol) and the mixture stirred for 15 mins. The resulting mixture was treated with 2-amino-2,3-dimethyl-butanenitrile (37 mg, 0.33 mmol) and stirring continued for 55 minutes. The mixture was diluted with water (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with water (10 mL), brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo* to afford a crude oil. The crude oil was adsorbed onto silica and purified by chromatography on silica eluting with 10-100% EtOAc in heptane to yield an oil. The oil was triturated with ether to afford the titled compound as a white solid.

[0758] 1H NMR (250 MHz, DMSO-d6) δ 10.75 (s, 1H), 8.69 (s, 1H), 8.51 (d, J = 5.5 Hz, 1H), 8.21 (d, J = 1.9 Hz, 1H), 7.86 (dd, J = 5.5, 2.2 Hz, 1H), 7.37 - 7.25 (m, 2H), 7.07 - 6.95 (m, 1H), 3.75 (s, 3H), 3.73 (s, 2H), 2.63 - 2.53 (m, 1H), 1.61 (s, 3H), 1.08 (d, J = 6.8 Hz, 3H), 0.97 (d, J = 6.8 Hz, 3H).

[0759] LC-MS (Method E): Rt 1.21 mins; MS m/z 415.1/417.1 = [M+H]+ (95% @215 nm)

Step 2: 4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1-cyano-1,2-dimethyl-propyl) pyridine-2-carboxam ide

[0760] A cooled (0°C) solution 4-[[2-(5-chloro-2-methoxy-phenyl)acetyl]amino]-N-(1-cyano-1,2-dimethyl-propyl) pyridine-2-carboxamide (step 1) (84 mg, 0.19 mmol) in DCM (2 mL) was treated with 1M BBr3 in DCM (962 μL, 0.96 mmol) and stirred at room temperature for 15 mins. The reaction was quenched with methanol (1 mL) the resulting mixture was reduced *in vacuo.* The residue was redissolved in EtOAc and washed with saturated NaHCO3 and brine. The organic layer was separated, dried over Na_2SO_4 and concentrated *in vacuo.* The residue was dissolved in DMSO:MeOH (800 μl, 1:1), filtered and purified via preparative HPLC (acidic pH, standard elution method). The product fractions were combined, concentrated *in vacuo* and the residue re-dissolved in MeCN:H2O (5 mL, 1:2) and freeze dried to afford the titled compound as a white powder.

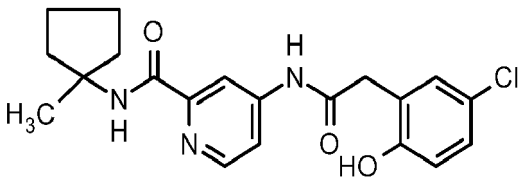
[0761] 1H NMR (500 MHz, DMSO-d6) δ 10.76 (s, 1H), 9.83 (s, 1H), 8.68 (s, 1H), 8.51 (d, J = 5.6 Hz, 1H), 8.21 (d, J = 2.0 Hz, 1H), 7.87 (dd, J = 5.5, 2.2 Hz, 1H), 7.22 (d, J = 2.7 Hz, 1H), 7.12 (dd, J = 8.6, 2.7 Hz, 1H), 6.81 (d, J = 8.6 Hz, 1H), 3.68 (s, 2H), 2.56 (hept, J = 6.8 Hz, 1H), 1.61 (s, 3H), 1.08 (d, J = 6.8 Hz, 3H), 0.97 (d, J = 6.8 Hz, 3H).

[0762] LC-MS (Method A): Rt 3.25 mins; MS m/z 401.2/403.2 = [M+H]+ (100% @215 nm)

Example 38

4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1-methylcyclopentyl)pyridine-2-carboxamide

[0763]



[0764] 4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxylic acid (Example 31 step 1) (100 mg, 0.33 mmol) and DIPEA (0.23 mL, 1.3 mmol) were suspended in DMF (2.1 mL) and treated with 1-methylcyclopentanamine hydrochloride (66 mg, 0.49 mmol) followed by HATU (149 mg, 0.39 mmol) and the mixture stirred at room temperature for 24 hours. The resulting mixture was diluted with EtOAc (10 mL) and washed with sat. aq $NaHCO_3$ (10 mL), water (10ml), brine (10 mL), dried over Na_2SO_4 and concentrated in *vacuo.* The residue was dissolved in MeOH (800 μl), filtered and purified by preparative HPLC (acidic pH, early elution method) to afford the titled compound as a white solid.

[0765] 1H NMR (500 MHz, DMSO-d6) δ 10.69 (s, 1H), 9.82 (s, 1H), 8.44 (d, J = 5.5 Hz, 1H), 8.17 (d, J = 2.1 Hz, 1H),

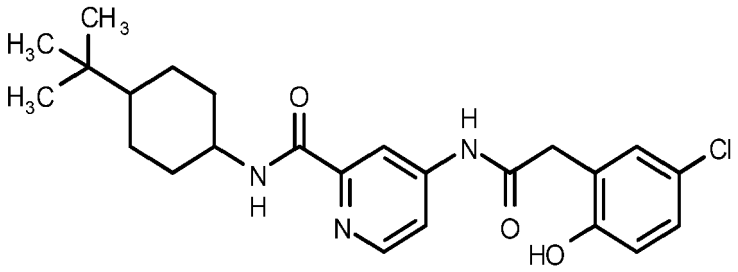
8.10 (s, 1H), 7.81 (dd, J = 5.5, 2.2 Hz, 1H), 7.21 (d, J = 2.7 Hz, 1H), 7.12 (dd, J = 8.6, 2.7 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 3.67 (s, 2H), 2.14-2.05 (m, 2H), 1.70-1.60 (m, 6H), 1.43 (s, 3H).

[0766] LC-MS (Method A): Rt 3.54 mins; MS m/z 388.2/390.2 = [M+H]+ (100% @ 215nm)

Example 39

N-(4-tert-Butylcyclohexyl)-4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (1:1 mixture cis/trans)

[0767]



[0768] 4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxylic acid (Example 31 step 1) (150 mg, 0.49 mmol) and DIPEA (0.26 mL, 1.47 mmol) were suspended in DMF (1.95 mL) and treated with 4-tert-butylcyclohexanamine (1:1 mixture cis/trans) (91 mg, 0.59 mmol) and HATU (223 mg, 0.59 mmol) and the mixture was stirred for 3 hours. The mixture was diluted with EtOAc (10 mL) and the organics were washed with saturated aqueous $NaHCO_3$ (2 x 10 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was dissolved in DMSO:MeCN (800 μl, 1:1), filtered and purified by preparative HPLC (acidic pH, early elution method). The product fractions were combined, neutralised with saturated sodium bicarbonate and extracted with EtOAc (3 x 20 mL). The combined organic extracts where concentrated *in vacuo* to afford the titled compound as a pale yellow solid.

[0769] 1H NMR (500 MHz, DMSO-d6) δ 10.95 - 10.61 (m, 2H), 9.93 - 9.68 (m, 2H), 8.49 (d, J = 5.6 Hz, 1H), 8.46 (d, J = 5.5 Hz, 1H), 8.36 (d, J = 8.7 Hz, 1H), 8.28 (d, J = 7.6 Hz, 1H), 8.21 (d, J = 2.0 Hz, 1H), 8.19 (d, J = 2.1 Hz, 1H), 7.83 (d, J = 2.1 Hz, 1H), 7.81 (d, J = 2.2 Hz, 1H), 7.24 -7.19 (m, 2H), 7.13 (d, J = 2.6 Hz, 1H), 7.12 (d, J = 2.7 Hz, 1H), 6.80 (d, J = 8.6 Hz, 2H), 4.13-4.07 (m, 1H), 3.68 - 3.65 (m, 4H), 1.93- 1.83 (m, 4H), 1.81 -1.73 (m, 2H), 1.69- 1.60 (m, 2H), 1.60-1.51 (m, 2H), 1.42 - 1.33 (m, 2H), 1.24 (s, 1H), 1.17 -1.03 (m, 5H), 1.03-0.97 (m, 1H), 0.89-0.83 (m, 18H). Contains a 1:1 mixture of the cis and trans products.

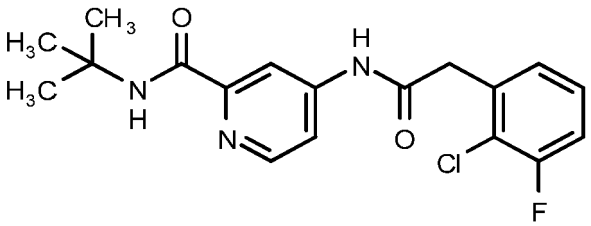
[0770] LC-MS (Method A): Rt 4.34 mins; MS m/z 444.4/446.4 = [M+H]+ (42% @ 215nm)

[0771] LC-MS (Method A): Rt 4.36 mins; MS m/z 444.4/446.4 = [M+H]+ (52% @ 215nm)

Example 40

N-tert-Butyl-4-[[2-(2-chloro-3-fluoro-phenyl)acetyl]amino]pyridine-2-carboxamide

[0772]



[0773] To a solution of 2-(2-chloro-3-fluoro-phenyl)acetic acid (146 mg, 0.78 mmol) in THF (3 mL) was added DIPEA (271 μL, 1.55 mmol), 4-amino-N-tert-butyl-pyridine-2-carboxamide (Example 3 step 1) (100 mg, 0.52 mmol) and HATU (236 mg, 0.62 mmol) and the mixture was stirred at room temperature for 90 mins. The resulting mixture was partitioned between EtOAc (20 mL) and water (20 mL) and the aqueous portion extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed with water (20 mL), brine (20 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The

residue was purified by chromatography on silica eluting with EtOAc in heptane to afford the titled compound as white amorphous solid.

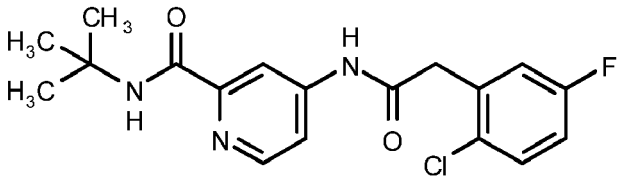
[0774] 1H NMR (500 MHz, Chloroform-d) δ 8.40 (d, J = 5.5 Hz, 1H), 8.18 (dd, J = 5.5, 2.1 Hz, 1H), 8.11 (s, 1H), 8.01 (s, 1H), 7.75 (d, J = 2.1 Hz, 1H), 7.30-7.23 (m, 1H), 7.21 -7.10 (m, 2H), 3.94 (s, 2H), 1.47 (s, 9H).

[0775] LC-MS (Method A): Rt 3.49 mins; MS m/z 364.2/366.2 = [M+H]+ (100%@215)

Example 40.1

N-tert-Butyl-4-[[2-(2-chloro-5-fluoro-phenyl)acetyl]amino]pyridine-2-carboxamide

[0776]



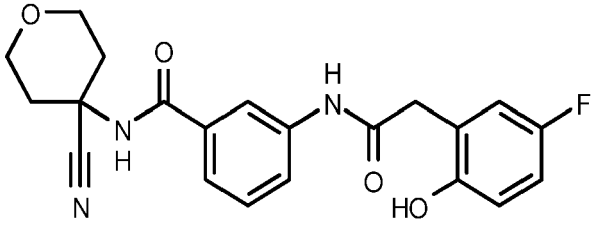
[0777] The titled compound was prepared from 4-amino-N-tert-butyl-pyridine-2-carboxamide (Example 3 step 1) and 2-(2-chloro-5-fluoro-phenyl)acetic acid analogously to Example 40.

[0778] 1H NMR (500 MHz, DMSO-d6) δ 10.90 (s, 1H), 8.46 (d, J = 5.5 Hz, 1H), 8.18 (d, J = 2.1 Hz, 1H), 8.03 (s, 1H), 7.80 (dd, J = 5.5, 2.2 Hz, 1H), 7.51 (dd, J = 8.8, 5.3 Hz, 1H), 7.36 (dd, J = 9.4, 3.1 Hz, 1H), 7.20 (td, J = 8.5, 3.1 Hz, 1H), 3.93 (s, 2H), 1.40 (s, 9H). LC-MS (Method A): Rt 3.51 mins; MS m/z 364 = [M+H]+

Example 41*

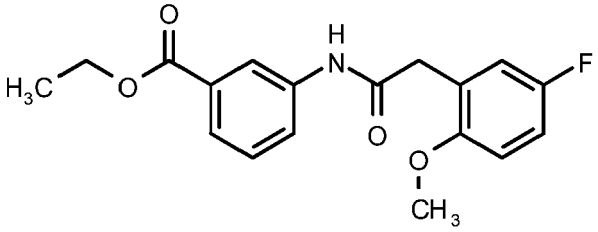
N-(4-Cyanotetrahydropyran-4-yl)-3-[[2-(5-fluoro-2-hydroxy-phenyl)acetyl]amino] benzamide

[0779]



Step 1: Ethyl 3-[[2-(5-fluoro-2-methoxy-phenyl)acetyl]amino]benzoate

[0780]



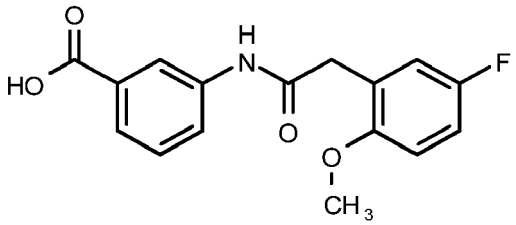
[0781] A mixture of ethyl 3-aminobenzoate (300 mg, 1.82 mmol) and 2-(5-fluoro-2-methoxyphenyl)acetic acid (334 mg, 1.82 mmol) in 1,4-dioxane (5 mL) was treated with 50% T3P® solution in EtOAc (2.31 mL, 1.82 mmol) and TEA (634 μL, 3.63 mmol). After stirring at room temperature for 2 hours, the mixture was partitioned between water (20 mL) and EtOAc (20 mL). The organic layer was separated, dried over Na2SO4 and concentrated *in vacuo*. Purification of the crude residue by chromatography on silica eluting with EtOAc in heptane afforded the titled compound as a white solid.

[0782] 1H NMR (500 MHz, DMSO-d6) δ 10.31 (s, 1H), 8.26 (t, J = 1.8 Hz, 1H), 7.86 -7.82 (m, 1H), 7.63 (dt, J = 7.79, 1.2 Hz, 1H), 7.45 (t, J = 7.9 Hz, 1H), 7.11 (dd, J = 9.2, 3.1 Hz, 1H), 7.07 (td, J = 8.6, 3.2 Hz, 1H), 6.98 (dd, J = 9.0, 4.6 Hz, 1H), 4.31 (q, J = 7.1 Hz, 2H), 3.75 (s, 3H), 3.66 (s, 2H), 1.31 (t, J = 7.1 Hz, 3H).

[0783] LC-MS (Method E): Rt 1.20 mins; MS m/z 332.1 = [M+H]+ (100% @ 215nm)

Step 2: 3-[[2-(5-Fluoro-2-methoxy-phenyl)acetyl]amino]benzoic acid

[0784]

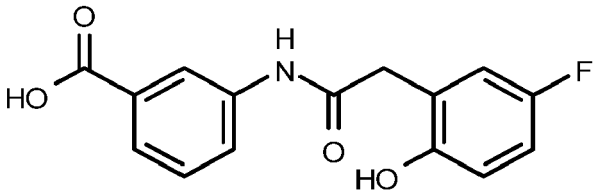


[0785] Ethyl 3-[[2-(5-fluoro-2-methoxy-phenyl)acetyl]amino]benzoate (step 1) (470 mg, 1.42 mmol) in THF (3 mL) and MeOH (1 mL) was treated with 2M aqueous LiOH solution (2.84 mL, 5.67 mmol) and the reaction mixture was stirred at room temperature for 2 hours. The volatile solvents were removed *in vacuo* and the aqueous portion was diluted with water (100 mL) and acidified with 2M HCl solution to pH 2. The resulting precipitate was collected by filtration, washed with water (30 mL) and under vacuum to afford the titled compound as a white solid.

[0786] 1H NMR (500 MHz, DMSO-d6) 5 12.92 (s, 1H), 10.26 (s, 1H), 8.23(t, J = 1.7 Hz, 1H), 7.84 - 7.78 (m, 1H), 7.63-7.58 (m, 1H), 7.42 (t, J = 7.9 Hz, 1H), 7.11 (dd, J = 9.2, 3.1 Hz, 1H), 7.07 (td, J = 8.6, 3.2 Hz, 1H), 6.98 (dd, J = 9.0, 4.7 Hz, 1H), 3.75 (s, 3H), 3.66 (s, 2H). LC-MS (Method E): Rt 1.02 mins; MS m/z 304.0 = [M+H]+ (98% @ 215nm)

Step 3: 3-[[2-(5-Fluoro-2-hydroxy-phenyl)acetyl]amino]benzoic acid

[0787]



[0788] To a solution of 3-[[2-(5-fluoro-2-methoxy-phenyl)acetyl]amino]benzoic acid (step 2)(400 mg, 1.29 mmol) in DCM (5 mL) was added 1M BBr3 in DCM (5.17 mL, 5.17 mmol) the reaction mixture was stirred at room temperature for 3 hours. The resulting mixture was concentrated *in vacuo* and the crude residue was partitioned between water (60 mL) and EtOAc (60 mL). The organic layer was separated, dried over Na_2SO_4 and concentrated in *vacuo* to afford the titled compound as a grey-purple solid.

[0789] 1H NMR (500 MHz, DMSO-d6) δ 12.91 (s, 1H), 10.25 (s, 1H), 9.47 (s, 1H), 8.24 (t, 1.7 Hz, 1H), 7.87 - 7.79 (m, 1H), 7.62 - 7.59 (m, 1H), 7.42 (t, J = 7.9 Hz, 1H), 7.00 (dd, J = 9.4, 3.1 Hz, 1H), 6.89 (td, J = 8.6, 3.2 Hz, 1H), 6.77 (dd, J = 8.8, 4.9 Hz, 1H), 3.62 (s, 2H). LC-MS (Method E): Rt 0.98 mins; MS m/z 290.0= [M+H]+ (89% @ 215nm)

Step 4: N-(4-Cyanotetrahydropyran-4-yl)-3-[[2-(5-fluoro-2-hydroxy-phenyl)acetyl]amino] benzamide

[0790] The titled compound was prepared from 3-[[2-(5-Fluoro-2-hydroxyphenyl)acetyl]amino]benzoic acid (step 3) and 4-aminotetrahydropyran-4-carbonitrile analogously to Example 1.1 step 3.

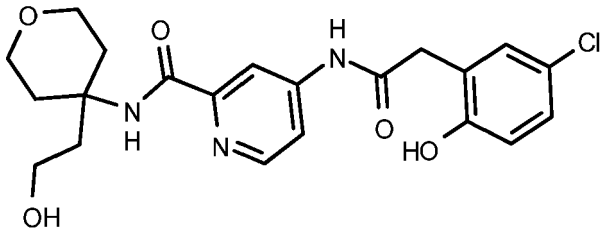
[0791] 1H NMR (500 MHz, DMSO-d6) δ 10.27 (s, 1H), 9.58 (s, 1H), 8.83 (s, 1H), 8.05 (t, J = 1.8 Hz, 1H), 7.86 - 7.79 (m, 1H), 7.52 (d, J = 7.8, 1.3 Hz, 1H), 7.42 (t, J = 7.9 Hz, 1H), 7.00 (dd, J = 9.4, 3.2 Hz, 1H), 6.89 (td, J = 8.6, 3.2 Hz, 1H), 6.78 (dd, J = 8.8, 4.9 Hz, 1H), 3.87 (dt, J = 12.2, 4.0 Hz, 2H), 3.63 (s, 2H), 3.62 - 3.56 (m, 2H), 2.35 - 2.28 (m, 2H), 2.04-1.97 (m, 2H).

[0792] LC-MS (Method A): Rt 2.41 mins; MS m/z 398.2 = [M+H]+ (97% @ 215nm)

Example 42

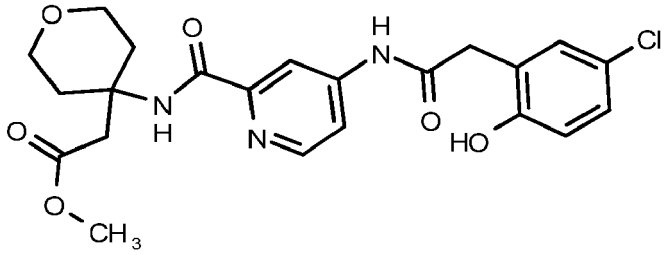
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[4-(2-hydroxyethyl) tetrahydropyran-4-yl]pyridine-2-carboxamide

[0793]



Step 1: Methyl 2-[4-[[4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carbonyl]amino]tetrahydropyran-4-yl]acetate

[0794]



[0795] The titled compound was prepared from methyl 2-(4-aminotetrahydropyran-4-yl)acetate and 4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxylic acid (Example 31 step 1) analogously to Example 33.

[0796] 1H NMR (500 MHz, DMSO-d6) 5 8.47 (d, J = 5.6 Hz, 1H), 8.19-8.17 (m, 2H), 7.81 (dd, J = 5.5, 2.2 Hz, 1H), 7.20 (d, J = 2.6 Hz, 1H), 7.10 (dd, J = 8.6, 2.7 Hz, 1H), 6.78 (d, J = 8.6 Hz, 1H), 3.71 - 3.66 (m, 2H), 3.66 (s, 2H), 3.53 - 3.45 (m, 5H), 2.91 (s, 2H), 2.33 - 2.27 (m, 2H), 1.79 - 1.72 (m, 2H).

[0797] LC-MS (Method E): Rt 1.06 mins; MS m/z 462.1 = [M+H]+ (87% @ 215nm)

Step 2: 4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[4-(2-hydroxyethyl) tetrahydropyran-4-yl]pyridine-2-carboxamide

[0798] A cooled (-78°C) solution of methyl 2-[4-[[4-[[2-(5-chloro-2-hydroxy-phenyl) acetyl]amino]pyridine-2-carbonyl]amino]tetrahydropyran-4-yl]acetate (step 1) (50 mg, 0.11 mmol) in anhydrous THF (2 mL) was treated with 2.4M lithium aluminium hydride in THF (90 μL, 0.22 mmol) and stirred at -78°C for 10 mins. A further portion of 2.4 M lithium aluminium hydride in THF (45 μL, 0.11 mmol) was added and stirring continued at -78°C for 5 minutes. The resulting mixture was allowed to warm to room temperature and stirred for 16 hours. 2M NaOH (3 mL) was added and the mixture was extracted with EtOAc (10 mL). The organic phase was washed with Rochelle Salt solution (2 x 10 mL), dried over Na_2SO_4 and concentrated *in vacuo.* Purification by preparative HPLC (acidic pH, standard elution method) afforded the titled compound as an off-white solid.

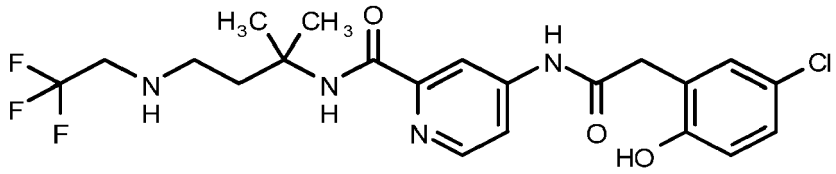
[0799] 1H NMR (500 MHz, DMSO-d6) δ 10.70 (s, 1H), 9.87 (s, 1H), 8.47 (d, J = 5.5 Hz, 1H), 8.18 (d, J = 1.9 Hz, 1H), 8.15 (s, 1H), 7.83 (dd, J = 5.5, 2.2 Hz, 1H), 7.22 (d, J = 2.7 Hz, 1H), 7.12 (dd, J = 8.6, 2.7 Hz, 1H), 6.81 (d, J = 8.6 Hz, 1H), 4.38 (s, 1H), 3.68 - 3.62 (m, 4H), 3.51 - 3.45 (m, 4H), 2.31 - 2.24 (m, 2H), 1.99 (t, J = 7.0 Hz, 2H), 1.68 - 1.61 (m, 2H).

[0800] LC-MS (Method A): Rt 2.32 mins; MS m/z 434.2/434.6 = [M+H]+ (100% @ 215nm)

Example 43

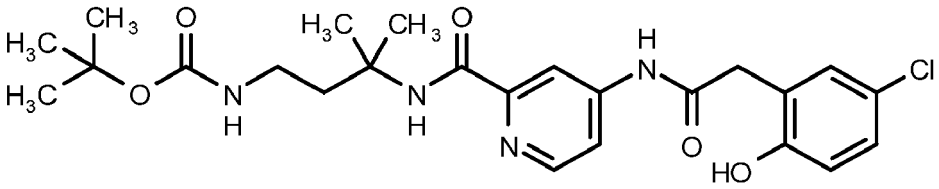
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[1,1-dimethyl-3-(2,2,2-trifluoro ethylamino)propyl] pyridine-2-carboxamide

[0801]



Step 1: tert-Butyl N-[3-[[4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carbonyl]am ino]-3-methyl-butyl]carbamate

[0802]



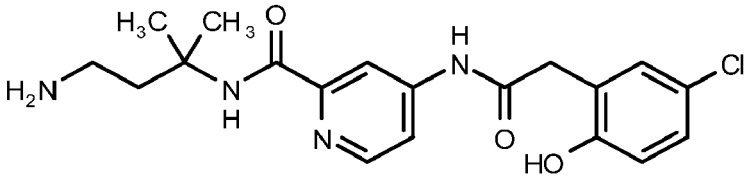
[0803] The titled compound was prepared from tert-butyl N-(3-amino-3-methyl-butyl)carbamate and 4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxylic acid (Example 31 step 1) analogously to Example 33.

[0804] 1H NMR (500 MHz, DMSO-d6) δ = 1.33 (s, 9H), 1.37 (s, 6H), 1.85 - 1.93 (m, 2H), 2.91 - 2.98 (m, 2H), 3.66 (s, 2H), 6.73 (s, 1H), 6.79 (d, J=8.6, 1H), 7.11 (dd, J=8.6, 2.7, 1H), 7.20 (d, J=2.7, 1H), 7.81 (dd, J=5.5, 2.2, 1H), 8.00 (s, 1H), 8.17 (d, J=2.0, 1H), 8.44 (d, J=5.5, 1H), 10.84 (s, 1H).

[0805] LC-MS (Method E): Rt 1.18 mins; MS m/z 491/493 = [M+H]+ (92% @ 215 nm)

Step 2: N-(3-Amino-1,1-dimethyl-propyl)-4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl] am i no]pyridi ne-2-carboxam ide

[0806]



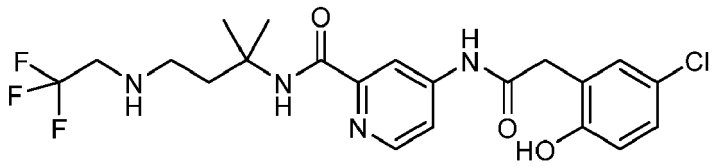
[0807] tert-Butyl N-[3-[[4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carbonyl] amino]-3-methyl-butyl]carbamate (step 1) (302 mg, 0.62 mmol) was dissolved in 20% TFA in DCM (2.0 mL) and the mixture was agitated at room temperature for 18 hours. The resulting mixture was loaded under gravity onto a 2 g Isolute® SCX-2 cartridge washing the column with 1:1 DCM/MeOH (100 mL). The product was eluted with 1:1 DCM/ 1M NH_3 in MeOH (100 mL) to afford the titled compound as a white crystalline solid

[0808] 1H NMR (500 MHz, DMSO-d6) δ 11.13 (s, 1H), 8.59 (s, 1H), 8.42 (d, J = 5.5 Hz, 1H), 8.15 (d, J = 2.1 Hz, 1H), 7.79 (dd, J = 5.5, 2.2 Hz, 1H), 7.18 (d, J = 2.6 Hz, 1H), 7.09 (dd, J = 8.6, 2.7 Hz, 1H), 6.76 (d, J = 8.6 Hz, 1H), 3.65 (s, 2H), 2.65 - 2.63 (m, 2H), 1.83 - 1.77 (m, 2H), 1.39 (s, 6H).

[0809] LC-MS (Method E): Rt 0.86 mins; MS m/z 391.1/393.1 = [M+H]+ (99% @ 215nm)

Step 3: 4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[1,1-dimethyl-3-(2,2,2-trifluoro ethylamino)propyl]pyridine-2-carboxamide

[0810]



[0811] A solution of N-(3-amino-1,1-dimethyl-propyl)-4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl] amino]pyridine-2-carboxamide (step 2) (39 mg, 0.1 mmol) in THF (1 mL) was treated with 2,2,2-trifluoroethyl trifluoromethanesulfonate (0.015 mL, 0.10 mmol) and stirred at room temperature for 16 hours. A further portion of 2,2,2-trifluoroethyl trifluoromethanesulfonate (0.015 mL, 0.10 mmol) was added and the mixture was stirred for a further 2 hours. The reaction mixture was concentrated *in vacuo* and purification of the crude product by chromatography on silica eluting with 75% EtOAc in heptane (isocratic gradient) afforded the titled compound as a white solid.

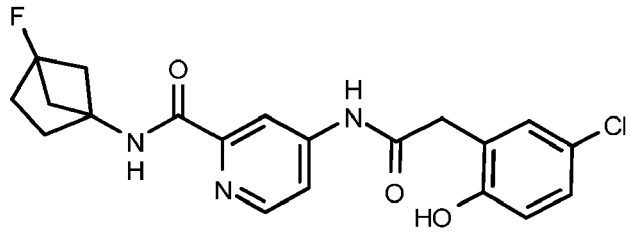
[0812] 1H NMR (500 MHz, DMSO-d6) δ 10.74 (s, 1H), 9.83 (s, 1H), 8.42 (d, J = 5.5 Hz, 1H), 8.36 (s, 1H), 8.15 (d, J = 2.1 Hz, 1H), 7.80 (dd, J = 5.5, 2.2 Hz, 1H), 7.21 (d, J = 2.7 Hz, 1H), 7.11 (dd, J = 8.6, 2.7 Hz, 1H), 6.79 (d, J = 8.6 Hz, 1H), 3.66 (s, 2H), 3.22 - 3.15 (m, 2H), 2.67 - 2.64 (m, 2H), 2.35 - 2.31 (m, 1H), 1.90 - 1.85 (m, 2H), 1.38 (s, 6H).

[0813] LC-MS (Method A): Rt 2.10 mins; MS m/z 473.2/475.2 = [M+H]+ (100% @ 215nm)

Example 44

4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(4-fluoro-1-bicyclo[2.1.1] hexanyl)pyridine-2-carboxamide

[0814]



[0815] To a solution of 4-fluorobicyclo[2.1.1]hexan-1-amine hydrochloride (21 mg, 0.14 mmol), DIPEA (0.09 mL, 0.52 mmol) and 4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino] pyridine-2-carboxylic acid (Example 31 step 1) (40 mg, 0.13 mmol) in DMF (1 mL) was added HATU (55 mg, 0.14 mmol) and the reaction mixture stirred at room temperature for 2 hours. The resulting mixture was diluted with EtOAc (10 mL) and water (10 mL). The organic layer was separated, dried over Na_2SO_4 and concentrated *in vacuo.* The residue was dissolved in DMSO:MeCN:H2O (1.4 mL, 3:3:1), filtered and purified by preparative HPLC (basic pH, early elution method) to afford the titled compound as an off-white solid.

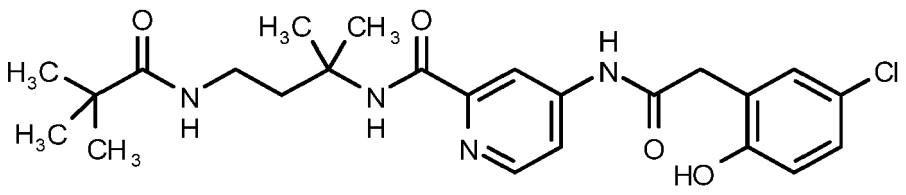
[0816] 1H NMR (500 MHz, Methanol-d4) δ 8.47 (dd, J = 5.5, 0.5 Hz, 1H), 8.14 (dd, J = 1.7, 0.5 Hz, 1H), 7.91 (dd, J = 5.5, 2.2 Hz, 1H), 7.20 (d, J = 2.6 Hz, 1H), 7.11 (dd, J = 8.6, 2.6 Hz, 1H), 6.79 (d, J = 8.6 Hz, 1H), 3.73 (s, 2H), 2.22-2.11 (m, 4H), 2.09-2.05 (dd, 2H), 1.96 - 1.89 (m, 2H).

[0817] LC-MS (Method A): Rt 3.21 mins; MS m/z 404.3/406.3 = [M+H]+ (100% @ 215nm)

Example 45

4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[3-(2,2-dimethylpropanoyl amino)-1, 1-dimethyl-propyl]pyridine-2-carboxamide

[0818]



[0819] The titled compound was prepared from N-(3-amino-1,1-dimethyl-propyl)-4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Example 43 step 2) and 2,2-dimethylpropanoic acid analogously to Example 33.

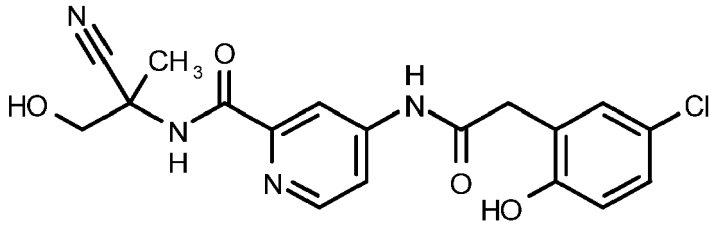
[0820] 1H NMR (500 MHz, DMSO-d6) δ 10.68 (s, 1H), 9.80 (s, 1H), 8.45 (d, J = 5.5 Hz, 1H), 8.19 (d, J = 2.0 Hz, 1H), 8.02 (s, 1H), 7.81 (dd, J = 5.5, 2.2 Hz, 1H), 7.40 (t, J = 5.5 Hz, 1H), 7.22 (d, J = 2.7 Hz, 1H), 7.12 (dd, J = 8.6, 2.7 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 3.67 (s, 2H), 3.12-3.02 (m, 2H), 1.95- 1.87 (m, 2H), 1.39 (s, 6H), 1.04 (s, 9H).

[0821] LC-MS (Method A): Rt 3.0 mins; MS m/z 475.4/477.4 = [M+H]+ (100% @ 215nm)

Example 46

4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1-cyano-2-hydroxy-1-methylethyl)pyridine-2-carboxamide

[0822]



[0823] 4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxylic acid (Example 31 step 1) (120 mg, 0.39 mmol) and DIPEA (273 μL, 1.57 mmol) were suspended in THF (2 mL) and treated with 2-amino-3-hydroxy-2-methyl-propanenitrile hydrochloride (64 mg, 0.47 mmol) followed by HATU (179 mg, 0.47 mmol). After stirring at room temperature for 18 hours, the resulting mixture was partitioned between DCM (10 ml) and water (10 ml). The organic portion was separated, dried over Na_2SO_4, filtered and concentrated *in vacuo.* The residue was purified by chromatography on silica eluting with 0-100% TBME in heptane 0-100% TBME in MeOH. The resulting residue was dissolved in DMSO:MeOH (1200 μl, 1:1) and purified by preparative HPLC (acidic pH, early elution method) and the product fractions were concentrated *in vacuo* to remove the volatile organics. The resulting aqueous mixture was treated with sat. aq. $NaHCO_3$ (3 mL) and DCM (5 ml) and agitated until clear. The organic portion was separated by filtration through a hydrophobic PTFE fritted tube and concentrated *in vacuo* to afford the titled compound as a white crystalline solid.

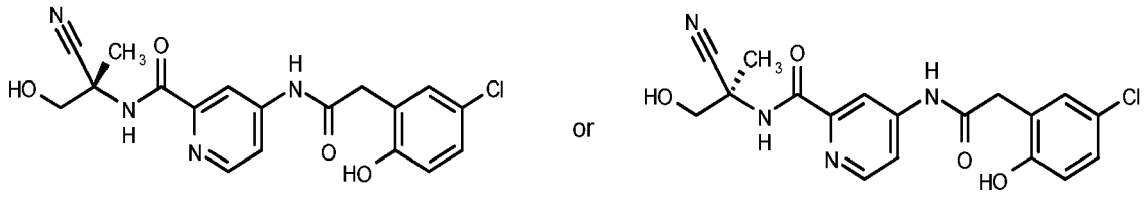
[0824] 1H NMR (500 MHz, DMSO-d6) δ 10.80 (s, 1H), 9.80 (s, 1H), 8.72 (s, 1H), 8.50 (d, J = 5.6 Hz, 1H), 8.23 (d, J = 2.0 Hz, 1H), 7.87 (dd, J = 5.5, 2.2 Hz, 1H), 7.22 (d, J = 2.7 Hz, 1H), 7.12 (dd, J = 8.6, 2.7 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 5.90 (t, J = 5.8 Hz, 1H), 3.81 (dd, J = 10.9, 5.4 Hz, 1H), 3.73 (dd, J = 10.9, 5.2 Hz, 1H), 3.68 (s, 2H), 1.66 (s, 3H).

[0825] LC-MS (Method A): Rt 2.47 mins; MS m/z 389.3/391.2 = [M+H]+ (99% @ 215nm)

[0826] Chiral separation of racemic 4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1-cyano-2-hydroxy-1-methyl-ethyl)pyridine-2-carboxamide using Supercritical Fluid Chromatography [chiral phase column: 25% Ethanol: 75%CO_2 with Chiralpak IC 25cm column at 4ml/min] afforded the individual enantiomers:

Example 46a: 4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[(1S)-1 -cyano-2-hydroxy-1-methyl-ethyl]pyridine-2-carboxamide or 4-[[2-(5-chloro-2-hydroxyphenyl)acetyl]amino]-N-[(1R)-1-cyano-2-hydroxy-1-methyl-ethyl]pyridine-2-carboxamide

[0827]



(S)-isomer

or

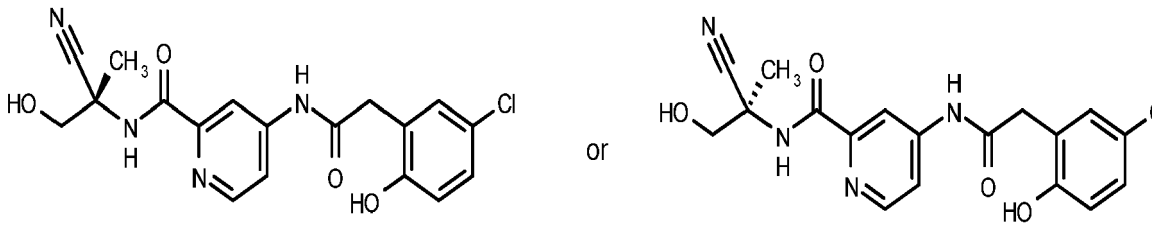
(R)-isomer

First eluted peak: SFC Retention Time = 8.89 mins; MS m/z 389.0/391.0

[0828] 1H NMR (500 MHz, DMSO-d6) δ 10.86 (s, 1H), 9.78 (s, 1H), 8.72 (s, 1H), 8.50 (d, J = 5.5 Hz, 1H), 8.22 (d, J = 2.0 Hz, 1H), 7.86 (dd, J = 5.5, 2.2 Hz, 1H), 7.21 (d, J = 2.7 Hz, 1H), 7.11 (dd, J = 8.6, 2.7 Hz, 1H), 6.79 (d, J = 8.6 Hz, 1H), 5.90 (t, J = 5.1 Hz, 1H), 3.81 (dd, J = 11.0, 4.6 Hz, 1H), 3.73 (dd, J = 11.3, 4.7 Hz, 1H), 3.67 (s, 2H), 1.66 (s, 3H). 100% e.e

Example 46b: 4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[(1S)-1-cyano-2-hydroxy-1-methyl-ethyl]pyridine-2-carboxamide or 4-[[2-(5-chloro-2-hydroxyphenyl)acetyl]amino]-N-[(1R)-1-cyano-2-hydroxy-1-methyl-ethyl]pyridine-2-carboxamide

[0829]



(S)-isomer (R)-isomer

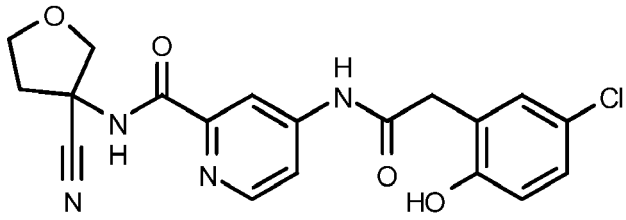
Second eluted peak: SFC Retention Time = 10.84 mins; MS m/z 389.0/391.0

[0830] 1H NMR (500 MHz, DMSO-d6) δ 10.98 (s, 1H), 9.82 (s, 1H), 8.72 (s, 1H), 8.50 (d, J = 5.5 Hz, 1H), 8.22 (d, J = 2.0 Hz, 1H), 7.86 (dd, J = 5.5, 2.1 Hz, 1H), 7.20 (d, J = 2.5 Hz, 1H), 7.10 (dd, J = 8.5, 2.7 Hz, 1H), 6.78 (d, J = 8.7 Hz, 1H), 5.90 (s, 1H), 3.82 (dd, J = 10.7, 3.3 Hz, 1H), 3.73 (dd, J = 10.4, 2.9 Hz, 1H), 3.67 (s, 2H), 1.66 (s, 3H). 88% e.e.

Example 47

4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(3-cyanotetrahydrofuran-3-yl)pyridine-2-carboxam ide

[0831]



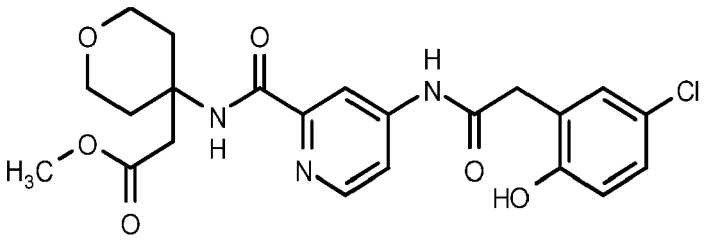
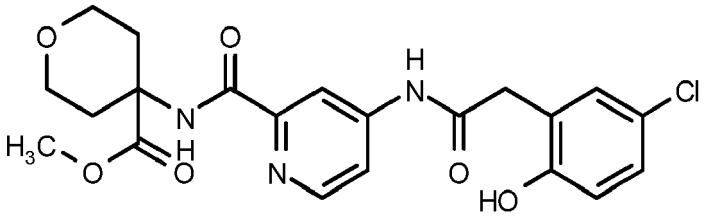
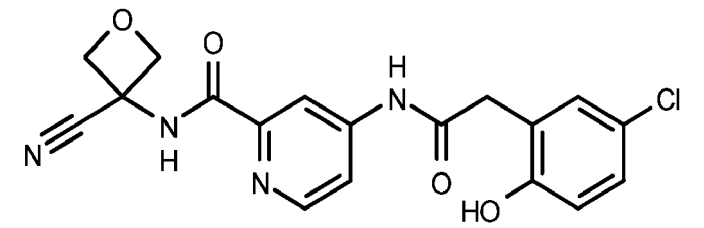
[0832] To a mixture comprising 3-aminotetrahydrofuran-3-carbonitrile hydrochloride (31 mg, 0.21 mmol) and 4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxylic acid (Example 31 step 1) (60 mg, 0.18 mmol, 90%) in DMF (2 mL) was added EDCI (74 mg, 0.39 mmol), HOAt (53 mg, 0.39 mmol) and DIPEA (123 μL, 0.7 mmol). The reaction mixture was stirred at room temperature for 30 minutes. The resulting mixture was diluted with water (10 mL) then acidified with 10% citric acid aqueous solution to pH 4 and extracted with DCM (10 mL). The organic layer was separated using a PTFE fritted tube and concentrated *in vacuo*. The crude residue was purified by preparative HPLC (acidic pH, early elution method) and the product fractions were freeze-dried to afford the titled compound as a white solid.

[0833] 1H NMR (500 MHz, DMSO-d6) δ 10.75 (s, 1H), 9.85 (s, 1H), 9.51 (s, 1H), 8.53 (d, J = 5.5 Hz, 1H), 8.22 (d, J = 1.9 Hz, 1H), 7.88 (dd, J = 5.5, 2.2 Hz, 1H), 7.22 (d, J = 2.7 Hz, 1H), 7.13 (dd, J = 8.6, 2.7 Hz, 1H), 6.81 (d, J = 8.6 Hz, 1H), 4.27 (d, J = 9.5 Hz, 1H), 4.04 (d, J = 9.5 Hz, 1H), 3.97-3.91 (m, 1H), 3.90-3.84 (m, 1H), 3.68 (s, 2H), 2.74-2.67 (m, 1H), 2.65-2.58 (m, 1H).

[0834] LC-MS (Method A): Rt 2.68 mins; MS m/z 401.1/403.1 = [M+H]+ (98% @ 215nm)

[0835] The compounds of the following tabulated Examples (Table 12) were prepared analogously to Example 47 by replacing 3-aminotetrahydrofuran-3-carbonitrile hydrochloride with the appropriate commercially available amine.

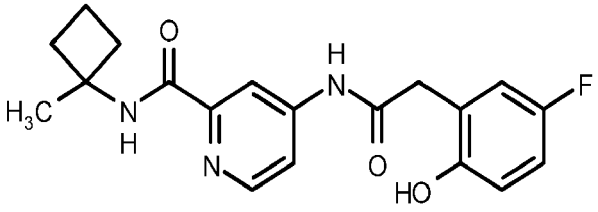
Table 12

Ex.	Structure and Name	1H NMR LCMS Retention Time, [M+H]+,
47.1	 Methyl2-[4-[[4-[[2-(5-chloro-2-hydroxy-phenyl) acetyl]amino]pyridine-2-carbonyl]amino]tetrahydropyran-4-yl]acetate	1H NMR (500 MHz, DMSO-d6) δ 10.71 (s, 1H), 9.84 (s, 1H), 8.49 (d, J = 5.5 Hz, 1H), 8.19 (m, 2H), 7.83 (dd, J = 5.5, 2.2 Hz, 1H), 7.23 (d, J = 2.6 Hz, 1H), 7.13 (dd, J = 8.6, 2.7 Hz, 1H), 6.81 (d, J = 8.6 Hz, 1H), 3.72 - 3.67 (m, 4H), 3.54 - 3.48 (m, 5H), 2.92 (s, 2H), 2.35 - 2.28 (m, 2H), 1.80 - 1.72 (m, 2H). LC-MS (Method A): Rt 2.80 mins; MS m/z 462.2/464.1 = [M+H]+ (98% @ 215nm)
47.2	 Methyl 4-[[4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl] amino]pyridine-2-carbonyl] amino]tetrahydropyran-4-carboxylate	1H NMR (500 MHz, DMSO-d6) δ 10.69 (s, 1H), 9.81 (s, 1H), 8.77 (s, 1H), 8.52 (d, J = 5.5 Hz, 1H), 8.16 (d, J = 2.0 Hz, 1H), 7.84 (dd, J = 5.5, 2.1 Hz, 1H), 7.22 (d, J = 2.7 Hz, 1H), 7.12 (dd, J = 8.6, 2.7 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 3.71 (dt, J = 11.7, 4.1 Hz, 2H), 3.67 (s, 2H), 3.61 (s, 3H), 3.60 - 3.55 (m, 2H), 2.13 - 2.08 (m, 2H), 2.06 - 1.99 (m, 2H). LC-MS (Method A): Rt 2.72 mins; MS m/z 448.2/450.2 = [M+H]+ (100% @ 215nm)
47.3	 4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(3-cyanooxetan-3-yl)pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.77 (br. s, 1H), 10.07 (s, 1H), 9.84 (br. s, 1H), 8.54 (d, J = 5.6 Hz, 1H), 8.22 (d, J = 1.9 Hz, 1H), 7.89 (dd, J = 5.5, 2.2 Hz, 1H), 7.22 (d, J = 2.7 Hz, 1H), 7.12 (dd, J = 8.6, 2.7 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 4.94 (d, J = 7.6 Hz, 2H), 4.84 (d, J = 7.6 Hz, 2H), 3.68 (s, 2H). LC-MS (Method A): Rt 2.59 mins; MS m/z 387.1/389.1 = [M+H]+ (98% @ 215nm)

Example 48

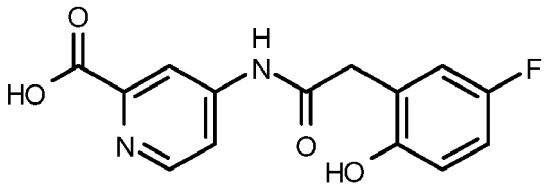
4-[[2-(5-Fluoro-2-hydroxy-phenyl)acetyl]amino]-N-(1-methylcyclobutyl)pyridine-2-carboxamide

[0836]



Steps 1-3: 4-[[2-(5-Fluoro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxylic acid

[0837]



[0838] The titled compound was prepared from methyl 4-aminopyridine-2-carboxylate and 2-(5-fluoro-2-methoxyphenyl)acetic acid analogously to Example 41 steps 1-3.

[0839] 1H NMR (500 MHz, DMSO-d6) δ 10.72 (s, 1H), 9.51 (s, 1H), 8.52 (d, J = 5.5 Hz, 1H), 8.28 (d, J = 1.7 Hz, 1H), 7.81 (dd, J = 5.5, 1.7 Hz, 1H), 7.02 (dd, J = 9.2, 3.0 Hz, 1H), 6.91 (td, J = 8.6, 3.1 Hz, 1H), 6.77 (dd, J = 8.8, 4.9 Hz, 1H), 3.67 (s, 2H).

[0840] LC-MS (Method E): Rt 0.76 mins; MS m/z 291.0 = [M+H]+ (84% @ 215nm)

Step 4: 4-[[2-(5-Fluoro-2-hydroxy-phenyl)acetyl]amino]-N-(1-methylcyclobutyl)pyridine-2-carboxamide

[0841] The titled compound was prepared from 4-[[2-(5-fluoro-2-hydroxyphenyl)acetyl]amino]pyridine-2-carboxylic acid (steps1-3) and 1-methylcyclobutanamine hydrochloride analogously to Example 47.

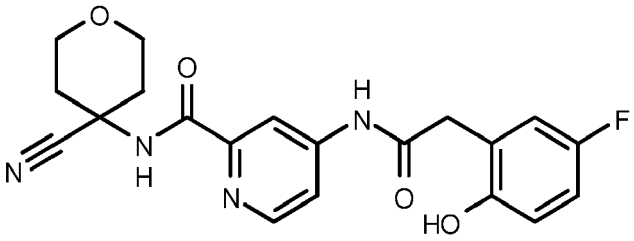
[0842] 1H NMR (500 MHz, DMSO-d6) δ 10.67 (s, 1H), 9.50 (s, 1H), 8.48 (s, 1H), 8.45 (d, J = 5.5 Hz, 1H), 8.16 (d, J = 2.1 Hz, 1H), 7.83 (dd, J = 5.5, 2.2 Hz, 1H), 7.01 (dd, J = 9.4, 3.2 Hz, 1H), 6.91 (td, J = 8.6, 3.2 Hz, 1H), 6.77 (dd, J = 8.8, 4.9 Hz, 1H), 3.67 (s, 2H), 2.43 - 2.35 (m, 2H), 2.03 - 1.96 (m, 2H), 1.84 - 1.77 (m, 2H), 1.47 (s, 3H).

[0843] LC-MS (Method A): Rt 3.00 mins; MS m/z 358.2/359.2 = [M+H]+ (95% @ 215nm)

Example 48.1

N-(4-Cyanotetrahydropyran-4-yl)-4-[[2-(5-fluoro-2-hydroxy-phenyl)acetyl]amino] pyridine-2-carboxamide

[0844]



[0845] The titled compound was prepared from 4-[[2-(5-fluoro-2-hydroxyphenyl)acetyl]amino]pyridine-2-carboxylic acid (Example 48, steps1-3) and 4-aminotetrahydropyran-4-carbonitrile analogously to Example 47.

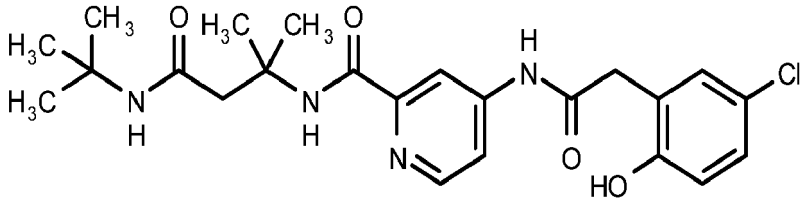
[0846] 1H NMR (500 MHz, DMSO-d6) δ 10.75 (s, 1H), 9.50 (s, 1H), 9.01 (s, 1H), 8.53 (d, J = 5.8 Hz, 1H), 8.24 (d, J = 1.8 Hz, 1H), 7.88 (dd, J = 5.5, 2.2 Hz, 1H), 7.03 (dd, J = 9.4, 3.2 Hz, 1H), 6.92 (td, J = 8.6, 3.2 Hz, 1H), 6.78 (dd, J = 8.8, 4.9 Hz, 1H), 3.87 (dt, J = 12.2, 3.8 Hz, 2H), 3.69 (s, 2H), 3.63 - 3.56 (m, 2H), 2.41 - 2.35 (m, 2H), 2.12 - 2.04 (m, 2H).

[0847] LC-MS (Method A): Rt 2.45 mins; MS m/z 399.2/400.2 = [M+H]+ (99% @ 215nm)

Example 49

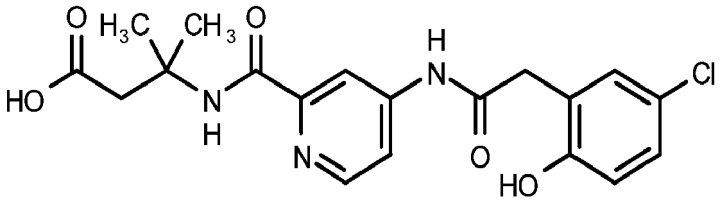
N-[3-(tert-Butylamino)-1,1-dimethyl-3-oxo-propyl]-4-[[2-(5-chloro-2-hydroxy-phenyl) acetyl]amino]pyridine-2-carboxamide

[0848]



Step 1: 3-[[4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carbonyl]amino]-3-methyl-butanoic acid

[0849]



[0850] A solution of ethyl 3-[[4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carbonyl]amino]-3-methyl-butanoate (Example 35.13)(688 mg, 1.57 mmol) in THF (7.5 mL) was treated with 2M aqueous sodium hydroxide (1.57 mL, 3.14 mmol) and the reaction mixture was stirred at room temperature for 2 hours. The resulting mixture was partitioned between DCM (25 ml) and water (10 mL) and 2M aqueous $KHSO_4$ (10 mL) was added.

[0851] The biphasic solution agitated until clarification of the solution. The organic layer was separated, dried over Na_2SO_4 and concentrated *in vacuo* to afford titled compound as a yellow viscous gel.

[0852] 1H NMR (500 MHz, DMSO-d6) δ = 12.21 (s, 1H), 10.67 (s, 1H), 9.80 (s, 1H), 8.44 (d, J=5.5, 1H), 8.39 (s, 1H), 8.17 (d, J=2.0, 1H), 7.81 (dd, J=5.5, 2.2, 1H), 7.22 (d, J=2.7, 1H), 7.12 (dd, J=8.6, 2.7, 1H), 6.79 (t, J=8.6, 1H), 3.67 (s, 2H), 2.73 (s, 2H), 1.48 (s, 6H). LC-MS (Method E): Rt 1.04 mins; MS m/z 406.2/408.1 = [M+H]+ (83% @ 215nm)

Step 2: N-[3-(tert-Butylamino)-1,1-dimethyl-3-oxo-propyl]-4-[[2-(5-chloro-2-hydroxyphenyl) acetyl]amino]pyridine-2-carboxamide

[0853] 3-[[4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carbonyl]amino]-3-methylbutanoic acid (step 1)(120 mg, 0.39 mmol) and DIPEA (205 μL, 1.17 mmol) were suspended in THF (2 mL) and treated with 2-methylpropan-2-amine (62 μL, 0.59 mmol) followed by HATU (179 mg, 0.47 mmol). The resulting mixture was stirred at room temperature for 42 hours and then partitioned between DCM (10 ml) and water (10 ml). The organic portion was separated by filtration through a hydrophobic PTFE fritted tube and concentrated *in vacuo.* Purification of the residue by preparative HPLC (acidic pH, early elution method) afforded the titled compound as a white crystalline solid.

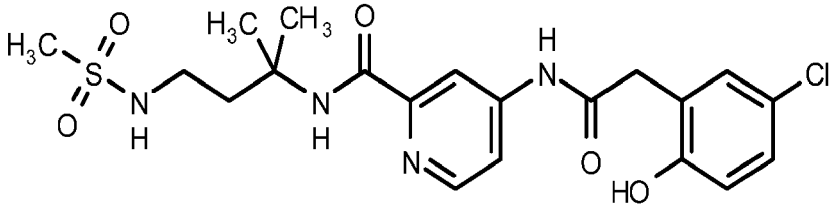
[0854] 1H NMR (500 MHz, DMSO-d6) δ 10.68 (s, 1H), 9.05 (s, 1H), 8.46 (d, J = 5.5 Hz, 1H), 8.28 (s, 1H), 8.19 (d, J = 2.0 Hz, 1H), 7.80 (dd, J = 5.5, 2.2 Hz, 1H), 7.59 (s, 1H), 7.22 (d, J = 2.7 Hz, 1H), 7.13 (dd, J = 8.6, 2.7 Hz, 1H), 6.81 (d, J = 8.6 Hz, 1H), 3.68 (s, 2H), 2.38 (s, 2H), 1.45 (s, 6H),

[0855] LC-MS (Method A): Rt 3.16 mins; MS m/z 461.3/463.3 = [M+H]+ (99% @ 215nm)

Example 50

4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[3-(methanesulfonamido)-1,1-dimethyl -propyl]pyridine-2-carboxamide

[0856]



[0857] A solution of N-(3-amino-1,1-dimethyl-propyl)-4-[[2-(5-chloro-2-hydroxyphenyl)acetyl]amino]pyridine-2-carboxamide (Example 43, step 2)(76 mg, 0.19 mmol) in THF (0.5 mL) was treated with K_2CO_3 (54 mg, 0.39 mmol) and the reaction mixture was stirred at room temperature. A solution of methane sulfonyl chloride (63.2 μL in 1000 μL in THF) was prepared and a 250 μL aliquot was added dropwise to the reaction mixture and stirred for 1 hour at room temperature. The resulting mixture was partitioned between DCM and water (8 mL 1:1) and the organic portion was separated by filtration through a hydrophobic PTFE fritted tube and concentrated *in vacuo.* The residue was dissolved in DMSO:MeOH (1200 μl, 1:1) and purified by (acidic pH, early elution method) and the first major product peak fractions were concentrated *in vacuo.* The resulting turbid aqueous mixture was treated with saturated aqueous $NaHCO_3$ (3 mL) and DCM (5 mL) and the biphasic solution was agitated until a clear biphasic solution was obtained. The organic portion was separated by filtration through a hydrophobic PTFE fritted tube and concentrated *in vacuo* to afford the titled compound as a white crystalline solid

[0858] 1H NMR (500 MHz, DMSO-d6) δ = 10.79 (s, 1H), 9.82 (s, 1H), 8.45 (d, J=5.5, 1H), 8.18 (d, J=1.9, 1H), 8.04 (s, 1H), 7.81 (dd, J=5.5, 2.2, 1H), 7.21 (d, J=2.7, 1H), 7.12 (dd, J=8.6, 2.7, 1H), 6.92 (t, J=5.8, 1H), 6.79 (d, J=8.6, 1H), 3.66 (s, 2H), 2.95 (dt, J=10.9, 5.9, 2H), 2.86 (s, 3H), 1.97 - 2.06 (m, 2H), 1.38 (s, 6H).

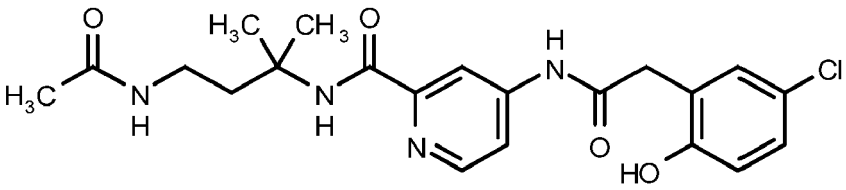
[0859] LC-MS (Method A): Rt 2.73 mins; MS m/z 469.2/471.2 = [M+H]+ (99% @ 215nm)

Example 51

N-(3-Acetamido-1,1-dimethyl-propyl)-4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]

amino]pyridine-2-carboxamide

[0860]



[0861] A solution of N-(3-amino-1,1-dimethyl-propyl)-4-[[2-(5-chloro-2-hydroxy-phenyl) acetyl]amino]pyridine-2-carboxamide; 2,2,2-trifluoroacetic acid (TFA salt of Example 43, step 2) (100 mg, 0.16 mmol) in THF (2.5 mL) was treated with DIPEA (113 μL, 0.65 mmol) followed by acetic anhydride (17 μL, 0.18 mmol) and the mixture was stirred at room temperature for 6 hours. 1M aqueous NaOH (0.5 mL) was added and stirring continued at room temperature for 1 hour. Further 1M aqueous NaOH (0.5 mL) was added followed by MeOH (~0.25 mL) and the mixture was stirred overnight. The resulting mixture was partitioned between DCM (5 mL) and water (3 mL) and the organic portion was separated. The aqueous layer was concentrated *in vacuo* and the crude residue was dissolved in 1:1 DCM/MeOH and purified by chromatography on silica eluting with 0-100% TBME in heptane followed by MeOH in TBME to afford the titled compound as a clear white crystalline solid.

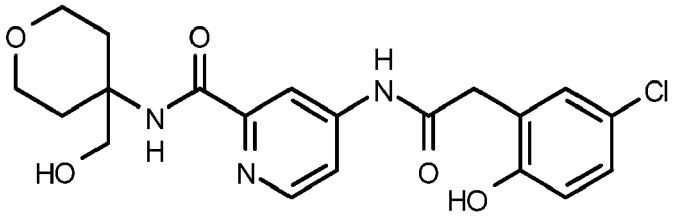
[0862] 1H NMR (500 MHz, DMSO-d6) δ = 8.40 (d, J=5.5, 1H), 8.11 (d, J=1.8, 1H), 8.02 (s, 1H), 7.81-7.79 (m, 1H), 7.75 (dd, J=5.5, 2.1, 1H), 7.08 (s, 1H), 7.00 (d, J=8.2, 1H), 6.64 (d, J=8.1, 1H), 4.09 (s, 1H), 3.58 (s, 2H), 3.00 - 3.09 (m, 2H), 1.88 - 1.95 (m, 2H), 1.73 (s, 3H), 1.38 (s, 6H).

[0863] LC-MS (Method A): Rt 2.51 mins; MS m/z 433.3/435.3 = [M+H]+ (97% @ 215nm)

Example 53

4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[4-(hydroxymethyl)tetrahydro pyran-4-yl]pyridine-2-carboxamide

[0864]



[0865] To a cooled (-78°C) solution of methyl 4-[[4-[[2-(5-chloro-2-hydroxyphenyl)acetyl]amino]pyridine-2-carbonyl]amino]tetrahydropyran-4-carboxylate (Example 47.2) (52 mg,0.1161 mmol) in THF (1.5 mL) under a nitrogen atmosphere was added dropwise a solution of 2.4M lithium aluminium hydride in THF (97 μL, 0.23 mmol). After stirring at -78°C for 45 minutes, the mixture was allowed to warm to room temperature and stirred for 1 hour. The solvent was removed *in vacuo* and purification by preparative HPLC (acidic pH, early elution method) afforded the titled compound as a white solid.

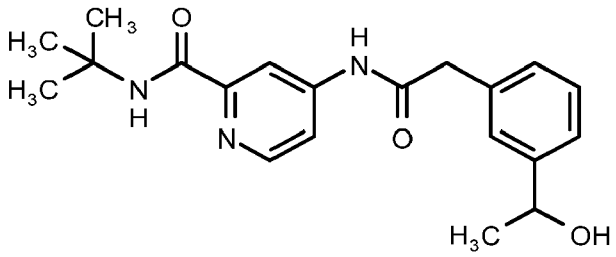
[0866] 1H NMR (500 MHz, DMSO-d6) δ 10.70 (s, 1H), 9.87 (s, 1H), 8.47 (d, J = 5.5 Hz, 1H), 8.19 (d, J = 2.0 Hz, 1H), 8.06 (s, 1H), 7.82 (dd, J = 5.5, 2.2 Hz, 1H), 7.22 (d, J = 2.7 Hz, 1H), 7.12 (dd, J = 8.6, 2.7 Hz, 1H), 6.81 (d, J = 8.6 Hz, 1H), 4.89 (s, 1H), 3.71 - 3.65 (m, 4H), 3.62 (s, 2H), 3.54 - 3.47 (m, 2H), 2.23 - 2.16 (m, 2H), 1.66 (ddd, J = 14.0, 10.2, 4.2 Hz, 2H).

[0867] LC-MS (Method A): Rt 2.33 mins; MS m/z 420.1/422.1 = [M+H]+ (98% @ 215nm)

Example 54

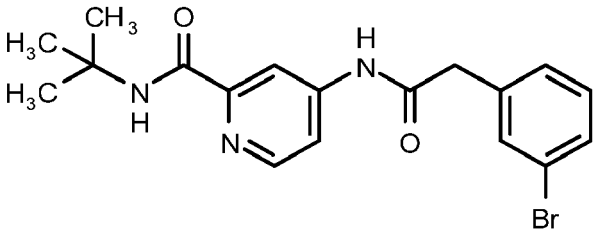
N-tert-Butyl-4-[[2-[3-(1-hydroxyethyl)phenyl]acetyl]amino]pyridine-2-carboxamide

[0868]



Step 1: 4-[[2-(3-Bromophenyl)acetyl]amino]-N-tert-butyl-pyridine-2-carboxamide

[0869]

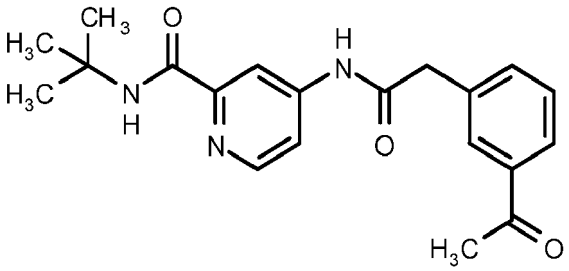


[0870] The titled compound was prepared from 2-(3-bromophenyl)acetic acid and 4-amino-N-tert-butyl-pyridine-2-carboxamide (Example 3 step 1) analogously to Example 21.

[0871] 1H NMR (250 MHz, DMSO-d6) δ 10.77 (s, 1H), 8.45 (d, J = 5.5 Hz, 1H), 8.17 (d, J = 1.9 Hz, 1H), 8.02 (s, 1H), 7.80 (dd, J = 5.5, 2.2 Hz, 1H), 7.57 - 7.54 (m, 1H), 7.47 (dt, J = 6.9, 2.1 Hz, 1H), 7.36 - 7.27 (m, 2H), 3.75 (s, 2H), 1.39 (s, 9H).
[0872] LC-MS (Method E): Rt 1.23 mins; MS m/z 390.1/392.1 = [M+H]+(98% @ 215 nm)

Step 2: 4-[[2-(3-Acetylphenyl)acetyl]amino]-N-tert-butyl-pyridine-2-carboxamide

[0873]



[0874] A solution of 4-[[2-(3-bromophenyl)acetyl]amino]-N-tert-butyl-pyridine-2-carboxamide (step 1)(200 mg, 0.51 mmol), 1-vinyloxybutane (332 μL, 2.56 mmol), triphenylphosphine (27 mg, 0.1 mmol) and TEA (107 μL, 0.61 mmol) in MeCN (1 mL) was degassed with nitrogen and treated with $Pd(OAc)_2$ (12 mg, 0.05 mmol). The mixture was sealed and heated at 100 °C overnight. Further portions of 1-vinyloxybutane (332 μL, 2.56 mmol), TEA (107 μL, 0.61 mmol), triphenylphosphine (27 mg, 0.1 mmol) and $Pd(OAc)_2$ (12 mg, 0.05 mmol) were added and heating continued at 100 °C for a further 8 hours. The resulting mixture was filtered through Celite® and washed with EtOAc. The filtrate was absorbed onto silica and purification by chromatography eluting with 0-100% EtOAc in heptane afforded the titled compound as an orange glassy solid.
[0875] 1H NMR (250 MHz, Chloroform-d) δ 8.34 (d, J = 5.6Hz, 1H), 8.11 (dd, J = 5.5, 2.3 Hz, 1H), 7.90 - 7.84 (m, 2H), 7.59 (s, 1H), 7.50 - 7.43 (m, 2H), 3.77 (s, 2H), 2.56 (s, 3H), 1.39 (s, 9H).
[0876] LC-MS (Method E): Rt 1.13 mins; MS m/z 354.1 = [M+H]+ (93% @ 215nm)

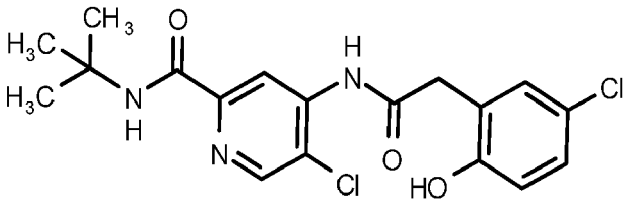
Step 3: N-tert-Butyl-4-[[2-[3-(1-hydroxyethyl)phenyl]acetyl]amino]pyridine-2-carboxamide

[0877] To a solution of 4-[[2-(3-acetylphenyl)acetyl]amino]-N-tert-butyl-pyridine-2-carboxamide (step 2) (45 mg, 0.12 mmol) in methanol (1 mL) at 0 °C was added $NaBH_4$ (4.5 mg, 0.12 mmol) and the mixture was allowed to warm to room temperature. After stirring for 1 hour, the reaction was quenched by addition of 3 drops of sat. $NaHCO_3$ solution and purification by preparative HPLC (acidic pH, standard elution method) afforded the titled compound as a colourless powder.
[0878] 1H NMR (500 MHz, Methanol-d4) δ 8.42 (d, J = 5.5 Hz, 1H), 8.14 (d, J = 2.1 Hz, 1H), 7.89 (dd, J = 5.5, 2.2 Hz, 1H), 7.37 (s, 1H), 7.33 - 7.22 (m, 3H), 4.85-4.79 (m , 1H), 3.74 (s, 2H), 1.47 (s, 9H), 1.43 (d, J = 6.5 Hz, 3H).
[0879] LC-MS (Method A): Rt 2.77 mins; MS m/z 356.3 = [M+H]+

Example 55

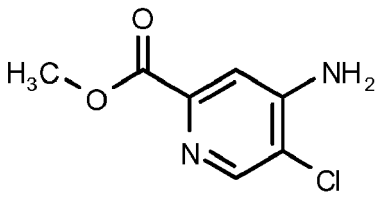
N-tert-Butyl-5-chloro-4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide

[0880]



Step 1: Methyl 4-amino-5-chloro-pyridine-2-carboxylate

[0881]

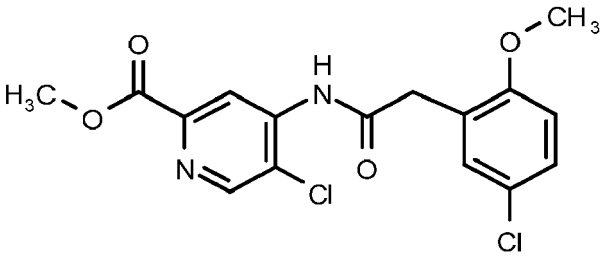


[0882] NCS (483 mg, 3.61 mmol) was added to a solution of methyl 4-aminopyridine-2-carboxylate (500 mg, 3.29 mmol) in DMF (10 mL) and the reaction mixture was stirred at 60°C overnight. The resulting mixture was diluted with EtOAc (50 mL) and washed with water (2 × 50 mL), brine (2 × 50 mL), dried over sodium sulfate and concentrated *in vacuo.* The resulting crude residue was purified by chromatography on KP-NH silica eluting 0-10% MeOH in DCM. The mixed fractions were combined and concentrated *in vacuo.* The resulting crude residue was further purified by chromatography on KP-NH silica eluting 0-100% EtOAc in heptane to afford the titled compound as a light pink solid.

[0883] 1H NMR (250 MHz, DMSO-d6) δ 8.22 (s, 1H), 7.42 (s, 1H), 6.68 (s, 2H), 3.82 (s, 3H). LC-MS (Method C): Rt 1.61 mins; MS m/z 186.8/188.8 = [M+H]+ (90% @ 215nm)

Step 2: Methyl 5-chloro-4-[[2-(5-chloro-2-methoxy-phenyl)acetyl]amino]pyridine-2-carboxylate

[0884]



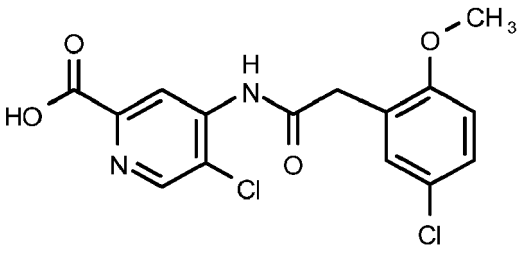
[0885] To a solution of 2-(5-chloro-2-methoxy-phenyl)acetic acid (106 mg, 0.53 mmol) and methyl 4-amino-5-chloro-pyridine-2-carboxylate (step 1) (100. mg, 0.48 mmol) in 1,4-dioxane (5 mL) was added TEA (0.17 mL, 0.96 mmol) followed by 50% T3P® solution in EtOAc (0.57 mL, 0.96 mmol). The resulting mixture was stirred at room temperature under an inert atmosphere overnight. The reaction mixture was diluted with EtOAc (20 mL) and washed with water (2 × 10 mL) and brine (10 mL). The organic portion was dried over Na_2SO_4 and concentrated *in vacuo.* The crude residue was purified by chromatography on silica eluting with 0-100% EtOAc in heptane to afford the titled compound as a white solid.

[0886] 1H NMR (250 MHz, DMSO-d6) δ 9.94 (s, 1H), 8.77 (s, 1H), 8.72 (s, 1H), 7.36 - 7.29 (m, 2H), 7.06 - 6.99 (m, 1H), 3.88 (s, 2H), 3.86 (s, 3H), 3.78 (s, 3H).

[0887] LC-MS (Method E): Rt 1.15 mins; MS m/z 369.0/371.0 = [M+H]+ (91% @ 215nm)

Step 3: 5-Chloro-4-[[2-(5-chloro-2-methoxy-phenyl)acetyl]amino]pyridine-2-carboxylic acid

[0888]



[0889] A solution of methyl 5-chloro-4-[[2-(5-chloro-2-methoxy-phenyl)acetyl]amino]pyridine-2-carboxylate (step 2)(106 mg, 0.26 mmol) in THF (3 mL) was treated with 1M NaOH (392 μL, 0.39 mmol) and stirred at room temperature for 2 hours. The resulting mixture was concentrated *in vacuo* and the residue dissolved in water (15 mL). The pH of was

adjusted to pH 5 by addition of 1M HCl and the resulting precipitate filtered and dried in a vacuum oven at 40°C to afford the titled compound as a white solid.

[0890] 1H NMR (250 MHz, DMSO-d6) δ 13.33 (br. s, 1H), 9.90 (s, 1H), 8.75 (s, 1H), 8.71 (s, 1H), 7.36 - 7.30 (m, 2H), 7.07 - 7.01 (m, 1H), 3.88 (s, 2H), 3.79 (s, 3H).

[0891] LC-MS (Method E): Rt 1.05 mins; MS m/z 355.0/357.0 = [M+H]+ (79% @ 215nm)

Step 4-5: N-tert-Butyl-5-chloro-4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide

[0892] The titled compound was prepared from 5-chloro-4-[[2-(5-chloro-2-methoxyphenyl)acetyl]amino]pyridine-2-carboxylic acid (step 3) and 2-methylpropan-2-amine analogously to Example 32, steps 1 and 2.

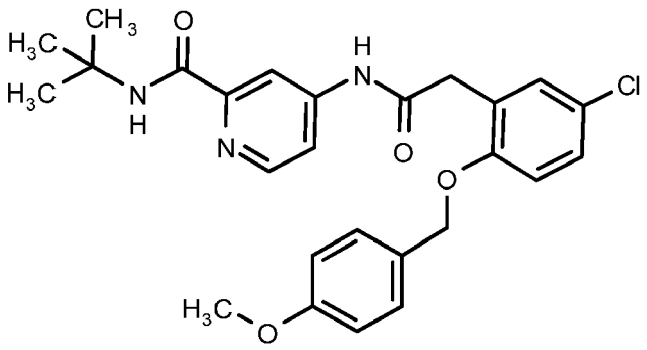
[0893] 1H NMR (500 MHz, DMSO-d6) δ 10.30-9.70 (m, 2H), 8.74 (s, 1H), 8.61 (s, 1H), 7.94 (s, 1H), 7.26 (d, J = 2.7 Hz, 1H), 7.15 (dd, J = 8.6, 2.7 Hz, 1H), 6.84 (d, J = 8.6 Hz, 1H), 3.81 (s, 2H), 1.39 (s, 9H).

[0894] LC-MS (Method A): Rt 3.64 mins; MS m/z 396.2/398.2 = [M+H]+ (97% @ 215nm)

Example 56

N-tert-Butyl-4-[[2-[5-chloro-2-[(4-methoxyphenyl)methoxy]phenyl]acetyl] amino]pyridine-2-carboxamide

[0895]



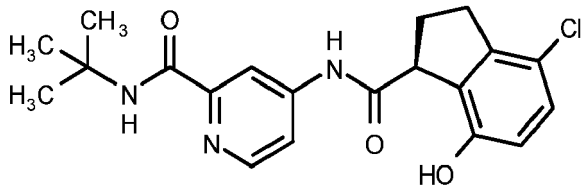
[0896] N-tert-Butyl-4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Example 3)(164 mg, 0.45 mmol) was suspended in anhydrous acetone (10 mL) and treated with K_2CO_3 (94 mg, 0.68 mmol) followed by 1-(bromomethyl)-4-methoxy-benzene (100 mg, 0.5 mmol). The reaction mixture was heated in a pressure tube at 50 °C overnight. The resulting mixture was concentrated *in vacuo* and then re-dissolved in EtOAc (25 mL). The mixture was washed with water (25 mL) and brine (25 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The solid was dissolved in EtOAc/ MeOH (2:1 ~15 mL) and the suspension was filtered and washed with EtOAc (20 mL) to afford the titled compound as a white solid.

[0897] 1H NMR (500 MHz, DMSO-d6) δ 10.65 (s, 1H), 8.45 (d, J = 5.5 Hz, 1H), 8.11 (d, J = 2.0 Hz, 1H), 8.05 (s, 1H), 7.82 (dd, J = 5.5, 2.2 Hz, 1H), 7.34 (d, J = 2.7 Hz, 1H), 7.30 (dd, J = 8.7, 2.7 Hz, 1H), 7.22 (d, J = 8.7 Hz, 2H), 7.09 (d, J = 8.8 Hz, 1H), 6.67 - 6.63 (m, 2H), 4.97 (s, 2H), 3.71 (s, 2H), 3.65 (s, 3H), 1.41 (s, 9H).

[0898] LC-MS (Method A): Rt 4.13 mins; MS m/z 482.3/484.3 = [M+H]+ (91% @ 215nm)

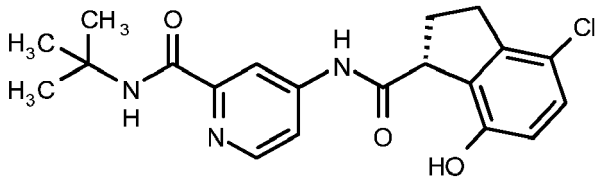
Example 57a: N-tert-butyl-4-[[(1S) or (1R)-4-chloro-7-hydroxy-indane-1-carbonyl]amino]pyridine-2-carboxamide and Example 57b: N-tert-butyl-4-[[(1S) or (1R)-4-chloro-7-hydroxy-indane-1-carbonyl]amino]pyridine-2-carboxamide

[0899]



(S)-isomer

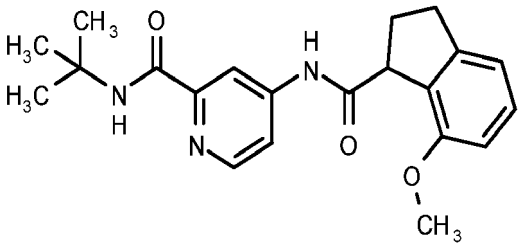
or



(R)-isomer

Step 1: N-tert-Butyl-4-[(7-methoxyindane-1-carbonyl)amino]pyridine-2-carboxamide

[0900]



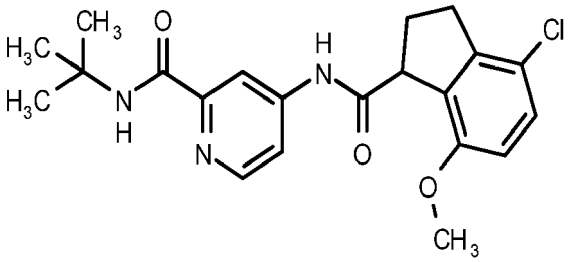
[0901] To a mixture of 4-amino-N-tert-butyl-pyridine-2-carboxamide (Example 3 step 1) (200 mg, 1.03 mmol) and 7-methoxyindane-1-carboxylic acid (199 mg, 1.03 mmol) in 1,4-dioxane (5 mL) was added 50% T3P® solution in EtOAc (1231 μL, 2.07 mmol) and TEA (362 μL, 2.07 mmol). The reaction mixture was stirred at room temperature under an inert atmosphere for 16 hours. The resulting mixture was diluted with EtOAc (20 mL) and the organic mixture was washed with water (20 mL), sat. $NaHCO_3$ (20 mL) and brine (20 mL). The organic portion was dried over Na_2SO_4 and concentrated *in vacuo.* The crude residue was purified by chromatography on KP-NH silica eluting with 0-80% heptane in EtOAc to afford the titled compound as a light pink foam.

[0902] 1H NMR (500 MHz, DMSO-d6) δ 10.67 (s, 1H), 8.44 (d, J = 5.5 Hz, 1H), 8.22 (d, J = 2.1 Hz, 1H), 8.03 (s, 1H), 7.83 (dd, J = 5.5, 2.2 Hz, 1H), 7.20 (t, J = 7.8 Hz, 1H), 6.87 (d, J = 7.4 Hz, 1H), 6.77 (d, J = 8.1 Hz, 1H), 4.12 (dd, J = 8.8, 5.4 Hz, 1H), 3.68 (s, 3H), 3.09 - 2.99 (m, 1H), 2.92-2.85 (m, 1H), 2.41 - 2.34 (m, 1H), 2.24 - 2.15 (m, 1H), 1.40 (s, 9H).

[0903] LC-MS (Method E): Rt 1.21 mins; MS m/z 368.1 = [M+H]+ (100% @ 215nm)

Step 2: N-tert-Butyl-4-[(4-chloro-7-methoxy-indane-1-carbonyl)amino]pyridine-2-carboxamide

[0904]



[0905] The titled compound was prepared from N-tert-butyl-4-[(7-methoxyindane-1-carbonyl)amino]pyridine-2-carboxamide (step 1) analogously to Example 24, step 2.

[0906] 1H NMR (250 MHz, Chloroform-d) δ 8.83 (s, 1H), 8.37 (d, J = 5.6 Hz, 1H), 8.20 (dd, J = 5.6, 2.2 Hz, 1H), 8.01 (s, 1H), 7.58 (d, J = 2.0 Hz, 1H), 7.19 (d, J = 8.7 Hz, 1H), 6.74 (d, J = 8.7 Hz, 1H), 4.22 (d, J = 7.5 Hz, 1H), 4.02 (s, 3H), 3.23 - 2.77 (m, 3H), 2.32-2.15 (m, 1H), 1.47 (s, 9H).

[0907] LC-MS (Method E): Rt 1.27 mins; MS m/z 402.1/404.1 = [M+H]+

Step 3: Example 57a: N-tert-butyl-4-[[(1S) or (1R)-4-chloro-7-hydroxy-indane-1-carbonyl]amino]pyridine-2-carboxamide and Example 57b: N-tert-butyl-4-[[(1S) or (1R)-4-chloro-7-hydroxy-indane-1-carbonyl]amino]pyridine-2-carboxamide

[0908] To a solution of N-tert-butyl-4-[(4-chloro-7-methoxy-indane-1-carbonyl)amino]pyridine-2-carboxamide (step 2) (50 mg, 0.12 mmol) in DCM (2 mL) was added 1M BBr_3 in DCM (249 μL, 0.25 mmol). The resulting mixture was stirred at room temperature under an inert atmosphere for 1 hour. Further 1M BBr_3 in DCM (249 μL, 0.25 mmol) was added and the mixture stirred for a further 24 hours. The reaction was quenched with water (1 mL) and concentrated *in vacuo.* The crude material was dissolved in EtOAc (20 mL) and the organic mixture was washed with sat. $NaHCO_3$ (20 mL), water (20 mL) and brine (20 mL). The organic portion was concentrated *in vacuo* to afford a racemic mixture

[0909] Chiral separation of racemic N-tert-butyl-4-[[4-chloro-7-hydroxy-indane-1-carbonyl]amino]pyridine-2-carboxamide using Supercritical Fluid Chromatography [chiral phase column (15% Ethanol: 95%CO2 with Chiralpak IC 25cm column at 15 ml/min)] afforded the individual enantiomers:

Example 57a: N-tert-butyl-4-[[(1S) or (1R)-4-chloro-7-hydroxy-indane-1-carbonyl]amino]pyridine-2-carboxamide

[0910] SFC retention Time: 6.00 mins

[0911] 1H NMR (500 MHz, DMSO-d6) δ 10.77 (br. s, 1H), 9.76 (br. s, 1H), 8.44 (d, J = 5.5 Hz, 1H), 8.19 (d, J = 2.0 Hz, 1H), 8.02 (s, 1H), 7.83 (dd, J = 5.5, 2.2 Hz, 1H), 7.07 (d, J = 8.5 Hz, 1H), 6.61 (d, J = 8.5 Hz, 1H), 4.18 (dd, J = 8.9, 5.2 Hz, 1H), 3.05-2.96 (m, 1H), 2.93 - 2.84 (m, 1H), 2.43 - 2.36 (m, 1H), 2.27 - 2.19 (m, 1H), 1.40 (s, 9H).

[0912] LC-MS (Method A): Rt 3.58 mins; MS m/z 388.2/390.2 = [M+H]+ (96% @ 215 nm)

Example 57b: N-tert-butyl-4-[[(1S) or (1R)-4-chloro-7-hydroxy-indane-1-carbonyl]amino]pyridine-2-carboxamide

[0913] SFC retention Time: 7.84 mins

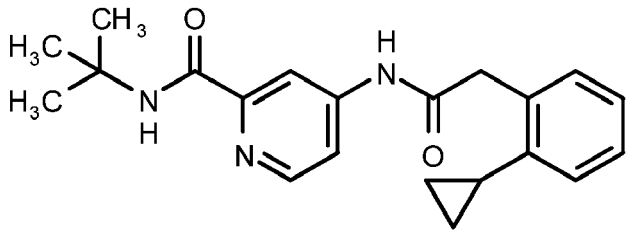
[0914] 1H NMR (500 MHz, DMSO-d6) δ 10.89 (br. s, 1H), 9.76 (br. s, 1H), 8.43 (d, J = 5.5 Hz, 1H), 8.19 (d, J = 2.1 Hz, 1H), 8.02 (s, 1H), 7.82 (dd, J = 5.5, 2.1 Hz, 1H), 7.06 (d, J = 8.5 Hz, 1H), 6.60 (d, J = 8.5 Hz, 1H), 4.18 (dd, J = 8.9, 5.1 Hz, 1H), 3.04 - 2.95 (m, 1H), 2.94 - 2.84 (m, 1H), 2.42 - 2.36 (m, 1H), 2.29 - 2.21 (m, 1H), 1.40 (s, 9H).

[0915] LC-MS (Method A): Rt 3.58 mins; MS m/z 388.2/390.2 = [M+H]+ (95% @ 215 nm)

Example 58

N-tert-Butyl-4-[[2-(2-cyclopropylphenyl)acetyl]amino]pyridine-2-carboxamide

[0916]



[0917] A mixture comprising 4-[[2-(2-bromophenyl)acetyl]amino]-N-tert-butyl-pyridine-2-carboxamide ((Example 23.13)(100 mg, 0.25 mmol), cyclopropylboronic acid (44 mg, 0.51 mmol), tripotassium phosphate (215 mg, 1.01 mmol) in toluene (5 mL) and water (0.5 mL) was degassed with nitrogen for 10 mins and treated with $Pd(OAc)_2$ (11 mg, 0.05 mmol) and $P(Cy)_3$ (28 mg, 0.1 mmol). The reaction mixture was sealed and heated at 100 °C for 5 hours. After cooling to room temperature, the mixture was filtered through Celite® and the filtrate diluted with EtOAc (10 mL) and water (10 mL). The organic layer was separated, dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was purified by preparative HPLC (basic pH, early elution method) followed by preparative HPLC (acidic pH, early elution method). Further purification using chromatography on silica eluting with 0-100% EtOAc in heptane afforded the titled compound as an off-white solid.

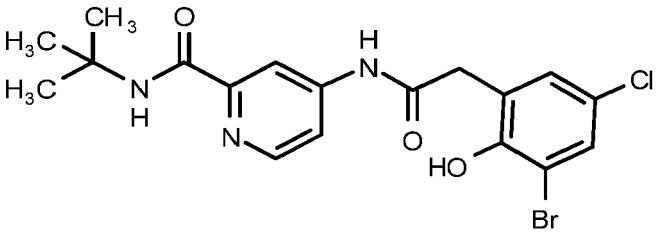
[0918] 1H NMR (500 MHz, Methanol-d4) δ 8.43 (dd, J = 5.6, 0.4 Hz, 1H), 8.13 (dd, J = 2.2, 0.4 Hz, 1H), 7.92 (dd, J = 5.5, 2.2 Hz, 1H), 7.23 (dd, J = 7.3, 1.5 Hz, 1H), 7.21 - 7.13 (m, 2H), 7.07 (dd, J = 7.3, 1.2 Hz, 1H), 3.98 (s, 2H), 2.01 - 1.91 (m, 1H), 1.47 (s, 9H), 0.95 - 0.82 (m, 2H), 0.67-0.58 (m, 2H).

[0919] LC-MS (Method A): Rt 3.69 mins; MS m/z 352.3 = [M+H]+ (99% @ 215nm)

Example 59

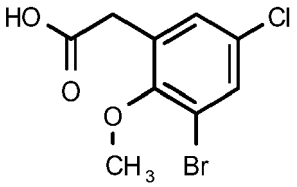
4-[[2-(3-Bromo-5-chloro-2-hydroxy-phenyl)acetyl]amino]-N-tert-butyl-pyridine-2-carboxamide

[0920]



Step 1: 2-(3-Bromo-5-chloro-2-methoxy-phenyl)acetic acid

[0921]



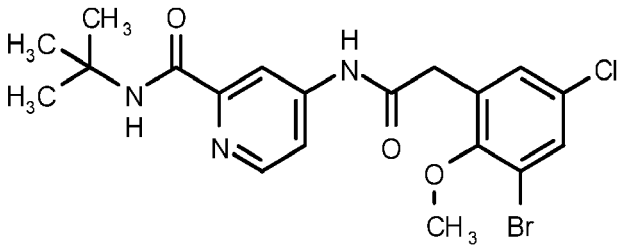
[0922] Bromine (8 mL, 139.34 mmol) was added to a stirred solution of 2-(5-chloro-2-methoxyphenyl)acetic acid (1 g, 4.98 mmol) in acetic acid (8 mL) and the mixture was stirred at room temperature for 1 hour. The reaction mixture was cooled to 0 °C and treated with EtOAc (50 mL) followed by saturated aqueous $Na_2S_2O_3$ (ca. 30 mL). The organic layer was separated and concentrated *in vacuo* to obtain a yellow gummy solid. The solid was purified by C18 reverse phase chromatography eluting with 10-100% (0.1% formic acid in water: 0.1% formic acid in MeCN) to afford the titled compound as an off-white solid.

[0923] 1H NMR (500 MHz, DMSO-d6) δ 12.53 (s, 1H), 7.67 (d, J = 2.6 Hz, 1H), 7.41 (d, J = 2.6 Hz, 1H), 3.73 (s, 3H), 3.65 (s, 2H).

[0924] LC-MS (Method E): Rt 1.08 mins; MS m/z not observed = [M+H]+ (100% @ 215nm)

Step 2: 4-[[2-(3-Bromo-5-chloro-2-methoxy-phenyl)acetyl]amino]-N-tert-butyl-pyridine-2-carboxamide

[0925]



[0926] To a stirred solution of 2-(3-bromo-5-chloro-2-methoxy-phenyl)acetic acid (step 1)(755 mg, 2.7 mmol), 4-amino-N-tert-butyl-pyridine-2-carboxamide (Example 3 step 1) (475. mg, 2.46 mmol) and TEA (644 μL, 3.69 mmol) in 1,4-dioxane (10 mL) was added 50% T3P® solution in EtOAc (2.19 mL, 3.69 mmol). The resulting mixture was stirred at room temperature for 2 hours and then diluted with water (40 mL) and EtOAc (50 mL). The organic layer was separated, washed with water (50 mL), dried over Na_2SO_4 and concentrated *in vacuo.* The crude material was purified by chromatography on silica eluting with 0-100% EtOAc in heptane to afford the titled compound as an off-white solid. 1H NMR (500 MHz, DMSO-d6) δ 10.83 (s, 1H), 8.47 (d, J = 5.5 Hz, 1H), 8.18 (d, J = 2.0 Hz, 1H), 8.04 (s, 1H), 7.82 (dd, J = 5.5, 2.2 Hz, 1H), 7.71 (d, J = 2.6 Hz, 1H), 7.48 (d, J = 2.6 Hz, 1H), 3.84 (s, 2H), 3.75 (s, 3H), 1.41 (s, 9H).

[0927] LC-MS (Method E): Rt 1.29 mins; MS m/z 454.0/456.0/458.0 = [M+H]+ (99% @ 215nm)

Step 3: 4-[[2-(3-Bromo-5-chloro-2-hydroxy-phenyl)acetyl]amino]-N-tert-butyl-pyridine-2-carboxamide

[0928] 1M BBr3 in DCM (0.2 mL, 0.2 mmol) was added to a stirred suspension of 4-[[2-(3-bromo-5-chloro-2-methoxy-phenyl)acetyl]amino]-N-tert-butyl-pyridine-2-carboxamide (step 2) (30 mg, 0.07 mmol) in DCM (1 mL) at 0°C. The mixture was allowed to warm to room temperature and stirred for 1 hour. The reaction was quenched by dropwise addition of sat. $NaHCO_3$ (20 mL) then diluted with EtOAc (20 mL). The organic layer was separated, dried over Na_2SO_4 and concentrated *in vacuo.* The crude product was purified by preparative HPLC (acidic pH, early elution method) and the product containing fractions were combined and lyophilised overnight to afford the titled compound as an off-white powder.

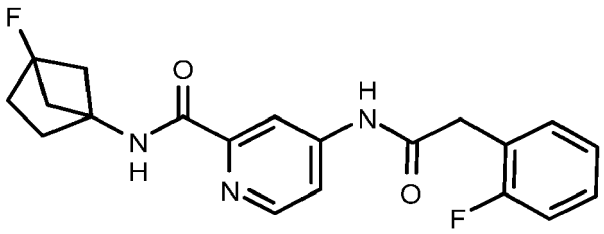
[0929] 1H NMR (500 MHz, DMSO-d6) δ 10.93 (s, 1H), 9.62 (s, 1H), 8.45 (d, J = 5.5 Hz, 1H), 8.15 (d, J = 2.0 Hz, 1H), 8.03 (s, 1H), 7.81 (dd, J = 5.5, 2.2 Hz, 1H), 7.52 (d, J = 2.6 Hz, 1H), 7.28 (d, J = 2.5 Hz, 1H), 3.78 (s, 2H), 1.40 (s, 9H).

[0930] LC-MS (Method A): Rt 3.81 mins; MS m/z 440.1/442.1 = [M+H]+ (99% @ 215nm)

Example 60

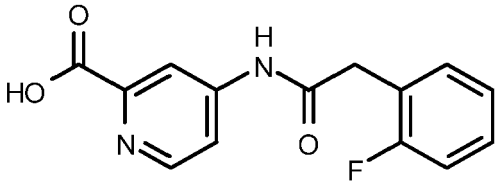
N-(4-Fluoro-1-bicyclo[2.1.1]hexanyl)-4-[[2-(2-fluorophenyl)acetyl]amino]pyridine-2-carboxamide

[0931]



Step 1-2: 4-[[2-(2-Fluorophenyl)acetyl]amino]pyridine-2-carboxylic acid

[0932]



[0933] The titled compound was prepared from 2-(2-fluorophenyl)acetic acid and methyl 4-aminopyridine-2-carboxylate analogously to Example 30 steps 1-2.

[0934] 1H NMR (500 MHz, DMSO-d6) δ 10.82 (s, 1H), 8.51 (d, J = 5.5 Hz, 1H), 8.23 (d, J = 1.8 Hz, 1H), 7.78 (dd, J = 5.5, 2.1 Hz, 1H), 7.39 (t, J = 7.6 Hz, 1H), 7.36 - 7.31 (m, 1H), 7.21 - 7.15 (m, 2H), 3.81 (s, 2H).

[0935] LC-MS (Method E): Rt 0.81 mins; MS m/z 275.0 = [M+H]+ (100% @ 215nm)

Step 3: N-(4-Fluoro-1-bicyclo[2.1.1]hexanyl)-4-[[2-(2-fluorophenyl)acetyl]amino]pyridine-2-carboxamide

[0936] The titled compound was prepared from 4-[[2-(2-fluorophenyl)acetyl]amino]pyridine-2-carboxylic acid (step 1-2) and 4-fluorobicyclo[2.1.1]hexan-1-amine hydrochloride analogously to Example 30 step 3.

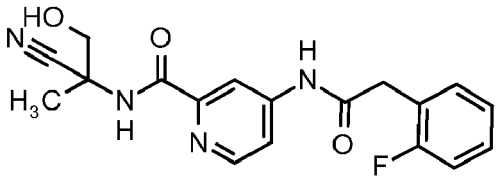
[0937] 1H NMR (500 MHz, DMSO-d6) δ 10.82 (s, 1H), 9.05 (s, 1H), 8.47 (d, J = 5.5 Hz, 1H), 8.16 (d, J = 2.0 Hz, 1H), 7.83 (dd, J = 5.5, 2.2 Hz, 1H), 7.40 (td, J = 7.6, 1.6 Hz, 1H), 7.36 - 7.31 (m, 1H), 7.21 - 7.15 (m, 2H), 3.81 (s, 2H), 2.13 - 2.05 (m, 4H), 1.99 - 1.95 (m, 2H), 1.87 - 1.82 (m, 2H).

[0938] LC-MS (Method A): Rt 3.22 mins; MS m/z 372.3 = [M+H]+ (98% @ 215nm)

Example 60.1

N-(1-Cyano-2-hydroxy-1-methyl-ethyl)-4-[[2-(2-fluorophenyl)acetyl]amino]pyridine-2-carboxamide

[0939]



[0940] The titled compound was prepared from 4-[[2-(2-fluorophenyl)acetyl]amino]pyridine-2-carboxylic acid (step 1-2) and 2-amino-3-hydroxy-2-methyl-propanenitrile hydrochloride analogously to Example 30 step 3.

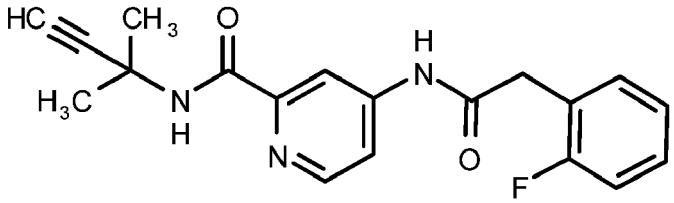
[0941] 1H NMR (500 MHz, DMSO-d6) δ 10.86 (s, 1H), 8.72 (s, 1H), 8.51 (d, J = 5.5 Hz, 1H), 8.23 (d, J = 2.1 Hz, 1H), 7.86 (dd, J = 5.5, 2.2 Hz, 1H), 7.43 - 7.37 (m, 1H), 7.37 - 7.28 (m, 1H), 7.22 - 7.14 (m, 2H), 5.99 - 5.79 (m, 1H), 3.86 - 3.78 (m, 3H), 3.72 (dd, J = 10.9, 4.7 Hz, 1H), 1.65 (s, 3H).

[0942] LC-MS (Method A): Rt 2.41 mins; MS m/z 357.2 = [M+H]+ (99% @ 215nm)

Example 60.2

N-(1,1-Dimethylprop-2-ynyl)-4-[[2-(2-fluorophenyl)acetyl]amino]pyridine-2-carboxamide

[0943]



[0944] The titled compound was prepared from 4-[[2-(2-fluorophenyl)acetyl]amino]pyridine-2-carboxylic acid (step 1-2) and 2-methylbut-3-yn-2-amine analogously to Example 30 step 3.

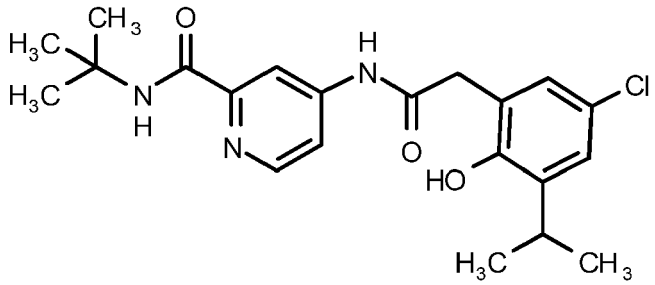
[0945] 1H NMR (500 MHz, DMSO-d6) δ 10.83 (s, 1H), 8.48 (d, J = 5.5 Hz, 1H), 8.32 (s, 1H), 8.19 (d, J = 2.1 Hz, 1H), 7.83 (dd, J = 5.5, 2.2 Hz, 1H), 7.43 - 7.37 (m, 1H), 7.37 - 7.30 (m, 1H), 7.22 - 7.15 (m, 2H), 3.82 (s, 2H), 3.21 (s, 1H), 1.64 (s, 6H).

[0946] LC-MS (Method A): Rt 3.08 mins; MS m/z 340.2 = [M+H]+ (99% @ 215nm)

Example 61

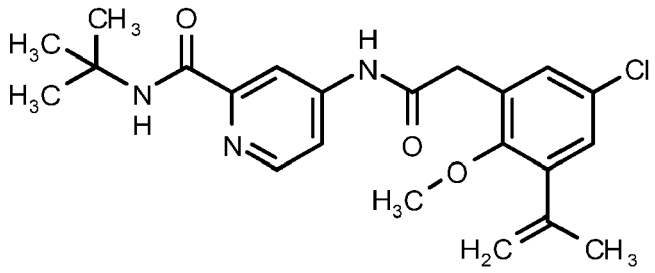
N-tert-Butyl-4-[[2-(5-chloro-2-hydroxy-3-isopropyl-phenyl)acetyl]amino]pyridine-2-carboxamide

[0947]



Step 1: N-tert-Butyl-4-[[2-(5-chloro-3-isopropenyl-2-methoxy-phenyl)acetyl]amino] pyridine-2-carboxamide

[0948]



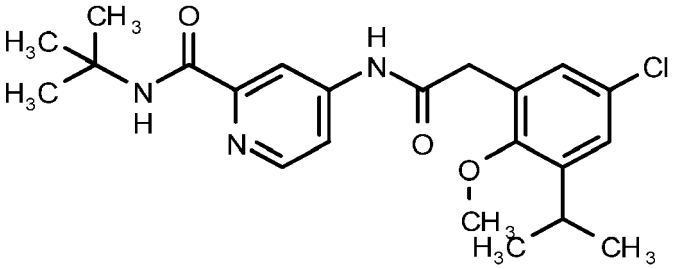
[0949] The titled compound was prepared from 4-[[2-(3-bromo-5-chloro-2-methoxyphenyl)acetyl]amino]-N-tert-butyl-pyridine-2-carboxamide (Example 59 step 2) and 2-isopropenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane analogously to Example 58.

[0950] 1H NMR (500 MHz, DMSO-d6) δ 10.84 - 10.75 (m, 1H), 8.48 - 8.42 (m, 1H), 8.23 - 8.17 (m, 1H), 8.03 (s, 1H), 7.84 - 7.79 (m, 1H), 7.33 (d, J = 2.7 Hz, 1H), 7.17 (d, J = 2.7 Hz, 1H), 5.25 - 5.22 (m, 1H), 5.17 - 5.15 (m, 1H), 3.77 (d, J = 2.8 Hz, 2H), 3.58 (s, 3H), 2.14 - 2.04 (m, 3H), 1.40 (s, 9H).

[0951] LC-MS (Method E): Rt 1.33 mins; MS m/z 416.1 = [M+H]+ (86% @ 215nm)

Step 2: N-tert-Butyl-4-[[2-(5-chloro-3-isopropyl-2-methoxy-phenyl)acetyl]amino]pyridine-2-carboxamide

[0952]



[0953] 10 % Pd/C (9 mg, 0.01 mmol) was added to a stirred solution of N-tert-butyl-4-[[2-(5-chloro-3-isopropenyl-2-methoxy-phenyl)acetyl]amino]pyridine-2-carboxamide (step 1) (120 mg, 0.17 mmol) in EtOH (10 mL). The resulting mixture was placed under an atmosphere of hydrogen and after stirring for 16 hours the mixture was filtered through Celite ® and washed through with EtOH (15 mL). The filtrate was concentrated *in vacuo* and purification by preparative HPLC (acidic pH, early elution method) afforded the titled compound as a pale yellow solid.

[0954] 1H NMR (500 MHz, DMSO-d6) δ 10.80 (s, 1H), 8.46 (d, J = 5.5 Hz, 1H), 8.19 (d, J = 2.0 Hz, 1H), 8.03 (s, 1H), 7.82 (dd, J = 5.5, 2.2 Hz, 1H), 7.26 (d, J = 2.7 Hz, 1H), 7.22 (d, J = 2.7 Hz, 1H), 3.77 (s, 2H), 3.66 (s, 3H), 3.21 (hept, J = 6.9 Hz, 1H), 1.40 (s, 9H), 1.18 (d, J = 6.9 Hz, 6H).

[0955] LC-MS (Method E): Rt 1.34 mins; MS m/z 418.2 = [M+H]+ (99% @ 215nm)

Step 3: N-tert-Butyl-4-[[2-(5-chloro-2-hydroxy-3-isopropyl-phenyl)acetyl]amino]pyridine-2-carboxamide

[0956] 1M BBr_3 in DCM (0.34 mL, 0.34 mmol) was added to a stirred suspension of N-tert-butyl-4-[[2-(5-chloro-3-isopropyl-2-methoxy-phenyl)acetyl]amino]pyridine-2-carboxamide (step 2)(48 mg, 0.11 mmol) in DCM (2 mL). The resulting mixture was stirred at room temperature for 1 hour. The reaction was quenched with MeOH (5 mL) and the mixture was concentrated *in vacuo.* The resulting residue was diluted with EtOAc (5 mL), washed with sat. $NaHCO_3$ (5 mL) and the organic portion was dried over Na_2SO_4 and concentrated *in vacuo.* The crude material was purified by preparative HPLC (acidic pH, early elution method) and the product fractions were combined, lyophilised overnight to afford the titled compound as an off-white powder.

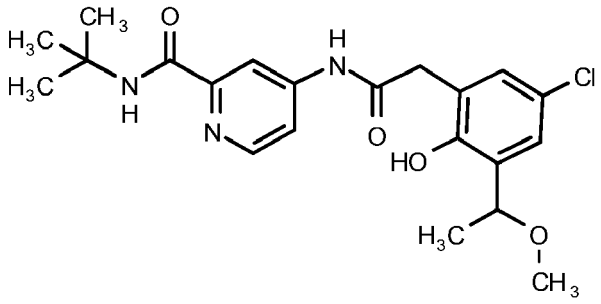
[0957] 1H NMR (500 MHz, DMSO-d6) δ 10.73 (s, 1H), 8.75 (s, 1H), 8.45 (d, J = 5.5 Hz, 1H), 8.18 (d, J = 1.9 Hz, 1H), 8.03 (s, 1H), 7.82 (dd, J = 5.5, 2.2 Hz, 1H), 7.10 - 7.01 (m, 2H), 3.74 (s, 2H), 3.29 - 3.22 (m, 1H), 1.40 (s, 9H), 1.14 (d, J = 6.8 Hz, 6H).

[0958] LC-MS (Method A): Rt 3.25 mins; MS m/z 356.3 = [M+H]+ (100% @ 215nm)

Example 62

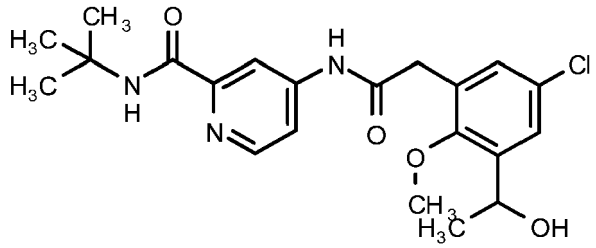
N-tert-Butyl-4-[[2-[5-chloro-2-hydroxy-3-(1-methoxyethyl)phenyl]acetyl]amino] pyridine-2-carboxamide

[0959]



Step 1: N-tert-Butyl-4-[[2-[5-chloro-3-(1-hydroxyethyl)-2-methoxy-phenyl]acetyl]amino] pyridine- 2-carboxamide

[0960]



[0961] The titled compound was prepared from 4-[[2-(3-bromo-5-chloro-2-methoxyphenyl)acetyl]amino]-N-tert-butyl-pyridine-2-carboxamide (Example 59, step 2) and 1-vinyloxybutane analogously to Example 54 steps 2-3.

[0962] 1H NMR (500 MHz, DMSO-d6) δ 10.80 (s, 1H), 8.45 (d, J = 5.5 Hz, 1H), 8.19 (d, J = 2.1 Hz, 1H), 8.03 (s, 1H), 7.81 (dd, J = 5.5, 2.2 Hz, 1H), 7.39 (d, J = 2.7 Hz, 1H), 7.27 (d, J = 2.7 Hz, 1H), 5.23 (d, J = 4.5 Hz, 1H), 5.06 - 4.87 (m,

1H), 3.77 (d, J = 2.6 Hz, 2H), 3.68 (s, 3H), 1.40 (s, 9H), 1.31 (d, J = 6.4 Hz, 3H).

[0963] LC-MS (Method E): Rt 1.18 mins; MS m/z 420.2/422.2 = [M+H]+ (100% @ 215nm)

Step 2: N-tert-Butyl-4-[[2-[5-chloro-2-hydroxy-3-(1-methoxyethyl)phenyl]acetyl]amino] pyridine-2-carboxamide

[0964] 1M BBr3 in DCM (0.5 mL, 0.5 mmol) was added to a cooled (0°C) suspension of N-tert-butyl-4-[[2-[5-chloro-3-(1-hydroxyethyl)-2-methoxy-phenyl]acetyl]amino]pyridine-2-carboxamide (70 mg, 0.17 mmol) in DCM (2 mL) and stirred at room temperature for 1 hour. The reaction was quenched by addition of sat $NaHCO_3$ (1 mL) then diluted with DCM (7 mL). The organic layer was separated, concentrated *in vacuo* and purification of the crude residue by preparative HPLC (acidic pH, early elution method) afforded the titled compound as an off-white powder.

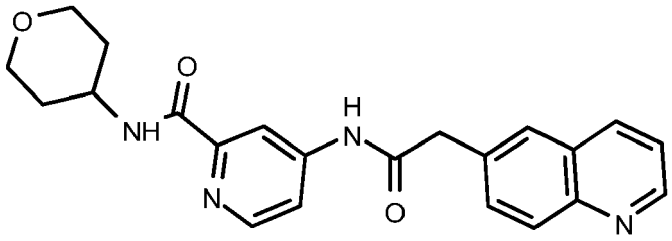
[0965] 1H NMR (500 MHz, DMSO-d6) δ 10.76 (s, 1H), 8.87 (s, 1H), 8.45 (d, J = 5.5 Hz, 1H), 8.18 (d, J = 1.9 Hz, 1H), 8.03 (s, 1H), 7.81 (dd, J = 5.5, 2.2 Hz, 1H), 7.15 (d, J = 2.7 Hz, 1H), 7.11 (d, J = 2.7 Hz, 1H), 4.68 (q, J = 6.3 Hz, 1H), 3.76 (s, 2H), 3.17 (s, 3H), 1.40 (s, 9H), 1.29 (d, J = 6.4 Hz, 3H).

[0966] LC-MS (Method A): Rt 3.80 mins; MS m/z 420.3 = [M+H]+ (100% @ 215nm)

Example 63

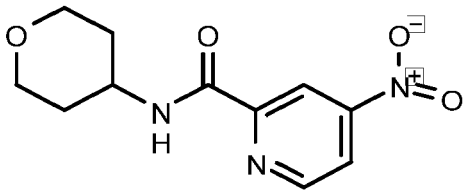
4-[[2-(6-Quinolyl)acetyl]amino]-N-tetrahydropyran-4-yl-pyridine-2-carboxamide

[0967]



Step 1: 4-Nitro-N-tetrahydropyran-4-yl-pyridine-2-carboxamide

[0968]

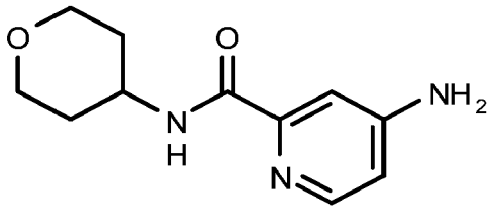


[0969] To a stirred solution of HATU (724 mg, 1.9 mmol) in DMF (1 mL) was added DIPEA (363 μL, 2.08 mmol) and 4-nitropyridine-2-carboxylic acid (320 mg, 1.9 mmol) and the mixture was stirred for 15 mins. Tetrahydropyran-4-amine (0.18 mL, 1.73 mmol) was added in one portion and the mixture was stirred at room temperature for 1 hour. The resulting mixture was washed with water (10 mL), $NaHCO_3$ (10 mL) and extracted with EtOAc (2 $\times$ 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* to afford the titled compound as a pale orange solid.

[0970] 1H NMR (500 MHz, DMSO-d6) δ = 1.70 - 1.75 (m, 4H), 3.37 - 3.44 (m, 2H), 3.88 (dt, J=11.2, 3.2, 2H), 4.05 (s, 1H), 8.33 (dd, J=5.3, 2.3, 1H), 8.53 (dd, J=2.3, 0.5, 1H), 8.92 (d, J=8.2, 1H), 9.02 (dd, J=5.3, 0.5, 1H).

Step 2: 4-Amino-N-tetrahydropyran-4-yl-pyridine-2-carboxamide

[0971]



[0972] A mixture comprising 4-nitro-N-tetrahydropyran-4-yl-pyridine-2-carboxamide (step 1) (338 mg, 1.35 mmol) and 10 % Pd-C (29 mg, 0.13 mmol) in EtOH (4 mL) was stirred under an atmosphere of hydrogen for 16 hours. The resulting mixture was filtered and the filtrate washed with EtOAc (2 × 10 mL). The combined organic extracts were concentrated in *vacuo* and purification of the crude residue by chromatography on silica eluting with 0-100% EtOAc in heptane afforded the titled compound as a pale orange solid.

[0973] 1H NMR (500 MHz, DMSO-d6) δ = 1.57 - 1.67 (m, 2H), 1.67 - 1.73 (m, 2H), 3.38 (td, J=11.6, 2.3, 2H), 3.81 - 3.88 (m, 2H), 3.90 - 3.99 (m, 1H), 6.30 (s, 2H), 6.58 (dd, J=5.6, 2.4, 1H), 7.21 (d, J=2.3, 1H), 8.01 (d, J=5.5, 1H), 8.37 (d, J=8.4, 1H).

[0974] LC-MS (Method C): Rt 0.32 mins; MS m/z 222.0 = [M+H]+ (98% @ 215nm)

Step 3: 4-[[2-(6-Quinolyl)acetyl]amino]-N-tetrahydropyran-4-yl-pyridine-2-carboxamide

[0975] A mixture of 4-amino-N-tetrahydropyran-4-yl-pyridine-2-carboxamide (step 2) (104 mg, 0.47 mmol) and 2-(6-quinolyl)acetic acid (87.99 mg, 0.47 mmol) in 1,4-dioxane (2mL) was treated with 50% T3P® solution in EtOAc (1118 μL, 0.94 mmol) and TEA (164 μL, 0.94 mmol). After stirring at room temperature for 1.5 hours, the mixture was concentrated in *vacuo*. The crude residue was washed with water (15 mL), $NaHCO_3$ (10 mL) and extracted with EtOAc (2 × 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by chromatography on silica eluting with 0-20% EtOAc/MeOH afforded the titled compound an off-white solid.

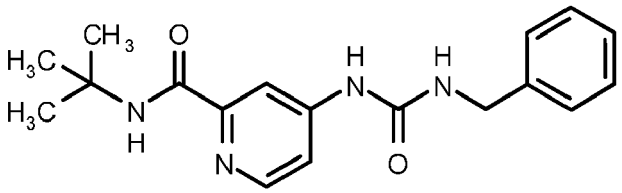
[0976] 1H NMR (500 MHz, DMSO-d6) δ = 1.64 - 1.73 (m, 4H), 3.38 (td, J=11.4, 3.2, 2H), 3.83 - 3.89 (m, 2H), 3.95 (s, 2H), 3.97 - 4.05 (m, 1H), 7.50 - 7.55 (m, 1H), 7.74 (dd, J=8.7, 2.0, 1H), 7.84 (dd, J=5.5, 2.2, 1H), 7.90 (d, J=1.7, 1H), 7.99 (d, J=8.6, 1H), 8.22 (d, J=2.0, 1H), 8.35 (d, J=7.4, 1H), 8.49 (d, J=5.5, 1H), 8.58 (d, J=8.4, 1H), 8.88 (dd, J=4.2, 1.7, 1H), 10.86 (s, 1H).

[0977] LC-MS (Method A): Rt 1.51 mins; MS m/z 391.0 = [M+H]+ (99% @ 215nm)

Example 64

4-(Benzylcarbamoylamino)-N-tert-butyl-pyridine-2-carboxamide

[0978]

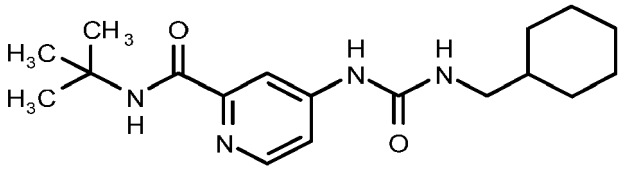
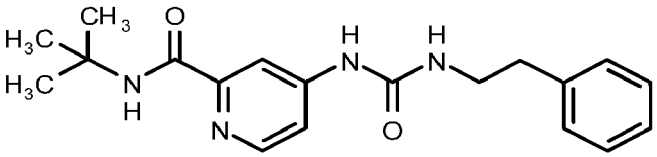
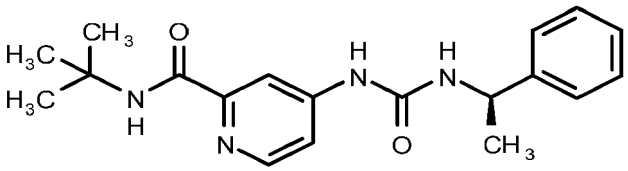
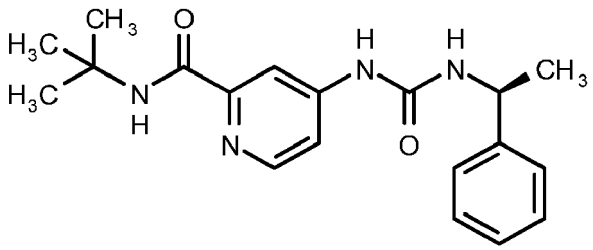
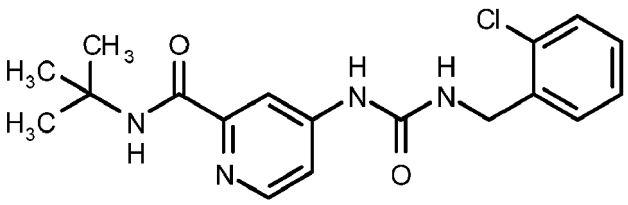


[0979] A mixture of isocyanatomethylbenzene (72 μL, 0.52 mmol) and 4-amino-N-tert-butylpyridine-2-carboxamide (Example 3 step 1)(100 mg, 0.52 mmol) in anhydrous DMF (1 mL) was stirred at 80°C overnight. The resulting mixture was concentrated *in vacuo* and the residue partitioned between EtOAc (2 mL) and brine (2 mL). The organic portion was separated and the aqueous layer was re-extracted with EtOAc (2 mL).The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was dissolved in DMSO:MeCN:H_2O (1.1 mL, 5:4:1), filtered and purified by preparative HPLC (acidic pH, early elution method) to afford the titled compound as an off-white solid. 1H NMR (250 MHz, DMSO-d6) δ 9.34 (s, 1H), 8.31 (d, J = 5.6 Hz, 1H), 8.05 - 7.97 (m, 2H), 7.62 (dd, J = 5.6, 2.3 Hz, 1H), 7.38 - 7.20 (m, 5H), 6.97 (t, J = 5.9 Hz, 1H), 4.32 (d, J = 5.9 Hz, 2H), 1.39 (s, 9H).

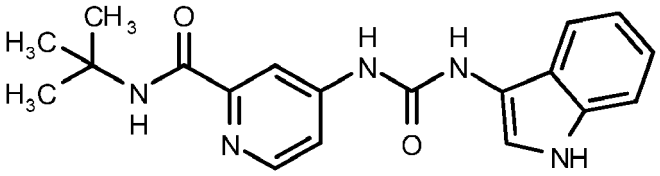
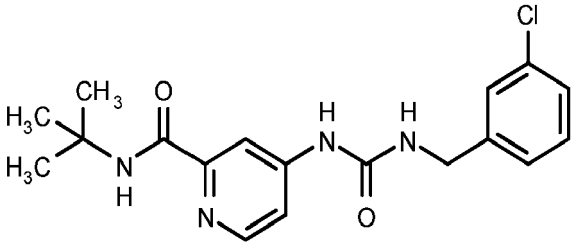
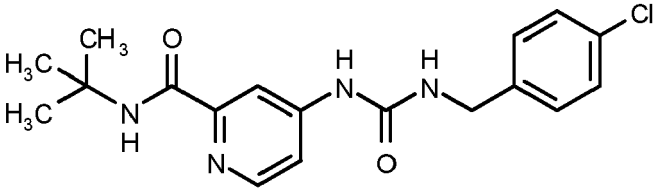
[0980] LC-MS (Method A): Rt 2.74 mins; MS m/z 327.3 = [M+H]+ (98% @ 215nm)

[0981] The compounds of the following tabulated Examples (Table 13) were prepared from 4-amino-N-tert-butyl-pyridine-2-carboxamide (Example 3 step 1) and the appropriate isocyanate analogously to Example 64

Table 13

Ex.	Structure and Name	1H NMR LCMS Retention Time, [M+H]+,
64.1	 N-tert-Butyl-4-(cyclohexylmethylcarbamoyl amino)pyridine-2-carboxamide	1H NMR (250 MHz, DMSO-d6) δ 9.10 (s, 1H), 8.30 (d, J = 5.5 Hz, 1H), 8.01 (s, 1H), 7.96 (d, J = 2.0 Hz, 1H), 7.58 (dd, J = 5.6, 2.3 Hz, 1H), 6.43 (t, J = 5.8 Hz, 1H), 2.96 (t, J = 6.3 Hz, 2H), 1.75 - 1.55 (m, 5H), 1.48 - 1.31 (m, 10H), 1.29 - 1.08 (m, 3H), 0.99 - 0.80 (m, 2H). LC-MS (Method A): Rt 3.21 mins; MS m/z 333.3 = [M+H]+ (98% @ 215nm)
64.2	 N-tert-Butyl-4-(2-phenylethylcarbamoyl amino)pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 9.23 (s, 1H), 8.30 (d, J = 5.6 Hz, 1H), 8.01 (s, 1H), 7.97 (d, J = 2.1 Hz, 1H), 7.60 (dd, J = 5.6, 2.2 Hz, 1H), 7.33 - 7.29 (m, 2H), 7.26 - 7.17 (m, 3H), 6.42 (t, J = 5.6 Hz, 1H), 3.39 - 3.34 (m, 2H), 2.77 (t, J = 7.2 Hz, 2H), 1.39 (s, 9H). LC-MS (Method A): Rt 2.91 mins; MS m/z 341.3 = [M+H]+ (95% @ 215nm)
64.3	 N-tert-Butyl-4-[[(1R)-1-phenylethyl]carbamoyl amino]pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 9.10 (s, 1H), 8.30 (d, J = 5.6 Hz, 1H), 8.00 (s, 1H), 7.95 (d, J = 2.2 Hz, 1H), 7.57 (dd, J = 5.6, 2.3 Hz, 1H), 7.37 - 7.33 (m, 4H), 7.26-7.22 (m, 1H), 6.93 (d, J = 7.8 Hz, 1H), 4.84 (p, J = 7.0 Hz, 1H), 1.41 (d, J = 7.0 Hz, 3H), 1.38 (s, 9H). LC-MS (Method A): Rt 2.92 mins; MS m/z 341.4 = [M+H]+ (98% @ 215nm)
64.4	 N-tert-Butyl-4-[[(1S)-1-phenylethyl] carbamoylamino]pyridine-2-carboxamide	1H NMR (500 MHz, Methanol-d4) δ 8.34 (d, J = 5.7 Hz, 1H), 7.94 - 7.89 (m, 1H), 7.75 (dd, J = 5.7, 2.1 Hz, 1H), 7.41 - 7.31 (m, 4H), 7.30 - 7.22 (m, 1H), 4.95 (q, J = 7.0 Hz, 1H), 1.51 (d, J = 7.0 Hz, 3H), 1.48 (s, 9H). LC-MS (Method A): Rt 2.91 mins; MS m/z 341.3 = [M+H]+ (99% @ 215nm)
64.5	 N-tert-Butyl-4-[(2-chlorophenyl) methylcarbamoylamino]pyridine-2-carboxamide	1H NMR (500 MHz, Methanol-d4) δ 8.34 (d, J = 5.3 Hz, 1H), 7.92 (s, 1H), 7.79 - 7.73 (m, 1H), 7.45 (dd, J = 7.4, 1.8 Hz, 1H), 7.42 (dd, J = 7.6, 1.6 Hz, 1H), 7.35 - 7.24 (m, 2H), 4.52 (s, 2H), 1.48 (s, 9H). LC-MS (Method A): Rt 3.07 mins; MS m/z 361.2/363.2 = [M+H]+ (100% @ 215nm)

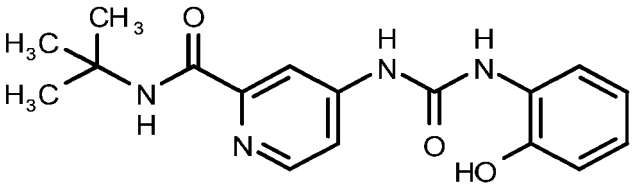
(continued)

Ex.	Structure and Name	1H NMR LCMS Retention Time, [M+H]+,
64.6	 N-tert-butyl-4-(1H-indol-3-ylcarbamoyl amino)pyridine-2-carboxamide	1H NMR (500 MHz, Methanol-d4) δ 8.38 (d, J = 5.6 Hz, 1H), 8.29 (s, 1H), 7.99 (d, J = 2.0 Hz, 1H), 7.85 (dd, J = 5.6, 2.2 Hz, 1H), 7.55 (dt, J = 8.1, 0.9 Hz, 1H), 7.50 (s, 1H), 7.40 - 7.35 (m, 1H), 7.19 - 7.12 (m, 1H), 7.11 - 7.03 (m, 1H), 1.50 (s, 9H). LC-MS (Method A): Rt 2.68 mins; MS m/z 352.3 = [M+H]+ (99% @ 215nm)
64.7	 N-tert-Butyl-4-[(3-chlorophenyl)methyl carbamoylamino]pyridine-2-carboxamide	1H NMR (500 MHz, Methanol-d4) δ 8.38 - 8.33 (m, 1H), 7.96 - 7.91 (m, 1H), 7.77 (dd, J = 5.6, 2.3 Hz, 1H), 7.38 (s, 1H), 7.38 (t, J = 1.5 Hz, 1H), 7.31 - 7.25 (m, 2H), 4.42 (s, 2H), 1.49 (s, 9H). LC-MS (Method A): Rt 3.12 mins; MS m/z 361.3/363.3 = [M+H]+ (100% @ 215nm)
64.8	 N-tert-butyl-4-[(4-chlorophenyl)methyl carbamoylamino]pyridine-2-carboxamide	1H NMR (500 MHz, Methanol-d4) δ 8.37 - 8.32 (m, 1H), 7.95 - 7.91 (m, 1H), 7.77 (dd, J = 5.6, 2.3 Hz, 1H), 7.35 (s, 4H), 4.41 (s, 2H), 1.49 (s, 9H). LC-MS (Method A): Rt 3.12 mins; MS m/z 361.3/363.2 = [M+H]+ (100% @ 215nm)

Example 65

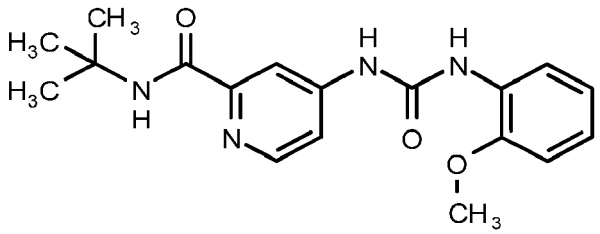
N-tert-Butyl-4-[(2-hydroxyphenyl)carbamoylamino]pyridine-2-carboxamide

[0982]



Step 1: N-tert-Butyl-4-[(2-methoxyphenyl)carbamoylamino]pyridine-2-carboxamide

[0983]



[0984] The titled compound was prepared from 1-isocyanato-2-methoxy-benzene and 4-amino-N-tert-butyl-pyridine-2-carboxamide (Example 3 step 1) analogously to Example 64.

[0985] 1H NMR (500 MHz, DMSO-d6) δ 9.95 (s, 1H), 8.43 - 8.37 (m, 2H), 8.11 (dd, J = 8.0, 1.6 Hz, 1H), 8.06 - 8.03 (m, 2H), 7.63 (dd, J = 5.5, 2.3 Hz, 1H), 7.06 - 6.98 (m, 2H), 6.92 (td, J = 7.8, 1.5 Hz, 1H), 3.89 (s, 3H), 1.41 (s, 9H).

[0986] LC-MS (Method A): Rt 3.21 mins; MS m/z 343.2 = [M+H]+ (100% @ 215nm)

Step 2: N-tert-Butyl-4-[(2-hydroxyphenyl)carbamoylamino]pyridine-2-carboxamide

[0987] N-tert-Butyl-4-[(2-methoxyphenyl)carbamoylamino]pyridine-2-carboxamide (step 1) (41 mg, 0.12 mmol) was added to a suspension of 1M BBr3 in DCM (532 μL, 0.53 mmol) in DCM (1 mL) at 0 °C - 5°C. After stirring at room temperature for 2.5 hours, the mixture was concentrated *in vacuo* and the residue partitioned between EtOAc (4 mL) and water (4 mL). The pH of the aqueous layer was adjusted to pH 5-6 with sat. aq. $NaHCO_3$ and the organic layer separated, washed with brine (2 mL), dried over Na_2SO_4 and concentrated *in vacuo.* The residue was dissolved in MeCN:H_2O (1.1 mL, 4:1), filtered and purified by preparative HPLC (acidic pH, early elution method) to afford the titled compound as a beige solid.

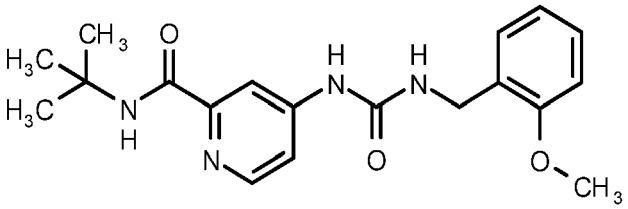
[0988] 1H NMR (250 MHz, DMSO-d6) δ 10.38 - 9.64 (m, 2H), 8.50 - 8.26 (m, 2H), 8.07 - 7.99 (m, 3H), 7.63 (dd, J = 5.6, 2.3 Hz, 1H), 6.89 - 6.72 (m, 3H), 1.40 (s, 9H).

[0989] LC-MS (Method A): Rt 2.72 mins; MS m/z 329.3 = [M+H]+ (100% @ 215nm)

Example 65.1

N-tert-Butyl-4-[(2-methoxyphenyl)methylcarbamoylamino]pyridine-2-carboxamide

[0990]



[0991] The titled compound was prepared from 4-amino-N-tert-butyl-pyridine-2-carboxamide (Example 3 step 1) and 1-(isocyanatomethyl)-2-methoxy-benzene analogously to Example 65 step 1.

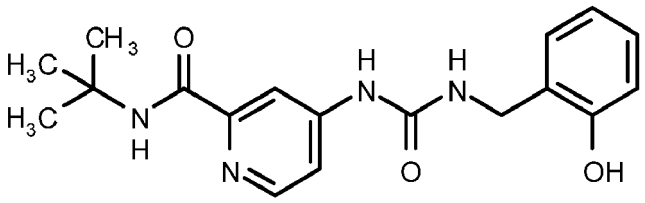
[0992] 1H NMR (500 MHz, DMSO-d6) δ 9.33 (s, 1H), 8.31 (d, J = 5.6 Hz, 1H), 8.02 (s, 1H), 7.98 (d, J = 2.1 Hz, 1H), 7.60 (dd, J = 5.6, 2.3 Hz, 1H), 7.29 - 7.21 (m, 2H), 7.03 - 6.99 (m, 1H), 6.94 - 6.88 (m, 1H), 6.75 (t, J = 5.9 Hz, 1H), 4.28 (d, J = 5.9 Hz, 2H), 3.84 (s, 3H), 1.40 (s, 9H).

[0993] LC-MS (Method A): Rt 2.86 mins; MS m/z 357.3 = [M+H]+ (99% @ 215nm)

Example 65.2

N-tert-Butyl-4-[(2-hydroxyphenyl)methylcarbamoylamino]pyridine-2-carboxamide

[0994]



[0995] The titled compound was prepared from N-tert-butyl-4-[(2-methoxyphenyl)methylcarbamoylamino]pyridine-2-carboxamide (Example 65.1) analogously to Example 65 step 2

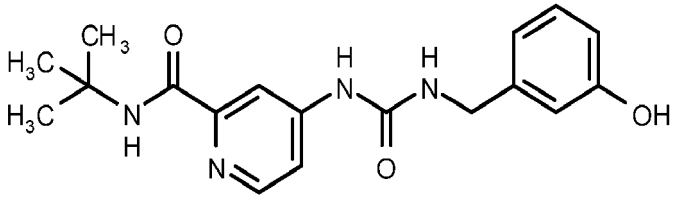
[0996] 1H NMR (500 MHz, DMSO-d6) δ 9.60 (s, 1H), 9.31 (s, 1H), 8.31 (d, J = 5.6 Hz, 1H), 8.01 (s, 1H), 7.96 (d, J = 2.1 Hz, 1H), 7.60 (dd, J = 5.6, 2.3 Hz, 1H), 7.16 (dd, J = 7.5, 1.5 Hz, 1H), 7.08 (td, J = 7.8, 1.7 Hz, 1H), 6.82 (dd, J = 8.0, 1.0 Hz, 1H), 6.76 (td, J = 7.4, 1.1 Hz, 1H), 6.72 (t, J = 5.9 Hz, 1H), 4.24 (d, J = 5.8 Hz, 2H), 1.39 (s, 9H).

[0997] LC-MS (Method A): Rt 2.56 mins; MS m/z 343.2 = [M+H]+ (97% @ 215nm)

Example 65.3

N-tert-Butyl-4-[(3-hydroxyphenyl)methylcarbamoylamino]pyridine-2-carboxamide

[0998]



[0999] The titled compound was prepared from 4-amino-N-tert-butyl-pyridine-2-carboxamide (Example 3 step 1) and 1-(isocyanatomethyl)-3-methoxy-benzene analogously to Example 65 steps 1 and 2.

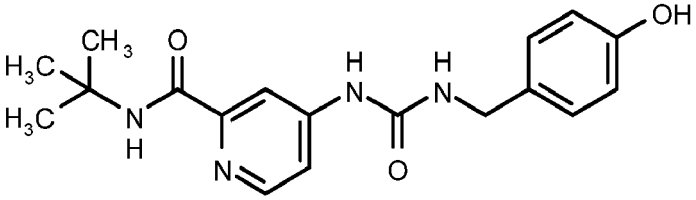
[1000] 1H NMR (500 MHz, Methanol-d4) δ 8.34 (d, J = 5.6 Hz, 1H), 7.92 (d, J = 2.1 Hz, 1H), 7.77 (dd, J = 5.6, 2.2 Hz, 1H), 7.16 (t, J = 7.8 Hz, 1H), 6.83 - 6.77 (m, 2H), 6.72 - 6.65 (m, 1H), 4.35 (s, 2H), 1.48 (s, 9H).

[1001] LC-MS (Method A): Rt 2.24 mins; MS m/z 343.3 = [M+H]+ (96% @ 215nm)

Example 65.4

N-tert-Butyl-4-[(4-hydroxyphenyl)methylcarbamoylamino]pyridine-2-carboxamide

[1002]



[1003] The titled compound was prepared from 4-amino-N-tert-butyl-pyridine-2-carboxamide (Example 3 step 1) and 1-(isocyanatomethyl)-4-methoxy-benzene analogously to Example 65 steps 1 and 2.

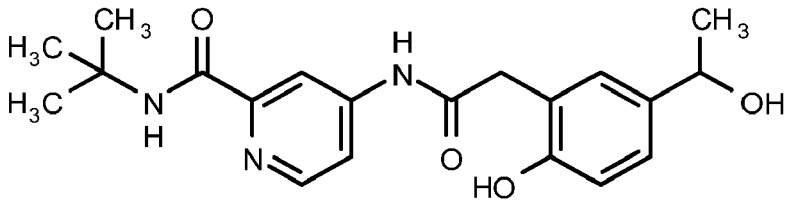
[1004] 1H NMR (500 MHz, Methanol-d4) δ 8.34 (d, J = 5.6 Hz, 1H), 7.91 (d, J = 1.9 Hz, 1H), 7.77 (dd, J = 5.6, 2.3 Hz, 1H), 7.21 - 7.14 (m, 2H), 6.80 - 6.73 (m, 2H), 4.31 (s, 2H), 1.48 (s, 9H).

[1005] LC-MS (Method A): Rt 2.16 mins; MS m/z 343.3 = [M+H]+ (98% @ 215nm)

Example 66

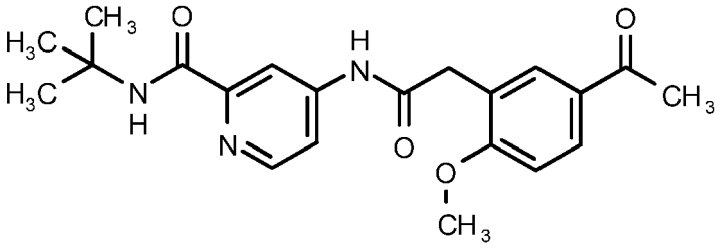
N-tert-Butyl-4-[[2-[2-hydroxy-5-(1-hydroxyethyl)phenyl]acetyl]amino]pyridine-2-carboxamide

[1006]



Step 1: 4-[[2-(5-Acetyl-2-methoxy-phenyl)acetyl]amino]-N-tert-butyl-pyridine-2-carboxamide

[1007]



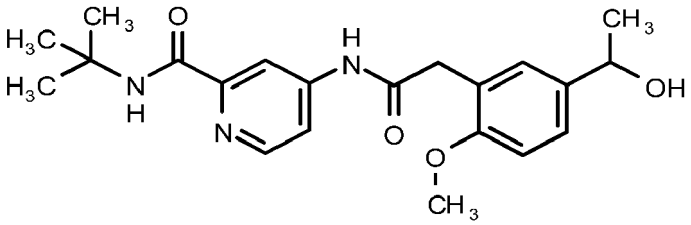
[1008] 4-[[2-(5-Bromo-2-methoxy-phenyl)acetyl]amino]-N-tert-butyl-pyridine-2-carboxamide (Example 6, step 1) (985 mg, 2.34 mmol), ZnF_2 (218 mg, 1.87 mmol) and $Pd(dba)_2$ (135 mg, 0.23 mmol) were dissolved in anhydrous DMF (10 mL) at room temperature and degassed with N_2 in a sealed pressure vial. To the mixture was added tri-tert-butylphosphine (1M in toluene, 0.47 mL, 0.47 mmol) followed by trimethyl(vinyloxy)silane (0.42 mL, 2.81 mmol) and the vial heated at 70 °C overnight. Additional trimethyl(vinyloxy)silane (105 μL, 0.70 mmol) was added and the mixture heated at 70°C for a further 4 hours. After cooling to room temperature, the mixture was diluted with TBME (40 mL) and filtered through a pad of kieselguhr. The filtrate was concentrated *in vacuo* and purification of the residue by chromatography on silica eluting with 0-100% TBME in heptane afforded the titled compound as a yellow solid.

[1009] 1H NMR (500 MHz, Chloroform-d) δ 8.40 - 8.37 (m, 1H), 8.21 (dd, J = 5.6, 2.2 Hz, 1H), 7.99 - 7.92 (m, 3H), 7.83 (s, 1H), 7.53 (d, J = 2.2 Hz, 1H), 7.02 (d, J = 8.6 Hz, 1H), 4.02 (s, 3H), 3.78 (s, 2H), 2.58 (s, 3H), 1.47 (s, 9H).

[1010] LC-MS (Method E): Rt 1.11 mins; MS m/z 384.1 = [M+H]+ (78% @ 215nm)

Step 2: N-tert-Butyl-4-[[2-[5-(1-hydroxyethyl)-2-methoxyphenyl]acetyl]amino]pyridine-2-carboxamide

[1011]



[1012] A solution of 4-[[2-(5-acetyl-2-methoxy-phenyl)acetyl]amino]-N-tert-butyl-pyridine-2-carboxamide (step 1) (45 mg, 0.09 mmol) in MeOH (1 mL) was treated with $NaBH_4$ (4 mg, 0.1 mmol) and stirred at room temperature for 2 hours. The reaction was quenched by addition to 10% aq. $H3PO_4$ (1 mL) and the mixture extracted with EtOAc (2 × 2 mL). The combined organic extracts were washed with water (2 mL) and brine (2 mL), dried over Na_2SO_4 and concentrated *in vacuo* to afford the titled compound as an off-white solid.

[1013] 1H NMR (500 MHz, DMSO-d6) δ 10.66 (s, 1H), 8.44 (d, J = 5.5 Hz, 1H), 8.19 (d, J = 2.0 Hz, 1H), 8.04 (s, 1H),

7.81 (dd, J = 5.5, 2.2 Hz, 1H), 7.23 - 7.17 (m, 2H), 6.94 - 6.89 (m, 1H), 4.65 (q, J = 6.4 Hz, 1H), 3.73 (s, 3H), 3.68 (s, 2H), 1.40 (s, 9H), 1.29 (d, J = 6.4 Hz, 3H)

[1014] LC-MS (Method E): Rt 1.06 mins; MS m/z 386.1 = [M+H]+ (97% @ 215nm)

Step 3: N-tert-Butyl-4-[[2-[2-hydroxy-5-(1-hydroxyethyl)phenyl]acetyl]amino]pyridine-2-carboxamide

[1015] N-tert-butyl-4-[[2-[5-(1-hydroxyethyl)-2-methoxy-phenyl]acetyl]amino]pyridine-2-carboxamide (step 2) (39 mg, 0.09 mmol) was added to a suspension of 1M BBr3 in DCM (303 μL, 0.3 mmol) in DCM (1 mL) in DCM (1 mL) at 0 - 5°C. After stirring at room temperature for 2 hours, the mixture was concentrated *in vacuo* and the residue partitioned between EtOAc (4 mL) and water (4 mL). The pH of the aqueous layer was adjusted to pH 5-6 with sat. aq. $NaHCO_3$ and the organic layer separated, washed with brine (2 mL), dried over Na_2SO_4 and concentrated *in vacuo.* The residue was dissolved in MeCN:H_2O (1.1 mL, 4:1), filtered and purified by preparative HPLC (acidic pH, early elution method) to afford the titled compound as a beige powder.

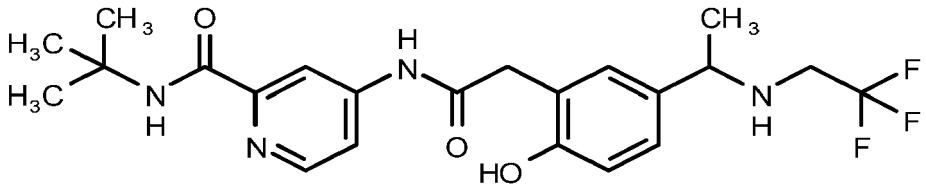
[1016] 1H NMR (500 MHz, DMSO-d6) δ 10.64 (br. s, 1H), 9.34 (br. s, 1H), 8.43 (d, J = 5.5 Hz, 1H), 8.18 (d, J = 1.9 Hz, 1H), 8.03 (s, 1H), 7.82 (dd, J = 5.5, 2.2 Hz, 1H), 7.12 (d, J = 2.1 Hz, 1H), 7.03 (dd, J = 8.2, 2.2 Hz, 1H), 6.73 (d, J = 8.2 Hz, 1H), 4.93 (d, J = 4.1 Hz, 1H), 4.63 - 4.57 (m, 1H), 3.64 (s, 2H), 1.40 (s, 9H), 1.27 (d, J = 6.4 Hz, 3H).

[1017] LC-MS (Method A): Rt 2.45 mins; MS m/z 372.3 = [M+H]+ (99% @ 215nm)

Example 67

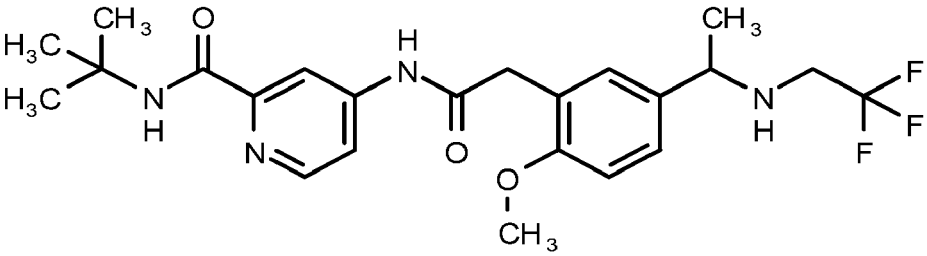
N-tert-Butyl-4-[[2-[2-hydroxy-5-[1-(2,2,2-trifluoroethylamino)ethyl]phenyl] acetyl]amino]pyridine-2-carboxamide

[1018]



Step 1: N-tert-Butyl-4-[[2-[2-methoxy-5-[1-(2,2,2-trifluoroethylamino)ethyl]phenyl]acetyl] **am**ino]pyridine-2-carboxamide

[1019]



[1020] To a solution of 4-[[2-(5-acetyl-2-methoxy-phenyl)acetyl]amino]-N-tert-butyl-pyridine-2-carboxamide (Example 66 step 1)(73 mg, 0.15 mmol) in dichloroethane (1.5 mL) was added the 2,2,2-trifluoroethanamine (14 μL, 0.18 mmol) and acetic acid (17 μL, 0.3 mmol) and the mixture was stirred at room temperature for 30 mins. Sodium triacetoxyborohydride (40 mg, 0.19 mmol) was added and the reaction mixture stirred at room temperature overnight. The resulting mixture was concentrated *in vacuo* and the residue dissolved in EtOAc (4 mL). The mixture was washed with sat. aq. $NaHCO_3$ (4 mL), brine (4 mL), dried over Na_2SO_4 and concentrated *in vacuo.* The residue was purified by preparative HPLC (acidic pH, early elution method) and the product fractions were combined and the pH was adjusted to pH8 using sat. aq. $NaHCO_3$. The mixture was extracted with DCM using a hydrophobic phase separator and the filtrate was concentrated *in vacuo* to afford the titled compound as an off-white solid.

[1021] LC-MS (Method E): Rt 1.07 mins; MS m/z 467.2 = [M+H]+ (99% @ 215nm)

Step 2: N-tert-Butyl-4-[[2-[2-hydroxy-5-[1-(2,2,2-trifluoroethylamino)ethyl]phenyl] acetyl]amino]pyridine-2-carboxamide

[1022] The titled compound was prepared from N-tert-Butyl-4-[[2-[2-methoxy-5-[1-(2,2,2-trifluoroethylamino)ethyl]phenyl]acetyl] amino]pyridine-2-carboxamide (step 1) analogously to Example 66 step 3.

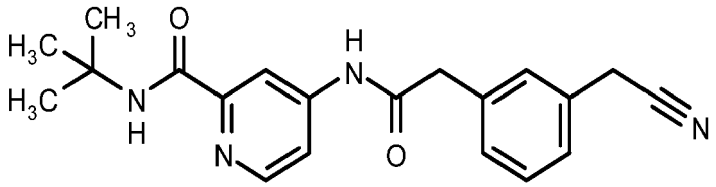
[1023] 1H NMR (500 MHz, DMSO-d6) δ 10.63 (s, 1H), 9.39 (s, 1H), 8.43 (d, J = 5.5 Hz, 1H), 8.18 (d, J = 2.1 Hz, 1H), 8.03 (s, 1H), 7.82 (dd, J = 5.5, 2.2 Hz, 1H), 7.08 (d, J = 2.0 Hz, 1H), 7.04 (dd, J = 8.2, 2.2 Hz, 1H), 6.75 (d, J = 8.2 Hz, 1H), 3.71 - 3.62 (m, 3H), 3.03 - 2.91 (m, 2H), 2.67 (q, J = 8.7, 8.1 Hz, 1H), 1.40 (s, 9H), 1.23 (d, J = 6.6 Hz, 3H).

[1024] LC-MS (Method A): Rt 2.22 mins; MS m/z 453.3 = [M+H]+ (97% @ 215nm)

Example 68

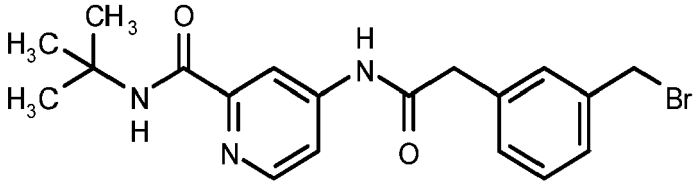
N-tert-Butyl-4-[[2-[3-(cyanomethyl)phenyl]acetyl]amino]pyridine-2-carboxamide

[1025]



Step 1: 4-[[2-[3-(Bromomethyl)phenyl]acetyl]amino]-N-tert-butyl-pyridine-2-carboxamide

[1026]



[1027] The titled compound was prepared from 2-[3-(bromomethyl)phenyl]acetic acid and 4-amino-N-tert-butyl-pyridine-2-carboxamide (Example 3 step 1) analogously to Example 3.5b step 1.

[1028] LC-MS (Method E): Rt 1.20 mins; MS m/z 404.0/406.0 = [M+H]+ (44% @ 215nm)

Step 2: N-tert-Butyl-4-[[2-[3-(cyanomethyl)phenyl]acetyl]amino]pyridine-2-carboxamide

[1029] 4-[[2-[3-(Bromomethyl)phenyl]acetyl]amino]-N-tert-butyl-pyridine-2-carboxamide (Step 1) (50 mg, 0.05 mmol) was treated with sodium cyanide (5 mg, 0.11 mmol) and tetrabutylammonium bromide (2 mg, 0.01 mmol) in a 1:1 mixture of DCM : water (2 mL) and stirred at room temperature for 18 hours. The resulting mixture was diluted with sat. aq. $NaHCO_3$ (5 mL) and extracted into DCM (3 $\times$ 5 mL). The combined organic extracts were concentrated *in vacuo* and the residue was dissolved in DMSO:MeCN (800 μl, 1:1), filtered and purified by preparative HPLC (acidic pH, early elution method) to afford the titled compound as a colourless glassy solid.

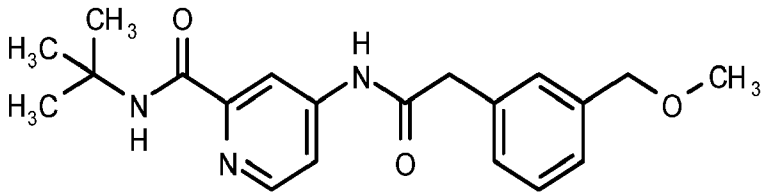
[1030] 1H NMR (500 MHz, DMSO-d6) δ 10.78 (s, 1H), 8.45 (d, J = 5.5 Hz, 1H), 8.18 (d, J = 2.0 Hz, 1H), 8.02 (s, 1H), 7.81 (dd, J = 5.5, 2.2 Hz, 1H), 7.36 (t, J = 7.6 Hz, 1H), 7.33 - 7.28 (m, 2H), 7.24 (d, J = 7.7 Hz, 1H), 4.04 (s, 2H), 3.74 (s, 2H), 1.39 (s, 9H).

[1031] LC-MS (Method A): Rt 3.04 mins; MS m/z 351.2 = [M+H]+ (96% @ 215nm)

Example 69

N-tert-Butyl-4-[[2-[3-(methoxymethyl)phenyl]acetyl]amino]pyridine-2-carboxamide

[1032]



[1033] A vessel was charged with 4-[[2-(3-bromophenyl)acetyl]amino]-N-tert-butyl-pyridine-2-carboxamide (Example 54 step 1)(50 mg, 0.13 mmol) $PdCl_2$dppf (3 mg), potassium trifluoro(methoxymethyl)boranuide (0.45 mL, 0.26 mmol) 2M aq. sodium carbonate (0.26 mL, 0.51 mmol) and heated at 80 °C for 16 hours. The mixture was allowed to cool to room temperature, poured onto water (20 mL) and extracted into EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo.* The residue was dissolved in DMSO:MeCN (800 μl, 1:1), filtered and purified by preparative HPLC (acidic pH, early elution method) to afford the titled compound as an off-white solid.

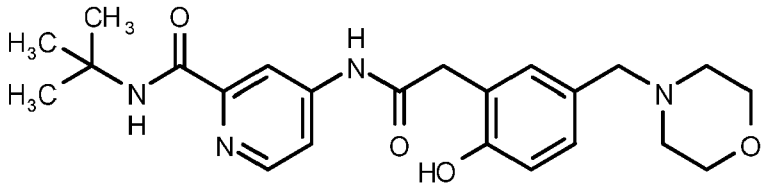
[1034] 1H NMR (500 MHz, DMSO-d6) δ 10.76 (s, 1H), 8.44 (d, J = 5.5 Hz, 1H), 8.18 (d, J = 2.1 Hz, 1H), 8.02 (s, 1H), 7.81 (dd, J = 5.5, 2.2 Hz, 1H), 7.34 - 7.27 (m, 2H), 7.25 (d, J = 7.7 Hz, 1H), 7.20 (d, J = 7.5 Hz, 1H), 4.40 (s, 2H), 3.71 (s, 2H), 3.29 (s, 3H), 1.39 (s, 9H).

[1035] LC-MS (Method C): Rt 3.18 mins; MS m/z 356.3 = [M+H]+ (94% @ 215nm)

Example 70

N-tert-Butyl-4-[[2-[2-hydroxy-5-(morpholinomethyl)phenyl]acetyl]amino]pyridine-2-carboxamide

[1036]



[1037] The titled compound was prepared from 4-[[2-(5-bromo-2-methoxy-phenyl)acetyl]amino]-N-tert-butyl-pyridine-2-carboxamide (Example 6 step 1) and potassium trifluoro(morpholinomethyl)boranuide analogously to Example 27 steps 3 and 4.

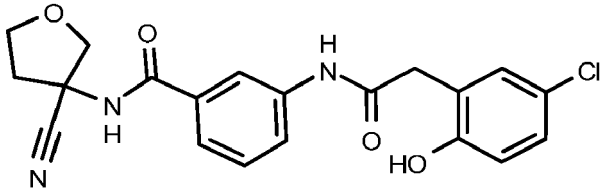
[1038] 1H NMR (500 MHz, DMSO-d6) δ 10.64 (br s, 1H), 9.43 (br s, 1H), 8.43 (d, J = 5.5 Hz, 1H), 8.18 (d, J = 2.1 Hz, 1H), 8.03 (s, 1H), 7.81 (dd, J = 5.5, 2.2 Hz, 1H), 7.06 (d, J = 2.0 Hz, 1H), 6.99 (dd, J = 8.1, 2.1 Hz, 1H), 6.74 (d, J = 8.1 Hz, 1H), 3.64 (s, 2H), 3.55 - 3.51 (m, 4H), 2.34 - 2.25 (m, 4H), 1.40 (s, 9H).

[1039] LC-MS (Method A): Rt 1.66 mins; MS m/z 427.4 = [M+H]+ (98% @ 215nm)

Example 71*

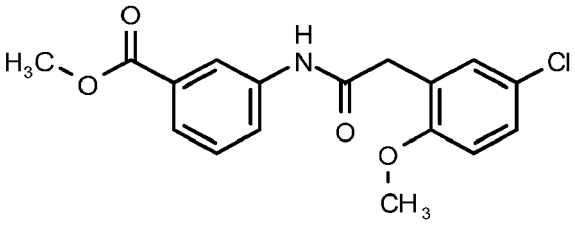
3-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(3-cyanotetrahydrofuran-3-yl)benzamide

[1040]



Step 1: Methyl 3-[[2-(5-chloro-2-methoxy-phenyl)acetyl]amino]benzoate

[1041]



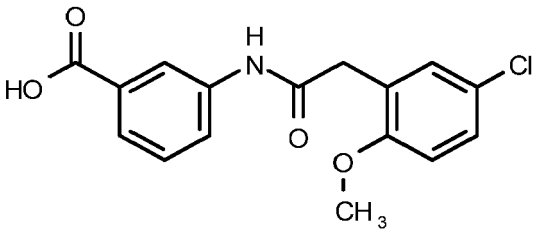
[1042] A solution comprising methyl 3-aminobenzoate (1 g, 6.62 mmol) and 2-(5-chloro-2-methoxy-phenyl)acetic acid (1.39 g, 6.95 mmol) in DMF (10 mL) was treated with DIPEA (1.73 mL, 9.92 mmol) followed by HATU (3019 mg, 7.94 mmol) and stirred at room temperature for 1 hour. The resulting mixture was diluted with water (50 mL) and EtOAc (60 mL) to form a biphasic solution. Heptane (15 ml) was added and the organic portion was separated, washed with water, dried over Na_2SO_4 and concentrated *in vacuo.* The residue was treated with TBME (50 ml) and the resultant suspension filtered, washing with through with TBME and dried *in vacuo* to afford the titled compound as an off-white powdery solid.

[1043] 1H NMR (500 MHz, DMSO-d6) δ 10.31 (s, 1H), 8.28 (t, J = 1.8 Hz, 1H), 7.84 - 7.80 (m, 1H), 7.63 (dt, J = 7.7, 1.2 Hz, 1H), 7.45 (t, J = 7.9 Hz, 1H), 7.29 (dd, J = 6.5, 2.9 Hz, 2H), 7.03 - 6.98 (m, 1H), 3.84 (s, 3H), 3.76 (s, 3H), 3.66 (s, 2H).

[1044] LC-MS (Method E): Rt 1.17 mins; MS m/z 334.0/336.0 = [M+H]+ (98% @ 215nm)

Step 2: 3-[[2-(5-Chloro-2-methoxy-phenyl)acetyl]amino]benzoic acid

[1045]



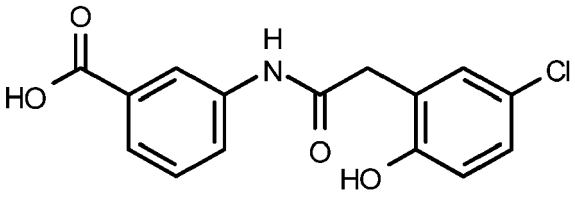
[1046] The titled compound was prepared from methyl 3-[[2-(5-chloro-2-methoxyphenyl)acetyl]amino]benzoate (step 1) analogously to Example 41 step 2.

[1047] 1H NMR (500 MHz, DMSO-d6) δ 12.82 (s, 1H), 10.26 (s, 1H), 8.22 (s, 1H), 7.81 (dd, J = 8.1, 1.1 Hz, 1H), 7.61 (dt, J = 7.7, 1.2 Hz, 1H), 7.41 (t, J = 7.9 Hz, 1H), 7.29 (dd, J = 6.9, 2.7 Hz, 2H), 7.03 - 6.98 (m, 1H), 3.76 (s, 3H), 3.66 (s, 2H).

[1048] LC-MS (Method E): Rt 1.06 mins; MS m/z 319.9/321.7 = [M+H]+ (99% @ 215nm)

Step 3: 3-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]benzoic acid

[1049]



[1050] The titled compound was prepared from 3-[[2-(5-chloro-2-methoxyphenyl)acetyl]amino]benzoic acid (step 2) analogously to Example 41 step 3.

[1051] 1H NMR (500 MHz, DMSO-d6) δ 12.91 (br s, 1H), 10.25 (s, 1H), 9.78 (s, 1H), 8.23 (t, J = 1.8 Hz, 1H), 7.82 (dd, J = 8.1, 1.1 Hz, 1H), 7.61 (dt, J = 7.7, 1.2 Hz, 1H), 7.42 (t, J = 7.9 Hz, 1H), 7.21 (d, J = 2.7 Hz, 1H), 7.11 (dd, J = 8.6, 2.7 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 3.62 (s, 2H).

[1052] LC-MS (Method E): Rt 1.01 mins; MS m/z 305.9/308.0 = [M+H]+ (99% @ 215nm)

Step 4: 3-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(3-cyanotetrahydrofuran-3-yl)benzamide

[1053] To a solution of 3-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]benzoic acid (step 3) (150 mg, 0.49 mmol), 3-aminotetrahydrofuran-3-carbonitrile hydrochloride (73 mg, 0.49 mmol) and DIPEA (343 μL, 1.96 mmol) in DMF (1.5 mL) was added HATU (224 mg, 0.59 mmol) and the reaction mixture was stirred at room temperature for 16 hours. The resulting mixture was diluted with EtOAc and washed with 1M NaOH (3 x 20 mL). The aqueous layer was extracted into EtOAc (2 x 10 mL), then acidified with 1M HCl and the remaining product extracted into EtOAc (3 x 30 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo.* Purification by preparative HPLC (acidic pH, early elution method) afforded the titled compound as an off-white solid.

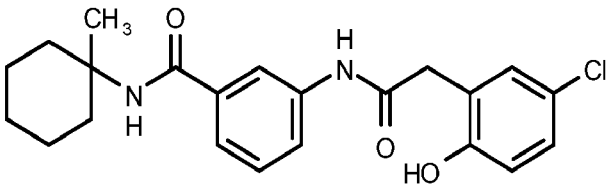
[1054] 1H NMR (500 MHz, DMSO-d6) δ 10.29 (s, 1H), 9.82 (br s, 1H), 9.21 (s, 1H), 8.08 (t, J = 1.8 Hz, 1H), 7.81 (dd, J = 8.1, 1.1 Hz, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.43 (t, J = 7.9 Hz, 1H), 7.21 (d, J = 2.7 Hz, 1H), 7.11 (dd, J = 8.6, 2.7 Hz, 1H), 6.81 (d, J = 8.6 Hz, 1H), 4.26 (d, J = 9.5 Hz, 1H), 3.96 (d, J = 9.5 Hz, 1H), 3.94 - 3.86 (m, 2H), 3.62 (s, 2H), 2.62 - 2.55 (m, 2H).

[1055] LC-MS (Method A): Rt 2.64 mins; MS m/z 400.3/402.2 = [M+H]+ (99% @ 215nm)

Example 71.1*

3-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1-methylcyclohexyl)benzamide

[1056]



[1057] The titled compound was prepared from 3-[[2-(5-chloro-2-hydroxyphenyl)acetyl]amino]benzoic acid (Example 71 step 3) and 1-methylcyclohexanamine analogously to Example 71.

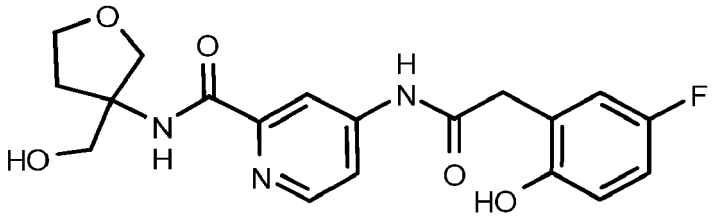
[1058] 1H NMR (500 MHz, Methanol-d4) δ 7.94 (t, J = 1.8 Hz, 1H), 7.75 - 7.72 (m, 1H), 7.51 - 7.47 (m, 1H), 7.42 (t, J = 7.9 Hz, 1H), 7.24 (d, J = 2.6 Hz, 1H), 7.12 (dd, J = 8.6, 2.6 Hz, 1H), 6.83 (s, 1H), 3.72 (s, 2H), 2.27 (d, J = 13.1 Hz, 2H), 1.68- 1.56 (m, 5H), 1.54 - 1.47 (m, 2H), 1.46 (s, 3H), 1.45 - 1.36 (m, 1H).

[1059] LC-MS (Method A): Rt 3.58 mins; MS m/z 401.2/403.2 = [M+H]+ (96% @ 215nm)

Example 72

4-[[2-(5-Fluoro-2-hydroxy-phenyl)acetyl]amino]-N-[3-(hydroxymethyl)tetrahydro furan-3-yl]pyridine-2-carboxamide

[1060]



[1061] The titled compound was prepared from 4-[[2-(5-fluoro-2-hydroxyphenyl)acetyl]amino]pyridine-2-carboxylic acid (Example 49 steps 1-3) and (3-aminotetrahydrofuran-3-yl)methanol analogously to Example 35.

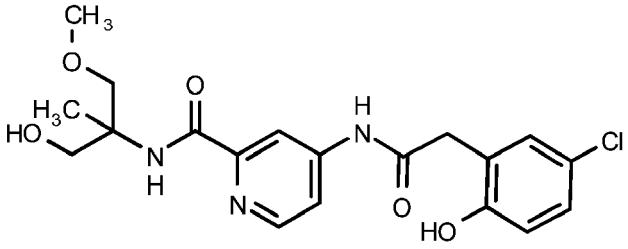
[1062] 1H NMR (500 MHz, DMSO-d6) δ 9.52 (br s, 1H), 8.47 (d, J = 5.5 Hz, 1H), 8.42 (s, 1H), 8.20 (d, J = 2.1 Hz, 1H), 7.83 (dd, J = 5.5, 2.2 Hz, 1H), 7.02 (dd, J = 9.4, 3.2 Hz, 1H), 6.91 (td, J = 8.6, 3.2 Hz, 1H), 6.79 - 6.75(m, 1H), 5.17 (s, 1H), 3.90 - 3.77 (m, 4H), 3.67 (s, 2H), 3.62 (s, 2H), 2.35 - 2.29 (m, 1H), 2.01 - 1.95 (m, 1H).

[1063] LC-MS (Method A): Rt 1.99 mins; MS m/z 390.2/392.3 = [M+H]+ (100% @ 215nm)

Example 73

4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[1-(hydroxymethyl)-2-methoxy-1-methyl-ethyl]pyridine-2-carboxamide

[1064]



[1065] The titled compound was prepared from 4-[[2-(5-chloro-2-hydroxyphenyl)acetyl]amino]pyridine-2-carboxylic acid (Example 31, step 1) and 2-amino-3-methoxy-2-methyl-propan-1-ol hydrochloride (prepared according to Tetrahedron, Volume 56, Issue 23, 2 June 2000, Pages 3799-3816) analogously to Example 35.

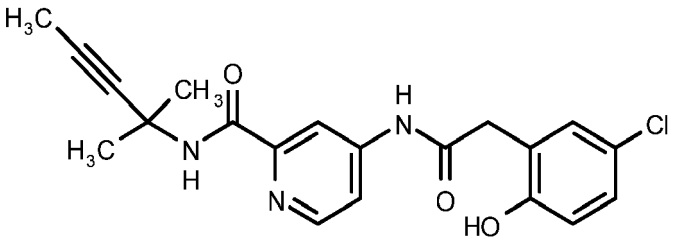
[1066] 1H NMR (500 MHz, Methanol-d4) δ 8.45 (dd, J = 5.5, 0.5 Hz, 1H), 8.19 - 8.14 (m, 1H), 7.91 (dd, J = 5.5, 2.2 Hz, 1H), 7.20 (d, J = 2.6 Hz, 1H), 7.10 (dd, J = 8.6, 2.6 Hz, 1H), 6.79 (d, J = 8.6 Hz, 1H), 3.83 (d, J = 11.1 Hz, 1H), 3.76 - 3.69 (m, 3H), 3.65 (d, J = 9.1 Hz, 1H), 3.59 (d, J = 9.1 Hz, 1H), 3.42 (s, 3H), 1.44 (s, 3H).

[1067] LC-MS (Method A): Rt 2.63 mins; MS m/z 408.2 = [M+H]+ (99% @ 215nm)

Example 73.1

4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1,1-dimethylbut-2-ynyl) pyridine-2-carboxamide

[1068]



[1069] The titled compound was prepared from 4-[[2-(5-chloro-2-hydroxyphenyl)acetyl]amino]pyridine-2-carboxylic acid (Example 31, step 1) and 2-methylpent-3-yn-2-amine hydrochloride (prepared according to WO 03048128A1 page 55) analogously to Example 73.

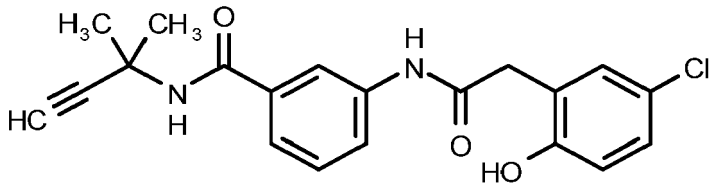
[1070] 1H NMR (500 MHz, DMSO-d6) δ 10.70 (br s, 1H), 9.81 (br s, 1H), 8.46 (d, J = 5.5 Hz, 1H), 8.25 (s, 1H), 8.18 (d, J = 2.0 Hz, 1H), 7.82 (dd, J = 5.5, 2.2 Hz, 1H), 7.22 (d, J = 2.7 Hz, 1H), 7.12 (dd, J = 8.6, 2.7 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 3.67 (s, 2H), 1.78 (s, 3H), 1.63 (s, 6H).

[1071] LC-MS (Method A): Rt 3.31 mins; MS m/z 386.3/388.2 = [M+H]+ (97% @ 215nm)

Example 74*

3-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1,1-dimethylprop-2-ynyl)benzamide

[1072]



[1073] 2-Methylbut-3-yn-2-amine (49 mg, 0.59 mmol) and 3-[[2-(5-chloro-2-hydroxyphenyl)acetyl]amino]benzoic acid (Example 71, step 3)(150 mg, 0.49 mmol) were dissolved in DMF (1 mL) and treated with TEA (0.26 mL, 1.47 mmol) followed by HATU (224 mg, 0.59 mmol) and stirred for 2 hours. The resulting mixture was diluted with EtOAc and washed with sat. aq. Na_2CO_3 (10 mL). The aqueous layer was extracted with EtOAc (2 x 10 mL) and the combined organic extracts were washed with 1M NaOH (3 x 20 mL). The aqueous layer was acidified with 1M HCl and the remaining product extracted into EtOAc (3 x 30 mL). The combined organic extracts were neutralised with a saturated aqueous sodium bicarbonate wash, dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by preparative HPLC (acidic pH, early elution method) to afford the titled compound as an off-white foamy solid.

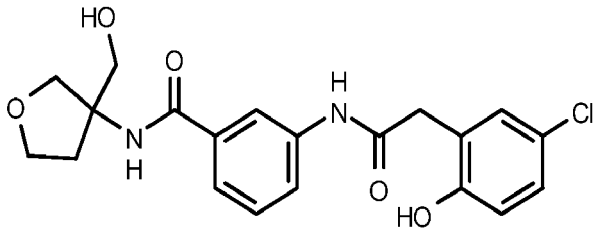
[1074] 1H NMR (500 MHz, DMSO-d6) δ 10.21 (s, 1H), 9.79 (s, 1H), 8.20 (s, 1H), 7.94 (t, J = 1.8 Hz, 1H), 7.80 - 7.74 (m, 1H), 7.47 - 7.42 (m, 1H), 7.36 (t, J = 7.9 Hz, 1H), 7.20 (d, J = 2.7 Hz, 1H), 7.11 (dd, J = 8.6, 2.7 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 3.61 (s, 2H), 3.08 (s, 1H), 1.59 (s, 6H).

[1075] LC-MS (Method A): Rt 2.92 mins; MS m/z 371.2/373.2 = [M+H]+ (97% @ 215nm)

Example 74.1*

3-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[3-(hydroxymethyl)tetra hydrofuran-3-yl]benzamide

[1076]



[1077] The titled compound was prepared from 3-[[2-(5-chloro-2-hydroxyphenyl)acetyl]amino]benzoic acid (Example 71, step 3) and (3-aminotetrahydrofuran-3-yl)methanol analogously to Example 74.

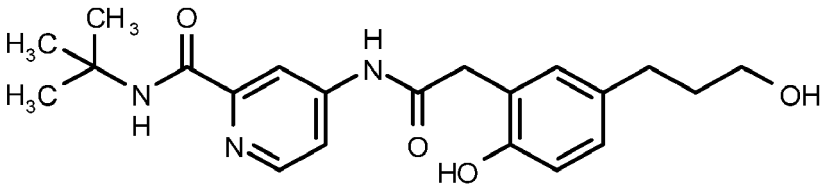
[1078] 1H NMR (500 MHz, DMSO-d6) δ 10.20 (s, 1H), 9.80 (s, 1H), 8.12 (s, 1H), 7.95 (t, J = 1.8 Hz, 1H), 7.81 - 7.74 (m, 1H), 7.53 - 7.47 (m, 1H), 7.36 (t, J = 7.9 Hz, 1H), 7.20 (d, J = 2.7 Hz, 1H), 7.11 (dd, J = 8.6, 2.7 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 4.97 (t, J = 5.8 Hz, 1H), 3.89 (d, J = 9.2 Hz, 1H), 3.81 - 3.73 (m, 3H), 3.67 (dd, J = 10.8, 5.7 Hz, 1H), 3.64 - 3.59 (m, 3H), 2.23 (dt, J = 12.8, 6.4 Hz, 1H), 2.05 (dt, J = 12.9, 7.7 Hz, 1H).

[1079] LC-MS (Method A): Rt 2.24 mins; MS m/z 405.2/407.2 = [M+H]+ (100% @ 215nm)

Example 75

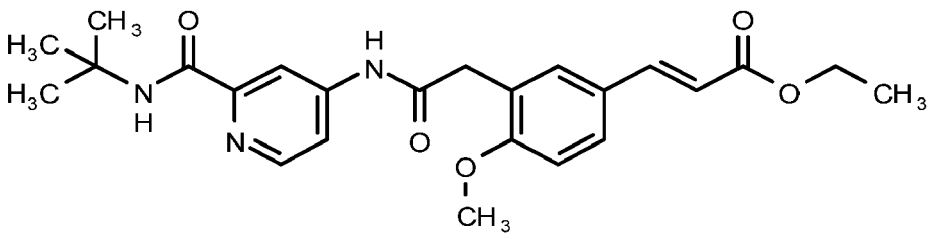
N-tert-Butyl-4-[[2-[2-hydroxy-5-(3-hydroxypropyl)phenyl]acetyl]amino]pyridine-2-carboxamide

[1080]



Step 1: Ethyl (E)-3-[3-[2-[[2-(tert-butylcarbamoyl)-4-pyridyl]amino]-2-oxo-ethyl]-4-methoxy-phenyl]prop-2-enoate

[1081]



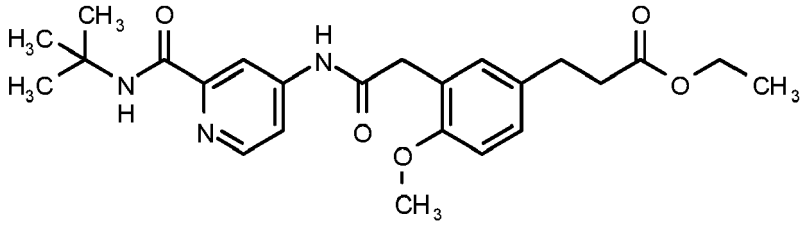
[1082] A mixture comprising 4-[[2-(5-bromo-2-methoxy-phenyl)acetyl]amino]-N-tert-butylpyridine-2-carboxamide (Example 6 step 1)(500 mg, 1.19 mmol), ethyl prop-2-enoate (0.52 mL, 4.76 mmol), $Pd_2(dba)_3$ (109 mg, 0.12 mmol), tri-o-tolyl phosphine (109 mg, 0.36 mmol), TEA (1.04 mL, 5.95 mmol) in DMF (10mL) under a nitrogen atmosphere was stirred at 90 °C for 18 hours. The resulting mixture was filtered, diluted with EtOAc (10 mL) and washed with brine (1 × 10 mL). The brine was re-extracted with EtOAc (2 × 10 mL) and the combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by chromatography on silica eluting with 0-100% EtOAc in heptane to afford the titled compound as an orange/brown solid.

[1083] 1H NMR (250 MHz, DMSO-d6) δ 10.69 (s, 1H), 8.44 (d, J = 5.6 Hz, 1H), 8.19 - 8.16 (m, 1H), 8.03 (s, 1H), 7.81 (dd, J = 5.5, 2.2 Hz, 1H), 7.67 - 7.60 (m, 2H), 7.56 (s, 1H), 7.04 (d, J = 9.2 Hz, 1H), 6.46 (d, J = 16.0 Hz, 1H), 4.17 (q, J = 7.1 Hz, 2H), 3.80 (s, 3H), 3.72 (s, 2H), 1.40 (s, 9H), 1.25 (t, J = 7.1 Hz, 3H).

[1084] LC-MS (Method E): Rt 1.23 mins; MS m/z 440.0 = [M+H]+ (65% @ 215nm)

Step 2: Ethyl 3-[3-[2-[[2-(tert-butylcarbamoyl)-4-pyridyl]amino]-2-oxo-ethyl]-4-methoxyphenyl]propanoate

[1085]



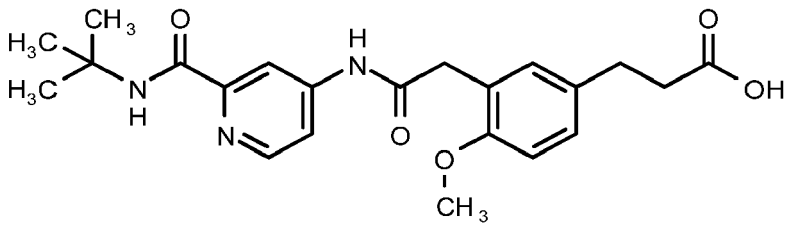
[1086] Ethyl (E)-3-[3-[2-[[2-(tert-butylcarbamoyl)-4-pyridyl]amino]-2-oxo-ethyl]-4-methoxyphenyl]prop-2-enoate (step 1)(625 mg, 0.92 mmol) in EtOH (9.24 mL) under nitrogen, was treated with 10 % Pd-C (50%w/w, 20 mg, 0.09 mmol) and placed under hydrogen. After stirring at room temperature for 19 hours, the mixture was filtered through kieselguhr (diatomaceous earth) and washed with through with EtOAc. The filtrate was concentrated *in vacuo* to afford the titled compound as an off-white solid.

[1087] 1H NMR (250 MHz, DMSO-d6) δ 10.64 (s, 1H), 8.43 (d, J = 5.5 Hz, 1H), 8.18 (d, J = 1.8 Hz, 1H), 8.03 (s, 1H), 7.81 (dd, J = 5.5, 2.2 Hz, 1H), 7.13 - 7.04 (m, 2H), 6.89 (d, J = 8.3 Hz, 1H), 4.02 (qd, J = 7.1, 1.1 Hz, 2H), 3.72 (s, 3H), 3.65 (s, 2H), 2.78 (t, J = 7.4 Hz, 2H), 2.60 - 2.52 (m, 2H), 1.40 (s, 9H), 1.14 (t, J = 7.2 Hz, 3H).

[1088] LC-MS (Method E): Rt 1.23 mins; MS m/z 442.3 = [M+H]+ (61% @ 215nm)

Step 3: 3-[3-[2-[[2-(tert-Butylcarbamoyl)-4-pyridyl]amino]-2-oxo-ethyl]-4-methoxy-phenyl] propanoic acid

[1089]



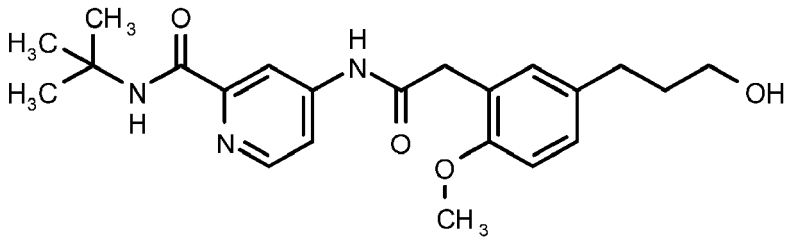
[1090] To a solution of ethyl 3-[3-[2-[[2-(tert-butylcarbamoyl)-4-pyridyl]amino]-2-oxo-ethyl]-4-methoxy-phenyl]propanoate (step 2) (332 mg, 0.75 mmol) in THF (4.3 mL)/water (1 mL), 1M LiOH (631 mg, 15.04 mmol) was added and the reaction mixture was stirred at room temperature for 5.5 hours. The resulting mixture was extracted with EtOAc and the aqueous layer was diluted with water and acidified to pH 3-4 with 6M HCl. The resulting mixture was extracted with EtOAc (3 × 25 ml) and the combined organic extracts were filtered, dried over Na_2SO_4 and concentrated *in vacuo* to afford the titled compound as a yellow oil.

[1091] 1H NMR (500 MHz, DMSO-d6) δ 10.64 (s, 1H), 8.43 (d, J = 5.5 Hz, 1H), 8.18 (d, J = 2.0 Hz, 1H), 8.03 (s, 1H), 7.81 (dd, J = 5.5, 2.2 Hz, 1H), 7.11 - 7.06 (m, 2H), 6.89 (d, J = 8.3 Hz, 1H), 3.72 (s, 3H), 3.66 (s, 2H), 2.75 (t, J = 7.7 Hz, 2H), 1.40 (s, 9H).

[1092] LC-MS (Method E): Rt 1.08 mins; MS m/z 414.2 = [M+H]+ (79% @ 215nm)

Step 4: N-tert-Butyl-4-[[2-[5-(3-hydroxypropyl)-2-methoxy-phenyl]acetyl]amino]pyridine-2-carboxamide

[1093]



[1094] To a cooled (0 °C) solution of 3-[3-[2-[[2-(tert-butylcarbamoyl)-4-pyridyl]amino]-2-oxoethyl]-4-methoxy-phenyl]propanoic acid (step 3)(196 mg, 0.47 mmol) in THF (3.96 mL) was added TEA (0.17 mL, 1.19 mmol) followed by the dropwise addition of methyl carbonochloridate (0.09 mL, 1.19 mmol). The reaction mixture was stirred for 30 minutes at 0 °C then treated with $NaBH_4$ (90 mg, 2.37 mmol) followed by dropwise addition of MeOH (0.5 mL). After stirring at 0°C for a further 90 minutes, the mixture was diluted with water and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with saturated $NaHCO_3$ (10 mL), brine (20 mL) then dried over Na_2SO_4 and concentrated *in vacuo.* The residue was purified by chromatography on silica eluting with 0-100% EtOAc in heptane to afford the titled compound as an off-white solid.

[1095] 1H NMR (500 MHz, DMSO-d6) δ 10.64 (s, 1H), 8.43 (d, J = 5.5 Hz, 1H), 8.18 (d, J = 2.1 Hz, 1H), 8.03 (s, 1H), 7.81 (dd, J = 5.5, 2.2 Hz, 1H), 7.08 - 7.03 (m, 2H), 6.88 (d, J = 8.3 Hz, 1H), 4.42 (t, J = 5.1 Hz, 1H), 3.72 (s, 3H), 3.66 (s, 2H), 3.40 (q, J = 6.4 Hz, 2H), 1.71 - 1.64 (m, 2H), 1.40 (s, 9H).

[1096] LC-MS (Method E): Rt 1.09 mins; MS m/z 400.1 = [M+H]+ (100% @ 215nm)

Step 5: N-tert-Butyl-4-[[2-[2-hydroxy-5-(3-hydroxypropyl)phenyl]acetyl]amino]pyridine-2-carboxamide

[1097] The titled compound was prepared from N-tert-butyl-4-[[2-[5-(3-hydroxypropyl)-2-methoxy-phenyl]acetyl]amino]pyridine-2-carboxamide (step 4) analogously to Example 41 step 3.

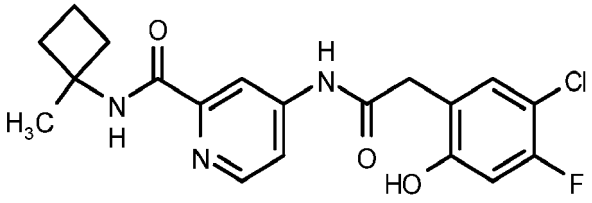
[1098] 1H NMR (500 MHz, Methanol-d4) δ 8.41 (d, J = 5.5 Hz, 1H), 8.10 (d, J = 2.0 Hz, 1H), 7.90 (dd, J = 5.5, 2.2 Hz, 1H), 7.02 (d, J = 2.0 Hz, 1H), 6.96 (dd, J = 8.2, 2.2 Hz, 1H), 6.74 (d, J = 8.2 Hz, 1H), 3.70 (s, 2H), 3.55 (t, J = 6.5 Hz, 2H), 2.63 - 2.54 (m, 2H), 1.84 - 1.75 (m, 2H), 1.47 (s, 9H).

[1099] LC-MS (Method A): Rt 2.57 mins; MS m/z 386.3 = [M+H]+ (97% @ 215nm)

Example 76

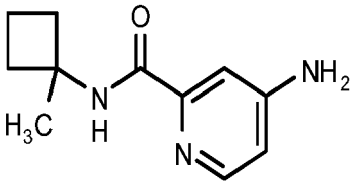
4-[[2-(5-Chloro-4-fluoro-2-hydroxy-phenyl)acetyl]amino]-N-(1-methylcyclo butyl)pyridine-2-carboxamide

[1100]



Step 1: 4-Amino-N-(1-methylcyclobutyl)pyridine-2-carboxamide

[1101]



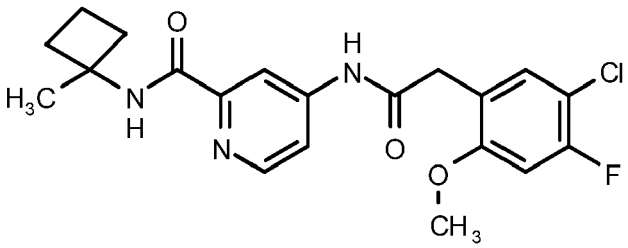
[1102] 4-Aminopyridine-2-carboxylic acid (700 mg, 5.07 mmol) and DIPEA (3.54 mL, 20.27 mmol) were suspended in DMF (39 mL) and treated with 1-methylcyclobutanamine hydrochloride (924 mg, 7.6 mmol) and HATU (2312 mg, 6.08 mmol). After stirring at room temperature for 4 days the reaction mixture was filtered and the solid washed with DMF (2 × 2 mL). The filtrate was concentrated *in vacuo* and the crude residue dissolved in EtOAc (20 mL) and washed with sat. $NaHCO_3$ solution (20 mL). The aqueous layer was re-extracted with EtOAc (20 mL) and the combined organic layers were washed with brine (2 × 20 mL), dried over Na_2SO_4 and concentrated *in vacuo.* Purification of the crude residue by C18 reverse phase chromatography eluting with 5-100% MeCN in water afforded the titled compound as a white solid

[1103] 1H NMR (500 MHz, DMSO-d6) δ 8.42 (s, 1H), 7.99 (d, J = 5.7 Hz, 1H), 7.17 (d, J = 2.3 Hz, 1H), 6.60 (dd, J = 5.7, 2.3 Hz, 1H), 6.53 (br s, 2H), 2.40 - 2.32 (m, 2H), 2.00 - 1.94 (m, 2H), 1.83 - 1.76 (m, 2H), 1.45 (s, 3H).

[1104] LC-MS (Method E): Rt 0.62 mins; MS m/z 206.0 = [M+H]+ (99% @ 215nm)

Step 2: 4-[[2-(5-Chloro-4-fluoro-2-methoxy-phenyl)acetyl]amino]-N-(1-methylcyclobutyl)pyridine-2-carboxamide

[1105]



[1106] A solution of 4-amino-N-(1-methylcyclobutyl)pyridine-2-carboxamide (step 1)(81 mg, 0.4 mmol) and 2-(5-chloro-4-fluoro-2-methoxy-phenyl)acetic acid (100 mg, 0.36 mmol) in DMF (1.9 mL) was treated with TEA (0.16 mL, 0.9 mmol) and T3P® (50% solution in EtOAc) (0.21 mL, 0.72 mmol) and stirred at room temperature for 17 hours. The reaction was quenched with sat $NaHCO_3$ (2 mL) and extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4 and concentrated in *vacuo.* The residue was purified by chromatography on silica eluting with 0-100% EtOAc in heptane to afford the titled compound as an off-white solid.

[1107] 1H NMR (500 MHz, Methanol-d4) δ 8.49 - 8.47 (m, 1H), 8.15 (dd, *J* = 2.2, 0.4 Hz, 1H), 7.92 (dd, J = 5.5, 2.2 Hz, 1H), 7.37 (d, J = 8.4 Hz, 1H), 6.97 (d, J = 11.2 Hz, 1H), 3.86 (s, 3H), 3.74 (s, 2H), 2.49 (dd, J = 9.7, 2.4 Hz, 2H), 2.19 - 2.13 (m, 2H), 1.99 - 1.93 (m, 2H), 1.59 (s, 3H).

[1108] LC-MS (Method E): Rt 1.22 mins; MS m/z 406.1/408.2 = [M+H]+ (79% @ 215nm)

Step 3: 4-[[2-(5-Chloro-4-fluoro-2-hydroxy-phenyl)acetyl]amino]-N-(1-methylcyclo butyl)pyridine-2-carboxamide

[1109] The titled compound was prepared from 4-[[2-(5-chloro-4-fluoro-2-methoxyphenyl)acetyl]amino]-N-(1-methylcyclobutyl)pyridine-2-carboxamide (step 2) analogously to Example 41 step 3.

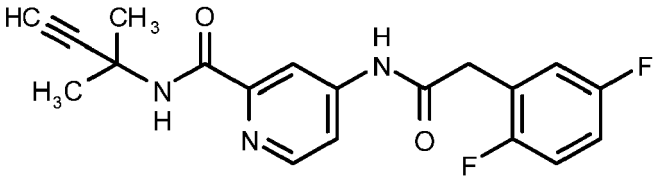
[1110] 1H NMR (500 MHz, DMSO-d6) δ 10.76 (br s, 1H), 10.32 (br s, 1H), 8.48 - 8.43 (m, 2H), 8.13 (d, J = 2.1 Hz, 1H), 7.81 (dd, J = 5.5, 2.2 Hz, 1H), 7.35 (d, J = 8.7 Hz, 1H), 6.75 (d, J = 11.0 Hz, 1H), 3.65 (s, 2H), 2.43 - 2.38 (m, 2H), 2.03 - 1.96 (m, 2H), 1.85 - 1.77 (m, 2H), 1.47 (s, 3H).

[1111] LC-MS (Method A): Rt 3.34 mins; MS m/z 392.2/394.2 = [M+H]+ (100% @ 215nm)

Example 77

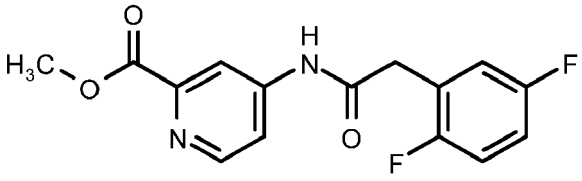
4-[[2-(2,5-Difluorophenyl)acetyl]amino]-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide

[1112]



Step 1: Methyl 4-[[2-(2,5-difluorophenyl)acetyl]amino]pyridine-2-carboxylate

[1113]



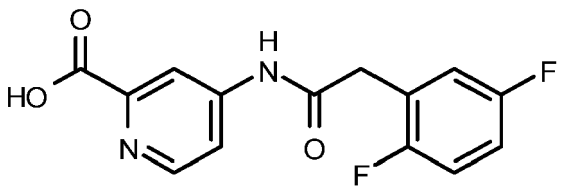
[1114] 2-(2,5-Difluorophenyl)acetic acid (407 mg, 2.37 mmol) was dissolved in thionyl chloride (1.8 mL, 20.43 mmol) and the mixture heated at 70 °C for 1h. The resulting mixture was concentrated *in vacuo* and the residue azeotropically dried with toluene. The crude acid chloride was dissolved in DCM (4 mL) and added dropwise to a cooled (0°C) solution of methyl 4-aminopyridine-2-carboxylate (300 mg, 1.97 mmol) and DIPEA (0.69 mL, 3.94 mmol) in DCM (6 mL). The mixture was allowed to warm to room temperature and stirred overnight. The resulting mixture was transferred to a separating funnel and washed sequentially with water (10 mL) and sat. $NaHCO_3$ solution (10 mL). The organic portion was separated, dried over Na_2SO_4 and concentrated *in vacuo.* Purification of the crude material by chromatography on silica eluting with 50-100% EtOAc in heptane afforded the titled compound as a colourless glass.

[1115] 1H NMR (500 MHz, Chloroform-d) δ 8.56 (d, J = 5.2 Hz, 1H), 8.04 (s, 1H), 7.89 - 7.81 (m, 2H), 7.12 - 7.06 (m, 2H), 7.04 - 6.99 (m, 1H), 3.98 (s, 3H), 3.76 - 3.74 (m, 2H)

[1116] LC-MS (Method E): Rt 0.99 mins; MS m/z 307.0 = [M+H]+

Step 2: 4-[[2-(2,5-Difluorophenyl)acetyl]amino]pyridine-2-carboxylic acid

[1117]



[1118] To a solution of methyl 4-[[2-(2,5-difluorophenyl)acetyl]amino]pyridine-2-carboxylate (step 1)(364 mg, 1.07 mmol) in THF (2 mL)/MeOH(2 mL)/water (2 mL) was added 1M LiOH (31 mg, 1.28 mmol) and the mixture stirred at room temperature overnight. A further 0.5 equivalent of 1M LiOH was added and stirring continued for 2 hours. The resulting mixture was acidified to pH 2 using 1M HCl solution (2 mL) resulting in the formation of a precipitate. Water (5 mL) was added to the mixture, stirred for 5 mins and the solid was filtered and dried in a vacuum oven to afford the titled compound as a colourless powder. 1H NMR (500 MHz, DMSO-d6) δ 10.87 (s, 1H), 8.55 (d, J = 5.5 Hz, 1H), 8.27 (d, J = 2.0 Hz, 1H), 7.79 (dd, J = 5.6, 2.2 Hz, 1H), 7.31 - 7.27 (m, 1H), 7.26 - 7.22 (m, 1H), 7.20 - 7.15 (m, 1H), 3.83 (s, 2H).
[1119] LC-MS (Method E): Rt 0.83 mins; MS m/z 293.0 = [M+H]+

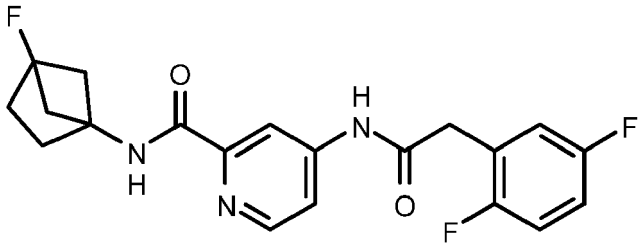
Step 3: 4-[[2-(2,5-Difluorophenyl)acetyl]amino]-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide

[1120] To a solution of 4-[[2-(2,5-difluorophenyl)acetyl]amino]pyridine-2-carboxylic acid (step 2) (50 mg, 0.16 mmol) and DIPEA (60 μL, 0.34 mmol) in DMF (1 mL) was added HATU (68 mg, 0.18 mmol) and the mixture stirred for 5 mins then treated with 2-methylbut-3-yn-2-amine (19 μL, 0.18 mmol). The resulting mixture was stirred at room temperature for 1 hour and then diluted with EtOAc. The mixture was washed with 1M HCl solution, brine, dried over Na_2SO_4 and concentrated *in vacuo.* The crude residue was purified by preparative HPLC to afford the titled compound as a colourless powder.
[1121] 1H NMR (500 MHz, DMSO-d6) δ 10.85 (s, 1H), 8.48 (d, J = 5.5 Hz, 1H), 8.32 (s, 1H), 8.18 (d, J = 1.9 Hz, 1H), 7.82 (dd, J = 5.5, 2.2 Hz, 1H), 7.31 - 7.27 (m, 1H), 7.24 (dt, J = 9.1, 4.6 Hz, 1H), 7.21 - 7.14 (m, 1H), 3.83 (s, 2H), 3.21 (s, 1H), 1.64 (s, 6H).
[1122] LC-MS (Method A): Rt 3.16 mins; MS m/z 358.2 = [M+H]+

Example 77.1

4-[[2-(2,5-Difluorophenyl)acetyl]amino]-N-(4-fluoro-1-bicyclo[2.1.1]hexanyl) pyridine-2-carboxamide

[1123]

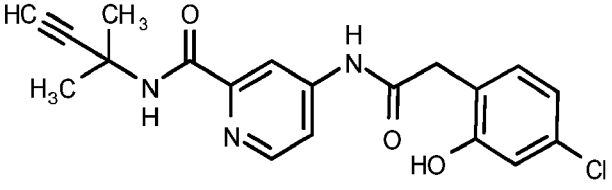


[1124] The titled compound was prepared from 4-[[2-(2,5-difluorophenyl)acetyl]amino]pyridine-2-carboxylic acid (Example 77 step 2) and 4-fluorobicyclo[2.1.1]hexan-1-amine hydrochloride analogously to Example 77 step 3.
[1125] 1H NMR (500 MHz, DMSO-d6) δ 10.83 (s, 1H), 9.05 (s, 1H), 8.48 (d, J = 5.5 Hz, 1H), 8.14 (d, J = 2.1 Hz, 1H), 7.82 (dd, J = 5.5, 2.2 Hz, 1H), 7.31 - 7.27 (m, 1H), 7.27 - 7.22 (m, 1H), 7.20 - 7.15 (m, 1H), 3.83 (s, 2H), 2.13 - 2.09 (m, 2H), 2.08 - 2.04 (m, 2H), 1.99 - 1.95 (m, 2H), 1.86 - 1.82 (m, 2H).
[1126] LC-MS (Method A): Rt 3.28 mins; MS m/z 390.2 = [M+H]+

Example 78

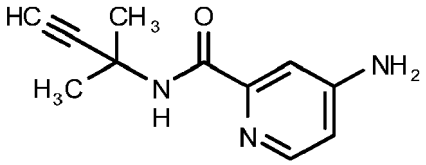
4-[[2-(4-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide

[1127]



Step 1: 4-Amino-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide

[1128]



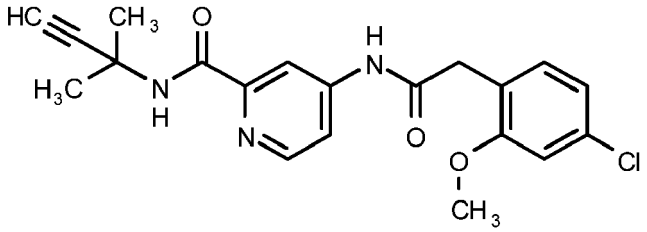
[1129] To a mixture of 4-aminopyridine-2-carboxylic acid (2 g, 14.48 mmol), TBTU (5.58 g, 17.38 mmol) and TEA (2.42 mL, 17.38 mmol) in DMF (36 mL) was added 2-methylbut-3-yn-2-amine (22.82 mL, 17.38 mmol) and the mixture was stirred at room temperature for 3 days. The reaction mixture was filtered and the filtrate concentrated *in vacuo*. The crude residue was dissolved in EtOAc (40 mL) and washed with sat. $NaHCO_3$ solution (40 mL). The aqueous was further extracted with EtOAc (40 mL) and the combined organic portions were washed with brine (2 × 40 mL), dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The crude material was triturated with the minimum amount of ether at 0°C to afford the titled compound as an off-white crystalline solid.

[1130] 1H NMR (500 MHz, DMSO-d6) δ 8.23 (s, 1H), 7.99 (d, J = 5.6 Hz, 1H), 7.19 (d, J = 2.3 Hz, 1H), 6.59 (dd, J = 5.6, 2.4 Hz, 1H), 6.36 (s, 2H), 3.19 (s, 1H), 1.62 (s, 6H).

[1131] LC-MS (Method F): Rt 1.28 mins; MS m/z 204.3 = [M+H]+

Step 2: 4-[[2-(4-Chloro-2-methoxy-phenyl)acetyl]amino]-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide

[1132]



[1133] The titled compound was prepared from 4-amino-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide (step 1) and 2-(4-chloro-2-methoxy-phenyl)acetic acid analogously to Example 3.5b.

[1134] 1H NMR (500 MHz, DMSO-d6) δ 10.71 (s, 1H), 8.47 (d, J = 5.5 Hz, 1H), 8.32 (s, 1H), 8.19 (d, J = 2.1 Hz, 1H), 7.83 (dd, J = 5.5, 2.2 Hz, 1H), 7.25 (d, J = 8.1 Hz, 1H), 7.07 (d, J = 2.0 Hz, 1H), 6.99 (dd, J = 8.0, 2.0 Hz, 1H), 3.79 (s, 3H), 3.70 (s, 2H), 3.21 (s, 1H), 1.65 (s, 6H).

[1135] LC-MS (Method A): Rt 3.44mins; MS m/z 386.2/388.2 = [M+H]+ (96% @ 215nm)

Step 3: 4-[[2-(4-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide

[1136] The titled compound was prepared from 4-[[2-(4-chloro-2-methoxy-phenyl)acetyl]amino]-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide(step 2) analogously to Example 3 step 3.

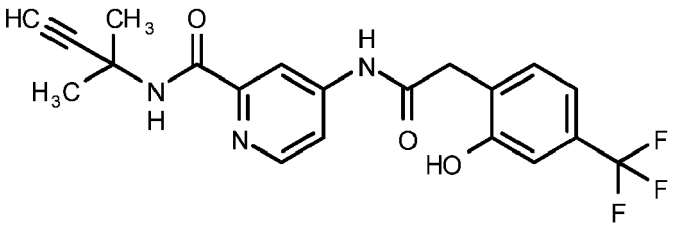
[1137] 1H NMR (500 MHz, DMSO-d6) δ 10.71 (br s, 1H), 10.04 (br s, 1H), 8.46 (d, J = 5.5 Hz, 1H), 8.31 (s, 1H), 8.18 (d, J = 1.9 Hz, 1H), 7.83 (dd, J = 5.5, 2.2 Hz, 1H), 7.17 (d, J = 7.8 Hz, 1H), 6.83 - 6.79 (m, 2H), 3.65 (s, 2H), 3.20 (s, 1H), 1.64 (s, 6H).

[1138] LC-MS (Method A): Rt 3.09 mins; MS m/z 372.2/374.2 = [M+H]+ (99% @ 215nm)

Example 78.1

N-(1,1-Dimethylprop-2-ynyl)-4-[[2-[2-hydroxy-4-(trifluoromethyl)phenyl]acetyl] amino]pyridine-2-carboxamide

[1139]



[1140] The titled compound was prepared from 4-amino-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide (Example 78, step 1) and 2-[2-methoxy-4-(trifluoromethyl)phenyl]acetic acid analogously to Example 78 steps 2 and 3.

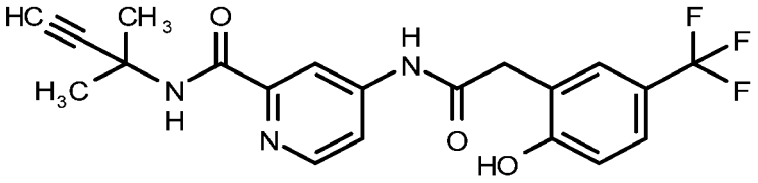
[1141] 1H NMR (500 MHz, DMSO-d6) δ 10.79 (s, 1H), 10.30 (s, 1H), 8.47 (d, J = 5.5 Hz, 1H), 8.31 (s, 1H), 8.19 (d, J = 2.0 Hz, 1H), 7.83 (dd, J = 5.5, 2.2 Hz, 1H), 7.38 (d, J = 7.8 Hz, 1H), 7.10 (d, J = 7.9 Hz, 1H), 7.07 (s, 1H), 3.76 (s, 2H), 3.21 (s, 1H), 1.64 (s, 6H).

[1142] LC-MS (Method A): Rt 3.27 mins; MS m/z 406.2 = [M+H]+ (98% @ 215nm)

Example 78.2

N-(1,1-Dimethylprop-2-ynyl)-4-[[2-[2-hydroxy-5-(trifluoromethyl)phenyl]acetyl] amino]pyridine-2-carboxamide

[1143]



[1144] The titled compound was prepared from 4-amino-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide (Example 78, step 1) and 2-[2-methoxy-5-(trifluoromethyl)phenyl]acetic acid analogously to Example 78 steps 2 and 3.

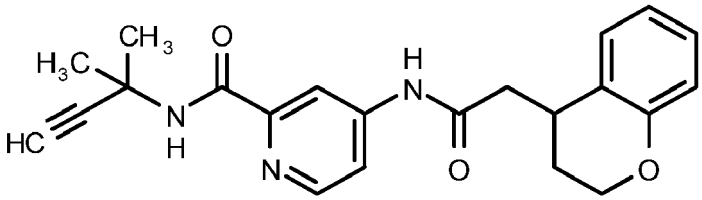
[1145] 1H NMR (500 MHz, DMSO-d6) δ 10.79 (s, 1H), 10.48 (s, 1H), 8.47 (d, J = 5.5 Hz, 1H), 8.32 (s, 1H), 8.19 (d, J = 2.0 Hz, 1H), 7.84 (dd, J = 5.5, 2.2 Hz, 1H), 7.54 (d, J = 2.2 Hz, 1H), 7.45 (dd, J = 8.5, 2.1 Hz, 1H), 6.96 (d, J = 8.4 Hz, 1H), 3.77 (s, 2H), 3.21 (s, 1H), 1.65 (s, 6H).

[1146] LC-MS (Method A): Rt 3.25 mins; MS m/z 406.2 = [M+H]+ (98% @ 215nm)

Example 79

4-[(2-Chroman-4-ylacetyl)amino]-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide

[1147]



[1148] The titled compound was prepared from 4-amino-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide (Example 78, step 1) and 2-chroman-4-ylacetic acid analogously to Example 3.5b

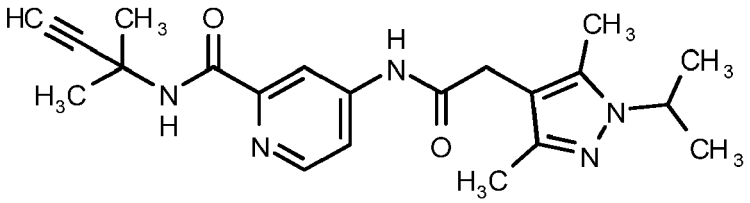
[1149] 1H NMR (500 MHz, Methanol-d4) δ 8.46 (d, J = 5.5 Hz, 1H), 8.19 (d, J = 1.7 Hz, 1H), 7.92 (dd, J = 5.5, 2.2 Hz, 1H), 7.16 (d, J = 7.7 Hz, 1H), 7.09 - 7.04 (m, 1H), 6.81 (td, J = 7.5, 1.2 Hz, 1H), 6.75 (dd, J = 8.2, 1.1 Hz, 1H), 4.22 - 4.18 (m, 2H), 3.44 (dq, J = 10.4, 5.1 Hz, 1H), 2.92 (dd, J = 14.7, 5.7 Hz, 1H), 2.73 (s, 1H), 2.62 (dd, J = 14.7, 9.3 Hz, 1H), 2.20 - 2.11 (m, 1H), 1.94 - 1.84 (m, 1H), 1.73 (s, 6H).

[1150] LC-MS (Method A): Rt 3.38 mins; MS m/z 378.3 = [M+H]+ (98% @ 215nm)

Example 79.1

N-(1,1-Dimethylprop-2-ynyl)-4-[[2-(1-isopropyl-3,5-dimethyl-pyrazol-4-yl)acetyl] amino]pyridine-2-carboxamide

[1151]



[1152] The titled compound was prepared from 4-amino-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide (Example 78, step 1) and 2-(1-isopropyl-3,5-dimethyl-pyrazol-4-yl)acetic acid analogously to Example 3.5b.

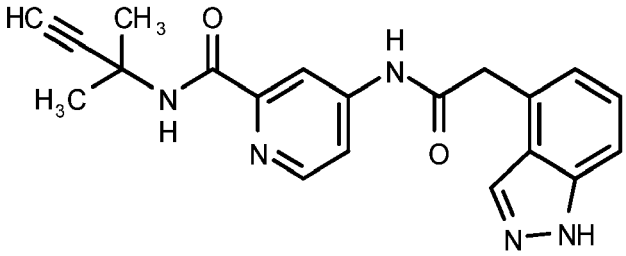
[1153] 1H NMR (500 MHz, DMSO-d6) δ 10.62 (s, 1H), 8.46 (d, 1H), 8.31 (s, 1H), 8.19 (d, J = 1.9 Hz, 1H), 7.84 (dd, J = 5.5, 2.2 Hz, 1H), 4.43 - 4.34 (m, 1H), 3.43 (s, 2H), 3.21 (s, 1H), 2.18 (s, 3H), 2.08 (s, 3H), 1.64 (s, 6H), 1.31 (d, J = 6.6 Hz, 6H).

[1154] LC-MS (Method A): Rt 2.54 mins; MS m/z 382.3 = [M+H]+ (100% @ 215nm)

Example 79.2

N-(1,1-Dimethylprop-2-ynyl)-4-[[2-(1H-indazol-4-yl)acetyl]amino]pyridine-2-carboxamide

[1155]



[1156] The titled compound was prepared from 4-amino-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide (Example 78, step 1) and 2-(1H-indazol-4-yl)acetic acid analogously to Example 3.5b.

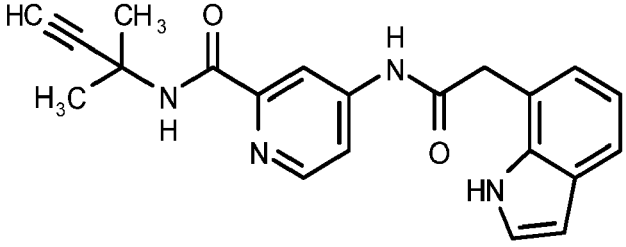
[1157] 1H NMR (500 MHz, Methanol-d4) δ 8.44 (dd, J = 5.4, 0.5 Hz, 1H), 8.19 (d, J = 1.0 Hz, 1H), 8.17 (dd, J = 2.3, 0.5 Hz, 2H), 7.93 (dd, J = 5.6, 2.2 Hz, 1H), 7.47 (d, J = 8.5 Hz, 1H), 7.36 (dd, J = 8.4, 7.0 Hz, 1H), 7.13 - 7.10 (m, 1H), 4.56 (br s, 1H), 4.08 (s, 2H), 2.72 (s, 1H), 1.72 (s, 6H).

[1158] LC-MS (Method A): Rt 2.51 mins; MS m/z 362.2 = [M+H]+

Example 79.3

N-(1,1-Dimethylprop-2-ynyl)-4-[[2-(1H-indo)-7-yl)acetyl]amino]pyridine-2-carboxamide

[1159]



[1160] The titled compound was prepared from 4-amino-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide (Example 78, step 1) and 2-(1H-indol-7-yl)acetic acid analogously to Example 3.5b.

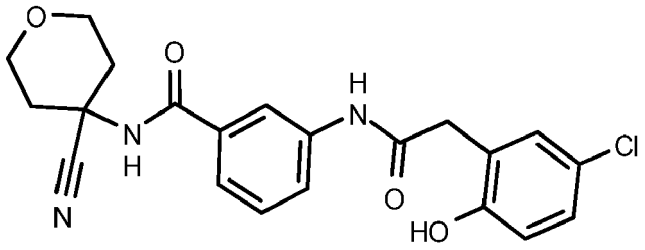
[1161] 1H NMR (500 MHz, DMSO-d6) δ 11.05 (br s, 1H), 10.82 (s, 1H), 8.48 (d, J = 5.5 Hz, 1H), 8.32 (s, 1H), 8.21 (d, J = 2.0 Hz, 1H), 7.86 (dd, J = 5.5, 2.1 Hz, 1H), 7.46 (d, J = 7.5 Hz, 1H), 7.36 (t, J = 2.7 Hz, 1H), 7.02 - 6.94 (m, 2H), 6.48 - 6.42 (m, 1H), 4.01 (s, 2H), 3.21 (s, 1H), 1.65 (s, 6H).

[1162] LC-MS (Method A): Rt 3.19 mins; MS m/z 361.2 = [M+H]+

Example 80*

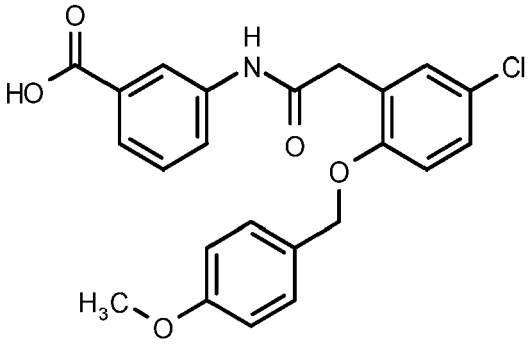
3-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(4-cyanotetrahydropyran-4-yl) benzamide

[1163]



Step 1: 3-[[2-[5-Chloro-2-[(4-methoxyphenyl)methoxy]phenyl]acetyl]amino]benzoic acid

[1164]

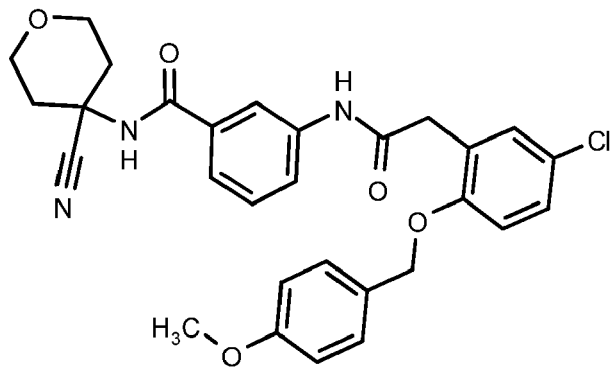


[1165] To a solution of 3-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]benzoic acid (Example 71 step 3)(464 mg, 1.046 mmol) in DMF (5 mL) was added K_2CO_3 (619 mg, 4.48 mmol) and 1-(bromomethyl)-4-methoxy-benzene (751 mg, 3.73 mmol) and the reaction mixture was stirred at room temperature for 1 hour. The resulting mixture was diluted with water (10 mL) to form a precipitate which was filtered and washed with water. The solid was dissolved in THF (7 mL) and treated with aq.1M LiOH (8.96 mL, 8.96 mmol) and stirred at room temperature for 20 hours. The volatile solvents were removed *in vacuo* causing the formation of a precipitate. The mixture was diluted with water (50 mL) and neutralised with aq.3M HCl solution. The precipitate was filtered and washed with water to afford the titled compound as an off-white solid.

[1166] 1H NMR (500 MHz, DMSO-d6) δ 10.24 (s, 1H), 8.20 (s, 1H), 7.82 (d, J = 8.9 Hz, 1H), 7.62 (dt, J = 7.7, 1.1 Hz, 1H), 7.42 (t, J = 7.9 Hz, 1H), 7.32 (d, J = 2.7 Hz, 1H), 7.30 - 7.24 (m, 3H), 7.08 (d, J = 8.8 Hz, 1H), 6.70 - 6.66 (m, 2H), 5.00 (s, 2H), 3.67 (s, 2H), 3.66 (s, 3H). LC-MS (Method E): Rt 1.18 mins; MS m/z 448.0/450.1 = [M+Na]+ (96% @ 215nm)

Step 2: 3-[[2-[5-Chloro-2-[(4-methoxyphenyl)methoxy]phenyl]acetyl]amino]-N-(4-cyanotetrahydropyran-4-yl)benzamide

[1167]



[1168] The titled compound was prepared from 3-[[2-[5-chloro-2-[(4-methoxyphenyl)methoxy]phenyl]acetyl]amino]benzoic acid (step 1) and 4-aminotetrahydropyran-4-carbonitrile analogously to Example 31 step 2.

[1169] 1H NMR (500 MHz, DMSO-d6) δ 10.26 (s, 1H), 8.82 (s, 1H), 8.04 (t, *J* = 1.7 Hz, 1H), 7.83 (d, J = 9.4 Hz, 1H), 7.56 (dt, J = 7.6, 1.1 Hz, 1H), 7.44 (t, J = 7.9 Hz, 1H), 7.32 (d, J = 2.7 Hz, 1H), 7.30 - 7.26 (m, 3H), 7.08 (d, J = 8.8 Hz, 1H), 6.73 - 6.70 (m, 2H, 5.00 (s, 2H), 3.90 - 3.84 (m, 2H), 3.68 (s, 2H), 3.67 (s, 3H), 3.63 - 3.57 (m, 2H), 2.33 (d, J = 13.5 Hz, 2H), 2.04 - 1.97 (m, 2H).

[1170] LC-MS (Method E): Rt 1.20 mins; MS m/z 556.1/558.0 = [M+H]+ (95% @ 215nm)

Step 3: 3-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(4-cyanotetrahydropyran-4-yl) benzamide

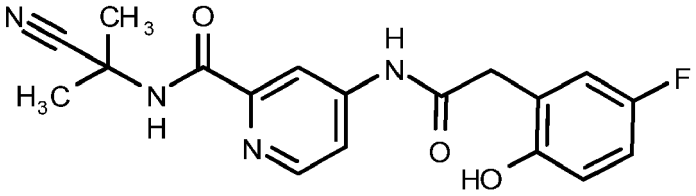
[1171] 3-[[2-[5-Chloro-2-[(4-methoxyphenyl)methoxy]phenyl]acetyl]amino]-N-(4-cyanotetra hydropyran-4-yl)benzamide (step 2)(70 mg, 0.13 mmol) was dissolved in 1M HCl in dioxane (1.97 mL, 1.97 mmol) and stirred at room temperature for 4 hours. The reaction mixture was diluted with EtOAc (5 mL) and water (5 mL). The organic portion was separated, dried over Na_2SO_4 and concentrated *in vacuo.* Purification of the crude material by preparative HPLC (acidic pH, standard elution method) afforded the titled compound as an off-white solid.

[1172] 1H NMR (500 MHz, DMSO-d6) δ 10.27 (s, 1H), 9.66 (br s, 1H), 8.82 (s, 1H), 8.04 (t, J = 1.8 Hz, 1H), 7.84 - 7.79 (m, 1H), 7.52 (dt, J = 7.6, 1.0 Hz, 1H), 7.42 (t, J = 7.9 Hz, 1H), 7.21 (d, J = 2.7 Hz, 1H), 7.11 (dd, J = 8.6, 2.7 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 3.91 - 3.83 (m, 2H), 3.62 (s, 2H), 3.62 - 3.57 (m, 2H), 2.35 - 2.29 (m, 2H), 2.04 - 1.97 (m, 2H). LC-MS (Method A): Rt 2.66 mins; MS m/z 414.2/416.2 = [M+H]+ (100% @ 215nm)

Example 81

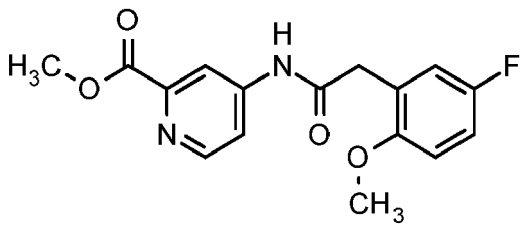
N-(1-Cyano-1-methyl-ethyl)-4-[[2-(5-fluoro-2-hydroxy-phenyl)acetyl]amino] pyridine-2-carboxamide

[1173]



Step 1: Methyl 4-[[2-(5-fluoro-2-methoxy-phenyl)acetyl]amino]pyridine-2-carboxylate

[1174]



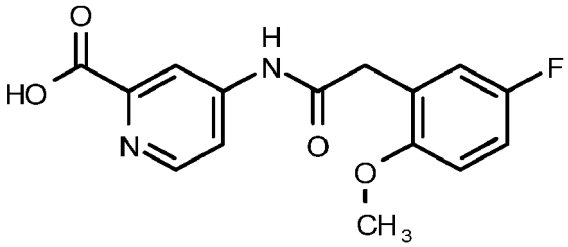
[1175] The titled compound was prepared from methyl 4-aminopyridine-2-carboxylate and 2-(5-fluoro-2-methoxy-phenyl)acetic acid analogously to Example 8 step 1.

[1176] 1H NMR (250 MHz, DMSO-d6) δ 10.71 (s, 1H), 8.54 (d, J = 5.5 Hz, 1H), 8.30 (d, J = 1.9 Hz, 1H), 7.77 (dd, J = 5.5, 2.2 Hz, 1H), 7.15 - 7.03 (m, 2H), 7.02 - 6.93 (m, 1H), 3.86 (s, 3H), 3.74 (s, 3H), 3.71 (s, 2H).

[1177] LC-MS (Method E): Rt 0.99 mins; MS m/z 319.0 (83% @ 215nm)

Step 2: 4-[[2-(5-Fluoro-2-methoxy-phenyl)acetyl]amino]pyridine-2-carboxylic acid

[1178]

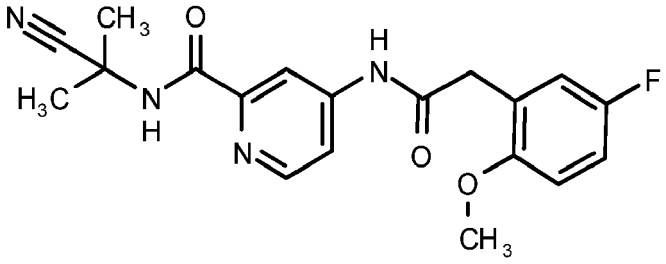


[1179] The titled compound was prepared from methyl 4-[[2-(5-fluoro-2-methoxyphenyl)acetyl]amino]pyridine-2-carboxylate (step 1) analogously to Example 7 step 2. 1H NMR (500 MHz, DMSO-d6) δ 10.77 (s, 1H), 8.53 (d, J = 5.6 Hz, 1H), 8.27 (d, J = 2.0 Hz, 1H), 7.80 (dd, J = 5.6, 2.2 Hz, 1H), 7.14 - 7.05 (m, 2H), 6.98 (dd, J = 9.0, 4.6 Hz, 1H), 3.74 (s, 3H), 3.72 (s, 2H).

[1180] LC-MS (Method A): Rt 0.87 mins; MS m/z 305.0 = [M+H]+

Step 3: N-(1-Cyano-1-methyl-ethyl)-4-[[2-(5-fluoro-2-methoxy-phenyl)acetyl]amino] pyridine-2-carboxamide

[1181]



[1182] The titled compound was prepared from 4-[[2-(5-fluoro-2-methoxyphenyl)acetyl]amino]pyridine-2-carboxylic acid (step 2) and 2-amino-2-methylpropanenitrile hydrochloride acid analogously to Example 77 step 3.

[1183] 1H NMR (500 MHz, DMSO-d6) δ 10.74 (s, 1H), 8.82 (s, 1H), 8.51 (d, J = 5.5 Hz, 1H), 8.22 (d, J = 1.9 Hz, 1H), 7.86 (dd, J = 5.5, 2.2 Hz, 1H), 7.17 - 7.05 (m, 2H), 6.99 (dd, J = 9.0, 4.6 Hz, 1H), 3.74 (s, 3H), 3.73 (s, 2H), 1.72 (s, 6H).

[1184] LC-MS (Method E): Rt 1.09mins; MS m/z 371.1 = [M+H]+ (87% @ 215nm)

Step 4: N-(1-Cyano-1-methyl-ethyl)-4-[[2-(5-fluoro-2-hydroxy-phenyl)acetyl]amino] pyridine-2-carboxamide

[1185] The titled compound was prepared from N-(1-cyano-1-methyl-ethyl)-4-[[2-(5-fluoro-2-methoxy-phenyl)acetyl]amino] pyridine-2-carboxamide (step 3) analogously to Example 3 step 3.

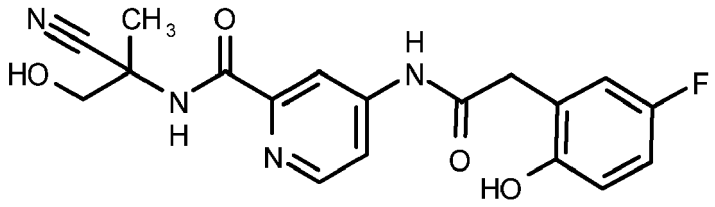
[1186] 1H NMR (500 MHz, DMSO-d6) δ 10.72 (br s, 1H), 9.52 (br s, 1H), 8.82 (s, 1H), 8.50 (d, J = 5.5 Hz, 1H), 8.22 (d, J = 2.0 Hz, 1H), 7.87 (dd, J = 5.5, 2.1 Hz, 1H), 7.02 (dd, J = 9.4, 3.1 Hz, 1H), 6.91 (td, J = 8.6, 3.2 Hz, 1H), 6.77 (dd, J = 8.8, 4.9 Hz, 1H), 3.68 (s, 2H), 1.72 (s, 6H).

[1187] LC-MS (Method A): Rt 2.53 mins; MS m/z 357.2 = [M+H]+ (99% @ 215nm)

Example 81.1

N-(1-Cyano-2-hydroxy-1-methyl-ethyl)-4-[[2-(5-fluoro-2-hydroxyphenyl)acetyl]amino] pyridine-2-carboxamide

[1188]



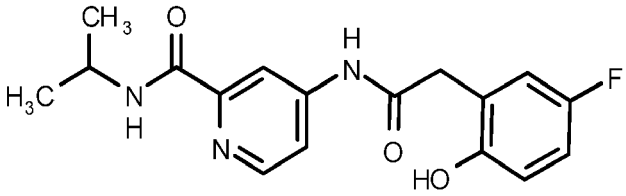
[1189] The titled compound was prepared from 4-[[2-(5-fluoro-2-methoxyphenyl)acetyl]amino]pyridine-2-carboxylic acid (Example 81 step 2) and 2-amino-3-hydroxy-2-methyl-propanenitrile analogously to Example 81 step 3 and 4.

[1190] 1H NMR (500 MHz, DMSO-d6) δ 10.76 (br s, 1H), 9.53 (br s, 1H), 8.73 (s, 1H), 8.50 (d, J = 5.5 Hz, 1H), 8.24 (d, J = 2.1 Hz, 1H), 7.87 (dd, J = 5.5, 2.2 Hz, 1H), 7.02 (dd, J = 9.3, 3.2 Hz, 1H), 6.95 - 6.87 (m, 1H), 6.78 (dd, J = 8.8, 4.9 Hz, 1H), 5.91 (t, J = 5.8 Hz, 1H), 3.82 (dd, J = 11.1, 5.2 Hz, 1H), 3.73 (dd, J = 10.9, 4.9 Hz, 1H), 3.68 (s, 2H), 1.66 (s, 3H). LC-MS (Method A): Rt 2.20 mins; MS m/z 373.3 = [M+H]+ (100% @ 215nm)

Example 81.2

4-[[2-(5-Fluoro-2-hydroxy-phenyl)acetyl]amino]-N-isopropyl-pyridine-2-carboxamide

[1191]



[1192] The titled compound was prepared from 4-[[2-(5-fluoro-2-methoxyphenyl)acetyl]amino]pyridine-2-carboxylic acid (Example 81 step 2) and analogously to Example 81 steps 3 and 4.

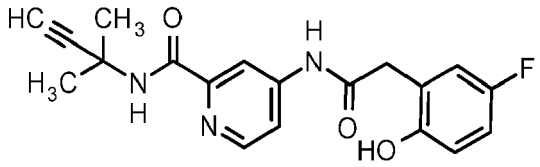
[1193] 1H NMR (500 MHz, DMSO-d6) δ 10.65 (br s, 1H), 9.50 (br s, 1H), 8.45 (d, J = 5.5 Hz, 1H), 8.37 (d, J = 8.4 Hz, 1H), 8.18 (d, J = 1.9 Hz, 1H), 7.81 (dd, J = 5.5, 2.2 Hz, 1H), 7.00 (dd, J = 9.4, 3.2 Hz, 1H), 6.95 - 6.86 (m, 1H), 6.76 (dd, J = 8.8, 4.9 Hz, 1H), 4.16 - 4.02 (m, 1H), 3.66 (s, 2H), 1.17 (d, J = 6.6 Hz, 6H).

[1194] LC-MS (Method A): Rt 2.56 mins; MS m/z 322.2 = [M+H]+ (100% @ 215nm)

Example 81.3

N-(1,1-Dimethylprop-2-ynyl)-4-[[2-(5-fluoro-2-hydroxy-phenyl)acetyl]amino] pyridine-2-carboxamide

[1195]



[1196] The titled compound was prepared from 4-[[2-(5-fluoro-2-methoxyphenyl)acetyl]amino]pyridine-2-carboxylic acid (Example 81 step 2) and 2-methylbut-3-yn-2-amine analogously to Example 81 steps 3 and 4.

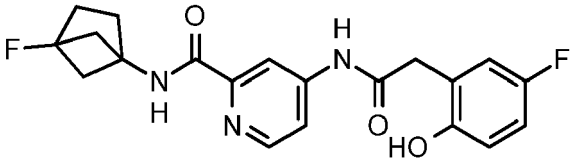
[1197] 1H NMR (500 MHz, DMSO-d6) δ 10.70 (br s, 1H), 9.52 (br s, 1H), 8.46 (d, J = 5.5 Hz, 1H), 8.31 (s, 1H), 8.18 (d, J = 2.0 Hz, 1H), 7.83 (dd, J = 5.5, 2.2 Hz, 1H), 7.01 (dd, J = 9.4, 3.2 Hz, 1H), 6.90 (td, J = 8.6, 3.2 Hz, 1H), 6.77 (dd, J = 8.8, 4.9 Hz, 1H), 3.67 (s, 2H), 3.20 (s, 1H), 1.64 (s, 6H).

[1198] LC-MS (Method A): Rt 2.84 mins; MS m/z 356.2 = [M+H]+ (97% @ 215nm)

Example 81.4

N-(4-Fluoro-1-bicyclo[2.1.1]hexanyl)-4-[[2-(5-fluoro-2-hydroxy-phenyl)acetyl]amino] pyridine-2-carboxamide

[1199]



[1200] The titled compound was prepared from 4-[[2-(5-fluoro-2-methoxyphenyl)acetyl]amino]pyridine-2-carboxylic acid (Example 81 step 2) and 4-fluorobicyclo[2.1.1]hexan-1-amine hydrochloride analogously to Example 81 steps 3 and 4.

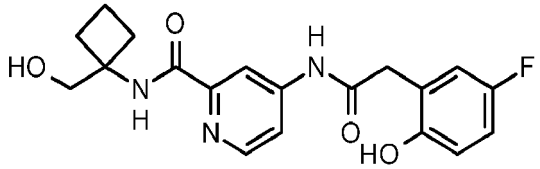
[1201] 1H NMR (500 MHz, DMSO-d6) δ 10.68 (s, 1H), 9.51 (br s, 1H), 9.04 (s, 1H), 8.46 (d, J = 5.5 Hz, 1H), 8.15 (d, J = 2.1 Hz, 1H), 7.84 (dd, J = 5.5, 2.1 Hz, 1H), 7.01 (dd, J = 9.3, 3.1 Hz, 1H), 6.91 (td, J = 8.6, 3.1 Hz, 1H), 6.77 (dd, J = 8.8, 4.9 Hz, 1H), 3.67 (s, 2H), 2.16 - 2.02 (m, 4H), 2.00 - 1.91 (m, 2H), 1.89 - 1.79 (m, 2H).

[1202] LC-MS (Method A): Rt 2.97 mins; MS m/z 388.2 = [M+H]+ (98% @ 215nm)

Example 81.5

4-[[2-(5-Fluoro-2-hydroxy-phenyl)acetyl]amino]-N-[1-(hydroxymethyl)cyclobutyl] pyridine-2-carboxamide

[1203]



[1204] The titled compound was prepared from 4-[[2-(5-fluoro-2-methoxyphenyl)acetyl]amino]pyridine-2-carboxylic acid (Example 81 step 2) and (1-aminocyclobutyl)methanol hydrochloride analogously to Example 81 steps 3 and 4.

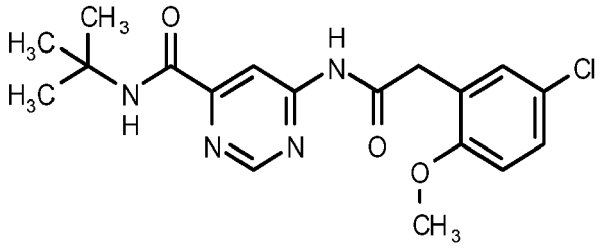
[1205] 1H NMR (500 MHz, DMSO-d6) δ 10.68 (s, 1H), 9.52 (s, 1H), 8.45 (d, J = 5.5 Hz, 1H), 8.40 (s, 1H), 8.18 (d, J = 2.1 Hz, 1H), 7.82 (dd, J = 5.5, 2.2 Hz, 1H), 7.01 (dd, J = 9.4, 3.2 Hz, 1H), 6.91 (td, J = 8.6, 3.2 Hz, 1H), 6.77 (dd, J = 8.8, 4.9 Hz, 1H), 5.00 (s, 1H), 3.67 (s, 2H), 3.61 (s, 2H), 2.09 - 2.01 (m, 2H), 1.88 - 1.79 (m, 1H), 1.78 - 1.67 (m, 1H).

[1206] LC-MS (Method A): Rt 2.33 mins; MS m/z 374.2 = [M+H]+ (96% @ 215nm)

Example 82*

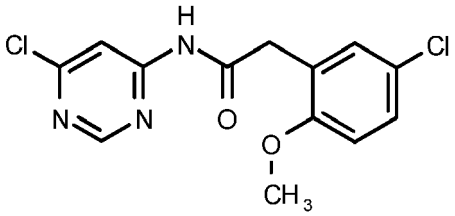
N-tert-Butyl-6-[[2-(5-chloro-2-methoxy-phenyl)acetyl]amino]pyrimidine-4-carboxamide

[1207]



Step 1: 2-(5-Chloro-2-methoxy-phenyl)-N-(6-chloropyrimidin-4-yl)acetamide

[1208]



[1209] A suspension of 6-chloropyrimidin-4-amine (250 mg, 1.93 mmol) and 2-(5-chloro-2-methoxy-phenyl)acetic acid (0.14 mL, 2.03 mmol) in 1,4-dioxane (2.5 mL) was treated wih DIPEA (1.01 mL, 5.79 mmol) followed by T3P® (50% in EtOAc) (2754 μL, 2.32 mmol) and the mixture was stirred at room temperature for 2 hours. The resulting mixture was partitioned between EtOAc (10 mL) and saturated aqueous $NaHCO_3$ (10 mL) and the organic portion was separated, washed with water, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by chromatography on silica eluting with a gradient of 0 to 100% EtOAc in heptane followed by 0 to 100% MeOH in EtOAc to afford the titled compound as an orange powdery solid.

[1210] 1H NMR (500 MHz, DMSO-d6) δ 11.40 (s, 1H), 8.77 (d, J = 1.0 Hz, 1H), 8.07 (d, J = 1.0 Hz, 1H), 7.33 - 7.29 (m, 2H), 7.03 - 6.98 (m, 1H), 3.79 (s, 2H), 3.74 (s, 3H).

[1211] LC-MS (Method E): Rt 1.14 mins; MS m/z 311.9/313.9 = [M+H]+ (100% @ 215nm)

Step 2: N-tert-Butyl-6-[[2-(5-chloro-2-methoxy-phenyl)acetyl]amino]pyrimidine-4-carboxamide

[1212] The following procedure was based on the literature reference: CA 2915356 Page 131. All reagents charged to COware equipment (carbon monoxide generating system): Chamber A: Aryl chloride, 2-methylpropan-2-amine, BINAP, $Pd(OAC)_2$, TEA 1,4-dioxane Chamber B: formic acid, MsCl, TEA, 1,4-dioxane

[1213] To chamber A was added 2-(5-chloro-2-methoxy-phenyl)-N-(6-chloropyrimidin-4-yl)acetamide (step 1) (202 mg, 0.65 mmol), $Pd(OAc)_2$ (15 mg, 0.06 mmol), 2-methylpropan-2-amine (95 mg, 1.29 mmol) and BINAP (81 mg, 0.13 mmol). The reaction vessel was flushed with nitrogen then 1,4-dioxane (2.5 mL) was added. To chamber B was added 1,4-dioxane (2.5 mL) followed by mesyl chloride (125 μL, 1.62 mmol) and formic acid (61 μL, 1.62 mmol) and the mixtures were stirred. To chamber A was added triethylamine (283 μL, 1.94 mmol) and to chamber B was added triethylamine (361 μL, 2.59 mmol) which quickly evolved CO gas. The COware equipment was heated at 80 °C for 22 hours and allowed to cool to room temperature. The mixture from chamber A was partitioned between DCM (5 mL) and water (5 mL) and the organic portion separated via filtration through a hydrophobic PTFE fritted tube. The filtrate was and concentrated in *vacuo* and the residue purified by preparative HPLC (acidic pH, standard elution method). The product fractions were combined and concentrated *in vacuo* to remove the volatile solvents. The aqueous residue was treated with DCM (10 mL) and saturated aqueous $NaHCO_3$ (10 mL) and the organic portion was separated by filtration through a hydrophobic PTFE fritted tube. The filtrate was concentrated *in vacuo* to afford the titled compound as a peach crystalline solid.

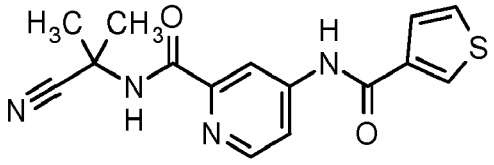
[1214] 1H NMR (500 MHz, DMSO-d6) δ 11.29 (s, 1H), 8.95 (d, J = 1.2 Hz, 1H), 8.53 (d, J = 1.2 Hz, 1H), 8.04 (s, 1H),), 7.33 - 7.29 (m, 2H), 7.03 - 6.99 (m, 1H), 3.80 (s, 2H), 3.74 (s, 3H), 1.39 (s, 9H).

[1215] LC-MS (Method A): Rt 3.56 mins; MS m/z 377.2/379.2 = [M+H]+ (97% @ 215nm)

Example 83

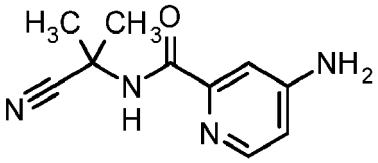
N-(1-Cyano-1-methyl-ethyl)-4-(thiophene-3-carbonylamino)pyridine-2-carboxamide

[1216]



Step 1: 4-Amino-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide

[1217]



[1218] To a mixture of 4-aminopyridine-2-carboxylic acid (15 g, 108.6 mmol), TBTU (41.84 g, 130.32 mmol) and triethylamine (37.84 mL, 271.5 mmol) in DMF (271.52 mL) was added 2-amino-2-methyl-propanenitrile hydrochloride (14.4 g, 119.46 mmol) and the mixture was stirred at room temperature for 3 days. The reaction mixture was filtered and the solid washed with DMF (2 × 30 mL). The combined filtrate was concentrated *in vacuo* and the crude residue dissolved in EtOAc (300 mL) and washed with sat. $NaHCO_3$ solution (2 × 300 mL). The aqueous portion was re-extracted with EtOAc (30 mL) and the organic layers were combined, washed with brine (160 mL × 2), dried over anhydrous Na_2SO_4 and concentrated *in vacuo.* Purification of the resulting solid by chromatography on silica eluting with 0-100% EtOAc in heptane yielded a solid which was triturated with ice cold TBME:heptane (3:1 mixture) to afford the titled compound as a colourless crytalline solid. 1H NMR (400 MHz, DMSO-d6) δ 8.60 (s, 1H), 8.03 (d, J = 5.6 Hz, 1H), 7.21 (d, J = 2.3 Hz, 1H), 6.62 (dd, J = 5.6, 2.4 Hz, 1H), 6.40 (s, 2H), 1.70 (s, 6H).

[1219] LCMS (Method E) Rt 0.35 mins; MS m/z 205.0 = [M+H]+

Step 2: N-(1-Cyano-1-methyl-ethyl)-4-(thiophene-3-carbonylamino)pyridine-2-carboxamide

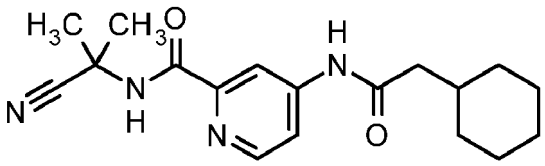
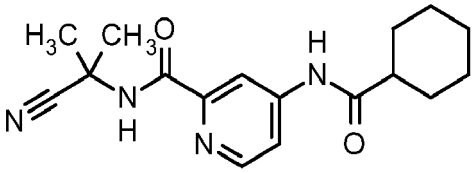
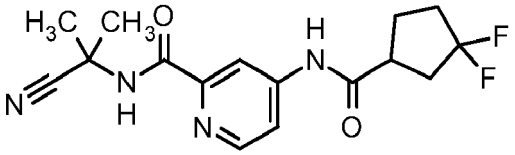
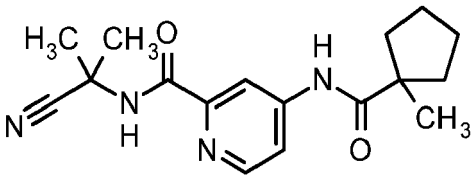
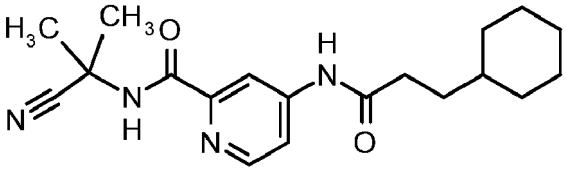
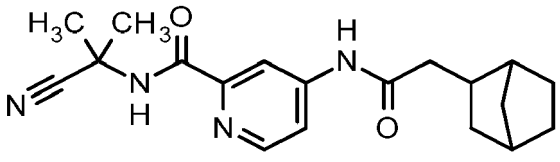
[1220] Oxalyl chloride (29 μL, 0.331 mmol) was added to a stirred solution of thiophene-3-carboxylic acid (47 mg, 0.368 mmol) dissolved in DMF (1 drop, ~5μL) in 1,4-dioxane (1 mL). The mixture was sealed and stirred at room temperature for 1 hour. The resulting acid chloride mixture was treated with a stock solution (1.6 mL) of 4-amino-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide (step 1) (45 mg, 0.22 mmol) and TEA (100 μL, 0.72 mmol) in 1,4-dioxane (1.5 mL). The mixture was re-sealed and stirred at room temperature overnight. The resulting mixture was concentrated *in vacuo* and purification of the crude residue by preparative HPLC (acidic pH, standard elution method) afforded the titled compound as an off-white powder.

[1221] 1H NMR (500 MHz, DMSO-d6) δ 10.63 (s, 1H), 8.85 (s, 1H), 8.56 (d, J = 5.5 Hz, 1H), 8.49 - 8.46 (m, 1H), 8.44 (d, J = 2.1 Hz, 1H), 8.09 (dd, J = 5.5, 2.2 Hz, 1H), 7.71 - 7.69 (m, 1H), 7.68 - 7.66 (m, 1H), 1.74 (s, 6H).

[1222] LCMS (Method A) Rt 2.60 mins; MS m/z 315.2 = [M+H]+ (99% @ 215 nm)

[1223] The compounds of the following tabulated Examples (Table 14) were prepared from 4-amino-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide (Example 83 step 1) analogously to Example 83 step 2 by replacing thiophene-3-carboxylic acid with the appropriate commercially available acid.

Table 14

Ex.	Structure and Name	1H NMR, LCMS Retention Time, [M+H]+,
83.1	 N-(1-Cyano-1-methyl-ethyl)-4-[(2-cyclohexylacetyl) amino] pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.50 (s, 1H), 8.81 (s, 1H), 8.49 (d, J = 5.5 Hz, 1H), 8.24 (d, J = 2.0 Hz, 1H), 7.84 (dd, J = 5.5, 2.2 Hz, 1H), 2.26 (d, J = 7.1 Hz, 2H), 1.83 - 1.75 (m, 1H), 1.72 (s, 6H), 1.71 - 1.64 (m, 4H), 1.63 - 1.58 (m, 1H), 1.28 - 1.09 (m, 3H), 1.03 - 0.93 (m, 2H).
83.2	 N-(1-Cyano-1-methyl-ethyl)-4-(cyclohexane carbonylamino) pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.46 (s, 1H), 8.81 (s, 1H), 8.49 (d, J = 5.5 Hz, 1H), 8.24 (d, J = 2.0 Hz, 1H), 7.87 (dd, J = 5.5, 2.2 Hz, 1H), 2.41 - 2.34 (m, 1H), 1.87 - 1.80 (m, 2H), 1.79 - 1.74 (m, 2H), 1.72 (s, 6H), 1.68 - 1.62 (m, 1H), 1.41 (qd, J = 12.4, 2.8 Hz, 2H), 1.33 - 1.14 (m, 3H).
83.3	 N-(1-Cyano-1-methyl-ethyl)-4-[(3,3-difluorocyclo pentanecarbonyl)amino]pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.65 (s, 1H), 8.83 (s, 1H), 8.52 (d, J = 5.5 Hz, 1H), 8.26 - 8.21 (m, 1H), 7.87 (dd, J = 5.5, 2.2 Hz, 1H), 3.16 (p, J = 8.6 Hz, 1H), 2.43 - 2.31 (m, 2H), 2.27 - 2.05 (m, 3H), 1.98 - 1.90 (m, 1H), 1.73 (s, 6H). LCMS (Method A) Rt 2.74 mins; MS m/z 337.3 = [M+H]+ (97% @ 215 nm)
83.4	 N-(1-Cyano-1-methyl-ethyl)-4-[(1-methylcyclo pentanecarbonyl) amino]pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 9.92 (s, 1H), 8.81 (s, 1H), 8.49 (d, J = 5.5 Hz, 1H), 8.36 (d, J = 2.1 Hz, 1H), 7.99 (dd, J = 5.5, 2.2 Hz, 1H), 2.18 - 2.07 (m, 2H), 1.73 (s, 6H), 1.70 - 1.56 (m, 4H), 1.55 - 1.49 (m, 2H), 1.32 (s, 3H). LCMS (Method A) Rt 3.08 mins; MS m/z 315.3 = [M+H]+ (100% @ 215 nm)
83.5	 N-(1-Cyano-1-methyl-ethyl)-4-(3-cyclohexyl propanoylamino) pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.51 (s, 1H), 8.81 (s, 1H), 8.49 (d, J = 5.5 Hz, 1H), 8.23 (d, J = 2.0 Hz, 1H), 7.84 (dd, J = 5.5, 2.2 Hz, 1H), 2.41 - 2.36 (m, 2H), 1.75 - 1.64 (m, 10H), 1.63 - 1.57 (m, 1H), 1.54 - 1.47 (m, 2H), 1.28 - 1.07 (m, 4H), 0.94 - 0.85 (m, 2H). LCMS (Method A) Rt 3.64 mins; MS m/z 343.3 = [M+H]+ (100% @ 215 nm)
83.6	 4-(2-{Bicyclo[2.2.1]heptan-2-yl}acetamido)-N-(1-cyano-1 -methylethyl)pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.50 (s, 1H), 8.81 (s, 1H), 8.49 (d, J = 5.5 Hz, 1H), 8.23 (d, J = 1.9 Hz, 1H), 7.84 (dd, J = 5.5, 2.2 Hz, 1H), 2.38 - 2.32 (m, 1H), 2.24 - 2.18 (m, 2H), 2.00 - 1.97 (m, 1H), 1.94 - 1.87 (m, 1H), 1.72 (s, 6H), 1.52 - 1.40 (m, 3H), 1.38 - 1.33 (m, 1H), 1.21 - 1.06 (m, 4H). LCMS (Method A) Rt 3.39 mins; MS m/z 341.3 = [M+H]+ (99% @ 215 nm)

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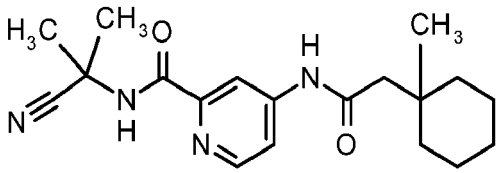
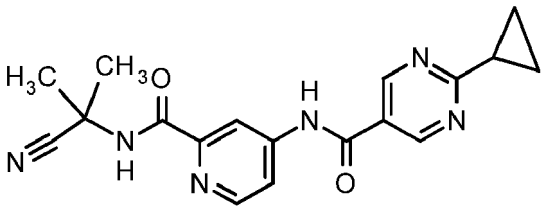
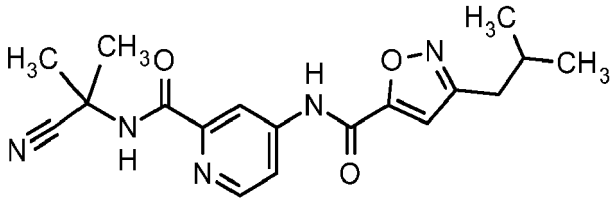
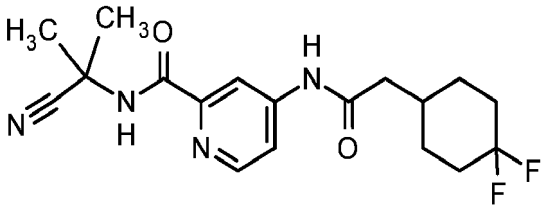
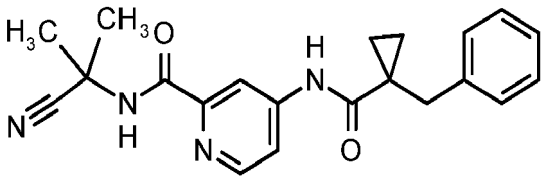
Ex.	Structure and Name	1H NMR, LCMS Retention Time, [M+H]+,
83.7	 N-(1-Cyano-1-methyl-ethyl)-4-[[2-(1-methylcyclo hexyl)acetyl] amino]pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.45 (s, 1H), 8.82 (s, 1H), 8.49 (d, J = 5.5 Hz, 1H), 8.24 (d, J = 2.0 Hz, 1H), 7.85 (dd, J = 5.5, 2.2 Hz, 1H), 2.29 (s, 2H), 1.72 (s, 6H), 1.52 - 1.36 (m, 7H), 1.36 - 1.27 (m, 3H), 1.02 (s, 3H). LCMS (Method A) Rt 3.56 mins; MS m/z 343.3 = [M+H]+ (100% @ 215 nm)
83.8	 N-[2-[(1-Cyano-1-methyl-ethyl)carbamoyl]-4-pyridyl]-2-cyclopropyl-pyrimidine-5-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 11.02 (s, 1H), 9.13 (s, 2H), 8.88 (s, 1H), 8.60 (d, J = 5.5 Hz, 1H), 8.42 (d, J = 2.0 Hz, 1H), 8.05 (dd, J = 5.5, 2.2 Hz, 1H), 2.35 - 2.29 (m, 1H), 1.74 (s, 6H), 1.20 - 1.15 (m, 2H), 1.13 - 1.09 (m, 2H). LCMS (Method A) Rt 2.56 mins; MS m/z 351.3 = [M+H]+ (99% @ 215 nm)
83.9	 N-[2-[(1-Cyano-1-methyl-ethyl)carbamoyl]-4-pyridyl]-3-isobutyl-isoxazole-5-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 11.28 (br. s, 1H), 8.88 (s, 1H), 8.60 (d, J = 5.5 Hz, 1H), 8.47 (d, J = 2.1 Hz, 1H), 8.03 (dd, J = 5.5, 2.2 Hz, 1H), 7.25 (s, 1H), 2.61 (d, J = 7.1 Hz, 2H), 2.05 - 1.96 (m, 1H), 1.74 (s, 6H), 0.94 (d, J = 6.7 Hz, 6H). LCMS (Method A) Rt 3.23 mins; MS m/z 356.3 = [M+H]+ (100% @ 215 nm)
83.10	 N-(1-Cyano-1-methyl-ethyl)-4-[[2-(4,4-difluorocyclo hexyl)acetyl] amino]pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.57 (s, 1H), 8.82 (s, 1H), 8.50 (d, J = 5.5 Hz, 1H), 8.24 (d, J = 2.0 Hz, 1H), 7.83 (dd, J = 5.5, 2.2 Hz, 1H), 2.35 (d, J = 7.1 Hz, 2H), 2.03 - 1.92 (m, 3H), 1.90 - 1.83 (m, 1H), 1.82 - 1.75 (m, 3H), 1.72 (s, 6H), 1.31 - 1.21 (m, 2H). LCMS (Method A) Rt 2.99 mins; MS m/z 365.3 = [M+H]+ (100% @ 215 nm)
83.11	 4-[(1-Benzylcyclopropanecarbonyl)amino]-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 9.94 (s, 1H), 8.80 (s, 1H), 8.46 (d, J = 5.5 Hz, 1H), 8.28 (d, J = 2.0 Hz, 1H), 7.90 (dd, J = 5.6, 2.2 Hz, 1H), 7.28 - 7.23 (m, 4H), 7.20 - 7.14 (m, 1H), 3.12 (s, 2H), 1.72 (s, 6H), 1.24 (q, J = 4.2 Hz, 2H), 0.87 (q, J = 4.4 Hz, 2H). LCMS (Method A) Rt 3.26 mins; MS m/z 363.3 = [M+H]+ (100% @ 215 nm)

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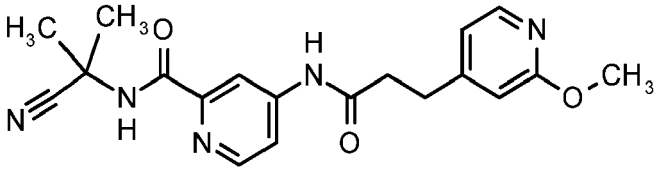
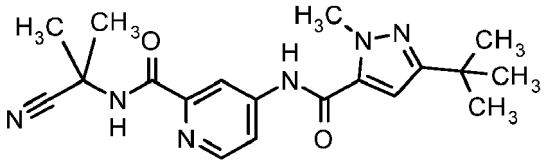
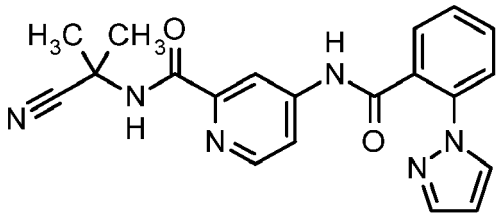
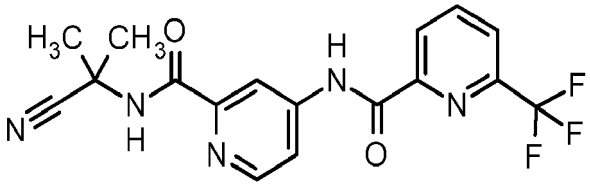
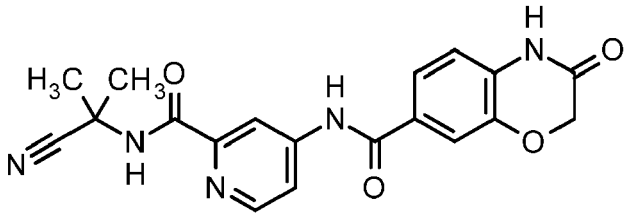
Ex.	Structure and Name	1H NMR, LCMS Retention Time, [M+H]+,
83.13	 N-(1-Cyano-1-methyl-ethyl)-4-[3-(2-methoxy-4-pyridyl) propanoylamino]pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.61 (s, 1H), 8.83 (s, 1H), 8.51 (d, J = 5.5 Hz, 1H), 8.22 (d, J = 2.0 Hz, 1H), 8.06 (d, J = 5.3 Hz, 1H), 7.83 (dd, J = 5.5, 2.2 Hz, 1H), 6.90 (dd, J = 5.3, 1.3 Hz, 1H), 6.70 (s, 1H), 3.82 (s, 3H), 2.91 (t, J = 7.5 Hz, 2H), 2.75 (t, J = 7.5 Hz, 2H), 1.73 (s, 6H). LCMS (Method A) Rt 2.29 mins; MS m/z 368.3 = [M+H]+ (97% @ 215 nm)
83.14	 4-[(5-tert-Butyl-2-methyl-pyrazole-3-carbonyl)amino]-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.66 (s, 1H), 8.86 (s, 1H), 8.58 - 8.55 (m, 1H), 8.45 - 8.41 (m, 1H), 8.05 (dd, J = 5.5, 2.2 Hz, 1H), 7.06 (s, 1H), 4.05 (s, 3H), 1.74 (s, 6H), 1.29 (s, 9H). LCMS (Method A) Rt 3.32 mins; MS m/z 369.3 = [M+H]+ (100% @ 215 nm)
83.15	 N-(1-Cyano-1-methyl-ethyl)-4-[(2-pyrazol-1-ylbenzoyl)amino] pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.86 (s, 1H), 8.83 (s, 1H), 8.51 (d, J = 5.5 Hz, 1H), 8.23 (d, J = 1.6 Hz, 1H), 8.19 (d, J = 2.4 Hz, 1H), 7.82 - 7.79 (m, 1H), 7.71 - 7.65 (m, 3H), 7.59 (d, J = 1.6 Hz, 1H), 7.55 - 7.51 (m, 1H), 6.47 - 6.45 (m, 1H), 1.73 (s, 6H). LCMS (Method A) Rt 2.50 mins; MS m/z 375.30 = [M+H]+ (98% @ 215 nm)
83.16	 N-[2-[(1-Cyano-1-methyl-ethyl)carbamoyl]-4-pyridyl]-6-(trifluoromethyl)pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 11.05 (s, 1H), 8.88 (s, 1H), 8.64 (d, J = 2.1 Hz, 1H), 8.62 (d, J = 5.5 Hz, 1H), 8.43 (d, J = 7.5 Hz, 1H), 8.38 (t, J = 7.8 Hz, 1H), 8.22 (d, 1H), 8.18 (dd, J = 5.5, 2.2 Hz, 1H), 1.75 (s, 6H). LCMS (Method A) Rt 3.23 mins; MS m/z 378.20 = [M+H]+ (100% @ 215 nm)
83.17	 N-[2-[(1-Cyano-1-methyl-ethyl)carbamoyl]-4-pyridyl]-3-oxo-4H-1,4-benzoxazine-7-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 11.04 (s, 1H), 10.68 (s, 1H), 8.85 (s, 1H), 8.56 (d, J = 5.5 Hz, 1H), 8.46 (d, J = 2.1 Hz, 1H), 8.09 (dd, J = 5.5, 2.2 Hz, 1H), 7.67 - 7.64 (m, 2H), 7.03 (d, J = 8.0 Hz, 1H), 4.68 (s, 2H), 1.74 (s, 6H). LCMS (Method A) Rt 2.32 mins; MS m/z 380.20 = [M+H]+ (94% @ 215 nm)

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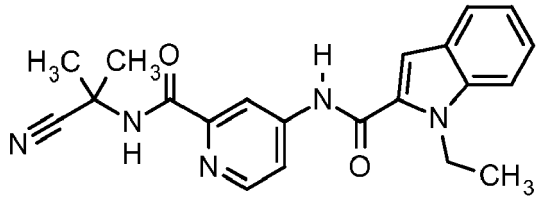
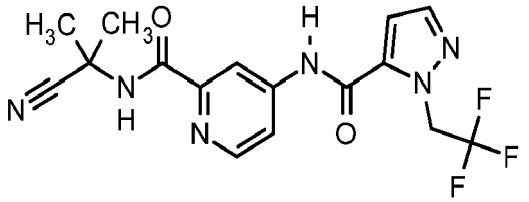
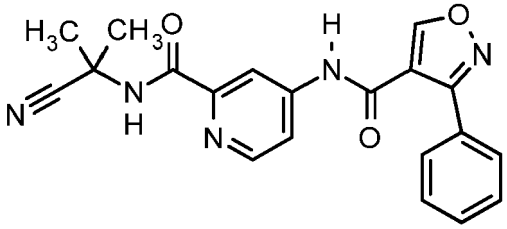
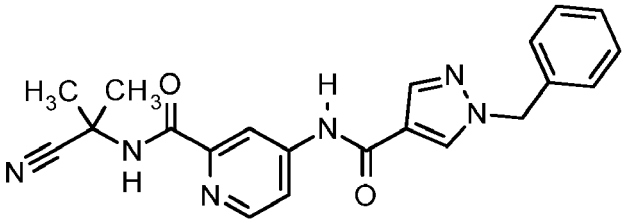
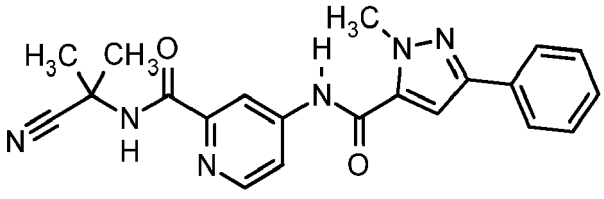
Ex.	Structure and Name	1H NMR, LCMS Retention Time, [M+H]+,
83.18	 N-[2-[(1-Cyano-1-methyl-ethyl)carbamoyl]-4-pyridyl]-1-ethyl-indole-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.86 (s, 1H), 8.86 (s, 1H), 8.57 (d, J = 5.5 Hz, 1H), 8.52 (d, J = 2.0 Hz, 1H), 8.07 (dd, J = 5.5, 2.2 Hz, 1H), 7.74 (d, J = 7.9 Hz, 1H), 7.62 (d, J = 8.4 Hz, 1H), 7.49 (s, 1H), 7.37 - 7.33 (m, 1H), 7.18 - 7.14 (m, 1H), 4.61 (q, J = 7.0 Hz, 2H), 1.75 (s, 6H), 1.34 (t, J = 7.0 Hz, 3H). LCMS (Method A) Rt 3.64 mins; MS m/z 376.3 = [M+H]+ (94% @ 215 nm)
83.19	 N-(1-Cyano-1-methyl-ethyl)-4-[[2-(2,2,2-trifluoroethyl)pyrazole-3-carbonyl]amino]pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.92 (s, 1H), 8.88 (s, 1H), 8.60 (d, J = 5.5 Hz, 1H), 8.44 (d, J = 2.1 Hz, 1H), 8.01 (dd, J = 5.5, 2.2 Hz, 1H), 7.81 (d, J = 2.0 Hz, 1H), 7.33 (d, J = 2.0 Hz, 1H), 5.53 (q, J = 8.9 Hz, 2H), 1.74 (s, 6H). LCMS (Method A) Rt 2.85 mins; MS m/z 381.3 = [M+H]+ (100% @ 215 nm)
83.20	 N-[2-[(1-Cyano-1-methyl-ethyl)carbamoyl]-4-pyridyl]-3-phenyl-isoxazole-4-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 11.07 (s, 1H), 9.64 (s, 1H), 8.87 (s, 1H), 8.57 (d, J = 5.5 Hz, 1H), 8.32 (d, J = 2.1 Hz, 1H), 7.91 (dd, J = 5.5, 2.2 Hz, 1H), 7.75 - 7.71 (m, 2H), 7.54 - 7.49 (m, 3H), 1.73 (s, 6H). LCMS (Method A) Rt 3.02 mins; MS m/z 376.3 = [M+H]+ (99% @ 215 nm)
83.21	 4-[(1-Benzylpyrazole-4-carbonyl)amino]-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.42 (s, 1H), 8.84 (s, 1H), 8.53 (d, J = 5.6 Hz, 2H), 8.36 (d, J = 2.1 Hz, 1H), 8.12 (s, 1H), 8.03 (dd, J = 5.6, 2.2 Hz, 1H), 7.40 - 7.36 (m, 2H), 7.34 - 7.28 (m, 3H), 5.41 (s, 2H), 1.73 (s, 6H). LCMS (Method A) Rt 2.89 mins; MS m/z 389.3 = [M+H]+ (100% @ 215 nm)
83.22	 N-(1-Cyano-1-methyl-ethyl)-4-[(2-methyl-5-phenyl-pyrazole-3-carbonyl)amino]pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.86 (s, 1H), 8.88 (s, 1H), 8.60 (d, J = 5.5 Hz, 1H), 8.46 (d, J = 2.1 Hz, 1H), 8.06 (dd, J = 5.5, 2.2 Hz, 1H), 7.85 - 7.80 (m, 2H), 7.58 (s, 1H), 7.47 (t, J = 7.7 Hz, 2H), 7.36 (t, J = 7.4 Hz, 1H), 4.16 (s, 3H), 1.75 (s, 6H). LCMS (Method A) Rt 3.44 mins; MS m/z 389.3 = [M+H]+ (100% @ 215 nm)

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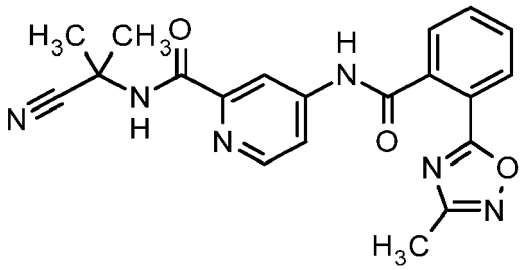
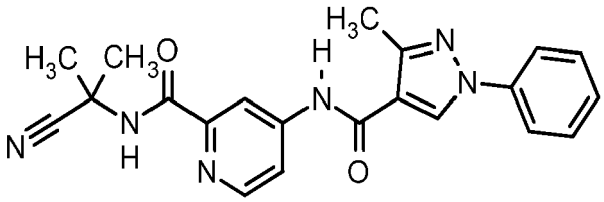
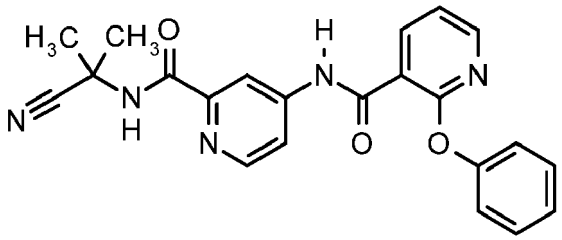
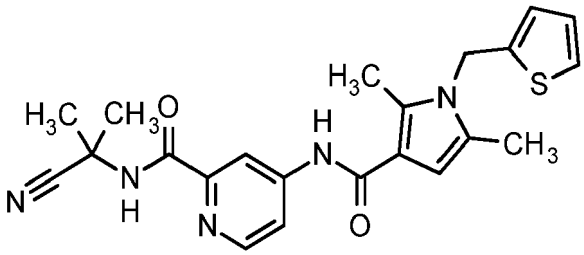
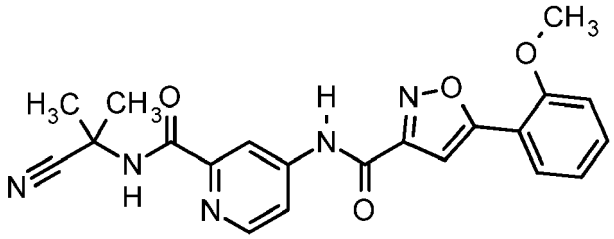
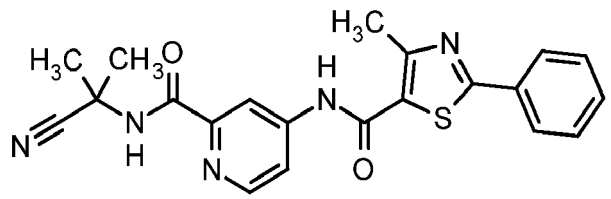
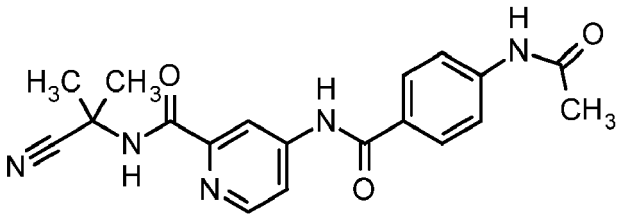
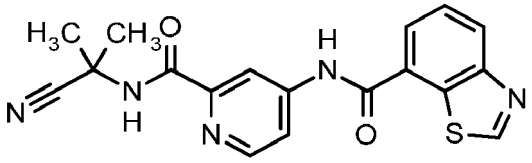
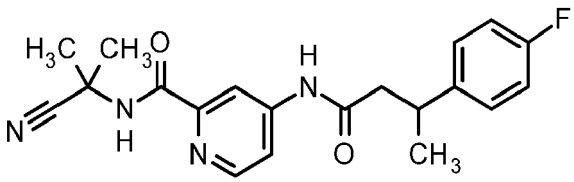
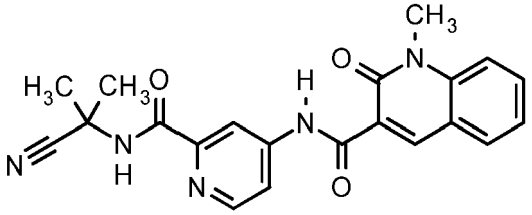
Ex.	Structure and Name	1H NMR, LCMS Retention Time, [M+H]+,
83.23	 N-(1-Cyano-1-methyl-ethyl)-4-[[2-(3-methyl-1,2,4-oxadiazol-5-yl)benzoyl]amino]pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 11.16 (s, 1H), 8.87 (s, 1H), 8.58 (d, J = 5.5 Hz, 1H), 8.31 (d, J = 1.9 Hz, 1H), 8.11 - 8.07 (m, 1H), 7.89 (dd, J = 5.5, 2.0 Hz, 1H), 7.85 - 7.76 (m, 3H), 2.32 (s, 3H), 1.74 (s, 6H). LCMS (Method A) Rt 2.61 mins; MS m/z 391.3 = [M+H]+ (96% @ 215 nm)
83.24	 N-(1-Cyano-1-methyl-ethyl)-4-[(3-methyl-1-phenyl-pyrazole-4-carbonyl)amino]pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.43 (s, 1H), 9.15 (s, 1H), 8.86 (s, 1H), 8.56 (d, J = 5.5 Hz, 1H), 8.35 (d, J = 2.1 Hz, 1H), 8.06 (dd, J = 5.5, 2.2 Hz, 1H), 7.83 - 7.79 (m, 2H), 7.59 - 7.54 (m, 2H), 7.39 (t, J = 7.4 Hz, 1H), 1.74 (s, 6H). Pyrazole CH3 behind DMSO peak at 2.50. LCMS (Method A) Rt 3.32 mins; MS m/z 389.3 = [M+H]+ (99% @ 215 nm)
83.25	 N-[2-[(1-Cyano-1-methyl-ethyl)carbamoyl]-4-pyridyl]-2-phenoxy-pyridine-3-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 11.11 (s, 1H), 8.87 (s, 1H), 8.58 (d, J = 5.5 Hz, 1H), 8.35 (d, J = 2.0 Hz, 1H), 8.27 (dd, J = 4.9, 1.9 Hz, 1H), 8.15 (dd, J = 7.4, 1.9 Hz, 1H), 7.99 (dd, J = 5.5, 2.1 Hz, 1H), 7.45 - 7.40 (m, 2H), 7.29 (dd, J = 7.4, 4.9 Hz, 1H), 7.25 - 7.20 (m, 3H), 1.73 (s, 6H). LCMS (Method A) Rt 3.24 mins; MS m/z 402.3 = [M+H]+ (100% @ 215 nm)
83.26	 N-(1-Cyano-1-methyl-ethyl)-4-[[2,5-dimethyl-1-(2-thienylmethyl) pyrrole-3-carbonyl]amino]pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 9.90 (s, 1H), 8.80 (s, 1H), 8.47 (d, J = 5.6 Hz, 1H), 8.44 (d, J = 2.1 Hz, 1H), 8.05 (dd, J = 5.6, 2.2 Hz, 1H), 7.45 (dd, J = 5.1, 1.2 Hz, 1H), 6.99 (dd, J = 5.1, 3.5 Hz, 1H), 6.92 (dd, J = 3.4, 1.0 Hz, 1H), 6.56 (s, 1H), 5.30 (s, 2H), 2.53 (s, 3H), 2.24 (s, 3H), 1.73 (s, 6H). LCMS (Method A) Rt 3.47 mins; MS m/z 422.3 = [M+H]+ (100% @ 215 nm)
83.27	 N-[2-[(1-Cyano-1-methyl-ethyl)carbamoyl]-4-pyridyl]-5-(2-methoxyphenyl)isoxazole-3-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 11.39 (s, 1H), 8.88 (s, 1H), 8.62 (d, J = 5.5 Hz, 1H), 8.56 (d, J = 2.1 Hz, 1H), 8.08 (dd, J = 5.5, 2.2 Hz, 1H), 7.95 (dd, J = 7.8, 1.7 Hz, 1H), 7.59 - 7.55 (m, 1H), 7.30 - 7.28 (m, 2H), 7.19 - 7.14 (m, 1H), 4.00 (s, 3H), 1.75 (s, 6H). LCMS (Method A) Rt 3.58 mins; MS m/z 406.2 = [M+H]+ (77% @ 215 nm)

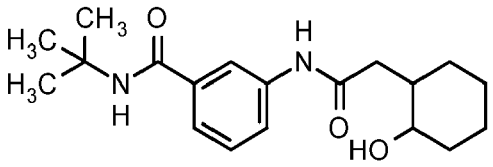
(continued)

Ex.	Structure and Name	1H NMR, LCMS Retention Time, [M+H]+,
83.28	 N-[2-[(1-Cyano-1-methyl-ethyl)carbamoyl]-4-pyridyl]-4-methyl-2-phenyl-thiazole-5-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.85 (s, 1H), 8.87 (s, 1H), 8.58 (d, J = 5.5 Hz, 1H), 8.40 (d, J = 2.1 Hz, 1H), 8.02 - 7.97 (m, 3H), 7.58 - 7.54 (m, 3H), 2.69 (s, 3H), 1.74 (s, 6H). LCMS (Method A) Rt 3.52 mins; MS m/z 406.2 = [M+H]+ (100% @ 215 nm)
83.29	 4-[(4-Acetamidobenzoyl)amino]-N-(1-cyano-1-methyl-ethyl) pyridine-2-carboxamide	LCMS (Method A) Rt 2.29 mins; MS m/z 366.2 = [M+H]+ (94% @ 215 nm)
83.30	 N-[2-[(1-Cyano-1-methyl-ethyl)carbamoyl]-4-pyridyl]-1,3-benzothiazole-7-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 11.13 (s, 1H), 9.54 (s, 1H), 8.90 (s, 1H), 8.62 (d, J = 5.5 Hz, 1H), 8.57 (d, J = 2.1 Hz, 1H), 8.45 (d, J = 7.5 Hz, 1H), 8.41 - 8.38 (m, 1H), 8.15 (dd, J = 5.5, 2.2 Hz, 1H), 7.81 (t, J = 7.8 Hz, 1H), 1.75 (s, 6H). LCMS (Method A) Rt 2.71 mins; MS m/z 366.2 = [M+H]+ (94% @ 215 nm)
83.31	 N-(1-Cyano-1-methyl-ethyl)-4-[3-(4-fluorophenyl) butanoylamino]pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.52 (s, 1H), 8.81 (s, 1H), 8.48 (d, J = 5.5 Hz, 1H), 8.20 (d, J = 2.0 Hz, 1H), 7.79 (dd, J = 5.5, 2.2 Hz, 1H), 7.34 - 7.28 (m, 2H), 7.15 - 7.07 (m, 2H), 3.30 - 3.26 (m, 1H), 2.68 - 2.62 (m, 2H), 1.72 (s, 6H), 1.25 (d, J = 7.0 Hz, 3H). LCMS (Method A) Rt 3.21 mins; MS m/z 369.3 = [M+H]+ (97% @ 215 nm)
83.32	 N-[2-[(1-Cyano-1-methyl-ethyl)carbamoyl]-4-pyridyl]-1-methyl-2-oxo-quinoline-3-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 12.52 (s, 1H), 9.02 (s, 1H), 8.89 (s, 1H), 8.60 (d, J = 5.4 Hz, 1H), 8.47 (s, 1H), 8.11 (d, J = 7.6 Hz, 1H), 7.90 (d, J = 3.7 Hz, 1H), 7.85 (t, J = 7.7 Hz, 1H), 7.74 (d, J = 8.5 Hz, 1H), 7.45 (t, J = 7.4 Hz, 1H), 3.82 (s, 3H), 1.75 (s, 6H). LCMS (Method A) Rt 3.33 mins; MS m/z 390.2 = [M+H]+ (99% @ 215 nm)

Example 84*

N-tert-Butyl-3-[[2-(2-hydroxycyclohexyl)acetyl]amino]benzamide

[1224]



[1225] HATU (268 mg, 0.7 mmol) was added to a stirred solution of 2-(2-oxocyclohexyl)acetic acid (100 mg, 0.64 mmol), 3-amino-N-tert-butyl-benzamide hydrochloride (146 mg, 0.64 mmol) and DIPEA (0.28 mL, 1.6 mmol) in DMF (2 mL) the resulting mixture was stirred at room temperature for 1 hour.The reaction mixture was diluted with EtOAc (10 mL) and water (10 mL). The aqueous layer was extracted with EtOAc (10 mL) and the combined organic extracts were washed with water (2 × 20 mL), brine (15 mL), dried over Na_2SO_4 and concentrated *in vacuo.* The crude material was then dissolved in MeOH (2 mL) and treated with $NaBH_4$ (36 mg, 0.96 mmol). The resulting mixture was stirred at room temperature for 10 minutes and then concentrated *in vacuo.* The crude residue was partitioned between water (20 mL) and EtOAc (20 mL). The organic layer was separated, dried over Na_2SO_4 and concentrated *in vacuo.* Purification by preparative HPLC (acidic pH, early elution method) afforded the titled compound as an off white powder as a 7:3 mixture of diastereoisomers.

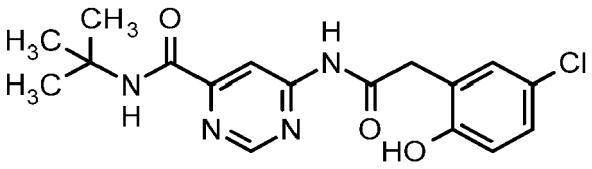
[1226] 1H NMR (400 MHz, DMSO-d6) δ 9.93 (s, 1H), 7.93 - 7.81 (m, 1H), 7.82 - 7.73 (m, 1H), 7.71 - 7.63 (m, 1H), 7.43 - 7.36 (m, 1H), 7.31 (t, J = 7.8 Hz, 1H), 4.70 - 4.18 (m, 1H), 3.74 - 2.93 (m, 1H), 2.87 - 2.35 (m, 1H), 2.27 - 1.97 (m, 1H), 1.96 - 1.77 (m, 1H), 1.76 - 0.88 (m, 17H).

[1227] LCMS (Method A) Rt 2.63 mins; MS m/z 333.3 = [M+H]+ (61% @ 215 nm); Rt 2.65 mins; MS m/z 333.3 = [M+H]+ (38% @215 nm)

Example 85*

N-tert-Butyl-6-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]pyrimidine-4-carboxamide

[1228]



[1229] The titled compound was prepared from N-tert-butyl-6-[[2-(5-chloro-2-methoxyphenyl)acetyl]amino]pyrimidine-4-carboxamide (Example 82) and analogously to Example 1 step 2.

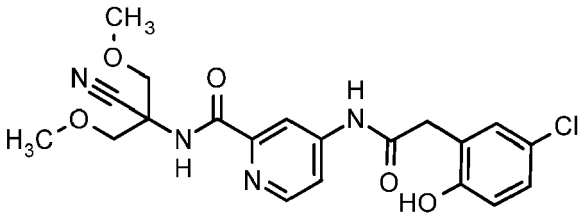
[1230] 1H NMR (500 MHz, DMSO-d6) δ 11.30 (s, 1H), 9.84 (s, 1H), 8.94 (d, J = 1.2 Hz, 1H), 8.54 (d, J = 1.2 Hz, 1H), 8.04 (s, 1H), 7.21 (d, J = 2.7 Hz, 1H), 7.11 (dd, J = 8.6, 2.7 Hz, 1H), 6.79 (d, J = 8.6 Hz, 1H), 3.75 (s, 2H), 1.39 (s, 9H).

[1231] LCMS (Method A) Rt 3.16 mins; MS m/z 363.2 = [M+H]+ (98% @ 215 nm)

Example 86

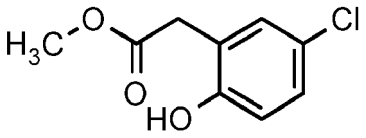
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[1-cyano-2-methoxy-1-(methoxy methyl)ethyl]pyridine-2-carboxamide

[1232]



Step 1: Methyl 2-(5-chloro-2-hydroxy-phenyl)acetate

[1233]

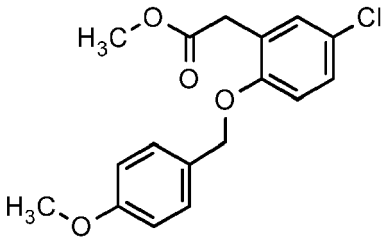


[1234] Methyl 2-(2-hydroxyphenyl)acetate (1.68 g, 10.11 mmol), NCS (1.35 g, 10.11 mmol) and triphenylphosphine sulfide (298 mg, 1.01 mmol) were dissolved in chloroform (40 mL) and stirred at room temperature for 1 hour. The resulting mixture was concentrated *in vacuo* and the residue dissolved in EtOAc (50 mL). The mixture was washed with water (2 × 50 mL), dried over anhydrous Na_2SO_4 and concentrated in *vacuo.* The residue was purified by chromatography on silica eluting with 0-50% EtOAc in heptane to afford the titled compound as a colourless viscous oil that solidified upon standing at room temperature. 1H NMR (500 MHz, DMSO-d6) δ 9.81 (br. s, 1H), 7.18 (d, J = 2.7 Hz, 1H), 7.11 (dd, J = 8.6, 2.7 Hz, 1H), 6.79 (d, J = 8.6 Hz, 1H), 3.59 (s, 3H), 3.56 (s, 2H).

[1235] LC-MS (Method E): Rt 1.02 mins; MS m/z no ionisaton observed

Step 2: Methyl 2-[5-chloro-2-[(4-methoxyphenyl)methoxy]phenyl]acetate

[1236]



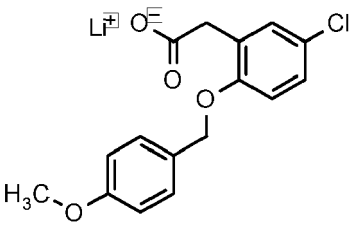
[1237] Methyl 2-(5-chloro-2-hydroxy-phenyl)acetate (step 1)(1.83 mL, 7.76 mmol) was suspended in anhydrous acetone (50 mL) and treated with K_2CO_3 (1.61 g, 11.64 mmol) followed by 1-(bromomethyl)-4-methoxy-benzene (1.2 mL, 8.55 mmol). After heating at reflux (60°C) for 2 hours, the mixture was concentrated *in vacuo.* The residue was dissolved in EtOAc (50 mL) and washed with water (50 mL), brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo.* The resulting crude residue was purified by chromatography on silica eluting with 0-25% EtOAc in heptane to afford the titled compound as a viscous yellow oil.

[1238] 1H NMR (500 MHz, DMSO-d6) δ 7.32 - 7.27 (m, 4H), 7.07 (d, J = 8.6 Hz, 1H), 6.96 - 6.92 (m, 2H), 5.01 (s, 2H), 3.75 (s, 3H), 3.62 (s, 2H), 3.55 (s, 3H).

[1239] LC-MS (Method E): Rt 1.23 mins; MS m/z no ionization observed = [M+H]+

Step 3: Lithium 2-[5-chloro-2-[(4-methoxyphenyl)methoxy]phenyl]acetate

[1240]



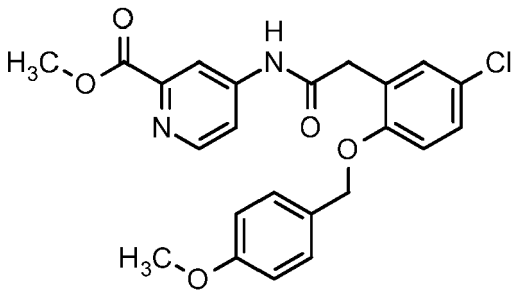
[1241] Methyl 2-[5-chloro-2-[(4-methoxyphenyl)methoxy]phenyl]acetate (step 2) (2.4 g, 6.57 mmol) was dissolved in THF (5 mL) and treated with 2M aqueous lithium hydroxide hydrate solution (3.45 mL, 6.9 mmol). After stirring at room temperature for 1 hour, MeOH (5 mL) was added to the bi-phasic mixture and stirring continued at room temperature

for 1 hour. Additional lithium hydroxide hydrate (13.8 mg, 0.33 mmol, 0.05 eq.) was added and the solution was stirred for another hour. A further portion of lithium hydroxide hydrate (13.8 mg, 0.33 mmol, 0.05 eq.) was added and stirring continued for 1 hour. The resulting mixture was concentrated *in vacuo* and azeotroped with MeCN (3 × 50 mL). The solid was suspended in diethyl ether (50 mL), filtered, washed with diethyl ether (2 × 25 mL) and dried under suction to afford the titled compound as a white powdery solid.

[1242] 1H NMR (500 MHz, DMSO-d6) δ 7.40 - 7.36 (m, 2H), 7.22 (d, J = 2.7 Hz, 1H), 7.07 (dd, J = 8.7, 2.8 Hz, 1H), 6.94 - 6.89 (m, 3H), 4.97 (s, 2H), 3.75 (s, 3H), 3.17 (s, 2H). LC-MS (Method E): Rt 1.17 mins; MS m/z 260.9 = [M-H]- (95% @ 215nm) [major mass ion observed for the decarboxylated ion fragment]

Step 4: Methyl 4-[[2-[5-chloro-2-[(4-methoxyphenyl)methoxy]phenyl]acetyl] amino]pyridine-2-carboxylate

[1243]



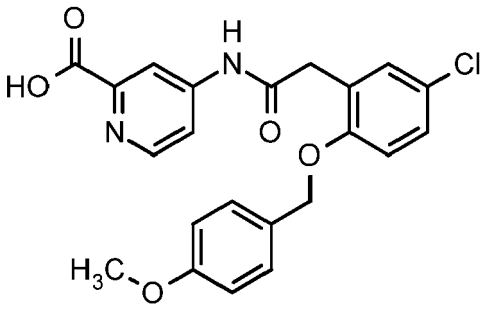
[1244] To a mixture of lithium 2-[5-chloro-2-[(4-methoxyphenyl)methoxy]phenyl]acetate (step 3) (1.5 g, 4.8 mmol) and methyl 4-aminopyridine-2-carboxylate (0.8 g, 5.28 mmol) in anhydrous 1,4-dioxane (50 mL) was added simultaneously 50% T3P® solution in EtOAc (5.71 mL, 9.59 mmol) and TEA (3.35 mL, 19.19 mmol). The reaction mixture was stirred at room temperature, for 1 hour and then quenched by careful addition of $NaHCO_3$ (50 mL). H_2O (10 mL) was added to dissolve excess salts and the mixture was extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo.* Purification by chromatography on NH-silica eluting with a gradient of 0 - 100% EtOAc in heptane afforded the titled compound as an off-white solid.

[1245] 1H NMR (500 MHz, DMSO-d6) δ 10.65 (s, 1H), 8.54 (d, J = 5.4 Hz, 1H), 8.21 (d, J = 2.0 Hz, 1H), 7.75 (dd, J = 5.5, 2.1 Hz, 1H), 7.33 (d, J = 2.7 Hz, 1H), 7.30 (dd, J = 8.7, 2.7 Hz, 1H), 7.22 (d, J = 8.7 Hz, 2H), 7.09 (d, J = 8.7 Hz, 1H), 6.65 - 6.61 (m, 2H), 4.97 (s, 2H), 3.87 (s, 3H), 3.70 (s, 2H), 3.64 (s, 3H).

[1246] LC-MS (Method F): Rt 1.63 mins; MS m/z 441.2/443.2 = [M+H]+ (100% @ 215nm)

Step 5: 4-[[2-[5-Chloro-2-[(4-methoxyphenyl)methoxy]phenyl]acetyl]amino]pyridine-2-carboxylic acid

[1247]



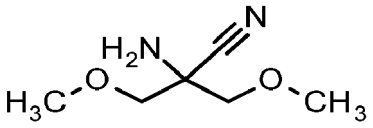
[1248] Methyl 4-[[2-[5-chloro-2-[(4-methoxyphenyl)methoxy]phenyl]acetyl]amino]pyridine-2-carboxylate (step 4) (1.98 g, 4.49 mmol) was dissolved in THF (2.5 mL) and MeOH (2.5mL) and treated with a 2M aqueous lithium hydroxide hydrate solution(2.47 mL, 4.94 mmol) and stirred at room temperature for 1 hour. Additional THF (2.5 mL), MeOH (2.5 mL) and water (2.5 mL) were added and stirring continued at room temperature overnight. The resulting mixture was diluted with EtOAc (50 mL) and water (50 mL). The pH was adjusted to pH 5 using 2M $KHS0_4$ (2 mL) and the precipitate was filtered. The filter cake was washed with water (20 mL), EtOAc (20 mL), diethyl ether (20 mL) and dried under vacumn to afford the titled compound as a white solid.

[1249] 1H NMR (500 MHz, DMSO-d6) δ 10.61 (s, 1H), 8.43 (d, J = 5.5 Hz, 1H), 8.11 (d, J = 1.7 Hz, 1H), 7.75 (dd, J = 5.6, 2.1 Hz, 1H), 7.33 (d, J = 2.6 Hz, 1H), 7.30 (dd, J = 8.7, 2.6 Hz, 1H), 7.23 (d, J = 8.6 Hz, 2H), 7.08 (d, J = 8.8 Hz, 1H), 6.68 - 6.64 (m, 2H), 4.98 (s, 2H), 3.71 (s, 2H), 3.65 (s, 3H) [OH not observed].

[1250] LC-MS (Method E): Rt 1.04 mins; MS m/z 427.0/429.0 = [M+H]+ (98% @ 215nm)

Step 6: 2-Amino-3-methoxy-2-(methoxymethyl)propanenitrile

[1251]



[1252] To a suspension of 1,3-dimethoxypropan-2-one (400 mg, 3.39 mmol) in 7M ammonia in MeOH (4.84 mL, 33.86 mmol) was added ammonium chloride (226 mg, 4.23 mmol) followed by sodium cyanide (207 mg, 4.23 mmol). After stirring at room temperature for 15 minutes, water (2.4 mL) was added and stirring continued for 3 hours. The mixture was diluted with EtOAc (30 mL) and washed with sat. sodium carbonate solution (3 × 20 mL) and brine (2 × 20 mL). The organic portion was separated, dried over Na_2SO_4 and concentrated in vacuo to afford the titled compound as a colorless oil.

[1253] 1H NMR (500 MHz, Methanol-d4) δ 3.55 (d, J = 9.5 Hz, 2H), 3.45 (d, J = 9.5 Hz, 2H), 3.45 (s, 6H)

[1254] LC-MS (Method E): Rt 0.66 mins; MS m/z 145.1= [M+H]+ (67% @ 215nm)

Step 7: 4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[1-cyano-2-methoxy-1-(methoxymethyl)ethyl]pyridine-2-carboxamide

[1255] To a solution of DIPEA (0.25 mL, 1.41 mmol), 4-[[2-[5-chloro-2-[(4-methoxyphenyl)methoxy]phenyl]acetyl]amino]pyridine-2-carboxylic acid (step 5) (200 mg, 0.47 mmol) and 50% T3P® solution in EtOAc (0.6 mL, 0.94 mmol) in DMF (2 mL) was added 2-amino-3-methoxy-2-(methoxymethyl)propanenitrile (step 6)(101 mg, 0.7 mmol) and the reaction mixture was stirred at room temperature for 6 hours. The resulting mixture was diluted with EtOAc (10 mL) and washed with brine (10 mL). The aqueous layer was re-extracted with EtOAc (10 mL) and the combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo.* The crude residue was dissolved in dioxane (2 mL) and treated with 4N HCl in dioxane (2 mL, 8.0 mmol). After stirring at room temperature for 2 hours, the mixture was concentrated *in vacuo* and purification of the crude product by preparative HPLC (acidic pH, early elution method) afforded the titled compound as an off white solid.

[1256] 1H NMR (500 MHz, Methanol-d4) δ 8.48 (d, J = 5.5 Hz, 1H), 8.21 (d, J = 1.8 Hz, 1H), 7.96 (dd, J = 5.5, 2.2 Hz, 1H), 7.21 (d, J = 2.6 Hz, 1H), 7.11 (dd, J = 8.6, 2.6 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 4.00 (d, J = 9.5 Hz, 2H), 3.83 (d, J = 9.5 Hz, 2H), 3.73 (s, 2H), 3.50 (s, 6H).

[1257] LC-MS (Method A): Rt 3.09 mins; MS m/z 433.1= [M+H]+ (98% @ 215nm)

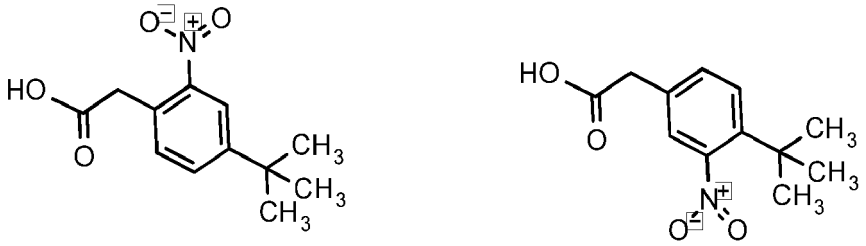
Example 87

4-[[2-(3-Amino-4-tert-butyl-phenyl)acetyl]amino]-N-tert-butyl-pyridine-2-carboxamide and

Example 88 4-[[2-(2-amino-4-tert-butyl-phenyl)acetyl]amino]-N-tert-butyl-pyridine-2-carboxamide

Step 1: A mixture of 2-(4-tert-butyl-2-nitro-phenyl)acetic acid and 2-(4-tert-butyl-3-nitrophenyl)acetic acid

[1258]



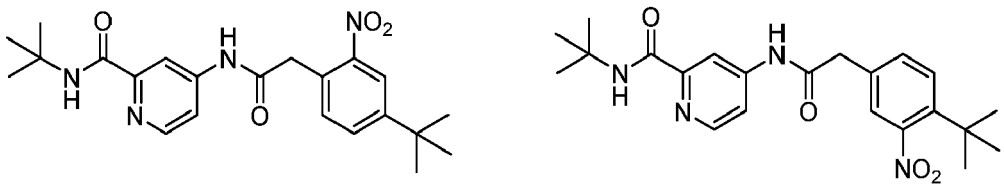
[1259] A stirred solution of 2-(4-tert-butylphenyl)acetic acid (1.0 g, 5.2 mmol) in water (5 mL) was treated dropwise with nitric acid (0.65 mL, 15.6 mmol) and sulfuric acid (0.55 mL, 10.4 mmol) and the mixture was stirred at room temperature for 10 hours. The resulting mixture was diluted with EtOAc (10 mL) and washed with brine (10 mL). The organic portion was separated, washed with brine (2 mL), dried over Na_2SO_4 and concentrated *in vacuo.* Purification by chromatography on silica eluting with 0-100% EtOAc in heptane afforded the titled mixture as a yellow oil.

[1260] 1H NMR (500 MHz, DMSO-d6) δ 8.01 (d, J = 2.1 Hz, 1H), 7.76 (dd, J = 8.0, 2.1 Hz, 1H), 7.61 (d, J = 8.1 Hz, 1H), 7.48 (d, J = 8.1 Hz, 1H), 7.48 - 7.42 (m, 2H), 3.95 (s, 2H), 3.66 (s, 2H), 1.34 (s,9H), 1.33 (s, 9H).

[1261] LC-MS (Method E): Rt 1.13 mins; MS m/z = no ionisation observed

Step 2: A mixture of N-tert-butyl-4-[[2-(4-tert-butyl-2-nitro-phenyl)acetyl]amino]pyridine-2-carboxamide and N-tert-butyl-4-[[2-(4-tert-butyl-3-nitro-phenyl)acetyl]amino]pyridine-2-carboxamide

[1262]



[1263] To a solution of DIPEA (1.36 mL, 7.76 mmol), 50% T3P® solution in EtOAc (0.6 mL, 5.17 mmol) and a mixture of 2-(4-tert-butyl-2-nitro-phenyl)acetic acid and 2-(4-tert-butyl-3-nitrophenyl)acetic acid (step 1) (720 mg, 3.03 mmol) in DMF (5 mL) was added 4-amino-N-tert-butyl-pyridine-2-carboxamide (645 mg, 3.34 mmol) and the reaction mixture was stirred at room temperature for 6 hours. The resulting mixture was diluted with EtOAc (10 mL) and washed with brine (10 mL). The aqueous layer was re-extracted with EtOAc (10 mL) and the combined extracts were dried over Na_2SO_4 and concentrated *in vacuo* to afford the titled compounds as a yellow oil.

[1264] 1H NMR (500 MHz, DMSO-d6) δ 10.81 (m, 2H), 8.46 (m, 2H), 8.16 (m, 2H), 8.03 (m, 3H), 7.84 - 7.74 (m, 3H), 7.64 (d, J = 8.1 Hz, 1H), 7.55 - 7.47 (m, 3H), 4.15 (s, 2H), 3.81 (s, 2H), 1.40 (s, 18H), 1.34 (s, 18H).

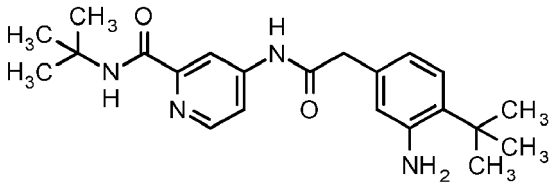
[1265] LC-MS (Method E): Rt 1.29 mins; MS m/z 413.5= [M+H]+ (100% @ 215nm)

Step 3: 4-[[2-(3-Amino-4-tert-butyl-phenyl)acetyl]amino]-N-tert-butyl-pyridine-2-carboxamide and 4-[[2-(2-amino-4-tert-butyl-phenyl)acetyl]amino]-N-tert-butyl-pyridine-2-carboxamide

[1266] To a mixture of N-tert-butyl-4-[[2-(4-tert-butyl-2-nitro-phenyl)acetyl]amino]pyridine-2-carboxamide and N-tert-butyl-4-[[2-(4-tert-butyl-3-nitro-phenyl)acetyl]amino]pyridine-2-carboxamide (step 2)(950 mg, 2.3 mmol) in EtOH (5 mL) was added 10 % Pd-C (123 mg, 1.15 mmol) and the mixture was stirred under an atmosphere of hydrogen for 18 hours. The resulting mixture was filtered through Celite® and washed through with methanol. The filtrate was concentrated *in vacuo* and purification of the crude by preparative HPLC (basic pH, early elution method) afforded the following compounds as white solids:

Example 87: 4-[[2-(3-Amino-4-tert-butyl-phenyl)acetyl]amino]-N-tert-butyl-pyridine-2-carboxamide

[1267]

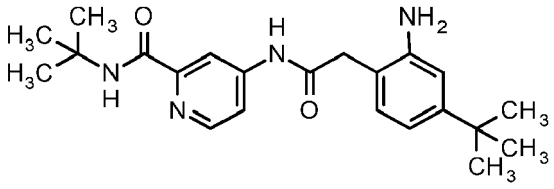


[1268] 1H NMR (500 MHz, DMSO-d6) δ 10.67 (s, 1H), 8.44 (d, J = 5.5 Hz, 1H), 8.19 (d, J = 2.0 Hz, 1H), 8.03 (s, 1H), 7.82 (dd, J = 5.5, 2.2 Hz, 1H), 7.00 (d, J = 8.0 Hz, 1H), 6.59 (d, J = 1.9 Hz, 1H), 6.48 (dd, J = 8.0, 1.9 Hz, 1H), 4.76 (s, 2H), 3.50 (s, 2H), 1.40 (s, 9H), 1.31 (s, 9H).

[1269] LC-MS (Method A): Rt 3.56 mins; MS m/z 383.3= [M+H]+ (100% @ 215nm)

Example 88: 4-[[2-(2-Amino-4-tert-butyl-phenyl)acetyl]amino]-N-tert-butyl-pyridine-2-carboxamide

[1270]



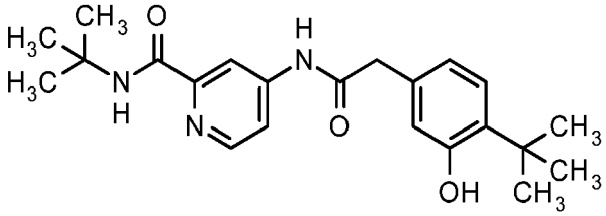
[1271] 1H NMR (500 MHz, DMSO-d6) δ 10.69 (s, 1H), 8.45 (d, J = 5.5 Hz, 1H), 8.18 (d, J = 2.1 Hz, 1H), 8.03 (s, 1H), 7.81 (dd, J = 5.5, 2.2 Hz, 1H), 6.97 (d, J = 8.0 Hz, 1H), 6.73 (d, J = 2.0 Hz, 1H), 6.59 (dd, J = 7.9, 2.0 Hz, 1H), 4.96 (s, 2H), 3.52 (s, 2H), 1.40 (s, 9H), 1.22 (s, 9H).

[1272] LC-MS (Method A): Rt 3.58 mins; MS m/z 383.3= [M+H]+ (99% @ 215nm)

Example 89

N-tert-Butyl-4-[[2-(4-tert-butyl-3-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide

[1273]



[1274] To a cooled (0 °C) solution of 4-[[2-(3-amino-4-tert-butyl-phenyl)acetyl]amino]-N-tert-butylpyridine-2-carboxamide (Example 87) (100 mg, 0.26 mmol) in water (0.2 mL) was added sulfuric acid (0.02 mL, 0.29 mmol) in water (0.3 mL) followed by sodium nitrite (20 mg, 0.29 mmol) in water (0.5 mL). After stirring at 5 °C for 3 hours, copper sulfate pentahydrate (326 mg, 1.31 mmol) and copper (I) oxide (112.23 mg, 0.78 mmol) in water (0.5 mL) were added and the mixture stirred at room temperature for 12 hours. The resulting mixture was diluted with EtOAc (10 mL) and water (10 mL). The organic layer was separated, dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude material by preparative HPLC (acidic pH early elution method) afforded the titled compound as a white solid.

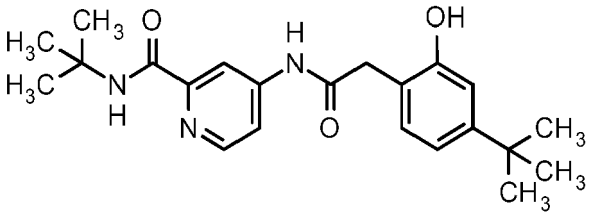
[1275] 1H NMR (400 MHz, DMSO-d6) δ 10.71 (s, 1H), 9.30 (s, 1H), 8.45 (d, J = 5.5 Hz, 1H), 8.20 (d, J = 2.1 Hz, 1H), 8.03 (s, 1H), 7.81 (dd, J = 5.5, 2.2 Hz, 1H), 7.08 (d, J = 8.0 Hz, 1H), 6.76 (d, J = 1.7 Hz, 1H), 6.68 (dd, J = 7.9, 1.7 Hz, 1H), 3.56 (s, 2H), 1.40 (s, 9H), 1.32 (s, 9H).

[1276] LC-MS (Method A): Rt 3.76 mins; MS m/z 384.2= [M+H]+ (99% @ 215nm)

Example 90

N-tert-Butyl-4-[[2-(4-tert-butyl-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide

[1277]



[1278] The titled compound was prepared from 4-[[2-(2-amino-4-tert-butyl-phenyl)acetyl]amino]-N-tert-butyl-pyridine-2-carboxamide (Example 88) analogously to Example 89.

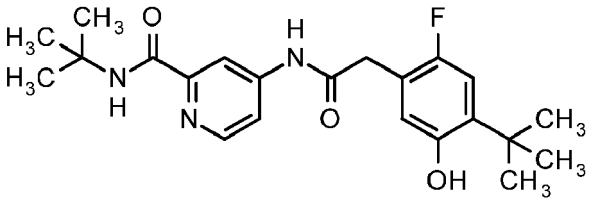
[1279] 1H NMR (500 MHz, DMSO-d6) δ 10.64 (s, 1H), 9.36 (s, 1H), 8.44 (d, J = 5.5 Hz, 1H), 8.18 (d, J = 2.0 Hz, 1H), 8.03 (s, 1H), 7.83 (dd, J = 5.5, 2.2 Hz, 1H), 7.06 (d, J = 7.9 Hz, 1H), 6.84 (d, J = 1.9 Hz, 1H), 6.79 (dd, J = 7.9, 1.9 Hz, 1H), 3.61 (s, 2H), 1.40 (s, 9H), 1.25 (s, 9H).

[1280] LC-MS (Method A): Rt 3.76 mins; MS m/z 384.2= [M+H]+ (100% @ 215nm)

Example 91

N-tert-Butyl-4-[[2-(4-tert-butyl-2-fluoro-5-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide

[1281]



[1282] To a solution of N-tert-butyl-4-[[2-(2-fluoro-5-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Example 3.13b) (300 mg, 0.87 mmol) in DCM (12 mL) was added tert-butanol (332 μL, 3.47 mmol) and H_2SO_4 (250 μL, 0.87 mmol) and the mixture stirred at room temperature for 1 hour. The resulting mixture was concentrated *in vacuo* and partitioned between EtOAc (20 mL) and water (20 mL). The organic portion was separated, washed with brine (20 mL) and concentrated *in vacuo.* Purification of the residue by preparative HPLC (acidic pH, standard elution method) afforded the titled compound as a white solid.

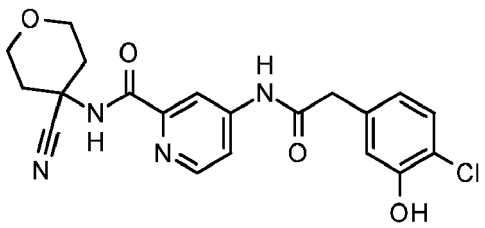
[1283] 1H NMR (500 MHz, DMSO-d6) δ 10.78 (s, 1H), 9.31 (s, 1H), 8.46 (d, J = 5.5 Hz, 1H), 8.19 (d, J = 2.0 Hz, 1H), 8.03 (s, 1H), 7.80 (dd, J = 5.5, 2.2 Hz, 1H), 6.87 (d, J = 11.9 Hz, 1H), 6.74 (d, J = 7.0 Hz, 1H), 3.65 (s, 2H), 1.40 (s, 9H), 1.32 (s, 9H).

[1284] LC-MS (Method A): Rt 3.89 mins; MS m/z 402.3= [M+H]+ (96% @ 215nm)

Example 92

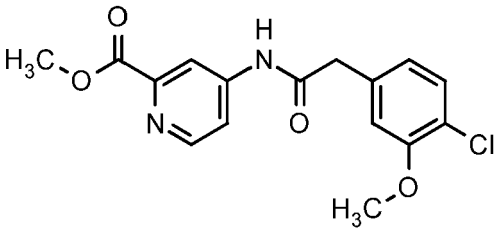
4-[[2-(4-Chloro-3-hydroxy-phenyl)acetyl]amino]-N-(4-cyanotetrahydropyran-4-yl)pyridine-2-carboxamide

[1285]



Step 1: Methyl 4-[[2-(4-chloro-3-methoxy-phenyl)acetyl]amino]pyridine-2-carboxylate

[1286]



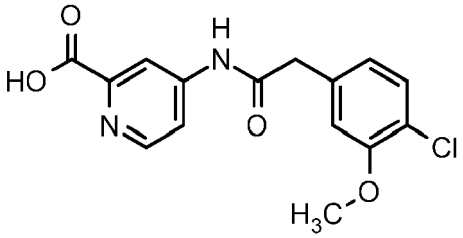
[1287] The titled compound was prepared from 2-(4-chloro-3-methoxy-phenyl)acetic acid and methyl 4-aminopyridine-2-carboxylate analogously to Example 41 step 1.

[1288] 1H NMR (400 MHz, DMSO-d6) δ 10.77 (s, 1H), 8.55 (d, J = 5.5 Hz, 1H), 8.29 (d, J = 2.0 Hz, 1H), 7.78 (dd, J = 5.5, 2.1 Hz, 1H), 7.36 (d, J = 8.1 Hz, 1H), 7.12 (d, J = 1.7 Hz, 1H), 6.91 (dd, J = 8.1, 1.7 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.73 (s, 2H).

[1289] LC-MS (Method E): Rt 1.03 mins; MS m/z 335.0/337.0 = [M+H]+ (95% @ 215nm)

Step 2: 4-[[2-(4-Chloro-3-methoxy-phenyl)acetyl]amino]pyridine-2-carboxylic acid

[1290]

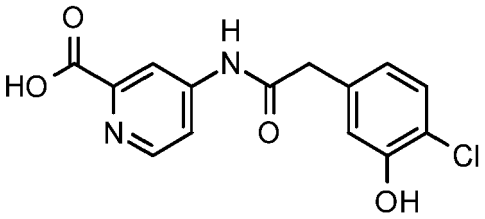


[1291] The titled compound was prepared from methyl 4-[[2-(4-chloro-3-methoxyphenyl)acetyl]amino]pyridine-2-carboxylate (step 1) analogously to Example 41 step 2. 1H NMR (500 MHz, DMSO-d6) δ 10.77 (s, 1H), 8.53 (d, J = 5.5 Hz, 1H), 8.26 (d, J = 2.0 Hz, 1H), 7.79 (dd, J = 5.5, 2.2 Hz, 1H), 7.36 (d, J = 8.1 Hz, 1H), 7.13 (d, J = 1.8 Hz, 1H), 6.91 (dd, J = 8.1, 1.9 Hz, 1H), 3.85 (s, 3H), 3.73 (s, 2H).

[1292] LC-MS (Method E): Rt 0.88 mins; MS m/z 321.0/322.9 = [M+H]+ (100% @ 215nm)

Step 3: 4-[[2-(4-Chloro-3-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxylic acid

[1293]



[1294] The titled compound was prepared from 4-[[2-(4-Chloro-3-methoxyphenyl)acetyl]amino]pyridine-2-carboxylic acid (step 2) and BBr_3 analogously Example 31 step 1.

[1295] LC-MS (Method E): Rt 0.80 mins; MS m/z 306.9/308.9 = [M+H]+ (62% @ 215nm)

Step 4: 4-[[2-(4-Chloro-3-hydroxy-phenyl)acetyl]amino]-N-(4-cyanotetrahydropyran-4-yl)pyridine-2-carboxamide

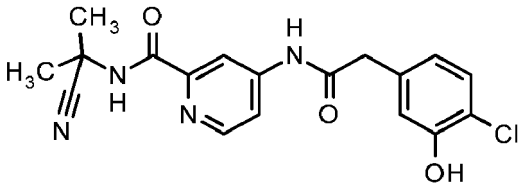
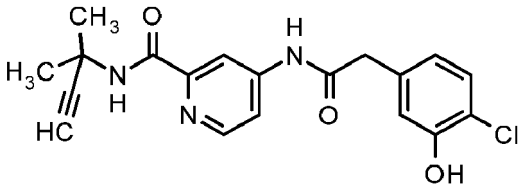
[1296] To a solution of 4-[[2-(4-chloro-3-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxylic acid (step 3)(65%, 50 mg, 0.11 mmol), 4-aminotetrahydropyran-4-carbonitrile (16 mg, 0.13 mmol) and DIPEA (0.04 mL, 0.21 mmol) in DMF (0.5 mL) was added HATU (48 mg, 0.13 mmol). The resulting mixture was stirred at room temperature for 1 hour. The reaction mixture was diluted with 0.5 M NaOH (aq., 0.4 mL), stirred for 5 min then acidified to pH 5 with 2M aqueous HCl. The aqueous layer was extracted with EtOAc (2 × 5 mL) and the combined organic extracts were washed with water (5 mL), dried over Na_2SO_4 and concentrated *in vacuo.* Purification by preparative HPLC (acidic pH, early elution method) followed by lyophilisation of the clean fractions afforded the titled compound as an off white powder.

[1297] 1H NMR (500 MHz, DMSO-d6) δ 10.79 (s, 1H), 10.11 (br s, 1H), 9.00 (s, 1H), 8.53 (d, J = 5.5 Hz, 1H), 8.23 (d, J = 2.1 Hz, 1H), 7.85 (dd, J = 5.5, 2.2 Hz, 1H), 7.26 (d, J = 8.1 Hz, 1H), 6.94 (d, J = 1.9 Hz, 1H), 6.76 (dd, J = 8.2, 1.9 Hz, 1H), 3.90 - 3.82 (m, 2H), 3.63 (s, 2H), 3.62 - 3.53 (m, 2H), 2.39 - 2.33 (m, 2H), 2.13 - 2.00 (m, 2H).

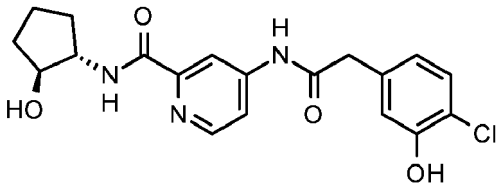
[1298] LC-MS (Method A): Rt 2.50 mins; MS m/z 415.1/417.1 = [M+H]+ (100% @ 215nm)

[1299] The compounds of the following tabulated Examples (Table 15) were prepared from 4-[[2-(4-chloro-3-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxylic acid (Example 92, step 3) analogously to Example 92 step 4 by replacing 4-aminotetrahydropyran-4-carbonitrile with the appropriate commercially available amine.

Table 15

Ex.	Structure and Name	1H NMR LCMS Retention Time, [M+H]+,
92.1	 4-[[2-(4-Chloro-3-hydroxyphenyl)acetyl] amino]-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.79 (s, 1H), 10.14 (br s, 1H), 8.83 (s, 1H), 8.51 (d, J = 5.5 Hz, 1H), 8.23 (d, J = 2.0 Hz, 1H), 7.85 (dd, J = 5.5, 2.2 Hz, 1H), 7.26 (d, J = 8.1 Hz, 1H), 6.94 (s, 1H), 6.76 (d, J = 7.5 Hz, 1H), 3.63 (s, 2H), 1.72 (s, 6H). LC-MS (Method A): Rt 2.63 mins; MS m/z 373.1/375.1 = [M+H]+ (95% @ 215nm)
92.2	 4-[[2-(4-Chloro-3-hydroxyphenyl)acetyl] amino]-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.76 (s, 1H), 10.12 (s, 1H), 8.47 (d, J = 5.5 Hz, 1H), 8.31 (s, 1H), 8.20 (d, J = 2.0 Hz, 1H), 7.82 (dd, J = 5.5, 2.2 Hz, 1H), 7.26 (d, J = 8.1 Hz, 1H), 6.94 (d, J = 2.0 Hz, 1H), 6.76 (dd, J = 8.2, 2.0 Hz, 1H), 3.63 (s, 2H), 3.21 (s, 1H), 1.64 (s, 6H). LC-MS (Method A): Rt 2.90 mins; MS m/z 372.1/374.1 = [M+H]+ (97% @ 215nm)

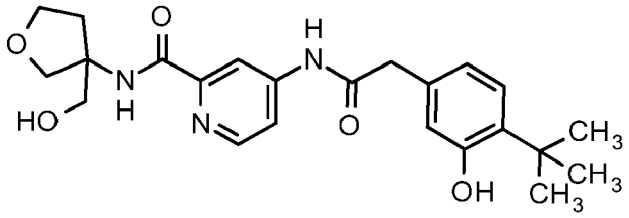
(continued)

Ex.	Structure and Name	1H NMR LCMS Retention Time, [M+H]+,
92.3	 4-[[2-(4-Chloro-3-hydroxyphenyl)acetyl] amino]-N-[(1s,2s)-2-hydroxycyclopentyl]pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.73 (s, 1H), 10.13 (s, 1H), 8.48 (d, J = 5.5 Hz, 1H), 8.44 (d, J = 7.6 Hz, 1H), 8.19 (d, J = 2.1 Hz, 1H), 7.81 (dd, J = 5.5, 2.2 Hz, 1H), 7.26 (d, J = 8.1 Hz, 1H), 6.95 (d, J = 1.9 Hz, 1H), 6.76 (dd, J = 8.2, 1.9 Hz, 1H), 4.80 (d, J = 4.5 Hz, 1H), 3.98 (dq, J = 13.1, 7.2, 6.4 Hz, 2H), 3.62 (s, 2H), 2.05 - 1.93 (m, 1H), 1.92 - 1.79 (m, 1H), 1.72 - 1.57 (m, 2H), 1.57 - 1.38 (m, 2H). LC-MS (Method A): Rt 2.37 mins; MS m/z 390.1/392.1 = [M+H]+ (99% @ 215nm)

Example 93

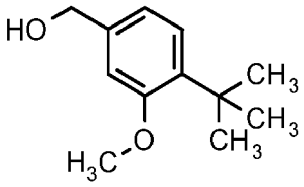
4-[[2-(4-tert-Butyl-3-hydroxy-phenyl)acetyl]amino]-N-[3-(hydroxymethyl) tetrahydrofuran-3-yl]pyridine-2-carboxamide

[1300]



Step 1: (4-tert-Butyl-3-methoxy-phenyl)methanol

[1301]

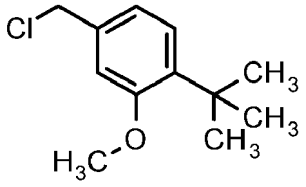


[1302] To a stirred solution of 4-tert-butyl-3-methoxy-benzoic acid (1.9 g, 9.12 mmol) in THF (20mL) was added 1M borane-THF (25.55 mL, 25.55 mmol) and the mixture was stirred at 50 °C for 1 hour. After cooling to room temperature, the reaction was quenched with methanol (10 mL) and the volatile solvent removed *in vacuo*. More methanol (10 mL) was added and the volatiles were removed *in vacuo*. This process was repeated once more to afford the titled compound as a pale yellow oil.

[1303] 1H NMR (400 MHz, DMSO-d6) δ 7.14 (d, J = 7.9 Hz, 1H), 6.94 (s, 1H), 6.81 (d, J = 7.8 Hz, 1H), 5.09 (s, 1H), 4.45 (s, 2H), 3.80 (s, 3H), 1.32 (s, 9H).

Step 2: 1-tert-Butyl-4-(chloromethyl)-2-methoxy-benzene

[1304]

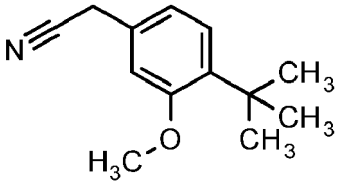


[1305] A stirred solution of (4-tert-butyl-3-methoxy-phenyl)methanol (step 1)(1.56 g, 8.03 mmol) and DMF (0.59 mL, 8.03 mmol) in DCM (20 mL) was treated dropwise with thionyl chloride (1.42 mL, 16.06 mmol) and the mixture stirred at room temperature for 1 hour. The resulting mixture was concentrated *in vacuo* and the residue diluted with EtOAc (10 mL) and washed with saturated $NaHCO_3$ (10 mL). The organic portion was separated, washed with brine (2 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the titled compound as a yellow oil.

[1306] 1H NMR (400 MHz, DMSO-d6) δ 7.21 (d, J = 7.9 Hz, 1H), 7.05 (d, J = 1.4 Hz, 1H), 6.94 (dd, J = 7.9, 1.6 Hz, 1H), 4.72 (s, 2H), 3.82 (s, 3H), 1.33 (s, 9H).

Step 3: 2-(4-tert-Butyl-3-methoxy-phenyl)acetonitrile

[1307]

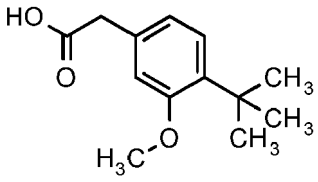


[1308] A solution of 1-tert-butyl-4-(chloromethyl)-2-methoxy-benzene (step 2)(1.7 g, 7.99 mmol) in DMF (10 mL) was treated with sodium cyanide (0.78 g, 15.98 mmol) and the resulting mixture stirred at room temperature for 8 hours. The mixture was diluted with EtOAc (30 mL) and washed with sat. sodium carbonate (3 $\times$ 20 mL) and brine (2 $\times$ 20 mL). The organic layer was separated, dried over sodium sulfate and concentrated *in vacuo* to afford the titled compound as a yellow oil.

[1309] 1H NMR (500 MHz, DMSO-d6) δ 7.22 (d, J = 7.9 Hz, 1H), 6.95 (d, J = 1.6 Hz, 1H), 6.86 (dd, J = 7.9, 1.7 Hz, 1H), 3.96 (s, 2H), 3.82 (s, 3H), 1.32 (s, 9H).

Step 4: 2-(4-tert-Butyl-3-methoxy-phenyl)acetic acid

[1310]



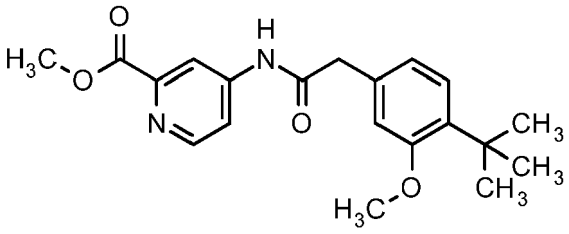
[1311] To a solution of 2-(4-tert-butyl-3-methoxy-phenyl)acetonitrile (step 3) (1.52 g, 7.48 mmol) H_2O (5 mL) was added lithium hydroxide hydrate (1.76 mL, 37.39 mmol) and the reaction mixture was heated at reflux for 10 hours. After cooling to room temperature, the mixture was acidified with concentrated HCl solution. The mixture was extracted with DCM (10 mL) and the combined organic extracts were dried over sodium sulphate and concentrated *in vacuo* to afford the titled compound as a pale yellow solid.

[1312] 1H NMR (400 MHz, DMSO-d6) δ 12.13 (s, 1H), 7.13 (d, J = 7.9 Hz, 1H), 6.87 (d, J = 1.6 Hz, 1H), 6.76 (dd, J = 7.9, 1.7 Hz, 1H), 3.79 (s, 3H), 3.51 (s, 2H), 1.32 (s, 9H).

[1313] LC-MS (Method E): Rt 1.14 mins; MS m/z 220.9 = [M+H]+ (99% @ 215nm)

Step 5: Methyl 4-[[2-(4-tert-butyl-3-methoxy-phenyl)acetyl]amino]pyridine-2-carboxylate

[1314]

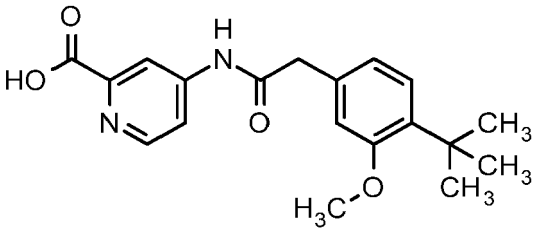


[1315] The titled compound was prepared from 2-(4-tert-butyl-3-methoxy-phenyl)acetic acid (step 4) and methyl 4-aminopyridine-2-carboxylate analogously to Example 30 step 1.

[1316] 1H NMR (500 MHz, DMSO-d6) δ 10.78 (s, 1H), 8.55 (d, J = 5.5 Hz, 1H), 8.31 (d, J = 2.0 Hz, 1H), 7.80 (dd, J = 5.5, 2.1 Hz, 1H), 7.16 (d, J = 7.9 Hz, 1H), 6.96 (d, J = 1.5 Hz, 1H), 6.84 (dd, J = 7.9, 1.6 Hz, 1H), 3.87 (s, 3H), 3.81 (s, 3H), 3.66 (s, 2H), 1.31 (s, 9H). LC-MS (Method E): Rt 1.19 mins; MS m/z 357.0 = [M+H]+ (97% @ 215nm)

Step 6: 4-[[2-(4-tert-Butyl-3-methoxy-phenyl)acetyl]amino]pyridine-2-carboxylic acid

[1317]



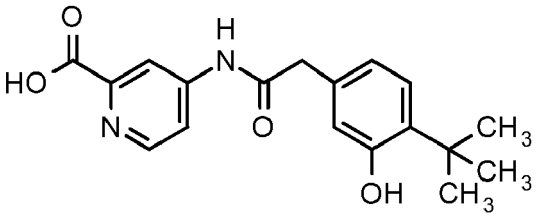
[1318] The titled compound was prepared from methyl 4-[[2-(4-tert-butyl-3-methoxyphenyl)acetyl]amino]pyridine-2-carboxylate (step 5) and lithium hydroxide hydrate analogously to Example 30 step 2.

[1319] 1H NMR (500 MHz, DMSO-d6) δ 10.87 (s, 1H), 8.54 (d, J = 5.6 Hz, 1H), 8.30 (d, J = 2.0 Hz, 1H), 7.84 (dd, J = 5.6, 2.2 Hz, 1H), 7.16 (d, J = 7.9 Hz, 1H), 6.97 (d, J = 1.6 Hz, 1H), 6.84 (dd, J = 7.9, 1.6 Hz, 1H), 3.81 (s, 3H), 3.68 (s, 2H), 1.31 (s, 9H)

[1320] LC-MS (Method E): Rt 1.03 mins; MS m/z 343.1 = [M+H]+ (94% @ 215nm)

Step 7: 4-[[2-(4-tert-Butyl-3-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxylic acid

[1321]



[1322] The titled compound was prepared from 4-[[2-(4-tert-butyl-3-methoxyphenyl)acetyl]amino]pyridine-2-carboxylic acid (step 6) and BBr3 analogously to Example 31 step 1.

[1323] 1H NMR (500 MHz, DMSO-d6) δ 11.12 (s, 1H), 9.32 (s, 1H), 8.60 (d, J = 6.0 Hz, 1H), 8.38 (d, J = 2.0 Hz, 1H), 7.98 (dd, J = 5.9, 2.1 Hz, 1H), 7.08 (d, J = 7.9 Hz, 1H), 6.76 (d, J = 1.7 Hz, 1H), 6.71 - 6.66 (m, 1H), 3.62 (s, 2H), 1.32 (s, 9H).

[1324] LC-MS (Method E): Rt 0.97 mins; MS m/z 329 = [M+H]+ (76% @ 215nm)

Step 8: 4-[[2-(4-tert-butyl-3-hydroxy-phenyl)acetyl]amino]-N-[3-(hydroxymethyl) tetrahydrofuran-3-yl]pyridine-2-carboxamide

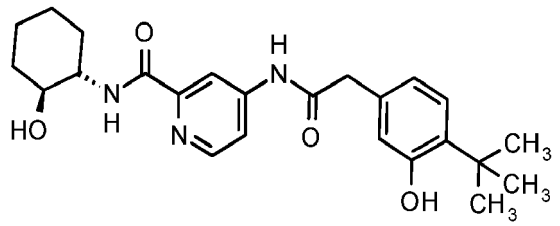
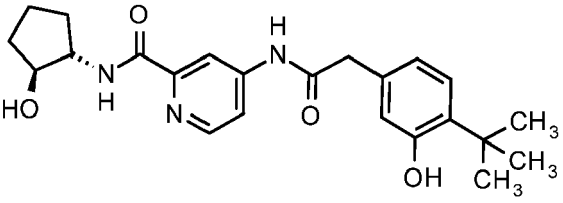
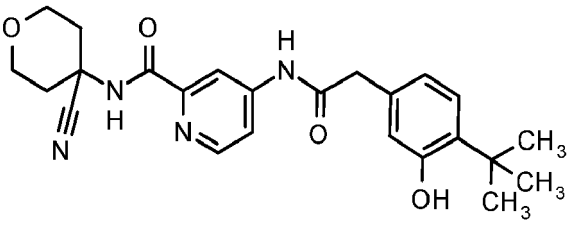
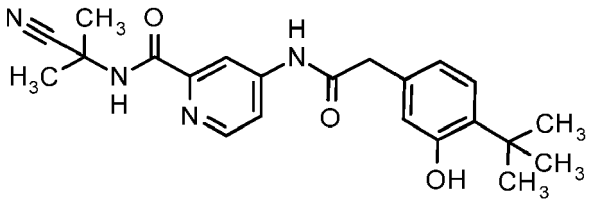
[1325] The titled compound was prepared from 4-[[2-(4-tert-butyl-3-hydroxyphenyl)acetyl]amino]pyridine-2-carboxylic acid (step 7) and (3-aminotetrahydrofuran-3-yl)methanol analogously to Example 31 step 2.

[1326] 1H NMR (500 MHz, DMSO-d6) δ 10.72 (s, 1H), 9.30 (s, 1H), 8.48 (d, J = 5.5 Hz, 1H), 8.41 (s, 1H), 8.22 (d, J = 2.1 Hz, 1H), 7.82 (dd, J = 5.5, 2.1 Hz, 1H), 7.08 (d, J = 8.0 Hz, 1H), 6.76 (d, J = 1.7 Hz, 1H), 6.68 (dd, J = 7.9, 1.6 Hz, 1H), 5.17 (t, J = 5.6 Hz, 1H), 3.90 - 3.76 (m, 4H), 3.61 (d, J = 5.2 Hz, 2H), 3.56 (s, 2H), 2.32 (ddd, J = 12.6, 7.6, 5.0 Hz, 1H), 1.98 (dt, J = 12.8, 7.8 Hz, 1H), 1.32 (s, 9H).

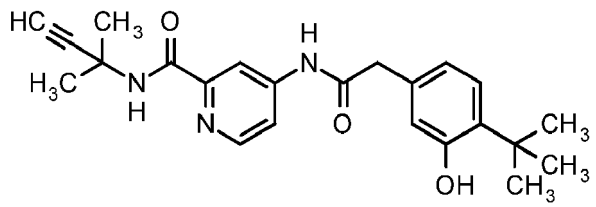
[1327] LC-MS (Method A): Rt 2.91 mins; MS m/z 428.3 = [M+H]+ (96% @ 215nm)

[1328] The compounds of the following tabulated Examples (Table 16) were prepared from 4-[[2-(4-tert-butyl-3-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxylic acid (Example 93, step 7) analogously to Example 93 step 8 by replacing (3-aminotetrahydrofuran-3-yl)methanol with the appropriate commercially available amine.

Table 16

Ex.	Structure and Name	1H NMR LCMS Retention Time, [M+H]+,
93.1	 4-[2-(4-tert-butyl-3-hydroxyphenyl)acetamido]-N-[(1S,2S)-2-hydroxycyclohexyl]pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.74 (s, 1H), 9.31 (s, 1H), 8.48 (d, J = 5.5 Hz, 1H), 8.34 (d, J = 8.1 Hz, 1H), 8.21 (d, J = 2.0 Hz, 1H), 7.84 (dd, J = 5.5, 2.2 Hz, 1H), 7.07 (d, J = 8.0 Hz, 1H), 6.77 (d, J = 1.6 Hz, 1H), 6.69 (dd, J = 8.0, 1.6 Hz, 1H), 4.69 (d, J = 5.5 Hz, 1H), 3.61 - 3.52 (m, 3H), 3.48 - 3.39 (m, 1H), 1.96 - 1.84 (m, 2H), 1.69 - 1.58 (m, 2H), 1.32 (s, 9H), 1.32 - 1.20 (m, 4H). LC-MS (Method A): Rt 3.24 mins; MS m/z 426.3 = [M+H]+ (100% @ 215nm)
93.2	 4-[2-(4-tert-butyl-3-hydroxyphenyl)acetamido]-N-[(1S,2S)-2-hydroxycyclopentyl]pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.76 (s, 1H), 9.31 (s, 1H), 8.48 (d, J = 5.5 Hz, 1H), 8.44 (d, J = 7.6 Hz, 1H), 8.21 (d, J = 1.9 Hz, 1H), 7.83 (dd, J = 5.5, 2.2 Hz, 1H), 7.07 (d, J = 8.0 Hz, 1H), 6.77 (d, J = 1.6 Hz, 1H), 6.69 (dd, J = 8.0, 1.7 Hz, 1H), 4.81 (d, J = 4.3 Hz, 1H), 4.05 - 3.93 (m, 2H), 3.56 (s, 2H), 2.05 - 1.95 (m, 1H), 1.91 - 1.80 (m, 1H), 1.74 - 1.58 (m, 2H), 1.56 - 1.42 (m, 2H), 1.32 (s, 9H). LC-MS (Method A): Rt 3.12 mins; MS m/z 412.3 = [M+H]+ (100% @ 215nm)
93.3	 4-[[2-(4-tert-Butyl-3-hydroxy-phenyl)acetyl]amino]-N-(4-cyanotetrahydropyran-4-yl)pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.77 (s, 1H), 9.30 (s, 1H), 9.01 (s, 1H), 8.54 (d, J = 5.5 Hz, 1H), 8.25 (d, J = 2.0 Hz, 1H), 7.87 (dd, J = 5.5, 2.2 Hz, 1H), 7.08 (d, J = 8.0 Hz, 1H), 6.77 (d, J = 1.7 Hz, 1H), 6.69 (dd, J = 8.0, 1.7 Hz, 1H), 3.87 (dt, J = 12.2, 3.8 Hz, 2H), 3.64 - 3.55 (m, 4H), 2.41 - 2.33 (m, 2H), 2.08 (ddd, J = 13.8, 10.3, 3.9 Hz, 2H), 1.32 (s, 9H). LC-MS (Method A): Rt 3.30 mins; MS m/z 437.2 = [M+H]+ (98% @ 215nm)
93.4	 4-[[2-(4-tert-Butyl-3-hydroxy-phenyl)acetyl]amino]-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.76 (s, 1H), 9.30 (s, 1H), 8.83 (s, 1H), 8.52 (d, J = 5.5 Hz, 1H), 8.25 (d, J = 2.0 Hz, 1H), 7.86 (dd, J = 5.5, 2.2 Hz, 1H), 7.08 (d, J = 8.0 Hz, 1H), 6.77 (d, J = 1.8 Hz, 1H), 6.69 (dd, J = 7.9, 1.8 Hz, 1H), 3.57 (s, 2H), 1.73 (s, 6H), 1.33 (s, 9H). LC-MS (Method A): Rt 3.41 mins; MS m/z 395.2 = [M+H]+ (99% @ 215nm)

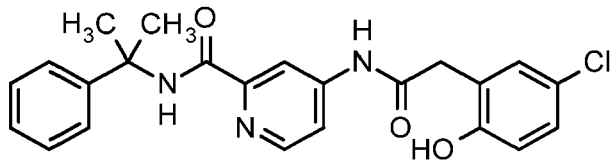
(continued)

Ex.	Structure and Name	1H NMR LCMS Retention Time, [M+H]+,
93.5	 4-[[2-(4-tert-Butyl-3-hydroxy-phenyl)acetyl]amino]-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide	1H NMR (500 MHz, DMSO-d6) δ 10.74 (s, 1H), 9.30 (s, 1H), 8.48 (d, J = 5.5 Hz, 1H), 8.32 (s, 1H), 8.21 (d, J = 2.0 Hz, 1H), 7.83 (dd, J = 5.5, 2.2 Hz, 1H), 7.08 (d, J = 8.0 Hz, 1H), 6.76 (d, J = 1.8 Hz, 1H), 6.69 (dd, J = 8.0, 1.8 Hz, 1H), 3.56 (s, 2H), 3.21 (s, 1H), 1.65 (s, 6H), 1.32 (s, 9H). LC-MS (Method A): Rt 3.64 mins; MS m/z 394.2 = [M+H]+ (96% @ 215nm)

Example 94

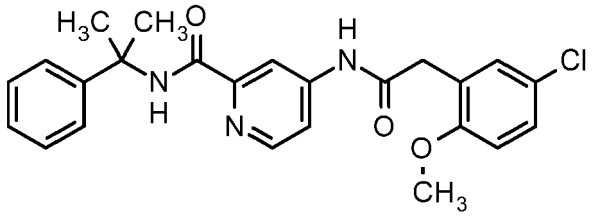
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1-methyl-1-phenyl-ethyl) pyridine-2-carboxamide

[1329]



Step 1: 4-[[2-(5-Chloro-2-methoxy-phenyl)acetyl]amino]-N-(1-methyl-1-phenylethyl)pyridine-2-carboxamide

[1330]



[1331] The titled compound was prepared from 4-[[2-(5-chloro-2-methoxyphenyl)acetyl]amino]pyridine-2-carboxylic acid (Example 8.1 step 2) and 2-phenylpropan-2-amine analogously to Example 86, step 7.

Step 2: 4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1-methyl-1-phenylethyl)pyridine-2-carboxamide

[1332] The titled compound was prepared from 4-[[2-(5-chloro-2-methoxy-phenyl)acetyl]amino]-N-(1-methyl-1-phenyl-ethyl)pyridine-2-carboxamide (step 1) and BBr3 analogously to Example 3 step 3.

[1333] 1H NMR (500 MHz, DMSO-d6) δ 10.77 (s, 1H), 9.80 (s, 1H), 8.56 (s, 1H), 8.49 (d, J = 5.5 Hz, 1H), 8.10 (d, J = 2.0 Hz, 1H), 7.84 (dd, J = 5.6, 2.2 Hz, 1H), 7.41 - 7.37 (m , 2H), 7.33 - 7.28 (m, 2H), 7.23 - 7.18 (m, 2H), 7.11 (dd, J = 8.6, 2.7 Hz, 1H), 6.79 (d, J = 8.6 Hz, 1H), 3.65 (s, 2H), 1.72 (s, 6H).

[1334] LC-MS (Method A): Rt 3.88 mins; MS m/z 424.2/426.2 = [M+H]+ (99% @ 215nm)

Biological example 95

Automated whole-cell patch clamp assay to detect TMEM16A activity in recombinant cells

Cell culture and preparation

[1335] Fisher rat thyroid (FRT) cells stably expressing human TMEM16A (TMEM16Aabc variant; Dr Luis Galietta,

Insituto Giannina, Italy) were cultured in T-75 flasks in Hams F-12 media with Coon's modification (Sigma) supplemented with 10% (v/v) foetal bovine serum, penicillin-streptomycin (10,000 U/mL/10000 μg/mL), G-418 (750μg/mL), L-glutamine (2 mM) and sodium bicarbonate solution (7.5% v/v). At ~90% confluence cells were harvested for experiments by detachment with a 2:1 (v/v) mixture of Detachin (BMS Biotechnology) and 0.25% (w/v) trypsin-EDTA. Cells were diluted to a density of 3.5 - 4.5 $\times$ 10^6 cells/mL with media consisting of CHO-S-SFM II (Sigma), 25 mM HEPES (Sigma) and Soy bean trypsin inhibitor (Sigma).

Whole-cell patch clamp recording

[1336] FRT-TMEM16A cells were whole-cell patch clamped using an automated planar patch clamp system (Qpatch, Sophion). Briefly, once high resistance (GOhm) seals were established between the cells and the planar recording array the patch was ruptured using suction pulses to establish the whole-cell recording configuration of the patch clamp technique. The assay employed the following solutions (all reagents Sigma):
Intracellular solution (mM): N-methyl-D-glucamine 130, $CaCl_2$ 18.2, $MgCl_2$ 1, HEPES 10, EGTA 10, BAPTA 20, Mg-ATP 2, pH 7.25, 325mOsm with sucrose.

[1337] Extracellular solution (mM): N-methyl-D-glucamine 130, $CaCl_2$ 2, $MgCl_2$ 1, HEPES 10, pH 7.3, 320 mOsm with sucrose.

[1338] The intracellular solution buffers intracellular calcium at levels required to give ~20% activation of the maximal TMEM16A mediated current (EC_{20} for calcium ions). Cells were voltage clamped at a holding potential of -70mV and a combined voltage step (to +70 mV)/ramp (-90 mv to +90 mV) was applied at 0.05 Hz. After a period of current stabilisation test compounds, solubilised in 100% (v/v) DMSO and subsequently diluted into extracellular solution, were applied to generate a cumulative concentration response curve. Each concentration of test compound was incubated for 5 minutes before addition of the next concentration. After the final concentration was tested a supramaximal concentration of either a known active positive modulator or the TMEM16A inhibitor, CaCCinhA01 (Del La Fuente *et al,* 2008) was added to define the upper and lower limits of the assay.

[1339] Compound activity was quantified by measuring the increase in current upon compound addition and expressing this as a percentage increase of baseline TMEM16A current level. Percentage increases in current were determined for each concentration and the data plotted as a function of concentration using either the Qpatch software or Graphpad Prism v6.05 providing the concentration which gave 50% of its maximal effect (EC_{50}) and maximum efficacy (percentage of baseline increase).

[1340] The method of calculating the results is illustrated in Figure 1, which shows an example trace from the Qpatch TMEM16A assay. In Figure 1, I_{BL} equals baseline current, $I_{[\#1]}$ equals the peak current during test compound concentration 1 incubation period and so on.

[1341] Peak TMEM16A current at +70mVwas plotted as a function of time over the assay period. Baseline current (I_{BL}) was measured after a period of stabilisation. The increase in current for each compound addition was determined by taking the peak current during the incubation period and subtracting the current from the previous recording period and then expressing this as a percentage of the baseline current. For test compound concentration 1 in Figure 1 this is:

$$(I_{[\#1]} - I_{BL} / I_{BL}) \times 100$$

[1342] For each additional concentration tested the increase in current was determined by subtracting the current from the previous incubation period and normalising the baseline value - for test concentration 2 in Figure 1 this is:

$$(I_{[\#2]} - I_{[\#1\}} / I_{BL}) \times 100$$

[1343] The values for each test concentration were plotted as a cumulative function of concentration eg. for test concentration two this would be the sum of the peak changes measured during concentration one plus concentration two.

[1344] The results obtained for the example compounds are shown in Table 8, from which it can be seen that the compounds of the present invention are capable of significantly increasing the TMEM16A current level.

Table 17 - % Potentiation shown by 3.33μM solution of Test Compounds and Calculated EC_{50} Values

(* denotes a reference compound that is not claimed)		
Example	**% Potentiation @ 3.33μM Avg**	**EC_{50} Avg (μM)**
1	203	0.21

(continued)

(* denotes a reference compound that is not claimed)		
Example	**% Potentiation @ 3.33μM Avg**	**EC_{50} Avg (μM)**
1.1*	182	0.56
1.2*	170	0.54
1.3	233	0.24
1.4	195	0.40
1.5*	149	0.34
1.6	255	0.06
1.7	239	0.15
1.8	300	0.41
1.9*	79	4.20
1.10	200	0.08
2*	262	0.27
2.1*	216	0.49
2.2*	158	1.61
2.3*	203	0.59
2.4*	53	
2.5*	51	1.34
2.6*	140	2.91
2.7*	51	8.19
2.8*	74	4.55
2.9*	148	0.99
2.10*	133	0.46
2.11*	126	0.43
2.12*	111	0.31
2.13*	126	0.46
2.14*	100	1.78
2.15*	163	0.49
2.16*	60	4.27
2.17*	172	0.27
2.18*	118	1.41
2.19*	249	0.46
3	287	0.11
3.1a	128	0.18
3.2a	116	0.16
3.3a	91	0.07
3.4a	206	0.14
3.5a	311	0.50
3.6a	546	0.37

(continued)

(* denotes a reference compound that is not claimed)		
Example	**% Potentiation @ 3.33μM Avg**	**EC_{50} Avg (μM)**
3.7a	135	0.28
3.5b	150	0.20
3.6b	205	0.12
3.7b	160	0.18
3.8b	203	0.30
3.9b	144	0.96
3.10b	159	0.46
3.11b	168	0.41
3.12b	143	0.34
3.13b	179	0.25
3.14b	251	0.04
3.15b	127	
3.16b	167	0.17
3.17b	227	0.12
4*	96	1.50
4.1*	79	2.17
4.2*	116	0.66
4.3*	151	1.53
4.4*	61	4.19
4.5*	138	0.70
4.6*	53	3.86
4.7*	68	
4.8*	55	2.07
4.9*	60	4.66
5	78	0.80
5.1	140	0.87
5.2	63	
5.3	152	0.88
5.4	57	
5.5	132	0.72
5.6	101	0.15
5.7	131	1.23
5.8	116	0.46
5.9	126	1.13
5.10	78	3.77
5.11	89	0.17
5.12	100	0.76

(continued)

(* denotes a reference compound that is not claimed)		
Example	**% Potentiation @ 3.33μM Avg**	**EC_{50} Avg (μM)**
5.13	94	1.14
5.14	128	0.76
5.15	87	
5.16	110	
5.17	94	0.65
5.18	79	0.46
5.19	75	1.85
5.20	221	0.57
5.21	172	0.51
5.22	94	
5.23	144	1.20
5.24	189	0.14
5.25	67	
5.26	110	1.20
5.27	84	
5.29	190	0.86
5.31	145	
5.32	285	
5.33	49	
5.34	185	0.64
5.35	106	0.18
5.36	44	0.06
5.37	117	0.15
5.38	231	0.15
5.39	147	
6	162	1.14
7*	153	0.65
7.1*	241	0.34
7.2	203	0.26
7.3*	125	0.20
7.4*	52	0.65
7.5*	239	0.28
7.6	285	0.10
7.7	234	0.13
7.8*	231	0.92
7.9	288	0.23
7.10*	218	0.36

(continued)

(* denotes a reference compound that is not claimed)		
Example	**% Potentiation @ 3.33μM Avg**	**EC_{50} Avg (μM)**
7.11	167	0.32
7.12	101	2.11
7.13	212	0.09
7.14	225	0.15
7.15	230	0.05
7.16	354	0.13
8*	88	3.02
8.1	155	0.59
8.2*	169	1.96
8.3	238	0.23
9*	149	0.23
9.1*	77	4.62
9.2	196	0.19
10	250	0.22
11*	76	0.90
12*	112	1.76
13	245	1.00
14*	58	
15	200	0.13
16*	63	
17*	173	1.49
18*	405	0.45
19	57	
20	111	0.22
21a	99	1.57
21b	164	1.08
22.1	114	
22.2	157	0.26
22.3	132	
23	93	
23.1	150	
23.2	87	
23.3	59	0.47
23.4	115	
23.5	110	
23.6	108	
23.7	98	

(continued)

(* denotes a reference compound that is not claimed)		
Example	**% Potentiation @ 3.33μM Avg**	**EC_{50} Avg (μM)**
23.8	122	
23.9	47	
23.11	101	
23.12	197	0.33
23.13	169	0.57
23.14	33	
23.15	147	1.19
23.16	68	1.40
24	68	
25	330	0.37
25.1	393	0.14
26	108	
27	90	
27.1	52	
27.2	300	
27.3	166	0.29
28	318	0.40
28.1	68	
30	113	1.22
30.1	245	0.14
30.2	221	0.18
30.3	100	0.25
30.3a	221	
30.4	95	0.75
30.5	63	
30.6	80	
30.7	124	0.34
30.8	121	0.70
30.9	100	0.47
30.10	265	
30.11	125	0.22
30.12	314	
30.13	205	0.38
31	223	0.12
31.2	110	0.01
31.3	205	0.21
31.3a	238	0.55

(continued)

(* denotes a reference compound that is not claimed)		
Example	**% Potentiation @ 3.33μM Avg**	**EC_{50} Avg (μM)**
31.4	186	0.02
32	171	
32.1	246	
32.2	183	0.34
32.3	288	0.29
32.4	187	0.71
32.5	177	0.59
32.6	153	0.82
32.7	111	0.20
32.8	79	
32.9	31	
33	245	0.24
34	245	0.09
35	180	0.19
35a	137	0.10
35b	190	0.31
35.1	51	
35.2	300	0.61
35.3	144	
35.4	138	
35.6	53	
35.7	97	
35.8	250	0.18
35.9	455	0.54
35.10	223	0.28
35.11	107	
35.12	158	0.42
35.13	191	0.35
35.14	172	0.27
35.15	158	0.15
35.16	85	0.33
35.17	153	0.15
35.18	147	0.43
35.19	248	0.47
35.20*	240	0.42
35.21*	200	0.41
35.22*	104	0.22

(continued)

(* denotes a reference compound that is not claimed)		
Example	**% Potentiation @ 3.33μM Avg**	**EC_{50} Avg (μM)**
35.24	120	0.01
35.25	126	0.10
35.26	157	
35.27	496	0.33
36	199	0.02
37	352	0.12
38	307	0.05
39	262	0.06
40	153	0.70
40.1	91	0.87
41*	38	
42	143	0.76
43	174	0.70
44	377	0.05
45	151	
46	275	0.25
46a	249	0.11
46b	215	
47	237	0.18
47.1	156	1.92
47.2	212	0.23
47.3	237	0.35
48	195	0.10
48.1	185	0.42
49	226	0.68
50	65	
51	54	
53	184	0.39
54	62	
55	114	
56	76	
57a	285	0.51
57b	162	0.67
58	217	
59	175	
60	126	0.35
60.1	60	

(continued)

(* denotes a reference compound that is not claimed)		
Example	**% Potentiation @ 3.33μM Avg**	**EC_{50} Avg (μM)**
60.2	169	0.20
61	85	
62	99	
63	37	
64	55	
64.1	78	
64.2	61	
64.3	70	
64.4	2	
64.5	143	0.45
64.6	0	
64.7	83	
64.8	97	
65	55	
65.1	75	0.47
65.2	73	0.48
65.3	33	
65.4	10	
66	130	
67	158	1.10
68	39	
69	47	
70	138	
71*	162	
71.1*	256	0.25
72	53	
73	196	0.31
73.1	389	0.28
74*	337	0.18
74.1*	49	
75	34	
76	366	0.22
77	139	0.41
77.1	151	0.54
78	98	0.02
78.1	238	0.05
78.2	86	0.02

(continued)

(* denotes a reference compound that is not claimed)		
Example	**% Potentiation @ 3.33μM Avg**	**EC_{50} Avg (μM)**
79	60	
79.1	45	
79.2	211	
79.3	64	0.24
80*	130	
81	151	0.37
81.1	108	
81.2	103	0.42
81.3	129	0.04
81.4	122	0.04
81.5	74	
82*	88	0.72
83	6	
83.1	159	
83.2	41	
83.3	16	
83.4	58	
83.5	185	
83.6	248	
83.7	147	
83.8	35	
83.9	18	
83.10	62	
83.11	13	
83.13	-1	
83.14	70	
83.15	-10	
83.16	60	
83.17	8	
83.18	16	
83.19	28	
83.20	9	
83.21	70	
83.22	85	
83.23	-11	
83.24	55	
83.25	-8	

(continued)

(* denotes a reference compound that is not claimed)		
Example	**% Potentiation @ 3.33μM Avg**	**EC_{50} Avg (μM)**
83.26	95	
83.27	-11	
83.28	20	
83.29	-9	
83.30	93	
83.31	78	
83.32	-16	
85*	155	0.35
86	593	0.35
87	332	0.22
88	270	0.24
89	366	0.09
90	219	0.12
92	133	0.11
92.1	151	0.14
92.2	71	0.01
93.1	207	0.05
93.2	220	0.04
93.3	130	0.06
93.4	476	0.07
93.5	136	0.02
94	516	0.34

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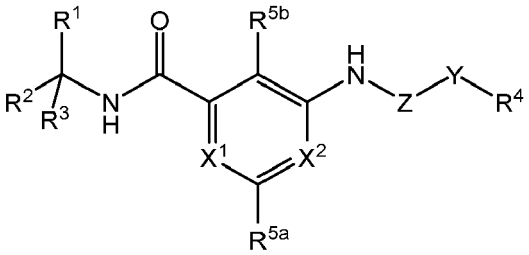
Claims

1. A compound of general formula (I) including all tautomeric forms all enantiomers and isotopic variants and salts and solvates thereof:



(I)

wherein:

R^1 is H, CN, $C(O)OR^{12}$, C_{1-3} alkyl, C_{2-3} alkenyl or C_{2-3} alkynyl, any of which alkyl, alkenyl or alkynyl groups are optionally substituted with one or more substituents, suitably one substituent, selected from fluoro, OR^{12}, $N(R^{12})_2$, $C(O)OR^{12}$, $C(O)N(R^{12})_2$, $C(O)R^{12}$ and $N(R^{13})C(O)R^{12}$;
wherein each R^{12} and R^{13} is independently selected from H, C_{1-6} alkyl and C_{1-6} fluoroalkyl
R^2 is H or C_{1-6} alkyl optionally substituted with OR^{12};
R^3 is:

C_{1-10} alkyl, C_{2-10} alkenyl or C_{2-10} alkynyl, any of which is optionally substituted with one or more substituents, suitably one substituent, selected from fluoro, CN, R^{14} OR^{14}, OR^{15}, $N(R^{15})_2$, $C(O)OR^{15}$, $C(O)N(R^{15})_2$, $N(R^{16})C(O)R^{15}$, $N(R^{15})S(O)_2R^{14}$, $N(R^{15})S(O)_2R^{16}$ and $N(R^{15})C(O)OR^{16}$; or
a 3- to 7-membered carbocyclic or heterocyclic ring system or a 6- to 10 membered aryl or 5- to 10-membered heteroaryl ring system, either of which is optionally substituted with one or more substituents selected from halo, CN, C_{1-4} alkyl, C_{1-4} haloalkyl, OR^{17} and $N(R^{17})_2$;

wherein R^{14} is a 6- to 10-membered aryl or 5- to 10-membered heteroaryl ring system or a 3- to 7-membered carbocyclic or heterocyclic ring system, any of which is optionally substituted with one or more substituents selected from halo, C_{1-4} alkyl, C_{1-4} haloalkyl, OR^{17} and $N(R^{17})_2$; wherein each R^{17} is independently H, C_{1-4} alkyl or C_{1-4} haloalkyl;
each R^{15} and R^{16} is independently H, C_{1-6} alkyl or C_{1-6} haloalkyl; or

R^2 and R^3 together with the carbon atom to which they are attached combine to form a 3-to 10-membered carbocyclic or heterocyclic ring system optionally substituted with one or more substituents selected from halo, CN, OR^9, $N(R^9)_2$, $C(O)OR^9$, $C(O)N(R^9)_2$, $C(O)R^9$, $N(R^9)C(O)R^9$ and C_{1-4} alkyl optionally substituted with halo, OR^9 or $N(R^9)_2$; or
R^1, R^2 and R^3 together with the carbon atom to which they are attached combine to form a bridged 5- to 10-membered carbocyclic or heterocyclic ring system or phenyl, any of which is optionally substituted with one or more substituents selected from halo, CN, OR^9, $N(R^9)_2$, $C(O)OR^9$, $C(O)N(R^9)_2$, $C(O)R^9$, $N(R^9)C(O)R^9$ and C_{1-4} alkyl optionally substituted with halo, OR^9 or $N(R^9)_2$;
each R^9 is independently selected from H, C_{1-6} alkyl or C_{1-6} haloalkyl;

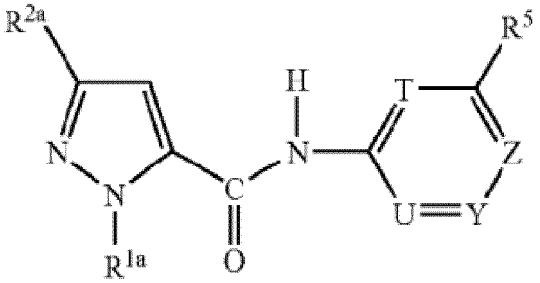
X^1 is N;
X^2 is CR^8
R^8 is H, halo, OH, $O(C_{1-4}$ alkyl), CN or NH_2;
Y is a bond or a straight C_{1-6} alkylene chain which is optionally substituted with one or more substituents R^{18}, wherein two substituents R^{18} may be attached to the same or to different carbon atoms;
wherein each R^{18} is independently C_{1-3} alkyl or C_{1-3} haloalkyl in which a $-CH_2-$ is optionally replaced with -NH- or -O- and wherein two R^{18} groups may combine with the atom or atoms to which they are attached to form a 3- to 6-membered carbocyclic or heterocyclic ring system;
Z is -C(O)- or -C(O)NH-;
R^4 is a 6- to 14-membered aryl, 5- to 14-membered heteroaryl or a 5- to 10-membered carbocyclic ring system, any of which is optionally substituted with one or more substituents selected from:

halo, CN, nitro, R^{19}, OR^{19}, OR^6, SR^6, NR^6R^7, $C(O)R^6$, $C(O)R^{19}$, $C(O)OR^6$, $C(O)N(R^6)(R^7)$, $N(R^7)C(O)R^6$;
C_{1-6} alkyl or $O(C_{1-6}$ alkyl), either of which is optionally substituted with one or more substituents selected from halo, CN, nitro, R^{19}, OR^6, SR^6, NR^6R^7, $C(O)R^6$ $C(O)OR^6$, $C(O)N(R^6)(R^7)$ and $N(R^7)C(O)R^6$; and when R^4 is not fully aromatic in character, oxo;

wherein R^{19} is 5- or 6-membered aryl or heteroaryl ring system or a 3- to 7-membered carbocyclic or heterocyclic ring system, any of which is optionally substituted with one or more substituents selected from halo, C_{1-4} alkyl, C_{1-4} haloalkyl, OH, $O(C_{1-4}$ alkyl), $O(C_{1-4}$ haloalkyl);
R^6 is H, C_{1-6} alkyl, C_{1-6} haloalkyl, benzyl, 3- to 7-membered carbocyclyl or 3- to 7-membered heterocyclyl;
R^7 is H, C_{1-6} alkyl or C_{1-6} haloalkyl; or
R^6 and R^7 together with the nitrogen atom to which they are attached may form a 4 to 7-membered heterocyclic ring optionally containing one or more further heteroatoms and optionally substituted with one or more substituents selected from oxo and halo; and

each of R^{5a} and R^{5b} is independently H, C_{1-4} alkyl or halo;
provided that:

when X^2 is CH, Z is -C(O)- and Y is a bond, R^4 is not a 5- to 10-membered heteroaryl ring linked to Y via a nitrogen atom, and
wherein the compounds of formula (A):

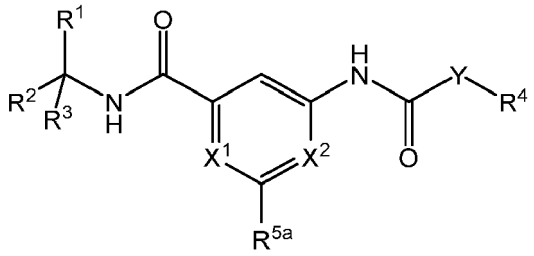


(A)

wherein R^{1a} is ethyl; R^{2a} is *tert*-butyl; T, U and Y are CH and Z is N; and R^5 is C(O)NHEt, $C(O)NH(CH_2)_2CH_3$, $C(O)NH(CH_2)_2CH_2F$, $C(O)NH(CH_2)_3CH_3$, $C(O)NH(CH_2)_3CH_2F$, $C(O)NHCH_2C{\equiv}CH$ or $C(O)NHCH_2CH{=}CH_2$ are disclaimed and any tautomeric forms, enantiomers and isotopic variants and salts and solvates of the compounds of Formula (A) are not disclaimed.

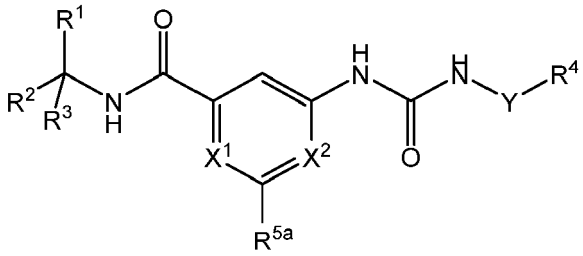
2. A compound according to claim 1, wherein:

Z is -C(O)- and R^{5b} is H, such that the compound is of formula (Iz):



(Iz)

wherein R^1, R^2, R^3, R^4, R^{5a}, X^1, X^2 and Y are as defined in claim 1; or
Z is -C(O)NH-, and R^{5b} is H such that the compound is of general formula (Iy):



(Iy)

wherein R^1, R^2, R^3, R^4, R^{5a}, X^1, X^2 and Y are as defined in claim 1.

3. A compound according to claim 1 or claim 2 wherein R^1 is H, CN, ethynyl or methyl, either of which is unsubstituted or is substituted with OH.

4. A compound according to any one of claims 1 to 3 wherein:

R^2 is methyl or ethyl; and
R^3 is C_{1-4} alkyl optionally substituted with one or more substituents selected from hydroxyl, methoxy, ethoxy, -C(O)O-(C_{1-4} alkyl) and -N(H)C(O)O-(C_{1-4} alkyl); or wherein:

R^3 is C_{1-10} alkyl or C_{2-3} alkynyl either of which is unsubstituted or substituted with a single substituent selected from fluoro, R^{14} OR^{14}, OR^{15}, $C(O)OR^{15}$, $N(R^{16})S(O)_2R^{15}$ and $N(R^{16})C(O)OR^{15}$; wherein
R^{14} is selected from phenyl, pyridyl and a 5- or 6-membered heterocyclic ring;
R^{15} is selected from H, or C_{1-4} alkyl; and
R^{16} is H; or
R^3 is a 3- to 7-membered carbocyclic or heterocyclic ring system, which is unsubstituted or substituted as defined in claim 1; or
R^3 is phenyl or pyridyl, either or which is unsubstituted or substituted with one or more substituents selected from OR^{17} and $N(R^{17})_2$, wherein each R^{17} is H or methyl.

5. A compound according to claim 4 wherein:

R^1 is methyl or CN and R^2 and R^3 are both methyl; or
R^2 and R^3 combine with the carbon atom to which they are attached to form a carbocyclic or heterocyclic ring system and R^1 is H, methyl, methyl substituted with OH, CN, ethynyl or $C(O)OR^{12}$, wherein R^{12} is as defined in claim 1.

6. A compound according to any one of claims 1 to 5 wherein Y is $-CH_2-$, $-CH_2CH_2-$,

$-CH(CH_3)CH_2-$, $-CH_2CH(CH_3)-$ or $-CH_2CH_2CH_2-$, especially $-CH_2-$; and/or
R^{5a} and R^{5b} are both H and/or
X^2 is CH; and/or wherein:

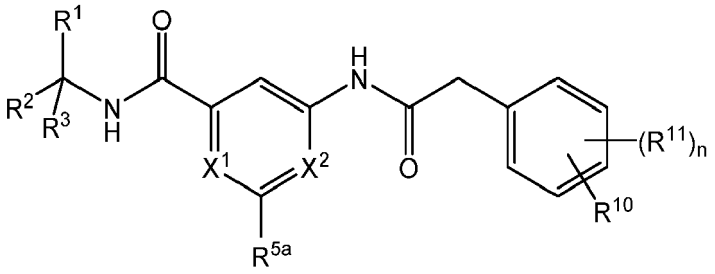
R^4 is a 6- to 11-membered aryl group selected from phenyl, naphthyl, indanyl, 1,2,3,4-tetrahydronaphthyl and benzocycloheptanyl, any of which is optionally substituted as defined in claim 1; or
R^4 is a 5- to 10-membered heteroaryl group selected from pyridyl, quinolinyl, quinoxalinyl, indazolyl, indolyl, benzoxazolyl, dihydrobenzofuranyl, furyl and thienyl, any of which is optionally substituted as defined in claim 1;
R^4 is a carbocyclyl group selected from cyclohexyl and adamantyl, any of which is optionally substituted as defined in claim 1; or
R^4 is phenyl optionally substituted with one or more substituents as defined in claim 1; or
R^4 is 5-10-membered heteroaryl selected from pyridyl, pyrrolyl, thienyl, furyl, benzoxazolyl, imidazolyl, indolyl or indazolyl any of which is optionally substituted as defined in claim 1.

7. A compound according to claim 6, wherein R^4 is phenyl which is substituted with an OH group at either the 2- or the 3-position and optionally with one or more further substituents selected from:

halo, CN, R^{19}, OR^{19};
OR^6, $C(O)OR^6$;
C_{1-4} alkyl or $O(C_{1-4}$ alkyl) either of which is optionally substituted with one or more substituents selected from halo, CN, R^{19}, OR^{19}, OR^6 and NR^6R^7;

wherein R^6 is H, C_{1-4} alkyl or C_{1-4} haloalkyl or, for a moiety NR^6R^7, R^6 and R^7 combine with the nitrogen atom to which they are attached to form a 5- or 6-membered heterocyclic ring, optionally containing one or more further heteroatoms and optionally substituted with one or more halo substituents;
R^7 is as defined in claim 1; and
R^{19} is a 3- to 6- membered carbocyclyl group or phenyl, either or which is optionally substituted with one or more substituents selected from halo, methyl and methoxy.

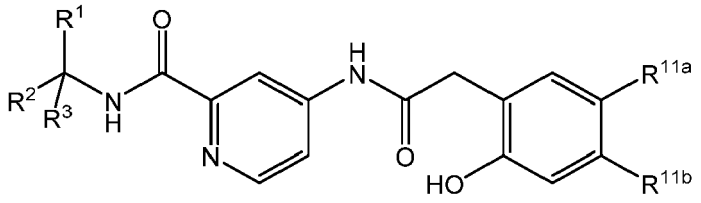
8. A compound according to any one of claims 1 to 7 wherein, Y is-CH_2-, R^4 is phenyl and the compound is a compound of general formula (Ia):



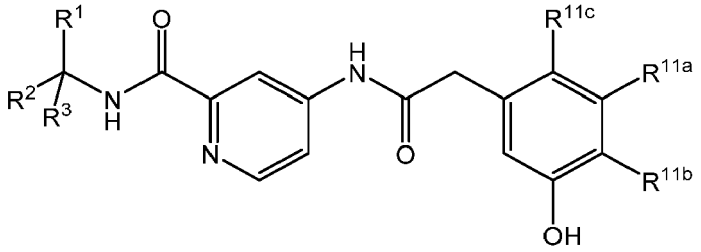
(Ia)

wherein

R^1, R^2, R^3, R^{5a}, X^1 and X^2 are as defined in claim 1;
R^{10} is H, OH, halo, C_{1-6} alkyl, -$O(C_{1-6}$ alkyl);
each R^{11} is independently H, halo, OH, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, -$O(C_{1-6}$ alkyl) or $C(O)O$-(C_{1-6} alkyl); and
n is 1 or 2; or
a compound of general formula (Id) or (Ie):



(Id)



(Ie)

wherein

R^1, R^2 and R^3, are as defined in claim 1;
R^{11a} is H, halo, C_{1-4} alkyl, C_{1-4} haloalkyl or C(O)O(C_{1-4} alkyl);
R^{11b} is H, halo, C_{1-4} alkyl or C_{1-4} haloalkyl; and
R^{11c} is H, halo, CN, C_{1-4} alkyl or C_{1-4} haloalkyl.

9. A compound according to claim 1 selected from:

N-tert-Butyl-4-[[2-(2-hydroxyphenyl)acetyl]amino]pyridine-2-carboxamide (Compound 1);
N-(1-Adamantyl)-4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide(Compound 1.3);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(3-methoxy-1,1-dimethylpropyl)pyridine-2-carboxamide (Compound 1.4);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1-methylcyclobutyl)pyridine-2-carboxamide (Compound 1.6);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1-methylcyclohexyl)pyridine-2-carboxamide (Compound 1.7);
tert-Butyl N-[3-[[4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carbonyl]amino]-3-methyl-butyl]carbamate (Compound 1.8);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-cyclohexyl-pyridine-2-carboxamide (Compound 1.10);
N-tert-Butyl-4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 3);
N-(1,1-Dimethylpropyl)-4-[[2-(4-fluoro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 3.1a);
N-tert-Butyl-4-[[2-(4-fluoro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 3.2a);
N-tert-Butyl-4-[[2-(2-chloro-6-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 3.3a);
4-[[2-(4-Bromo-5-chloro-2-hydroxy-phenyl)acetyl]amino]-N-tert-butyl-pyridine-2-carboxamide (Compound 3.4a);
4-[[2-(5-tert-Butyl-2-hydroxy-phenyl)acetyl]amino]-N-(1-cyanocyclobutyl)pyridine-2-carboxamide (Compound 3.5a);
4-[[2-(5-tert-Butyl-2-hydroxy-phenyl)acetyl]amino]-N-(1-methyl cyclobutyl)pyridine-2-carboxamide (Compound 3.6a);
N-tert-butyl-4-[2-(2,5-dibromo-3-fluoro-6-hydroxyphenyl)acetamido]pyridine-2-carboxamide (Compound 3.7a);
N-tert-Butyl-4-[[2-[2-hydroxy-5-(trifluoromethyl)phenyl]acetyl]amino]pyridine-2-carboxamide (Compound 3.5b);
N-tert-Butyl-4-[[2-(4-chloro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 3.6b);
N-tert-Butyl-4-[[2-[2-hydroxy-4-(trifluoro methyl)phenyl]acetyl]amino]pyridine-2-carboxamide (Compound 3.7b);
N-tert-Butyl-4-[[2-(2-hydroxy-5-methoxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 3.8b);

N-tert-Butyl-4-[(6-hydroxyindane-1-carbonyl)amino]pyridine-2-carboxamide (Compound 3.9b);
N-tert-Butyl-4-[(7-hydroxyindane-1-carbonyl)amino]pyridine-2-carboxamide (Compound 3.10b);
N-tert-Butyl-4-[[2-(2,5-dibromo-3-chloro-6-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 3.11b);
N-tert-Butyl-4-[[2-(3-hydroxyphenyl) acetyl]amino]pyridine-2-carboxamide (Compound 3.12b);
N-tert-Butyl-4-[[2-(2-fluoro-5-hydroxy-phenyl) acetyl]amino]pyridine-2-carboxamide (Compound 3.13b);
N-tert-Butyl-4-[[2-(4-chloro-3-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 3.14b);
N-tert-Butyl-4-[[2-(2-chloro-3-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 3.15b);
N-tert-Butyl-4-[[2-(2-chloro-5-hydroxy-phenyl) acetyl]amino]pyridine-2-carboxamide (Compound 3.16b);
N-tert-Butyl-4-[[2-(3-chloro-5-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 3.17b);
N-tert-Butyl-4-[[2-(2-thienyl)acetyl]amino]pyridine-2-carboxamide (Compound 5);
4-[[2-(2-Adamantyl)acetyl]amino]-N-tert-butyl-pyridine-2-carboxamide (Compound 5.1);
N-tert-Butyl-4-[[2-(4-fluoro-2-methoxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 5.2);
N-tert-Butyl-4-[[2-(5-chloro-2-fluoro-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 5.3);
N-tert-Butyl-4-[[2-(2-furyl)acetyl]amino] pyridine-2-carboxamide (Compound 5.4);
N-tert-Butyl-4-[[2-(3-chlorophenyl) acetyl]amino]pyridine-2-carboxamide (Compound 5.5);
N-tert-Butyl-4-[[2-(1H-indol-3-yl)acetyl] amino]pyridine-2-carboxamide (Compound 5.6);
N-tert-Butyl-4-[[2-(o-tolyl)acetyl] amino]pyridine-2-carboxamide (Compound 5.7);
N-tert-Butyl-4-[[2-(3,4-dichlorophenyl) acetyl]amino]pyridine-2-carboxamide (Compound 5.8);
N-tert-Butyl-4-[[2-(3-fluorophenyl)acetyl] amino]pyridine-2-carboxamide (Compound 5.9);
N-tert-Butyl-4-[[2-(5-chloro-2-methoxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 5.10);
N-tert-Butyl-4-[[2-(p-tolyl)acetyl] amino]pyridine-2-carboxamide (Compound 5.11);
N-tert-Butyl-4-[[2-(2-fluorophenyl) acetyl]amino]pyridine-2-carboxamide (Compound 5.12);
N-tert-Butyl-4-[[2-(4-fluorophenyl) acetyl]amino]pyridine-2-carboxamide (Compound 5.13);
N-tert-Butyl-4-[[2-(m-tolyl)acetyl] amino]pyridine-2-carboxamide (Compound 5.14);
4-[[2-(1,3-Benzoxazol-6-yl)acetyl] amino]-N-tert-butyl-pyridine-2-carboxamide (Compound 5.15);
N-tert-Butyl-4-[[2-(2-chloro-3-pyridyl) acetyl]amino]pyridine-2-carboxamide (Compound 5.16);
N-tert-Butyl-4-[[2-(2,6-dichlorophenyl) acetyl]amino]pyridine-2-carboxamide (Compound 5.17);
N-tert-Butyl-4-[[2-(4-chloro-3-fluoro-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 5.18);
N-tert-Butyl-4-[[2-(3,5-dichloro phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 5.19);
N-tert-Butyl-4-[[2-(2-chlorophenyl) acetyl]amino]pyridine-2-carboxamide (Compound 5.20);
N-tert-Butyl-4-[[2-(3-chloro-4-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 5.21);
N-tert-Butyl-4-(indane-1-carbonyl amino)pyridine-2-carboxamide (Compound 5.22);
N-tert-Butyl-4-[(2-quinoxalin-6-ylacetyl) amino]pyridine-2-carboxamide (Compound 5.23);
N-tert-Butyl-4-[[2-(2-naphthyl) acetyl]amino]pyridine-2-carboxamide (Compound 5.24);
N-tert-Butyl-4-(2,3-dihydrobenzofuran-3-carbonylamino)pyridine-2-carboxamide (Compound 5.25);
N-tert-Butyl-4-(6,7,8,9-tetrahydro-5H-benzo[7]annulene-5-carbonylamino) pyridine-2-carboxamide (Compound 5.26);
N-tert-Butyl-4-(tetralin-1-carbonylamino) pyridine-2-carboxamide (Compound 5.27);
N-tert-Butyl-4-[[2-(6-quinolyl)acetyl] amino]pyridine-2-carboxamide (Compound 5.29);
N-tert-butyl-4-[[1-(3-chlorophenyl) cyclopropanecarbonyl]amino]pyridine-2-carboxamide (Compound 5.31);
N-tert-Butyl-4-[[2-(2,3-dihydro-1,4-benzodioxin-6-yl)acetyl]amino]pyridine-2-carboxamide (Compound 5.32);
N-(1,1-Dimethylprop-2-ynyl)-4-[(2-isochroman-1-ylacetyl)amino]pyridine-2-carboxamide (Compound 5.33);
4-[[2-(4,4-Difluorocyclohexyl)acetyl]amino]-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide (Compound 5.34);
N-(1,1-Dimethylprop-2-ynyl)-4-[[2-[4-(trifluoromethyl)phenyl]acetyl]amino]pyridine-2-carboxamide (Compound 5.35);
N-(1,1-Dimethylprop-2-ynyl)-4-[[2-[3-(trifluoromethyl)-1H-pyrazol-4-yl]acetyl] amino] pyridine-2-carboxamide (Compound 5.36);
N-(1,1-Dimethylprop-2-ynyl)-4-[[2-[3-(trifluoromethyl)phenyl]acetyl]amino]pyridine-2-carboxamide (Compound 5.37);
N-(1,1-Dimethylprop-2-ynyl)-4-[[2-[2-(trifluoromethyl)phenyl]acetyl]amino]pyridine-2-carboxamide (Compound 5.38);
4-[[2-(2,3-Dihydro-1,4-benzoxazin-4-yl)acetyl]amino]-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide (Compound 5.39);
N-tert-Butyl-4-[[2-(5-cyano-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 6);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(1,1-dimethylbutyl)pyridine-2-carboxamide (Compound 7.2);

4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(1,1,2-trimethylpropyl)pyridine-2-carboxamide (Compound 7.6);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-isopropyl-pyridine-2-carboxamide (Compound 7.7);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(4-methyltetrahydropyran-4-yl)pyridine-2-carboxamide (Compound 7.9);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-tetrahydropyran-4-yl-pyridine-2-carboxamide (Compound 7.11);
4-[2-(5-Chloro-2-hydroxyphenyl)acetamido]-N-[(1s,4s)-4-hydroxycyclohexyl]pyridine-2-carboxamide (Compound 7.12);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-sec-butyl-pyridine-2-carboxamide (Compound 7.13);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(2-hydroxy-1,1,2-trimethylpropyl)pyridine-2-carboxamide (Compound 7.14);
N-(3-Bicyclo[1.1.1]pentanyl)-4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 7.15);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(1-cyanocyclobutyl)pyridine-2-carboxamide (Compound 7.16);
tert-Butyl-3-[[4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carbonyl]amino]piperidine-1-carboxylate (Compound 8.1);
tert-Butyl (1r,5s,6s)-6-{4-[2-(5-chloro-2-hydroxyphenyl)acetamido]pyridine-2-amido}-3-azabicyclo[3.1.0]hexane-3-carboxylate (Compound 8.3);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1,1-dimethylpropyl)pyridine-2-carboxamide (Compound 9.2);
N-tert-Butyl-4-[[2-(5-tert-butyl-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 10);
Methyl 3-[2-[[2-(tert-butylcarbamoyl)-4-pyridyl]amino]-2-oxo-ethyl]-4-hydroxy-benzoate (Compound 13);
N-tert-Butyl-4-[[2-(2-hydroxy-5-methyl-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 15);
N-tert-Butyl-4-[[2-(3-hydroxy-2-pyridyl)acetyl]amino]pyridine-2-carboxamide (Compound 19);
N-tert-Butyl-4-[[2-(5-fluoro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 20);
N-tert-Butyl-4-[[(1R) or (1S)-indane-1-carbonyl]amino]pyridine-2-carboxamide (Compound 21a);
N-tert-Butyl-4-[[(1R) or (1S)-indane-1-carbonyl]amino]pyridine-2-carboxamide (Compound 21b);
N-tert-Butyl-4-[(2-phenylacetyl)amino]pyridine-2-carboxamide (Compound 22);
4-(3,3-Dimethylbutanoylamino)-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide (Compound 22.1);
4-[(2-Cyclopentylacetyl)amino]-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide (Compound 22.2);
4-[[2-(3-Chloro-4-pyridyl)acetyl]amino]-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide (Compound 22.3);
4-[[2-(4-Chlorophenyl)acetyl]amino]-N-(1-cyanocyclopropyl)pyridine-2-carboxamide (Compound 23);
4-[[2-(3-Chlorophenyl)acetyl] amino]-N-(1-cyanocyclo propyl)pyridine-2-carboxamide (Compound 23.1);
4-[[2-(2-Chloro-5-fluoro-phenyl) acetyl] amino]-N-(1-cyanocyclo propyl)pyridine-2-carboxamide (Compound 23.2);
N-tert-Butyl-4-(indane-2-carbonyl amino)pyridine-2-carboxamide (Compound 23.3);
N-tert-Butyl-4-[[2-[2-(difluoromethoxy) phenyl]acetyl]amino]pyridine-2-carboxamide (Compound 23.4);
N-tert-Butyl-4-[[2-[2-(difluoromethyl) phenyl]acetyl]amino]pyridine-2-carboxamide (Compound 23.5);
N-tert-Butyl-4-[[2-(3,4-difluorophenyl) acetyl]amino]pyridine-2-carboxamide (Compound 23.6);
N-tert-Butyl-4-[[2-(3,5-difluorophenyl) acetyl]amino]pyridine-2-carboxamide (Compound 23.7);
N-tert-Butyl-4-[[2-(2,3-difluorophenyl) acetyl]amino]pyridine-2-carboxamide (Compound 23.8);
4-[[2-(2-Chlorophenyl)acetyl]amino]-N-tetrahydropyran-4-yl-pyridine-2-carboxamide (Compound 23.9);
N-(1-Cyanocyclobutyl)-4-[[2-(6-quinolyl) acetyl]amino]pyridine-2-carboxamide (Compound 23.11);
N-tert-Butyl-4-[[2-[2-(trifluoromethyl) phenyl]acetyl]amino]pyridine-2-carboxamide (Compound 23.12);
4-[[2-(2-Bromophenyl)acetyl]amino]-N-tert-butyl-pyridine-2-carboxamide (Compound 23.13);
N-tert-Butyl-4-[[2-(2-cyanophenyl) acetyl]amino]pyridine-2-carboxamide (Compound 23.14);
4-[[2-(2-Chlorophenyl)acetyl]amino]-N-(4-cyanotetrahydropyran-4-yl)pyridine-2-carboxamide (Compound 23.15);
N-(4-Cyanotetrahydropyran-4-yl)-4-[[2-(6-quinolyl)acetyl]amino]pyridine-2-carboxamide (Compound 23.16);
4-[[2-(2-Chloro-5-methoxy-phenyl)acetyl] amino]-N-(1-cyanocyclopropyl)pyridine-2-carboxamide (Compound 24);
N-(3-Bicyclo[1.1.1]pentanyl)-4-[[2-(5-tert-butyl-2-hydroxy-phenyl)acetyl]amino] pyridine-2-carboxamide (Compound 25);
-[[2-(5-tert-Butyl-2-hydroxy-phenyl)acetyl]amino]-N-(4-cyanotetrahydropyran-4-yl)pyridine-2-carboxamide (Compound 25.1);
N-tert-Butyl-4-[[2-(2-hydroxy-5-phenyl-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 26);

N-tert-Butyl-4-[[2-[5-chloro-2-hydroxy-4-(pyrrolidin-1-ylmethyl)phenyl]acetyl] amino]pyridine-2-carboxamide (Compound 27);
N-tert-Butyl-4-[[2-[4-[(tert-butylamino)methyl]-5-chloro-2-hydroxyphenyl]acetyl]amino]pyridine-2-carboxamide (Compound 27.1);
N-tert-Butyl-4-[[2-[5-chloro-2-hydroxy-4-(morpholinomethyl)phenyl]acetyl]amino]pyridine-2-carboxamide (Compound 27.2);
N-tert-Butyl-4-[[2-[5-chloro-4-[(3,3-difluoropyrrolidin-1-yl)methyl]-2-hydroxyphenyl]acetyl]amino]pyridine-2-carboxamide (Compound 27.3);
N-tert-butyl-4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]-5-fluoro-pyridine-2-carboxamide (Compound 28);
N-tert-Butyl-4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]-3-fluoro-pyridine-2-carboxamide (Compound 28.1);
4-[[2-(2-Chlorophenyl)acetyl]amino]-N-(1-cyanocyclobutyl)pyridine-2-carboxamide (Compound 30);
4-[[2-(2-Chlorophenyl)acetyl]amino]-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide (Compound 30.1);
4-[[2-(2-Chlorophenyl)acetyl]amino]-N-(4-fluoro-1-bicyclo[2.1.1]hexanyl)pyridine-2-carboxamide (Compound 30.2);
4-[[2-(2-Chlorophenyl)acetyl]amino]-N-(1-cyclopropyl-1-methyl-ethyl)pyridine-2-carboxamide (Compound 30.3);
4-[[2-(2-Chlorophenyl)acetyl]amino]-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide (Compound 30.3a);
4-[[2-(2-Chlorophenyl)acetyl]amino]-N-(1-methyl-3-bicyclo[1.1.1] pentanyl)pyridine-2-carboxamide (Compound 30.4);
4-[[2-(2-Chlorophenyl)acetyl]amino]-N-(1-cyano-3-bicyclo[1.1,1]pentanyl) pyridine-2-carboxamide (Compound 30.5);
4-[[2-(2-Chlorophenyl)acetyl]amino]-N-(2,2-difluorocyclopropyl)pyridine-2-carboxamide (Compound 30.6);
4-[[2-(2-Chlorophenyl)acetyl]amino]-N-(1-cyanocyclopropyl)pyridine-2-carboxamide (Compound 30.7);
4-[[2-(2-Clorophenyl)acetyl]amino]-N-(1-methylcyclopropyl)pyridine-2-carboxamide (Compound 30.8);
4-[[2-(2-Chlorophenyl)acetyl]amino]-N-(3-fluoro-1-bicyclo[1.1.1]pentanyl)pyridine-2-carboxamide (Compound 30.9);
4-[[2-(2-Chlorophenyl)acetyl]amino]-N-(2-fluoro-1,1-dimethyl-ethyl)pyridine-2-carboxamide (Compound 30.10);
4-[[2-(2-Chlorophenyl)acetyl]amino]-N-(4-ethynyltetrahydropyran-4-yl)pyridine-2-carboxamide (Compound 30.11);
4-[[2-(2-Chlorophenyl)acetyl]amino]-N-(1-cyanocyclopentyl)pyridine-2-carboxamide (Compound 30.12);
4-[[2-(2-Chlorophenyl)acetyl]amino]-N-(2,2-difluoro-1,1-dimethyl-ethyl)pyridine-2-carboxamide (Compound 30.13);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(4-cyanotetrahydropyran-4-yl)pyridine-2-carboxamide (Compound 31);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1-ethynylcyclopentyl)pyridine-2-carboxamide (Compound 31.2);
4-[2-(5-Chloro-2-hydroxyphenyl)acetamido]-N-[(1s,2s)-2-hydroxycyclohexyl] pyridine-2-carboxamide (Compound 31.3);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[(1S,2S)-2-hydroxycyclo hexyl]pyridine-2-carboxamide or 4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[(1R,2R)-2-hydroxycyclohexyl]pyridine-2-carboxamide (Compound 31.3a);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(4-ethynyltetrahydropyran-4-yl)pyridine-2-carboxamide (Compound 31.4);
N-[(6-Amino-2-pyridyl)methyl]-4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl] amino]pyridine-2-carboxamide (Compound 32);
12-[[4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carbonyl] amino]dodecanoic acid (Compound 32.1);
4-[[2-(5-Chloro-2-hydroxy-phenyl) acetyl]amino]-N-(3-pyridylmethyl)pyridine-2-carboxamide (Compound 32.2);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(2-pyridylmethyl)pyridine-2-carboxamide (Compound 32.3);
4-[[2-(5-Chloro-2-hydroxy-phenyl) acetyl]amino]-N-(4-pyridylmethyl)pyridine-2-carboxamide (Compound 32.4);
4-[[2-(5-Chloro-2-hydroxy-phenyl) acetyl]amino]-N-[(2-hydroxyphenyl) methyl]pyridine-2-carboxamide (Compound 32.5);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(1,1-dimethyl-2-morpholinoethyl)pyridine-2-carboxamide (Compound 32.6);
4-[[2-(5-Chloro-2-hydroxy-phenyl) acetyl]amino]-N-(2-hydroxy-1,1-dimethylethyl)pyridine-2-carboxamide (Compound 32.7);

4-[[2-(5-Chloro-2-hydroxy-phenyl) acetyl] amino]-N-(3,3-difluoro-4-piperidyl)pyridine-2-carboxamide (Compound 32.8);
4-[[2-(5-Chloro-2-hydroxy-phenyl) acetyl]amino]-N-(1H-imidazol-2-yl)pyridine-2-carboxamide (Compound 32.9);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[(1R,2R)-2-hydroxycyclopentyl] pyridine-2-carboxamide (Compound 33);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide (Compound 34);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[3-(hydroxymethyl) tetrahydrofuran-3-yl]pyridine-2-carboxamide (Compound 35);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[(3R)-3-(hydroxymethyl)tetrahydro furan-3-yl]pyridine-2-carboxamide or 4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]-N-[(3S)-3-(hydroxymethyl)tetrahydrofuran-3-yl]pyridine-2-carboxamide (Compound 35a);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[(3R)-3-(hydroxymethyl)tetrahydro furan-3-yl]pyridine-2-carboxamide or 4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]-N-[(3S)-3-(hydroxymethyl)tetrahydrofuran-3-yl]pyridine-2-carboxamide (Compound 35b);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(4-hydroxy-4-methyl-cyclohexyl) pyridine-2-carboxamide as a 6:4 mixture of stereoisomers (Compound 35.1);
4-[[2-(5-Chloro-2-hydroxy-phenyl) acetyl]amino]-N-[(1s,2r)-2-(hydroxy methyl)cyclohexyl]pyridine-2-carboxamide (Compound 35.2);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-[(1s,3r)-3-hydroxycyclopentyl] pyridine-2-carboxamide (Compound 35.3);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-[2-hydroxy-1-(hydroxy methyl)-1-methyl-ethyl]pyridine-2-carboxamide (Compound 35.4);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(3-hydroxycyclohexyl)pyridine-2-carboxamide as a mixture of stereoisomers (Compound 35.6);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(3-phenoxypropyl)pyridine-2-carboxamide (Compound 35.7);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(1-methylcyclo propyl)pyridine-2-carboxamide (Compound 35.8);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-[1-methyl-1-(2-pyridyl) ethyl]pyridine-2-carboxamide (Compound 35.9);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(3-phenylpropyl)pyridine-2-carboxamide (Compound 35.10);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-[2-hydroxy-1-(2-pyridyl)ethyl] pyridine-2-carboxamide (Compound 35.11);
4-[[2-(5-Chloro-2-hydroxy-phenyl) acetyl]amino]-N-[(5-methoxy-2-pyridyl)methyl]pyridine-2-carboxamide (Compound 35.12);
Ethyl 3-[[4-[[2-(5-chloro-2-hydroxy-phenyl) acetyl]amino]pyridine-2-carbonyl]amino]-3-methyl-butanoate (Compound 35.13);
4-[[2-(5-Chloro-2-hydroxy-phenyl) acetyl]amino]-N-(3-hydroxy-1,1-dimethylpropyl)pyridine-2-carboxamide (Compound 35.14);
N-Benzyl-4-[[2-(5-chloro-2-hydroxy-phenyl) acetyl]amino]pyridine-2-carboxamide (Compound 35.15);
4-[[2-(5-Chloro-2-hydroxy-phenyl) acetyl]amino]-N-phenyl-pyridine-2-carboxamide (Compound 35.16);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-[(1S,2S)-2-hydroxycyclopentyl]pyridine-2-carboxamide (Compound 35.17);
4-[[2-(5-Chloro-2-hydroxy-phenyl) acetyl]amino]-N-[(1R,2S)-2-hydroxy cyclopentyl]pyridine-2-carboxamide (Compound 35.18);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-[(1S,2R)-2-hydroxy cyclopentyl]pyridine-2-carboxamide (Compound 35.19);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1-ethynylcyclohexyl)pyridine-2-carboxamide (Compound 35.24);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[1-(hydroxymethyl)cyclobutyl]pyridine-2-carboxamide (Compound 35.25);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[3-(hydroxymethyl)oxetan-3-yl]pyridine-2-carboxamide (Compound 35.26);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1-cyano-2-methoxy-1-methylethyl)pyridine-2-carboxamide (Compound 35.27);

4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[(1-hydroxycyclobutyl)methyl]pyridine-2-carboxamide (Compound 35.28);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide (Compound 36);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1-cyano-1,2-dimethyl-propyl)pyridine-2-carboxamide (Compound 37);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1-methylcyclopentyl)pyridine-2-carboxamide (Compound 38);
N-(4-tert-Butylcyclohexyl)-4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 39);
N-tert-Butyl-4-[[2-(2-chloro-3-fluoro-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 40);
N-tert-Butyl-4-[[2-(2-chloro-5-fluoro-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 40.1);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[4-(2-hydroxyethyl) tetrahydropyran-4-yl]pyridine-2-carboxamide (Compound 42);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[1,1-dimethyl-3-(2,2,2-trifluoro ethylamino)propyl]pyridine-2-carboxamide (Compound 43);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(4-fluoro-1-bicyclo[2.1.1] hexanyl)pyridine-2-carboxamide (Compound 44);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[3-(2,2-dimethylpropanoyl amino)-1,1-dimethyl-propyl]pyridine-2-carboxamide (Compound 45);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1-cyano-2-hydroxy-1-methylethyl)pyridine-2-carboxamide (Compound 46);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[(1S)-1-cyano-2-hydroxy-1-methylethyl]pyridine-2-carboxamide or 4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]-N-[(1R)-1-cyano-2-hydroxy-1-methyl-ethyl]pyridine-2-carboxamide (Compound 46a);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[(1S)-1-cyano-2-hydroxy-1-methylethyl]pyridine-2-carboxamide or 4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]-N-[(1R)-1-cyano-2-hydroxy-1-methyl-ethyl]pyridine-2-carboxamide (Compound 46b);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(3-cyanotetrahydrofuran-3-yl)pyridine-2-carboxamide (Compound 47);
Methyl2-[4-[[4-[[2-(5-chloro-2-hydroxy-phenyl) acetyl]amino]pyridine-2-carbonyl]amino]tetrahydropyran-4-yl]acetate (Compound 47.1);
Methyl 4-[[4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carbonyl] amino]tetrahydropyran-4-carboxylate (Compound 47.2);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl] amino]-N-(3-cyanooxetan-3-yl)pyridine-2-carboxamide (Compound 47.3);
4-[[2-(5-Fluoro-2-hydroxy-phenyl)acetyl]amino]-N-(1-methylcyclobutyl)pyridine-2-carboxamide (Compound 48);
N-(4-Cyanotetrahydropyran-4-yl)-4-[[2-(5-fluoro-2-hydroxy-phenyl)acetyl]amino] pyridine-2-carboxamide (Compound 48.1);
N-[3-(tert-Butylamino)-1,1-dimethyl-3-oxo-propyl]-4-[[2-(5-chloro-2-hydroxy-phenyl) acetyl]amino]pyridine-2-carboxamide (Compound 49);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[3-(methanesulfonamido)-1,1-dimethyl -propyl]pyridine-2-carboxamide (Compound 50);
N-(3-Acetamido-1,1-dimethyl-propyl)-4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl] amino]pyridine-2-carboxamide (Compound 51);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[4-(hydroxymethyl)tetrahydro pyran-4-yl]pyridine-2-carboxamide (Compound 53);
N-tert-Butyl-4-[[2-[3-(1-hydroxyethyl)phenyl]acetyl]amino]pyridine-2-carboxamide (Compound 54);
N-tert-Butyl-5-chloro-4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 55);
N-tert-Butyl-4-[[2-[5-chloro-2-[(4-methoxyphenyl)methoxy]phenyl]acetyl] amino]pyridine-2-carboxamide (Compound 56);
N-tert-butyl-4-[[(1S) or (1R)-4-chloro-7-hydroxy-indane-1-carbonyl]amino]pyridine-2-carboxamide (Compound 57a);
N-tert-butyl-4-[[(1S) or (1R)-4-chloro-7-hydroxy-indane-1-carbonyl]amino]pyridine-2-carboxamide (Compound 57b);
N-tert-Butyl-4-[[2-(2-cyclopropylphenyl)acetyl]amino]pyridine-2-carboxamide (Compound 58);
4-[[2-(3-Bromo-5-chloro-2-hydroxy-phenyl)acetyl]amino]-N-tert-butyl-pyridine-2-carboxamide (Compound 59);

N-(4-Fluoro-1-bicyclo[2.1.1]hexanyl)-4-[[2-(2-fluorophenyl)acetyl]am ino]pyridine-2-carboxamide (Compound 60);
N-(1-Cyano-2-hydroxy-1-methyl-ethyl)-4-[[2-(2-fluorophenyl)acetyl]amino]pyridine-2-carboxamide (Compound 60.1);
N-(1,1-Dimethylprop-2-ynyl)-4-[[2-(2-fluorophenyl)acetyl]amino]pyridine-2-carboxamide (Compound 60.2);
N-tert-Butyl-4-[[2-(5-chloro-2-hydroxy-3-isopropyl-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 61);
N-tert-Butyl-4-[[2-[5-chloro-2-hydroxy-3-(1-methoxyethyl)phenyl]acetyl]amino] pyridine-2-carboxamide (Compound 62);
4-[[2-(6-Quinolyl)acetyl]amino]-N-tetrahydropyran-4-yl-pyridine-2-carboxamide (Compound 63);
4-(Benzylcarbamoylamino)-N-tert-butyl-pyridine-2-carboxamide (Compound 64);
N-tert-Butyl-4-(cyclohexylmethylcarbamoyl amino)pyridine-2-carboxamide (Compound 64.1);
N-tert-Butyl-4-(2-phenylethylcarbamoyl amino)pyridine-2-carboxamide (Compound 64.2);
N-tert-Butyl-4-[[(1R)-1-phenylethyl]carbamoyl amino]pyridine-2-carboxamide (Compound 64.3);
N-tert-Butyl-4-[[(1S)-1-phenylethyl] carbamoylamino]pyridine-2-carboxamide (Compound 64.4);
N-tert-Butyl-4-[(2-chlorophenyl) methylcarbamoylamino]pyridine-2-carboxamide (Compound 64.5);
N-tert-butyl-4-(1H-indol-3-ylcarbamoyl amino)pyridine-2-carboxamide (Compound 64.6);
N-tert-Butyl-4-[(3-chlorophenyl)methyl carbamoylamino]pyridine-2-carboxamide (Compound 64.7);
N-tert-butyl-4-[(4-chlorophenyl)methyl carbamoylamino]pyridine-2-carboxamide (Compound 64.8);
N-tert-Butyl-4-[(2-hydroxyphenyl)carbamoylamino]pyridine-2-carboxamide (Compound 65);
N-tert-Butyl-4-[(2-methoxyphenyl)methylcarbamoylamino]pyridine-2-carboxamide (Compound 65.1);
N-tert-Butyl-4-[(2-hydroxyphenyl)methylcarbamoylamino]pyridine-2-carboxamide (Compound 65.2);
N-tert-Butyl-4-[(3-hydroxyphenyl)methylcarbamoylamino]pyridine-2-carboxamide (Compound 65.3);
N-tert-Butyl-4-[(4-hydroxyphenyl)methylcarbamoylamino]pyridine-2-carboxamide (Compound 65.4);
N-tert-Butyl-4-[[2-[2-hydroxy-5-(1-hydroxyethyl)phenyl]acetyl]amino]pyridine-2-carboxamide (Compound 66);
N-tert-Butyl-4-[[2-[2-hydroxy-5-[1-(2,2,2-trifluoroethylamino)ethyl]phenyl] acetyl]amino]pyridine-2-carboxamide (Compound 67);
N-tert-Butyl-4-[[2-[3-(cyanomethyl)phenyl]acetyl]amino]pyridine-2-carboxamide (Compound 68);
N-tert-Butyl-4-[[2-[3-(methoxymethyl)phenyl]acetyl]amino]pyridine-2-carboxamide (Compound 69);
N-tert-Butyl-4-[[2-[2-hydroxy-5-(morpholinomethyl)phenyl]acetyl]amino]pyridine-2-carboxamide (Compound 70);
4-[[2-(5-Fluoro-2-hydroxy-phenyl)acetyl]amino]-N-[3-(hydroxymethyl)tetrahydro furan-3-yl]pyridine-2-carboxamide (Compound 72);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[1-(hydroxymethyl)-2-methoxy-1-methyl-ethyl]pyridine-2-carboxamide (Compound 73);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1,1-dimethylbut-2-ynyl) pyridine-2-carboxamide (Compound 73.1);
N-tert-Butyl-4-[[2-[2-hydroxy-5-(3-hydroxypropyl)phenyl]acetyl]amino]pyridine-2-carboxamide (Compound 75);
4-[[2-(5-Chloro-4-fluoro-2-hydroxy-phenyl)acetyl]amino]-N-(1-methylcyclo butyl)pyridine-2-carboxamide (Compound 76);
4-[[2-(2,5-Difluorophenyl)acetyl]amino]-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide (Compound 77);
4-[[2-(2,5-Difluorophenyl)acetyl]amino]-N-(4-fluoro-1-bicyclo[2.1.1]hexanyl) pyridine-2-carboxamide (Compound 77.1);
4-[[2-(4-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide (Compound 78);
N-(1,1-Dimethylprop-2-ynyl)-4-[[2-[2-hydroxy-4-(trifluoromethyl)phenyl]acetyl] amino]pyridine-2-carboxamide (Compound 78.1);
N-(1,1-Dimethylprop-2-ynyl)-4-[[2-[2-hydroxy-5-(trifluoromethyl)phenyl]acetyl] amino]pyridine-2-carboxamide (Compound 78.2);
4-[(2-Chroman-4-ylacetyl)amino]-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide (Compound 79);
N-(1,1-Dimethylprop-2-ynyl)-4-[[2-(1-isopropyl-3,5-dimethyl-pyrazol-4-yl)acetyl] amino]pyridine-2-carboxamide (Compound 79.1);
N-(1,1-Dimethylprop-2-ynyl)-4-[[2-(1H-indazol-4-yl)acetyl]amino]pyridine-2-carboxamide (Compound 79.2);
N-(1,1-Dimethylprop-2-ynyl)-4-[[2-(1H-indol-7-yl)acetyl]amino]pyridine-2-carboxamide (Compound 79.3);
N-(1-Cyano-1-methyl-ethyl)-4-[[2-(5-fluoro-2-hydroxy-phenyl)acetyl]amino] pyridine-2-carboxamide (Compound 81);
N-(1-Cyano-2-hydroxy-1-methyl-ethyl)-4-[[2-(5-fluoro-2-hydroxy-phenyl)acetyl]amino] pyridine-2-carboxamide (Compound 81.1);

4-[[2-(5-Fluoro-2-hydroxy-phenyl)acetyl]amino]-N-isopropyl-pyridine-2-carboxamide (Compound 81.2);
N-(1,1-Dimethylprop-2-ynyl)-4-[[2-(5-fluoro-2-hydroxy-phenyl)acetyl]amino] pyridine-2-carboxamide (Compound 81.3);
N-(4-Fluoro-1-bicyclo[2.1.1]hexanyl)-4-[[2-(5-fluoro-2-hydroxy-phenyl)acetyl]amino] pyridine-2-carboxamide (Compound 81.4);
4-[[2-(5-Fluoro-2-hydroxy-phenyl)acetyl]amino]-N-[1-(hydroxymethyl)cyclobutyl] pyridine-2-carboxamide (Compound 81.5);
N-(1-Cyano-1-methyl-ethyl)-4-(thiophene-3-carbonylamino)pyridine-2-carboxamide (Compound 83);
N-(1-Cyano-1-methyl-ethyl)-4-[(2-cyclohexylacetyl) amino]pyridine-2-carboxamide (Compound 83.1);
N-(1-Cyano-1-methyl-ethyl)-4-(cyclohexane carbonylamino)pyridine-2-carboxamide (Compound 83.2);
N-(1-Cyano-1-methyl-ethyl)-4-[(3,3-difluorocyclo pentanecarbonyl)amino]pyridine-2-carboxamide (Compound 83.3);
N-(1-Cyano-1-methyl-ethyl)-4-[(1-methylcyclo pentanecarbonyl)amino]pyridine-2-carboxamide (Compound 83.4);
N-(1-Cyano-1-methyl-ethyl)-4-(3-cyclohexyl propanoylamino)pyridine-2-carboxamide (Compound 83.5);
4-(2-{Bicyclo[2.2.1]heptan-2-yl}acetamido)-N-(1-cyano-1-methylethyl)pyridine-2-carboxamide (Compound 83.6);
N-(1-Cyano-1-methyl-ethyl)-4-[[2-(1-methylcyclo hexyl)acetyl]amino]pyridine-2-carboxamide (Compound 83.7);
N-[2-[(1-Cyano-1-methyl-ethyl)carbamoyl]-4-pyridyl]-2-cyclopropyl-pyrimidine-5-carboxamide (Compound 83.8);
N-[2-[(1-Cyano-1-methyl-ethyl)carbamoyl]-4-pyridyl]-3-isobutyl-isoxazole-5-carboxamide (Compound 83.9);
N-(1-Cyano-1-methyl-ethyl)-4-[[2-(4,4-difluorocyclo hexyl)acetyl]amino]pyridine-2-carboxamide (Compound 83.10);
4-[(1-Benzylcyclopropanecarbonyl)amino]-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide (Compound 83.11);
N-(1-Cyano-1-methyl-ethyl)-4-[3-(2-methoxy-4-pyridyl)propanoylamino]pyridine-2-carboxamide (Compound 83.13);
4-[(5-tert-Butyl-2-methyl-pyrazole-3-carbonyl)amino]-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide (Compound 83.14);
N-(1-Cyano-1-methyl-ethyl)-4-[(2-pyrazol-1-ylbenzoyl)amino]pyridine-2-carboxamide (Compound 83.15);
N-[2-[(1-Cyano-1-methyl-ethyl)carbamoyl]-4-pyridyl]-6-(trifluoromethyl)pyridine-2-carboxamide (Compound 83.16);
N-[2-[(1-Cyano-1-methyl-ethyl)carbamoyl]-4-pyridyl]-3-oxo-4H-1,4-benzoxazine-7-carboxamide (Compound 83.17);
N-[2-[(1-Cyano-1-methyl-ethyl)carbamoyl]-4-pyridyl]-1-ethyl-inldole-2-carboxamide (Compound 83.18);
N-(1-Cyano-1-methyl-ethyl)-4-[[2-(2,2,2-trifluoroethyl)pyrazole-3-carbonyl]amino]pyridine-2-carboxamide (Compound 83.19);
N-[2-[(1-Cyano-1-methyl-ethyl)carbamoyl]-4-pyridyl]-3-phenyl-isoxazole-4-carboxamide (Compound 83.20);
4-[(1-Benzylpyrazole-4-carbonyl)amino]-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide (Compound 83.21);
N-(1-Cyano-1-methyl-ethyl)-4-[(2-methyl-5-phenyl-pyrazole-3-carbonyl)amino]pyridine-2-carboxamide (Compound 83.22);
N-(1-Cyano-1-methyl-ethyl)-4-[[2-(3-methyl-1,2,4-oxadiazol-5-yl)benzoyl]amino]pyridine-2-carboxamide (Compound 83.23);
N-(1-Cyano-1-methyl-ethyl)-4-[(3-methyl-1-phenyl-pyrazole-4-carbonyl)amino]pyridine-2-carboxamide (Compound 83.24);
N-[2-[(1-Cyano-1-methyl-ethyl)carbamoyl]-4-pyridyl]-2-phenoxy-pyridine-3-carboxamide (Compound 83.25);
N-(1-Cyano-1-methyl-ethyl)-4-[[2,5-dimethyl-1-(2-thienylmethyl)pyrrole-3-carbonyl]amino]pyridine-2-carboxamide (Compound 83.26);
N-[2-[(1-Cyano-1-methyl-ethyl)carbamoyl]-4-pyridyl]-5-(2-methoxyphenyl)isoxazole-3-carboxamide (Compound 83.27);
N-[2-[(1-Cyano-1-methyl-ethyl)carbamoyl]-4-pyridyl]-4-methyl-2-phenyl-thiazole-5-carboxamide (Compound 83.28);
4-[(4-Acetamidobenzoyl)amino]-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide (Compound 83.29);
N-[2-[(1-Cyano-1-methyl-ethyl)carbamoyl]-4-pyridyl]-1,3-benzothiazole-7-carboxamide (Compound 83.30);
N-(1-Cyano-1-methyl-ethyl)-4-[3-(4-fluorophenyl) butanoylamino]pyridine-2-carboxamide (Compound 83.31);
N-[2-[(1-Cyano-1-methyl-ethyl)carbamoyl]-4-pyridyl]-1-methyl-2-oxo-quinoline-3-carboxamide (Compound

83.32);
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-[1-cyano-2-methoxy-1-(methoxy methyl)ethyl]pyridine-2-carboxamide (Compound 86);
4-[[2-(3-Amino-4-tert-butyl-phenyl)acetyl]amino]-N-tert-butyl-pyridine-2-carboxamide (Compound 87);
4-[[2-(2-Amino-4-tert-butyl-phenyl)acetyl]amino]-N-tert-butyl-pyridine-2-carboxamide (Compound 88);
N-tert-Butyl-4-[[2-(4-tert-butyl-3-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 89);
N-tert-Butyl-4-[[2-(4-tert-butyl-2-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 90);
N-tert-Butyl-4-[[2-(4-tert-butyl-2-fluoro-5-hydroxy-phenyl)acetyl]amino]pyridine-2-carboxamide (Compound 91);
4-[[2-(4-Chloro-3-hydroxy-phenyl)acetyl]amino]-N-(4-cyanotetrahydropyran-4-yl)pyridine-2-carboxamide (Compound 92);
4-[[2-(4-Chloro-3-hydroxy-phenyl)acetyl]amino]-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide (Compound 92.1);
4-[[2-(4-Chloro-3-hydroxy-phenyl)acetyl]amino]-N-(1,1-dimethylprop-2-ynyl) pyridine-2-carboxamide (Compound 92.2);
4-[[2-(4-Chloro-3-hydroxy-phenyl)acetyl]amino]-N-[(1s,2s)-2-hydroxycyclopentyl]pyridine-2-carboxamide (Compound 92.3);
4-[[2-(4-tert-Butyl-3-hydroxy-phenyl)acetyl]amino]-N-[3-(hydroxymethyl) tetrahydrofuran-3-yl]pyridine-2-carboxamide (Compound 93);
4-[[2-(4-tert-Butyl-3-hydroxy-phenyl)acetyl]amino]-N-[(2S)-2-hydroxycyclohexyl]pyridine-2-carboxamide (Compound 93.1);
4-[[2-(4-tert-Butyl-3-hydroxy-phenyl)acetyl]amino]-N-[(2S)-2-hydroxycyclopentyl]pyridine-2-carboxamide (Compound 93.2);
4-[[2-(4-tert-Butyl-3-hydroxy-phenyl)acetyl]amino]-N-(4-cyanotetrahydropyran-4-yl)pyridine-2-carboxamide (Compound 93.3);
4-[[2-(4-tert-Butyl-3-hydroxy-phenyl)acetyl]amino]-N-(1-cyano-1-methyl-ethyl)pyridine-2-carboxamide (Compound 93.4);
4-[[2-(4-tert-Butyl-3-hydroxy-phenyl)acetyl]amino]-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide (Compound 93.5); and
4-[[2-(5-Chloro-2-hydroxy-phenyl)acetyl]amino]-N-(1-methyl-1-phenyl-ethyl) pyridine-2-carboxamide (Compound 94);
and salts and solvates of any of the above.

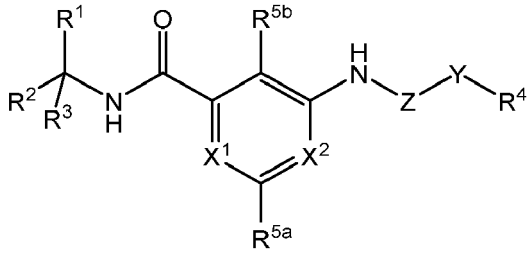
10. A compound according to claim 1 which is N-tert-Butyl-4-[[2-(5-chloro-2-hydroxyphenyl)acetyl]amino]pyridine-2-carboxamide (Compound 3) or a salt or solvate thereof.

11. A compound according to claim 1 which is 4-[[2-(5-Chloro-2-hydroxyphenyl)acetyl]amino]-N-[(3R)-3-(hydroxymethyl)tetrahydro furan-3-yl]pyridine-2-carboxamide or 4-[[2-(5-chloro-2-hydroxy-phenyl)acetyl]amino]-N-[(3S)-3-(hydroxymethyl)tetrahydrofuran-3-yl]pyridine-2-carboxamide (Compound 35a) or a salt or solvate thereof.

12. A compound according to claim 1 which is 4-[[2-(5-Chloro-2-hydroxyphenyl)acetyl]amino]-N-(1,1-dimethylprop-2-ynyl)pyridine-2-carboxamide (Compound 36) or a salt or solvate thereof.

13. A compound according to claim 1 which is N-(1,1-Dimethylprop-2-ynyl)-4-[[2-[3-(trifluoromethyl)-1H-pyrazol-4-yl]acetyl] amino] pyridine-2-carboxamide (Compound 5.36) or a salt or solvate thereof.

14. A compound of general formula (I) including all tautomeric forms all enantiomers and isotopic variants and salts and solvates thereof:



(I)

wherein:

R^1 is H, CN, C(O)OR ^{12}, C_{1-3} alkyl, C_{2-3} alkenyl or C_{2-3} alkynyl, any of which alkyl, alkenyl or alkynyl groups are optionally substituted with one or more substituents, suitably one substituent, selected from fluoro, OR^{12}, $N(R^{12})_2$, C(O)OR ^{12}, C(O)N(R^{12})$_2$, $C(O)R^{12}$ and $N(R^{13})C(O)R^{12}$;
wherein each R^{12} and R^{13} is independently selected from H, C_{1-6} alkyl and C_{1-6} fluoroalkyl
R^2 is H or C_{1-6} alkyl optionally substituted with OR^{12};
R^3 is:

C_{1-10} alkyl, C_{2-10} alkenyl or C_{2-10} alkynyl, any of which is optionally substituted with one or more substituents, suitably one substituent, selected from fluoro, CN, R^{14} OR^{14}, OR^{15}, $N(R^{15})_2$, $C(O)OR^{15}$, $C(O)N(R^{15})_2$, $N(R^{16})C(O)R^{15}$, $N(R^{15})S(O)_2R^{14}$, $N(R^{15})S(O)_2R^{16}$ and $N(R^{15})C(O)OR^{16}$; or
a 3- to 7-membered carbocyclic or heterocyclic ring system or a 6- to 10 membered aryl or 5- to 10-membered heteroaryl ring system, either of which is optionally substituted with one or more substituents selected from halo, CN, C_{1-4} alkyl, C_{1-4} haloalkyl, OR^{17} and $N(R^{17})_2$;

wherein R^{14} is a 6- to 10-membered aryl or 5- to 10-membered heteroaryl ring system or a 3- to 7-membered carbocyclic or heterocyclic ring system, any of which is optionally substituted with one or more substituents selected from halo, C_{1-4} alkyl, C_{1-4} haloalkyl, OR^{17} and $N(R^{17})_2$; wherein each R^{17} is independently H, C_{1-4} alkyl or C_{1-4} haloalkyl;
each R^{15} and R^{16} is independently H, C_{1-6} alkyl or C_{1-6} haloalkyl; or

R^2 and R^3 together with the carbon atom to which they are attached combine to form a 3-to 10-membered carbocyclic or heterocyclic ring system optionally substituted with one or more substituents selected from halo, CN, OR^9, $N(R^9)_2$, $C(O)OR^9$, $C(O)N(R^9)_2$, $C(O)R^9$, $N(R^9)C(O)R^9$ and C_{1-4} alkyl optionally substituted with halo, OR^9 or $N(R^9)_2$; or
R^1, R^2 and R^3 together with the carbon atom to which they are attached combine to form a bridged 5- to 10-membered carbocyclic or heterocyclic ring system or phenyl, any of which is optionally substituted with one or more substituents selected from halo, CN, OR^9, $N(R^9)_2$, $C(O)OR^9$, $C(O)N(R^9)_2$, $C(O)R^9$, $N(R^9)C(O)R^9$ and C_{1-4} alkyl optionally substituted with halo, OR^9 or $N(R^9)_2$;
each R^9 is independently selected from H, C_{1-6} alkyl or C_{1-6} haloalkyl;
X^1 is N;
X^2 is CR^8
R^8 is H, halo, OH, O(C_{1-4} alkyl), CN or NH_2;
Y is a bond or a straight C_{1-6} alkylene chain which is optionally substituted with one or more substituents R^{18}, wherein two substituents R^{18} may be attached to the same or to different carbon atoms;
wherein each R^{18} is independently C_{1-3} alkyl or C_{1-3} haloalkyl in which a -CH_2- is optionally replaced with -NH- or -O- and wherein two R^{18} groups may combine with the atom or atoms to which they are attached to form a 3- to 6-membered carbocyclic or heterocyclic ring system;
Z is -C(O)- or -C(O)NH-;
R^4 is a 6- to 14-membered aryl, 5- to 14-membered heteroaryl or a 5- to 10-membered carbocyclic ring system, any of which is optionally substituted with one or more substituents selected from:

halo, CN, nitro, R^{19}, OR^{19}, OR^6, SR^6, NR^6R^7, $C(O)R^6$, $C(O)R^{19}$, $C(O)OR^6$, $C(O)N(R^6)(R^7)$, $N(R^7)C(O)R^6$;
C_{1-6} alkyl or O(C_{1-6} alkyl), either of which is optionally substituted with one or more substituents selected from halo, CN, nitro, R^{19}, OR^6, SR^6, NR^6R^7, $C(O)R^6$ $C(O)OR^6$,

$C(O)N(R^6)(R^7)$ and $N(R^7)C(O)R^6$; and
when R^4 is not fully aromatic in character, oxo;

wherein R^{19} is 5- or 6-membered aryl or heteroaryl ring system or a 3- to 7-membered carbocyclic or heterocyclic ring system, any of which is optionally substituted with one or more substituents selected from halo, C_{1-4} alkyl, C_{1-4} haloalkyl, OH, $O(C_{1-4}$ alkyl), $O(C_{1-4}$ haloalkyl);
R^6 is H, C_{1-6} alkyl, C_{1-6} haloalkyl, benzyl, 3- to 7-membered carbocyclyl or 3- to 7-membered heterocyclyl;
R^7 is H, C_{1-6} alkyl or C_{1-6} haloalkyl; or
R^6 and R^7 together with the nitrogen atom to which they are attached may form a 4 to 7-membered heterocyclic ring optionally containing one or more further heteroatoms and optionally substituted with one or more substituents selected from oxo and halo; and

each of R^{5a} and R^{5b} is independently H, C_{1-4} alkyl or halo; or
a compound according to any one of claims 1 to 13;
for use in medicine, especially in the treatment or prophylaxis of diseases and conditions affected by modulation of TMEM16A, for example respiratory diseases and conditions, dry mouth (xerostomia), intestinal hypermobility, cholestasis and ocular conditions; and
wherein optionally the compound of general formula (I) is used in combination with an additional active agent useful in the treatment or prevention of respiratory conditions.

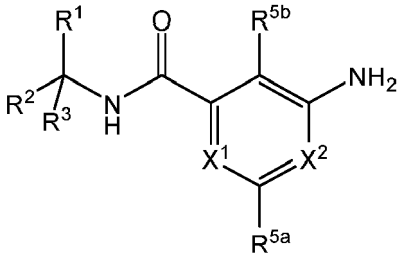
15. A compound for use according to claim 14, wherein the respiratory diseases and conditions are selected from cystic fibrosis, chronic obstructive pulmonary disease (COPD), chronic bronchitis, emphysema, bronchiectasis, including non-cystic fibrosis bronchiectasis, asthma and primary ciliary dyskinesia;

the dry mouth (xerostomia) results from Sjorgens syndrome, radiotherapy treatment or xerogenic drugs;
the intestinal hypermobility is associated with gastric dyspepsia, gastroparesis, chronic constipation or irritable bowel syndrome;
the ocular disease is dry eye disease.

16. A process for the preparation of a compound according to any one of claims 1 to 13 the process comprising:

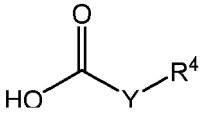
A. for a compound of general formula (I) in which Z is -C(O)-:

reacting a compound of general formula (II):



(II)

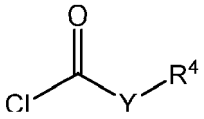
wherein R^1, R^2, R^3, R^{5a}, R^{5b}, X^1 and X^2 are as defined in claim 1;
with a compound of general formula (III):



(III)

wherein R^4 and Y are as defined in claim 1;
in the presence of a coupling agent; or

reacting a compound of general formula (II) with an acid chloride of general formula (IV):



(IV)

wherein R^4 and Y are as defined in claim 1; or

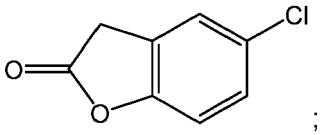
B. for compounds of general formula (I) in which Z is C(O)NH and Y is -C_{1-2} alkylene-:

reacting a compound of general formula (II) with a compound of general formula (XIV):

$$O=C=N\text{-}Y^1\text{-}R^4 \qquad \text{(XIV)}$$

wherein R^4 is as defined in claim 1 and Y^1 is -CH_2- or -CH_2CH_2-.

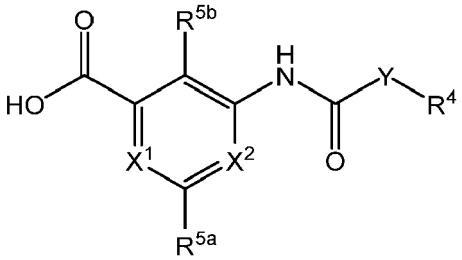
C. for compounds of general formula (Id) as defined in claim 8 in which R^{11a} is Cl and R^{11b} is H:
reacting a compound of general formula (II) with 5-chloro-2(3H)-benzofuranone, which has the structure:



;

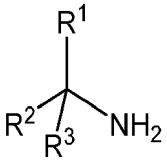
or

D. reacting a compound of general formula (X):



(X)

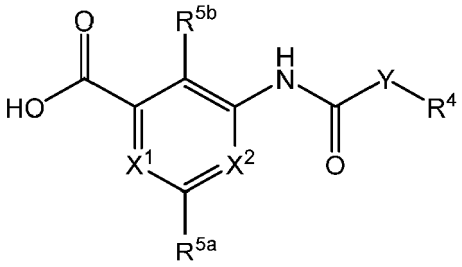
wherein X^1, X^2, Y, R^4, R^{5a} and R^{5b} are as defined in claim 1;
with a compound of general formula (VII):



(VII)

wherein R^1, R^2 and R^3 are as defined in claim 1; or

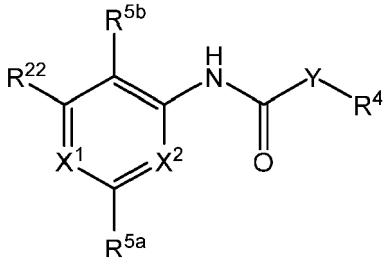
E. reacting a compound of general formula (X):



(X)

wherein X^1, X^2, Y, R^4, R^{5a} and R^{5b} are as defined in claim 1
with a compound of general formula (VII) as defined above; or

F. reacting a compound of general formula (XV):



(XV)

wherein X^1, X^2, Y, R^4, R^{5a} and R^{5b} are as defined in claim 1 and R^{22} is halo;
with an amine of general formula (VII) as defined above and carbon monoxide in the presence of a phosphorus ligand and a palladium catalyst; or

G. converting a compound of general formula (I) to another compound of general formula (I).

17. A pharmaceutical composition comprising a compound according to any one of claims 1 to 13 together with a pharmaceutically acceptable excipient and optionally further including an additional active agent useful in the treatment or prevention of respiratory conditions.

18. A product comprising a compound according to any one of claims 1 to 13 and an additional agent useful in the treatment or prevention of respiratory conditions as a combined preparation for simultaneous, sequential or separate use in the treatment of a disease or condition affected by modulation of TMEM16A.

19. A compound for use according to claim 14 or claim 15, a pharmaceutical composition according to claim 17 or a product according to claim 18, wherein the additional agent useful in the treatment or prevention of respiratory conditions is selected from:

β2 adrenoreceptor agonists such as metaproterenol, isoproterenol, isoprenaline, albuterol, salbutamol, formoterol, salmeterol, indacaterol, terbutaline, orciprenaline, bitolterol mesylate, pirbuterol, olodaterol, vilanterol and abediterol;
antihistamines, for example histamine H_1 receptor antagonists such as loratadine, cetirizine, desloratadine, levocetirizine, fexofenadine, astemizole, azelastine and chlorpheniramine or H_4 receptor antagonists;
dornase alpha;
corticosteroids such as prednisone, prednisolone, flunisolide, triamcinolone acetonide, beclomethasone dipropionate, budesonide, fluticasone propionate mometasone furoate and fluticasone furoate;
Leukotriene antagonists such as montelukast and zafirlukast;
anticholinergic compounds, particularly muscarinic antagonists such as ipratropium, tiotropium, glycopyrrolate, aclidinium and umeclidinium;
CFTR repair therapies (e.g. CFTR potentiators, correctors or amplifiers) such as Ivacaftor, QBW251, VX659, VX445, VX561/CPT-656, VX152, VX440, GLP2737, GLP2222, GLP2451, PTI438, PTI801, PTI808, FDL-169

and FDL-176and CFTR correctors such as Lumacaftor and Tezacaftor;
ENaC modulators, particularly ENaC inhibitors such as:

amiloride, VX-371, AZD5634, QBW276, SPX-101, BI443651, ETD001 and
compounds having a cation selected from:

2-[({3-amino-5*H*-pyrrolo[2,3-b]pyrazin-2-yl}formamido)ethyl]-6-(4-{bis[(2*S*,3*R*,4*R*,5*R*)-2,3,4,5,6-pentahydroxyhexyl]amino}piperidine-1-carbonyl)-1,3-diethyl-1*H*-1 ,3-benzodiazol-3-ium;
2-[({3-amino-5*H*-pyrrolo[2,3-b]pyrazin-2-yl}formamido) methyl]-6-{[2-(4-{bis[(2*S*,3*R*,4*R*,5*R*)-2,3,4,5,6-pentahydroxyhexyl]amino}piperidin-1-yl)ethyl]carbamoyl}-1,3-diethyl-1*H*-1,3-benzodiazol-3-ium;
2-[({3-amino-5*H*-pyrrolo[2,3-b]pyrazin-2-yl}formamido)methyl]-5-[4-({bis[(2*S*,3*R*,4*R*,5*R*)-2,3,4,5,6-pentahydroxyhexyl]amino}methyl)piperidine-1-carbonyl]-1,3-diethyl-1*H*-1,3-benzodiazol-3-ium;
2-[({3-amino-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl}formamido)methyl]-6-[(3*R*)-3-{bis[(2*S*,3*R*,4*R*,5*R*)-2,3,4,5,6-pentahydroxyhexyl]amino}pyrrolidine-1-carbonyl]-1,3-diethyl-1*H*-1,3-benzodiazol-3-ium;
2-[({3-amino-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl}formamido)methyl]-6-[(3*S*)-3-{bis[(2*S*,3*R*,4*R*,5*R*)-2,3,4,5,6-pentahydroxyhexyl]amino}pyrrolidine-1-carbonyl]-1,3-diethyl-1*H*-1,3-benzodiazol-3-ium;
2-[({3-amino-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl}formamido)methyl]-1,3-diethyl-6-{[(1*r*,4*r*)-4-{bis[(2S,3R,4R,5R)-2,3,4,5,6-pentahydroxyhexyl]amino}cyclohexyl]carbamoyl}-1*H*-1 ,3-benzodiazol-3-ium;
2-[({3-amino-5*H*-pyrrolo[2,3-*b*] pyrazin-2-yl}formamido)methyl]-1,3-diethyl-6-{[(1*s*,4*s*)-4-{bis[(2*S*,3*R*,4*R*,5*R*)-2,3,4,5,6-pentahydroxyhexyl]amino}cyclohexyl]carbamoyl}-1*H*-1,3-benzodiazol-3-ium;
and a suitable anion, for example halide, sulfate, nitrate, phosphate, formate, acetate, trifluoroacetate, fumarate, citrate, tartrate, oxalate, succinate, mandelate, methane sulfonate or p-toluene sulfonate;

antibiotics;
airway hydrating agents (osmoloytes) such as hypertonic saline and mannitol (Bronchitol®); and
mucolytic agents eg. N-acetyl cysteine.

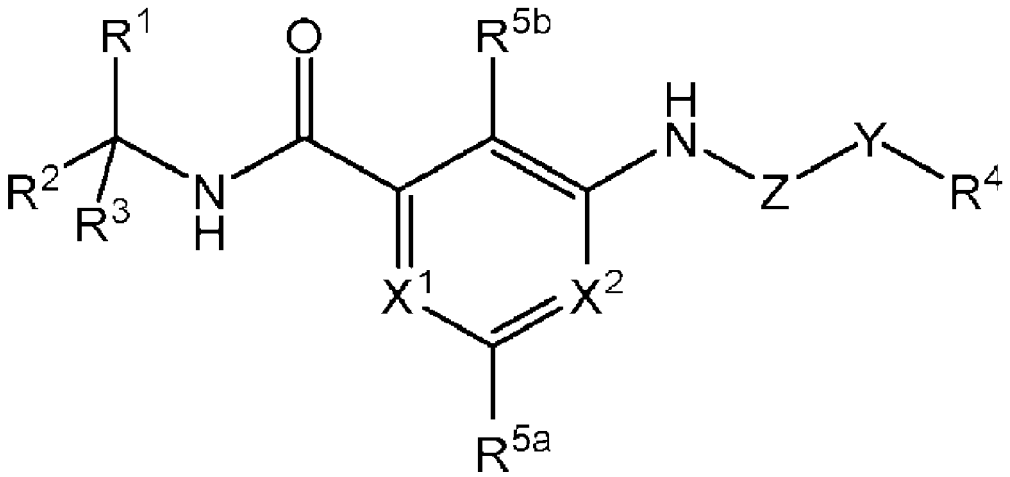
20. The compound of claim 2, wherein the compound is compound of Formula (Iz) and wherein Y is not a bond.

21. The compound of claim 1, wherein Y is a straight C_{1-3} alkylene optionally substituted with one or more substituents R^{18},wherein R^{18} is as defined above and wherein two substituents R^{18} may be attached to the same or to different carbon atoms.

22. The compound of claim 1, wherein R^4 is a 6- to 11-membered aryl group selected from phenyl, naphthyl, indanyl, 1,2,3,4-tetrahydronaphthyl and benzocycloheptanyl, any of which is optionally substituted as defined in claim 1.

Patentansprüche

1. Verbindung der allgemeinen Formel (I) einschließlich aller tautomeren Formen, aller Enantiomere und Isotopenvarianten sowie Salze und Solvate davon:



(I)

wobei:

R^1 für H, CN, C(O)OR^{12}, C_{1-3}-Alkyl, C_{2-3}-Alkenyl oder C_{2-3}-Alkinyl steht, wobei die Alkyl-, Alkenyl- bzw. Alkinylgruppen jeweils gegebenenfalls durch einen oder mehrere Substituenten, geeigneterweise einen Substituenten, ausgewählt aus Fluor, OR^{12}, $N(R^{12})_2$, C(O)OR^{12}, C(O)$N(R^{12})_2$, C(O)R^{12} und $N(R^{13})C(O)R^{12}$ substituiert sind;
wobei R^{12} und R^{13} jeweils unabhängig voneinander aus H, C_{1-6}-Alkyl und C_{1-6}-Fluoralkyl ausgewählt sind,
R^2 für H oder C_{1-6}-Alkyl, gegebenenfalls substituiert durch OR^{12}, steht;
R^3 für:

C_{1-10}-Alkyl, C_{2-10}-Alkenyl oder C_{2-10}-Alkinyl, jeweils gegebenenfalls substituiert durch einen oder mehrere Substituenten, geeigneterweise einen Substituenten, ausgewählt aus Fluor, CN, R^{14} OR^{14}, OR^{15}, $N(R^{15})_2$, C(O)OR^{15}, C(O)$N(R^{15})_2$, $N(R^{16})C(O)R^{15}$, $N(R^{15})S(O)_2R^{14}$, $N(R^{15})S(O)_2R^{16}$ und $N(R^{15})C(O)OR^{16}$; oder ein 3- bis 7-gliedriges carbocyclisches oder heterocyclisches Ringsystem oder ein 6- bis 10-gliedriges Aryl- oder 5- bis 10-gliedriges Heteroarylringsystem, die jeweils gegebenenfalls durch einen oder mehrere Substituenten ausgewählt aus Halogen, CN, C_{1-4}-Alkyl, C_{1-4}-Halogenalkyl, OR^{17} und $N(R^{17})_2$ substituiert sind, steht;

wobei R^{14} für ein 6- bis 10-gliedriges Aryl- oder 5-bis 10-gliedriges Heteroarylringsystem oder ein 3- bis 7-gliedriges carbocyclisches oder heterocyclisches Ringsystem steht, die jeweils gegebenenfalls durch einen oder mehrere Substituenten ausgewählt aus Halogen, C_{1-4}-Alkyl, C_{1-4}-Halogenalkyl, OR^{17} und $N(R^{17})_2$ substituiert sind; wobei R^{17} jeweils unabhängig für H, C_{1-4}-Alkyl oder C_{1-4}-Halogenalkyl steht;
R^{15} und R^{16} jeweils unabhängig voneinander für H, C_{1-6}-Alkyl oder C_{1-6}-Halogenalkyl stehen; oder

R^2 und R^3 zusammen mit dem Kohlenstoffatom, an das sie gebunden sind, ein 3- bis 10-gliedriges carbocyclisches oder heterocyclisches Ringsystem bilden, gegebenenfalls substituiert durch einen oder mehrere Substituenten ausgewählt aus Halogen, CN, OR^9, $N(R^9)_2$, C(O)OR^9, C(O)$N(R^9)_2$, C(O)R^9, $N(R^9)C(O)R^9$ und gegebenenfalls durch Halogen, OR^9 oder $N(R^9)_2$ substituiertem C_{1-4}-Alkyl; oder R^1, R^2 und R^3 zusammen mit dem Kohlenstoffatom, an das sie gebunden sind, ein verbrücktes 5- bis 10-gliedriges carbocyclisches oder heterocyclisches Ringsystem oder Phenyl bilden, jeweils gegebenenfalls substituiert durch einen oder mehrere Substituenten ausgewählt aus Halogen, CN, OR^9, $N(R^9)_2$, C(O)OR^9, C(O)$N(R^9)_2$, C(O)R^9, $N(R^9)C(O)R^9$ und gegebenenfalls durch Halogen, OR^9 oder $N(R^9)_2$ substituiertem C_{1-4}-Alkyl;
R^9 jeweils unabhängig aus H, C_{1-6}-Alkyl oder C_{1-6}-Halogenalkyl ausgewählt ist;
X^1 für N steht;
X^2 für CR^8 steht;
R^8 für H, Halogen, OH, O(C_{1-4}-Alkyl) , CN oder NH_2 steht;
Y für eine Bindung oder eine geradkettige C_{1-6}-Alkylenkette steht, die gegebenenfalls durch einen oder

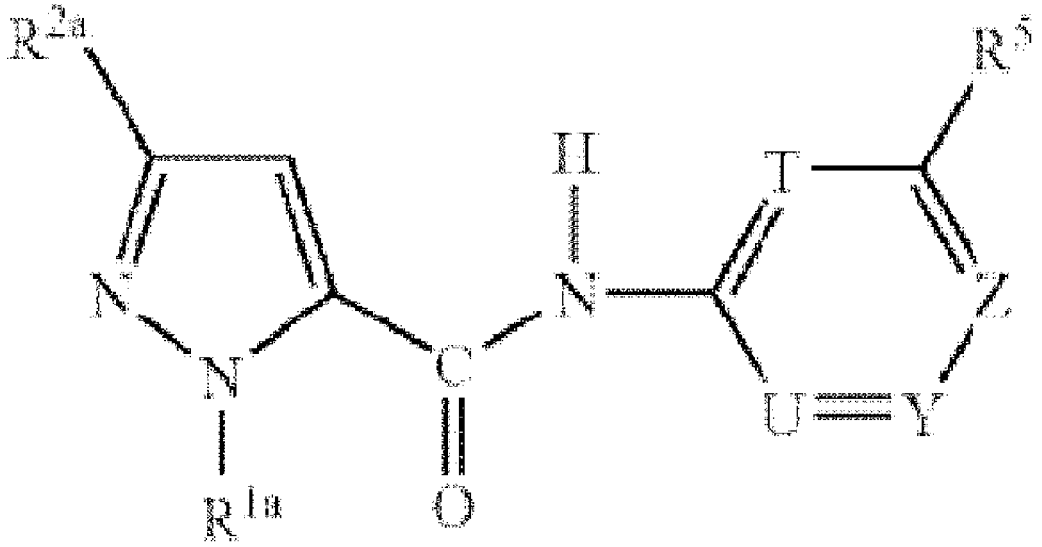
mehrere R^{18}-Substituenten substituiert ist, wobei zwei R^{18}-Substituenten an die gleichen oder an verschiedene Kohlenstoffatome gebunden sein können;
wobei R^{18} jeweils unabhängig für C_{1-3}-Alkyl oder C_{1-3}-Halogenalkyl, in welchem ein $-CH_2-$ gegebenenfalls durch -NH- oder -O- ersetzt ist, steht und wobei zwei R^{18}-Gruppen zusammen mit dem Atom bzw. den Atomen, an das/die sie gebunden sind, ein 3- bis 6-gliedriges carbocyclisches oder heterocyclisches Ringsystem bilden können;
Z für -C(O)- oder -C(O)NH- steht;
R^4 für ein 6- bis 14-gliedriges Aryl-, 5- bis 14-gliedriges Heteroaryl- oder ein 5- bis 10-gliedriges carbocyclisches Ringsystem steht, jeweils gegebenenfalls substituiert durch einen oder mehrere Substituenten ausgewählt aus:

Halogen, CN, Nitro, R^{19}, OR^{19}, OR^6, SR^6, NR^6R^7, $C(O)R^6$, $C(O)R^{19}$, $C(O)OR^6$, $C(O)N(R^6)(R^7)$, $N(R^7)C(O)R^6$;
C_{1-6}-Alkyl oder $O(C_{1-6}$-Alkyl), jeweils gegebenenfalls substituiert durch einen oder mehrere Substituenten ausgewählt aus Halogen, CN, Nitro, R^{19}, OR^6, SR^6, NR^6R^7, $C(O)R^6$, $C(O)OR^6$, $C(O)N(R^6)(R^7)$ und $N(R^7)C(O)R^6$; und,
wenn R^4 keinen vollaromatischen Charakter hat, Oxo;

wobei R^{19} für ein 5- oder 6-gliedriges Aryl- oder Heteroarylringsystem oder ein 3- bis 7-gliedriges carbocyclisches oder heterocyclisches Ringsystem steht, jeweils gegebenenfalls substituiert durch einen oder mehrere Substituenten ausgewählt aus Halogen, C_{1-4}-Alkyl, C_{1-4}-Halogenalkyl,OH, $O(C_{1-4}$-Alkyl), $O(C_{1-4}$-Halogenalkyl;
R^6 für H, C_{1-6}-Alkyl, C_{1-6}-Halogenalkyl, Benzyl, 3- bis 7-gliedriges Carbocyclyl oder 3- bis 7-gliedriges Heterocyclyl steht;
R^7 für H, C_{1-6}-Alkyl oder C_{1-6}-Halogenalkyl steht; oder R^6 und R^7 zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen 4- bis 7-gliedrigen heterocyclischen Ring bilden können, gegebenenfalls mit einem oder mehreren weiteren Heteroatomen und gegebenenfalls substituiert durch einen oder mehrere Substituenten ausgewählt aus Oxo und Halogen; und

R^{5a} und R^{5b} jeweils unabhängig voneinander für H, C_{1-4}-Alkyl oder Halogen stehen; mit der Maßgabe, dass:

wenn X^2 für CH steht, Z für -C(O)- steht und Y für eine Bindung steht, R^4 nicht für einen 5- bis 10-gliedrigen Heteroarylring steht, der über ein Stickstoffatom an Y gebunden ist,
mit Ausnahme der Verbindungen der Formel (A):

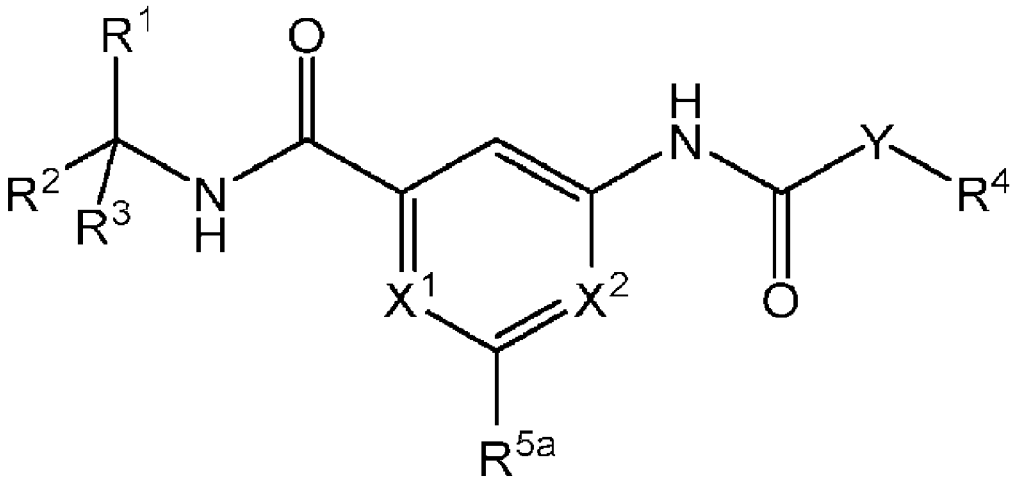


(A)

in denen R^{18} für Ethyl steht; R^{2a} für tert.-Butyl steht; T, U und Y für CH stehen und Z für N steht; und R^5 für C(O)NHEt, $C(O)NH(CH_2)_2CH_3$, $C(O)NH(CH_2)_2CH_2F$, $C(O)NH(CH_2)_3CH_3$, $C(O)NH(CH_2)_3CH_2F$, $C(O)NHCH_2C{=}CH$ oder $C(O)NHCH_2CH{=}CH_2$ steht, wobei jedoch die tautomeren Formen, Enantiomere und Isotopenvarianten sowie Salze und Solvate der Verbindungen der Formel (A) nicht ausgenommen sind.

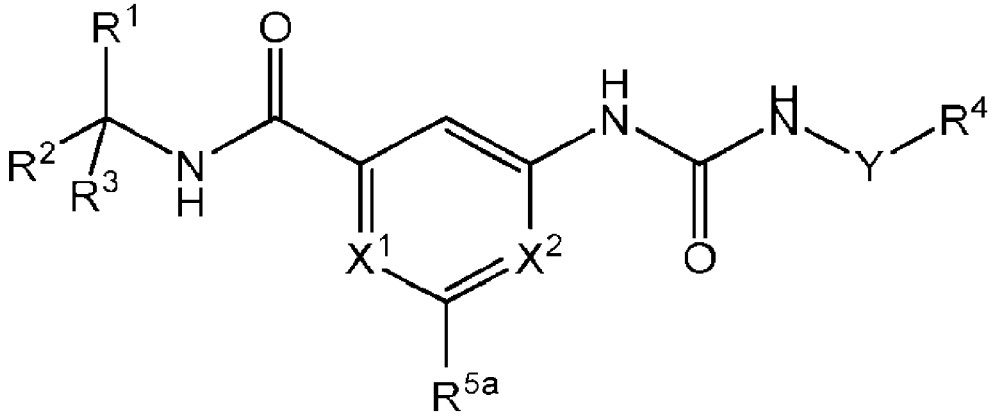
2. Verbindung nach Anspruch 1, wobei:

Z für -C(O)- steht und R^{5b} für H steht, so dass die Verbindung die Formel (Iz) aufweist:



(Iz)

wobei R^1, R^2, R^3, R^4, R^{5a}, X^1, X^2 und Y wie in Anspruch 1 definiert sind; oder
Z für -C(O)NH- steht und R^{5b} für H steht, so dass die Verbindung die allgemeine Formel (Iy) aufweist:



(Iy)

wobei R^1, R^2, R^3, R^4, R^{5a}, X^1, X^2 und Y wie in Anspruch 1 definiert sind.

3. Verbindung nach Anspruch 1 oder Anspruch 2, wobei R^1 für H, CN oder Ethinyl oder Methyl, jeweils unsubstituiert oder substituiert durch OH, steht.

4. Verbindung nach einem der Ansprüche 1 bis 3 wobei:

R^2 für Methyl oder Ethyl steht; und
R^3 für C_{1-4}-Alkyl steht, gegebenenfalls substituiert durch einen oder mehrere Substituenten ausgewählt aus Hydroxyl, Methoxy, Ethoxy, -C(O)O-(C_{1-4}-Alkyl) und -N (H) C (O)O-(C_{1-4}-Alkyl); oder wobei:

R^3 für C_{1-10}-Alkyl oder C_{2-3}-Alkinyl steht, jeweils gegebenenfalls unsubstituiert oder substituiert durch einen einzelnen Substituenten ausgewählt aus Fluor, R^{14}, OR^{14}, OR^{15}, $C(O)OR^{15}$, $N(R16)S(O)_2R^{15}$ und $N(R^{16})C(O)OR^{15}$; wobei R^{14} aus Phenyl, Pyridyl und einem 5- oder 6-gliedrigen heterocyclischen Ring ausgewählt ist;
R^{15} aus H oder C_{1-4}-Alkyl ausgewählt ist; und
R^{16} für H steht; oder
R^3 für ein 3- bis 7-gliedriges carbocyclisches oder heterocyclisches Ringsystem steht, das unsubstituiert oder wie in Anspruch 1 definiert ist; oder
R^3 für Phenyl oder Pyridyl steht, jeweils gegebenenfalls unsubstituiert oder substituiert durch einen einzelnen Substituenten ausgewählt aus OR^{17} und $N(R^{17})_2$, wobei R^{17} jeweils für H oder Methyl steht.

5. Verbindung nach Anspruch 4 wobei:

R^1 für Methyl oder CN steht und R^2 und R^3 beide für Methyl steht; oder
R^2 und R^3 zusammen mit dem Kohlenstoffatom, an das sie gebunden sind, ein carbocyclisches oder heterocyclisches Ringsystem bilden und R^1 für H, Methyl, Methyl substituiert durch OH, CN, Ethinyl oder $C(O)OR^{12}$ steht, wobei R^{12} wie in Anspruch 1 definiert ist.

6. Verbindung nach einem der Ansprüche 1 bis 5 wobei Y für -CH_2-, -CH_2CH_2-, -CH (CH_3) CH_2-, -CH_2CH (CH_3) - oder - $CH_2CH_2CH_2$-, insbesondere -CH_2-, steht; und/oder

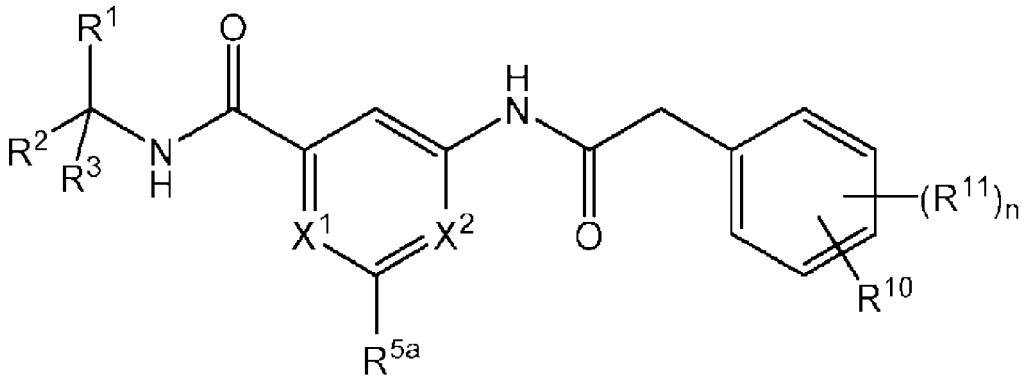
R^{5a} und R^{5b} beide für H stehen und/oder
X^2 für CH steht; und/oder wobei:

R^4 für eine 6- bis 11-gliedrige Arylgruppe ausgewählt aus Phenyl, Naphthyl, Indanyl, 1,2,3,4-Tetrahydronaphthyl und Benzocycloheptanyl steht, jeweils gegebenenfalls substituiert wie in Anspruch 1 definiert; oder
R^4 für eine 5- bis 10-gliedrige Heteroarylgruppe ausgewählt aus Pyridyl, Chinolinyl, Chinoxalinyl, Indazolyl, Indolyl, Benzoxazolyl, Dihydrobenzofuranyl, Furyl und Thienyl steht, jeweils gegebenenfalls substituiert wie in Anspruch 1 definiert;
R^4 für eine Carbocyclylgruppe ausgewählt aus Cyclohexyl und Adamantyl steht, jeweils gegebenenfalls substituiert wie in Anspruch 1 definiert; oder
R^4 für Phenyl steht, gegebenenfalls substituiert wie in Anspruch 1 definiert; oder
R^4 für 5- bis 10-gliedriges Heteroaryl ausgewählt aus Pyridyl, Pyrrolyl, Thienyl, Furyl, Benzoxazolyl, Imidazolyl, Indolyl oder Indazolyl steht, jeweils gegebenenfalls substituiert wie in Anspruch 1 definiert.

7. Verbindung nach Anspruch 6, wobei R^4 für Phenyl steht, substituiert durch eine OH-Gruppe entweder an der 2- oder der 3-Position und gegebenenfalls durch einen oder mehrere Substituenten ausgewählt aus:

Halogen, CN, R^{19}, OR^{19};
ORB, $C(O)OR^6$;
C_{1-4}-Alkyl oder O(C_{1-4}-Alkyl), jeweils gegebenenfalls substituiert durch einen oder mehrere Substituenten ausgewählt aus Halogen, CN, R^{19}, OR^{19}, OR^6 und NR^6R^7;
wobei R^6 für H, C_{1-4}-Alkyl oder C_{1-4}-Halogenalkyl steht oder, bei einer Gruppierung NR^6R^7, R^6 und R^7 zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen 5- oder 6-gliedrigen heterocyclischen Ring bilden, gegebenenfalls mit einem oder mehreren Heteroatomen und gegebenenfalls substituiert durch einen oder mehrere Halogensubstituenten;
R^7 wie in Anspruch 1 definiert ist; und
R^{19} für eine 3- bis 6-gliedrige Carbocyclylgruppe oder Phenyl steht, jeweils gegebenenfalls substituiert durch einen oder mehrere Substituenten ausgewählt aus Halogen, Methyl und Methoxy.

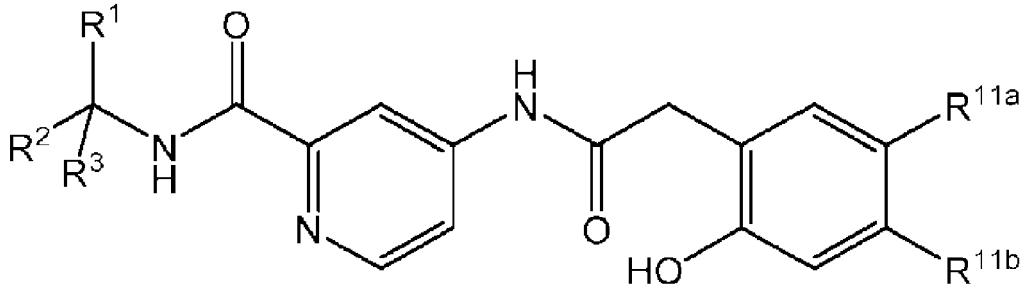
8. Verbindung nach einem der Ansprüche 1 bis 7, wobei Y für -CH_2- steht, R^4 für Phenyl steht und es sich bei der Verbindung um eine Verbindung der allgemeinen Formel (Ia) :



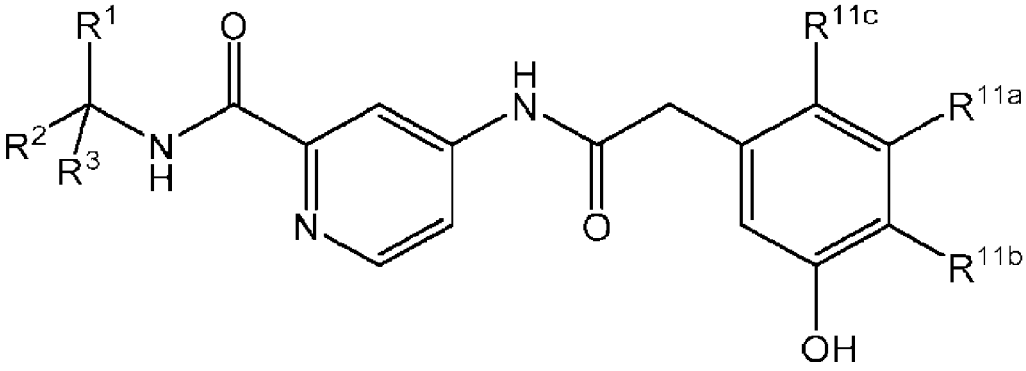
(Ia)

wobei

R^1, R^2, R^3, R^{5a}, X^1 und X^2 wie in Anspruch 1 definiert sind; R^{10} für H, OH, Halogen, C_{1-6}-Alkyl, -O (C_{1-6}-Alkyl) steht; R^{11} jeweils unabhängig für H, Halogen, OH, CN, C_{1-6}-Alkyl, C_{1-6}-Halogenalkyl, -O(C_{1-6}-Alkyl) oder C(O)O-(C_{1-6}-Alkyl) steht; und
n für 1 oder 2 steht; oder
eine Verbindung der allgemeinen Formel (Id) oder (Ie):



(Id)



(Ie)

wobei

R^1, R^2 und R^3 wie in Anspruch 1 definiert sind;
R^{11a} für H, Halogen, C_{1-4}-Alkyl, C_{1-4}-Halogenalkyl oder C(O)O(C_{1-4}-Alkyl) steht;
R^{11b} für H, Halogen, C_{1-4}-Alkyl oder C_{1-4}-Halogenalkyl steht; und

R^{11c} für H, Halogen, CN, C_{1-4}-Alkyl oder C_{1-4}-Halogenalkyl steht,
handelt.

9. Verbindung nach Anspruch 1, ausgewählt aus:

N-tert.-Butyl-4-[[2-(2-hydroxyphenyl)acetyl]amino]pyridin-2-carboxamid (Verbindung 1);
N-(1-Adamantyl)-4-[[2-(5-chlor-2-hydroxyphenyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 1.3);
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-(3-methoxy-1,1-dimethylpropyl)pyridin-2-carbonsäureamid (Verbindung 1.4);
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-(1-methylcyclobutyl)pyridin-2-carbonsäureamid (Verbindung 1.6) ;
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-(1-methylcyclohexyl)pyridin-2-carbonsäureamid (Verbindung 1.7);
N-[3-[[4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]pyridin-2-carbonyl]amino]-3 - methyl-butyl]carbamidsäure-tert.-butylester (Verbindung 1.8) ;
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-cyclohexylpyridin-2-carbonsäureamid (Verbindung 1.10);
N-tert.-Butyl-4-[[2-(5-chlor-2-hydroxyphenyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 3);
N-(1,1-Dimethylpropyl)-4-[[2-(4-fluor-2-hydroxyphenyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 3.1a);
N-tert.-Butyl-4-[[2-(4-fluor-2-hydroxyphenyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 3.2a);
N-tert.-Butyl-4-[[2-(2-chlor-6-hydroxyphenyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 3.3a);
4-[[2-(4-Brom-5-chlor-2-hydroxyphenyl)acetyl]amino]-N-tert.-Butyl-pyridin-2-carbonsäureamid (Verbindung 3.4a);
4-[[2-(5-tert.-Butyl-2-hydroxyphenyl)acetyl]amino]-N-(1-cyanocyclobutyl)pyridin-2-carbonsäureamid (Verbindung 3.5a);
4-[[2-(5-tert.-Butyl-2-hydroxyphenyl)acetyl]amino]-N-(1-methylcyclobutyl)pyridin-2-carbonsäureamid (Verbindung 3.6a);
N-tert.-Butyl-4-[2-(2,5-dibrom-3-fluor-6-hydroxyphenyl)acetamido]pyridin-2-carbonsäureamid (Verbindung 3.7a);
N-tert.-Butyl-4-[[2-[2-hydroxy-5-(trifluormethyl)phenyl]acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 3.5b);
N-tert.-Butyl-4-[[2-(4-chlor-2-hydroxyphenyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 3.6b);
N-tert.-Butyl-4-[[2-[2-hydroxy-4-(trifluormethyl)phenyl]acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 3.7b);
N-tert.-Butyl-4-[[2-(2-hydroxy-5-methoxyphenyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 3.8b);
N-tert.-Butyl-4-[(6-hydroxyindan-1-carbonyl)amino]pyridin-2-carbonsäureamid (Verbindung 3.9b);
N-tert.-Butyl-4-[(7-hydroxyindan-1-carbonyl)amino]pyridin-2-carbonsäureamid (Verbindung 3.10b);
N-tert.-Butyl-4-[[2-(2,5-dibrom-3-chlor-6-hydroxyphenyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 3.11b);
N-tert.-Butyl-4-[[2-(3-hydroxyphenyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 3.12b);
N-tert.-Butyl-4-[[2-(2-fluor-5-ydroxyphenyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 3.13b);
N-tert.-Butyl-4-[[2-(4-chlor-3-hydroxyphenyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 3.14b);
N-tert.-Butyl-4-[[2-(2-chlor-3-hydroxyphenyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 3.15b);
N-tert.-Butyl-4-[[2-(2-chlor-5-hydroxyphenyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 3.16b);
N-tert.-Butyl-4-[[2-(3-chlor-5-hydroxyphenyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 3.17b);
N-tert.-Butyl-4-[[2-(2-thienyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 5);
4-[[2-(2-Adamantyl)acetyl]amino]-N-tert.-butyl-pyridin-2-carbonsäureamid (Verbindung 5.1);
N-tert.-Butyl-4-[[2-(4-fluor-2-methoxyphenyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 5.2);
N-tert.-Butyl-4-[[2-(5-chlor-2-fluorphenyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 5.3);
N-tert.-Butyl-4-[[2-(2-furyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 5.4);
N-tert.-Butyl-4-[[2-(3-chlorphenyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 5.5);
N-tert.-Butyl-4-[[2-(1H-indol-3-yl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 5.6) ;
N-tert.-Butyl-4-[[2-(o-tolyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 5.7);
N-tert.-Butyl-4-[[2-(3,4-dichlorphenyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 5.8);
N-tert.-Butyl-4-[[2-(3-fluorphenyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 5.9);
N-tert.-Butyl-4-[[2-(5-chlor-2-methoxyphenyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 5.10);
N-tert.-Butyl-4-[[2-(p-tolyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 5.11);
N-tert.-Butyl-4-[[2-(2-fluorphenyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 5.12);

N-tert.-Butyl-4-[[2-(4-fluorphenyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 5.13);
N-tert.-Butyl-4-[[2-(m-tolyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 5.14);
4-[[2-(1,3-Benzoxazol-6-yl)acetyl]amino]-N-tert.-butyl-pyridin-2-carbonsäureamid (Verbindung 5.15);
N-tert.-Butyl-4-[[2-(2-chlor-3-pyridyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 5.16);
N-tert.-Butyl-4-[[2-(2,6-dichlorphenyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 5.17);
N-tert.-Butyl-4-[[2-(4-chlor-3-fluorphenyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 5.18);
N-tert.-Butyl-4-[[2-(3,5-dichlorphenyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 5.19);
N-tert.-Butyl-4-[[2-(2-chlorphenyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 5.20);
N-tert.-Butyl-4-[[2-(3-chlor-4-hydroxyphenyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 5.21);
N-tert.-Butyl-4-(indan-1-carbonylamino)pyridin-2-carbonsäureamid (Verbindung 5.22);
N-tert.-Butyl-4-[(2-chinoxalin-6-ylacetyl)amino]pyridin-2-carbonsäureamid (Verbindung 5.23) ;
N-tert.-Butyl-4-[[2-(2-naphthyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 5.24);
N-tert.-Butyl-4-(2,3-dihydrobenzofuran-3-carbonylamino)pyridin-2-carbonsäureamid (Verbindung 5.25) ;
N-tert.-Butyl-4-(6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-carbonylamino)carbonsäureamid (Verbindung 5.26);
N-tert.-Butyl-4-(tetralin-1-carbonylamino)pyridin-2-carbonsäureamid (Verbindung 5.27);
N-tert.-Butyl-4-[[2-(6-chinolyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 5.29);
N-tert.-Butyl-4-[[1-(3-chlorphenyl)cyclopropancarbonyl]amino]pyridin-2-carbonsäureamid (Verbindung 5.31);
N-tert.-Butyl-4-[[2-(2,3-dihydro-1,4-benzodioxin-6-yl)acetyl]amino]pyridin-2- carbonsäureamid (Verbindung 5.32) ;
N-(1,1-Dimethylprop-2-inyl)-4-[(2-isochroman-1-ylacetyl)amino]pyridin-2-carbonsäureamid (Verbindung 5.33) ;
4-[[2-(4,4-Difluorcyclohexyl)acetyl]amino]-N-(1,1-dimethylprop-2-inyl)pyridin-2-carbonsäureamid (Verbindung 5.34);
N-(1,1-Dimethylprop-2-inyl)-4-[[2-[4-(trifluormethyl)phenyl]acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 5.35);
N-(1,1-Dimethylprop-2-inyl)-4-[[2-[3-(trifluormethyl)-1H-pyrazol-4-yl] acetyl] amino]pyridin-2-carbonsäureamid (Verbindung 5.36);
N-(1,1-Dimethylprop-2-inyl)-4-[[2-[3-(trifluormethyl)phenyl]acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 5.37);
N-(1,1-Dimethylprop-2-inyl)-4-[[2-[2-(trifluormethyl)phenyl]acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 5.38);
4-[[2-(2,3-Dihydro-1,4-benzoxazin-4-yl)acetyl]amino]-N-(1,1-dimethylprop-2-inyl)pyridin-2-carbonsäureamid (Verbindung 5.39);
N-tert.-Butyl-4-[[2-(5-cyano-2-hydroxyphenyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 6);
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-(1,1-dimethylbutyl)pyridin-2-carbonsäureamid (Verbindung 7.2);
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-(1,1,2-trimethylpropyl)pyridin-2-carbonsäureamid (Verbindung 7.6);
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-isopropylpyridin-2-carbonsäureamid (Verbindung 7.7);
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-(4-methyltetrahydropyran-4-yl)pyridin-2-carbonsäureamid (Verbindung 7.9);
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-tetrahydropyran-4-yl-pyridin-2-carbonsäureamid (Verbindung 7.11);
4-[2-(5-Chlor-2-hydroxyphenyl)acetamido]-N-[(1s,4s)-4-hydroxycyclohexyl]pyridin-2-carbonsäureamid (Verbindung 7.12) ;
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-sek.-butylpyridin-2-carbonsäureamid (Verbindung 7.13);
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-(2-hydroxy-1,1,2-trimethylpropyl)pyridin-2-carbonsäureamid (Verbindung 7.14);
N-(3-Bicyclo[1.1.1]pentanyl)-4-[[2-(5-chlor-2-hydroxyphenyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 7.15);
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-(1-cyanocyclobutyl)pyridin-2-carbonsäureamid (Verbindung 7.16) ;
3-[[4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]pyridin-2-carbonyl]amino]piperidin-1-carbonsäure-tert.-butylester (Verbindung 8.1);
(1r,5s,6s)-6-{4-[2-(5-Chlor-2-hydroxyphenyl)acetamido]pyridin-2-amido}-3-azabicyclo[3.1.0]hexan-3-carbonsäure-tert.-butylester (Verbindung 8.3);
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-(1,1-dimethylpropyl)pyridin-2-carbonsäureamid (Verbindung 9.2);

N-tert.-Butyl-4-[[2-(5-tert.-butyl-2-hydroxyphenyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 10);
3-[2-[[2-(tert.-Butylcarbamoyl)-4-pyridyl]amino]-2-oxo-ethyl]-4-hydroxy-benzoesäuremethylester (Verbindung 13);
N-tert.-Butyl-4-[[2-(2-hydroxy-5-methylphenyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 15);
N-tert.-Butyl-4-[[2-(3-hydroxy-2-pyridyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 19);
N-tert.-Butyl-4-[[2-(5-fluor-2-hydroxyphenyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 20);
N-tert.-Butyl-4-[[(1R) - oder -(1S)-indan-1-carbonyl]amino]pyridin-2-carbonsäureamid (Verbindung 21a) ;
N-tert.-Butyl-4-[[(1R) - oder -(1S)-indan-1-carbonyl]amino]pyridin-2-carbonsäureamid (Verbindung 21b) ;
N-tert.-Butyl-4-[(2-phenylacetyl)amino]pyridin-2-carbonsäureamid (Verbindung 22);
4-(3,3-Dimethylbutanoylamino)-N-(1,1-dimethylprop-2-inyl)pyridin-2-carbonsäureamid (Verbindung 22.1);
4-[(2-Cyclopentylacetyl)amino]-N-(1,1-dimethylprop-2-inyl)pyridin-2-carbonsäureamid (Verbindung 22.2);
4-[[2-(3-Chlor-4-pyridyl)acetyl]amino]-N-(1,1-dimethylprop-2-inyl)pyridin-2-carbonsäureamid (Verbindung 22.3);
4-[[2-(4-Chlorphenyl)acetyl]amino]-N-(1-cyanocyclopropyl)pyridin-2-carbonsäureamid (Verbindung 23) ;
4-[[2-(3-Chlorphenyl)acetyl]amino]-N-(1-cyanocyclopropyl)pyridin-2-carbonsäureamid (Verbindung 23.1) ;
4-[[2-(2-Chlor-5-fluorphenyl)acetyl]amino]-N-(1-cyanocyclopropyl)pyridin-2-carbonsäureamid (Verbindung 23.2) ;
N-tert.-Butyl-4-(indan-2-carbonylamino)pyridin-2-carbonsäureamid (Verbindung 23.3);
N-tert.-Butyl-4-[[2-[2-(difluormethoxy)phenyl]acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 23.4);
N-tert.-Butyl-4-[[2-[2-(difluormethyl)phenyl]acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 23.5);
N-tert.-Butyl-4-[[2-(3,4-difluorphenyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 23.6);
N-tert.-Butyl-4-[[2-(3,5-difluorphenyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 23.7);
N-tert.-Butyl-4-[[2-(2,3-difluorphenyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 23.8);
4-[[2-(2-Chlorphenyl)acetyl]amino]-N-tetrahydropyran-4-yl-pyridin-2-carbonsäureamid (Verbindung 23.9);
N-(1-Cyanocyclobutyl)-4-[[2-(6-chinolyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 23.11);
N-tert.-Butyl-4-[[2-[2-(trifluormethyl)phenyl]acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 23.12);
4-[[2-(2-Bromphenyl)acetyl]amino]-N-tert.-butyl-pyridin-2-carbonsäureamid (Verbindung 23.13);
N-tert.-Butyl-4-[[2-(2-cyanophenyl)cetyl]amino]pyridin-2-carbonsäureamid (Verbindung 23.14);
4-[[2-(2-Chlorphenyl)acetyl]amino]-N-(4-cyanotetrahydropyran-4-yl)pyridin-2-carbonsäureamid (Verbindung 23.15);
N-(4-Cyanotetrahydropyran-4-yl)-4-[[2-(6-chinolyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 23.16);
4-[[2-(2-Chlor-5-methoxy-phenyl)acetyl]amino]-N-(1-cyanocyclopropyl)pyridin-2-carbonsäureamid (Verbindung 24) ;
N-(3-Bicyclo[1.1.1]pentanyl)-4-[[2-(5-tert.-butyl-2-hydroxyphenyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 25);
-[[2-(5-tert.-Butyl-2-hydroxyphenyl)acetyl]amino]-N-(4-cyanotetrahydropyran-4-yl)pyridin-2-carbonsäureamid (Verbindung 25.1);
N-tert.-Butyl-4-[[2-(2-hydroxy-5-phenyl-phenyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 26);
N-tert.-Butyl-4-[[2-[5-chlor-2-hydroxy-4-(pyrrolidin-1-ylmethyl)phenyl] acetyl] amino]pyridin-2-carbonsäureamid (Verbindung 27);
N-tert.-Butyl-4-[[2-[4-[(tert.-Butylamino)methyl]-5-chlor-2-hydroxyphenyl] acetyl] amino]pyridin-2-carbonsäureamid (Verbindung 27.1);
N-tert.-Butyl-4-[[2-[5-chlor-2-hydroxy-4-(morpholinomethyl)phenyl]acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 27.2);
N-tert.-Butyl-4-[[2-[5-chlor-4-[(3,3-difluorpyrrolidin-1-yl)methyl]-2-hydroxyphenyl] acetyl] amino]pyridin-2-carbonsäureamid (Verbindung 27.3);
N-tert.-Butyl-4-[[2-(5-chlor-2-hydroxyphenyl)acetyl]amino]-5-fluor-pyridin-2-carbonsäureamid (Verbindung 28);
N-tert.-Butyl-4-[[2-(5-chlor-2-hydroxyphenyl)acetyl]amino]-3-fluor-pyridin-2-carbonsäureamid (Verbindung 28.1);
4-[[2-(2-Chlorphenyl)acetyl]amino]-N-(1-cyanocyclobutyl)pyridin-2-carbonsäureamid (Verbindung 30) ;
4-[[2-(2-Chlorphenyl)acetyl]amino]-N-(1,1-dimethylprop-2-inyl)pyridin-2-carbonsäureamid(Verbindung 30.1);
4-[[2-(2-Chlorphenyl)acetyl]amino]-N-(4-fluor-1-bicyclo[2.1.1]hexanyl)pyridin-2-carbonsäureamid (Verbindung 30.2);
4-[[2-(2-Chlorphenyl)acetyl]amino]-N-(1-cyclopropyl-1-methylethyl)pyridin-2-carbonsäureamid (Verbindung 30.3);
4-[[2-(2-Chlorphenyl)acetyl]amino]-N-(1-cyano-1-methylethyl)pyridin-2-carbonsäureamid (Verbindung 30.3a);
4-[[2-(2-Chlorphenyl)acetyl]amino]-N-(1-methyl-3-bicyclo[1.1.1]pentanyl)pyridin-2-carbonsäureamid (Verbin-

dung 30.4);
4-[[2-(2-Chlorphenyl)acetyl]amino]-N-(1-cyano-3-bicyclo[1.1.1]pentanyl)pyridin-2-carbonsäureamid (Verbindung 30.5);
4-[[2-(2-Chlorphenyl)acetyl]amino]-N-(2,2-difluorcyclopropyl)pyridin-2-carbonsäureamid (Verbindung 30.6);
4-[[2-(2-Chlorphenyl)acetyl]amino]-N-(1-cyanocyclopropyl)pyridin-2-carbonsäureamid (Verbindung 30.7) ;
4-[[2-(2-Chlorphenyl)acetyl]amino]-N-(1-methylcyclopropyl)pyridin-2-carbonsäureamid (Verbindung 30.8) ;
4-[[2-(2-Chlorphenyl)acetyl]amino]-N-(3-fluor-1-bicyclo[1.1.1]pentanyl)pyridin-2-carbonsäureamid (Verbindung 30.9);
4-[[2-(2-Chlorphenyl)acetyl]amino]-N-(2-fluor-1,1-dimethylethyl)pyridin-2-carbonsäureamid (Verbindung 30.10) ;
4-[[2-(2-Chlorphenyl)acetyl]amino]-N-(4-ethinyltetrahydropyran-4-yl)pyridin-2-carbonsäureamid (Verbindung 30.11);
4-[[2-(2-Chlorphenyl)acetyl]amino]-N-(1-cyanocyclopentyl) pyridin-2-carbonsäureamid (Verbindung 30.12) ;
4-[[2-(2-Chlorphenyl)acetyl]amino]-N-(2,2-difluor-1,1-dimethylethyl)pyridin-2-carbonsäureamid (Verbindung 30.13) ;
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-(4-cyanotetrahydropyran-4-yl)pyridin-2-carbonsäureamid (Verbindung 31);
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-(1-ethinylcyclopentyl)pyridin-2-carbonsäureamid (Verbindung 31.2);
4-[2-(5-Chlor-2-hydroxyphenyl)acetamido]-N-[(1s,2s)-2-hydroxycyclohexyl]pyridin-2-carbonsäureamid (Verbindung 31.3) ;
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-[(1S,2S)-2-hydroxycyclohexyl]pyridin-2-carbonsäureamid oder 4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-[(1R,2R)-2-hydroxycyclohexyl]pyridin-2-carbonsäureamid (Verbindung 31.3a);
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-(4-ethinyltetrahydropyran-4-yl)pyridin-2-carbonsäureamid (Verbindung 31.4);
N-[(6-Amino-2-pyridyl)methyl]-4-[[2-(5-chlor-2-hydroxyphenyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 32);
12-[[4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]pyridin-2-carbonyl]amino]dodecansäure (Verbindung 32.1);
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-(3-pyridylmethyl)pyridin-2-carbonsäureamid (Verbindung 32.2) ;
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-(2-pyridylmethyl)pyridin-2-carbonsäureamid (Verbindung 32.3) ;
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-(4-pyridylmethyl)pyridin-2-carbonsäureamid (Verbindung 32.4) ;
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-[(2-hydroxyphenyl)methyl] pyridin-2-carbonsäureamid (Verbindung 32.5);
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-(1,1-dimethyl-2-morpholinoethyl)pyridin-2-carbonsäureamid (Verbindung 32.6);
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-(2-hydroxy-1,1-dimethylethyl)pyridin-2-carbonsäureamid (Verbindung 32.7);
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-(3,3-difluor-4-piperidyl)pyridin-2-carbonsäureamid (Verbindung 32.8);
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-(1H-imidazol-2-yl)pyridin-2-carbonsäureamid (Verbindung 32.9) ;
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-[(1R,2R)-2-hydroxycyclopentyl]pyridin-2-carbonsäureamid (Verbindung 33);
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-(1-cyano-1-methylethyl)pyridin-2-carbonsäureamid (Verbindung 34);
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-[3-(hydroxymethyl)tetrahydrofuran-3-yl]pyridin-2-carbonsäureamid (Verbindung 35);
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-[(3R)-3-(hydroxymethyl)tetrahydrofuran-3-yl]pyridin-2-carbonsäureamid oder 4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-[(3S)-3-(hydroxymethyl)tetrahydrofuran-3-yl]pyridin-2-carbonsäureamid (Verbindung 35a);
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-[(3R)-3-(hydroxymethyl)tetrahydro furan-3-yl]pyridin-2-carbonsäureamid oder 4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-[(3S)-3-(hydroxymethyl)tetrahydrofuran-3-yl]pyridin-2-carbonsäureamid (Verbindung 35b);
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-(4-hydroxy-4-methyl-cyclohexyl) s-pyridin-2-carbonsäurea-

mid als eine 6:4-Stereoisomerenmischung (Verbindung 35.1);
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-[(1s,2r)-2-(hydroxymethyl)cyclohexyl]pyridin-2-carbonsäureamid (Verbindung 35.2);
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-[(1s,3r)-3-hydroxycyclopentyl]pyridin-2-carbonsäureamid (Verbindung 35.3);
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-[2-hydroxy-1-(hydroxymethyl)-1-methylethyl]pyridin-2-carbonsäureamid (Verbindung 35.4);
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-(3-hydroxycyclohexyl)pyridin-2-carbonsäureamid als Stereoisomerenmischung (Verbindung 35.6);
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-(3-phenoxypropyl)pyridin-2-carbonsäureamid (Verbindung 35.7) ;
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-(1-methylcyclopropyl)pyridin-2-carbonsäureamid (Verbindung 35.8) ;
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-[1-methyl-1-(2-pyridyl)ethyl]pyridin-2-carbonsäureamid (Verbindung 35.9);
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-(3-phenylpropyl)pyridin-2-carbonsäureamid (Verbindung 35.10);
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-[2-hydroxy-1-(2-pyridyl)ethyl]pyridin-2-carboxamid (Verbindung 35.11);
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-[(5-methoxy-2-pyridyl)methyl]pyridin-2-carbonsäureamid (Verbindung 35.12);
3-[[4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl] amino]pyridin-2-carbonyl] amino]-3 - methylbutansäureethylester (Verbindung 35.13);
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-(3-hydroxy-1,1-dimethylpropyl)pyridin-2-carbonsäureamid (Verbindung 35.14);
N-Benzyl-4-[[2-(5-chlor-2-hydroxyphenyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 35.15);
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-phenyl-pyridin-2-carbonsäureamid (Verbindung 35.16);
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-[(1S,2S)-2-hydroxycyclopentyl]pyridin-2-carbonsäureamid (Verbindung 35.17);
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-[(1R,2S)-2-hydroxycyclopentyl]pyridin-2-carbonsäureamid (Verbindung 35.18);
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-[(1S,2R)-2-hydroxycyclopentyl]pyridin-2-carbonsäureamid (Verbindung 35.19);
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-(1-ethinylcyclohexyl)pyridin-2-carbonsäureamid (Verbindung 35.24) ;
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-[1-(hydroxymethyl)cyclobutyl]pyridin-2-carbonsäureamid (Verbindung 35.25);
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-[3-(hydroxymethyl)oxetan-3-yl]pyridin-2-carbonsäureamid (Verbindung 35.26);
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-(1-cyano-2-methoxy-1-methylethyl)pyridin-2-carbonsäureamid (Verbindung 35.27);
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-[(1-hydroxycyclobutyl) methyl] pyridin-2-carbonsäureamid (Verbindung 35.28);
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-(1,1-dimethylprop-2-inyl)pyridin-2-carbonsäureamid (Verbindung 36);
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-(1-cyano-1,2-dimethylpropyl)pyridin-2-carbonsäureamid (Verbindung 37);
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-(1-methylcyclopentyl)pyridin-2-carbonsäureamid (Verbindung 38) ;
N-(4-tert.-Butylcyclohexyl)-4-[[2-(5-chlor-2-hydroxyphenyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 39);
N-tert.-Butyl-4-[[2-(2-chlor-3-fluorphenyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 40);
N-tert.-Butyl-4-[[2-(2-chlor-5-fluorphenyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 40.1);
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-[4-(2-hydroxyethyl)tetrahydropyran-4-yl]pyridin-2-carbonsäureamid (Verbindung 42);
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-[1,1-dimethyl-3-(2,2,2-trifluorethylamino)propyl]pyridin-2-carbonsäureamid (Verbindung 43);
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-(4-fluor-1-bicyclo[2.1.1]hexanyl)pyridin-2-carbonsäureamid

(Verbindung 44);
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-[3-(2,2-dimethylpropanoylamino)-1,1-dimethylpropyl]pyridin-2-carbonsäureamid (Verbindung 45);
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-(1-cyano-2-hydroxy-1-methylethyl)pyridin-2-carbonsäureamid (Verbindung 46);
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-[(1S)-1-cyano-2-hydroxy-1-methylethyl]pyridin-2-carbonsäureamid oder 4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-[(1R)-1-cyano-2-hydroxy-1-methylethyl]pyridin-2-carbonsäureamid (Verbindung 46a);
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-[(1S)-1-cyano-2-hydroxy-1-methylethyl]pyridin-2-carbonsäureamid oder 4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-[(1R)-1-cyano-2-hydroxy-1-methylethyl]pyridin-2-carbonsäureamid (Verbindung 46b);
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-(3-cyanotetrahydrofuran-3-yl)pyridin-2-carbonsäureamid (Verbindung 47);
2-[4-[[4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]pyridin-2-carbonyl]amino]tetrahydropyran-4-yl]essigsäuremethylester (Verbindung 47.1);
4-[[4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]pyridin-2-carbonyl] amino]tetrahydropyran-4-carbonsäuremethylester (Verbindung 47.2);
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-(3-cyanooxetan-3-yl)pyridin-2-carbonsäureamid (Verbindung 47.3) ;
4-[[2-(5-Fluor-2-hydroxyphenyl)acetyl]amino]-N-(1-methylcyclobutyl)pyridin-2-carbonsäureamid (Verbindung 48) ;
N-(4-Cyanotetrahydropyran-4-yl)-4-[[2-(5-fluor-2-hydroxyphenyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 48.1);
N-[3-(tert.-Butylamino)-1,1-dimethyl-3-oxopropyl]-4-[[2-(5-chlor-2-hydroxyphenyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 49);
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-[3-(methansulfonamido)-1,1-dimethylpropyl]pyridin-2-carbonsäureamid (Verbindung 50);
N-(3-Acetamido-1,1-dimethylpropyl)-4-[[2-(5-chlor-2-hydroxyphenyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 51);
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-[4-(hydroxymethyl)tetrahydropyran-4-yl]pyridin-2-carbonsäureamid (Verbindung 53);
N-tert.-Butyl-4-[[2-[3-(1-hydroxyethyl)phenyl]acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 54);
N-tert.-Butyl-5-chlor-4-[[2-(5-chlor-2-hydroxyphenyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 55);
N-tert.-Butyl-4-[[2-[5-chlor-2-[(4-methoxyphenyl)methoxy]phenyl]acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 56);
N-tert.-Butyl-4-[[(1S)- oder -(1R)-4-chlor-7-hydroxyindan-1-carbonyl]amino]pyridin-2-carbonsäureamid (Verbindung 57a);
N-tert.-Butyl-4-[[(1S)- oder -(1R)-4-chlor-7-hydroxyindan-1-carbonyl]amino]pyridin-2-carbonsäureamid (Verbindung 57b);
N-tert.-Butyl-4-[[2-(2-cyclopropylphenyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 58);
4-[[2-(3-Brom-5-chlor-2-hydroxyphenyl)acetyl]amino]-N-tert.-butylpyridin-2-carbonsäureamid (Verbindung 59);
N-(4-Fluor-1-bicyclo[2.1.1]hexanyl)-4-[[2-(2-fluorphenyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 60);
N-(1-Cyano-2-hydroxy-1-methylethyl)-4-[[2-(2-fluorphenyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 60.1);
N-(1,1-Dimethylprop-2-inyl)-4-[[2-(2-fluorphenyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 60.2);
N-tert.-Butyl-4-[[2-(5-chloro-2-hydroxy-3-isopropylphenyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 61);
N-tert.-Butyl-4-[[2-[5-chlor-2-hydroxy-3-(1-methoxyethyl)phenyl]acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 62);
4-[[2-(6-Chinolyl)acetyl]amino]-N-tetrahydropyran-4-ylpyridin-2-carbonsäureamid (Verbindung 63);
4-(Benzylcarbamoylamino)-N-tert.-butylpyridin-2-carbonsäureamid (Verbindung 64);
N-tert.-Butyl-4-(cyclohexylmethylcarbamoylamino)pyridin-2-carbonsäureamid (Verbindung 64.1);
N-tert.-Butyl-4-(2-phenylethylcarbamoylamino)pyridin-2-carbonsäureamid (Verbindung 64.2);
N-tert.-Butyl-4-[[(1R)-1-phenylethyl]carbamoylamino]pyridin-2-carbonsäureamid (Verbindung 64.3);
N-tert.-Butyl-4-[[(1S)-1-phenylethyl]carbamoylamino]pyridin-2-carbonsäureamid (Verbindung 64.4);
N-tert.-Butyl-4-[(2-chlorphenyl)methylcarbamoylamino] pyridin-2-carbonsäureamid (Verbindung 64.5);
N-tert.-Butyl-4-(1H-indol-3-ylcarbamoylamino)pyridin-2-carbonsäureamid (Verbindung 64.6);

N-tert.-Butyl-4-[(3-chlorphenyl)methylcarbamoylamino] pyridin-2-carbonsäureamid (Verbindung 64.7);
N-tert.-Butyl-4-[(4-chlorphenyl)methylcarbamoylamino]pyridin-2-carbonsäureamid (Verbindung 64.8);
N-tert.-Butyl-4-[(2-hydroxyphenyl)carbamoylamino]pyridin-2-carbonsäureamid (Verbindung 65);
N-tert.-Butyl-4-[(2-methoxyphenyl)methylcarbamoylamino] pyridin-2-carbonsäureamid (Verbindung 65.1);
N-tert.-Butyl-4-[(2-hydroxyphenyl)methylcarbamoylamino] pyridin-2-carbonsäureamid (Verbindung 65.2);
N-tert.-Butyl-4-[(3-hydroxyphenyl)methylcarbamoylamino] pyridin-2-carbonsäureamid (Verbindung 65.3);
N-tert.-Butyl-4-[(4-hydroxyphenyl)methylcarbamoylamino] pyridin-2-carbonsäureamid (Verbindung 65.4);
N-tert.-Butyl-4-[[2-[2-hydroxy-5-(1-hydroxyethyl)phenyl]acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 66);
N-tert.-Butyl-4-[[2-[2-hydroxy-5-[1-(2,2,2-trifluorethylamino)ethyl]phenyl]acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 67);
N-tert.-Butyl-4-[[2-[3-(cyanomethyl)phenyl]acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 68);
N-tert.-Butyl-4-[[2-[3-(methoxymethyl)phenyl]acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 69);
N-tert.-Butyl-4-[[2-[2-hydroxy-5-(morpholinomethyl)phenyl]acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 70);
4-[[2-(5-Fluor-2-hydroxyphenyl)acetyl]amino]-N-[3-(hydroxymethyl)tetrahydrofuran-3-yl]pyridin-2-carbonsäureamid (Verbindung 72);
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-[1-(hydroxymethyl)-2-methoxy-1-methylethyl]pyridin-2-carbonsäureamid (Verbindung 73);
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-(1,1-dimethylbut-2-inyl)pyridin-2-carbonsäureamid (Verbindung 73.1);
N-tert.-Butyl-4-[[2-[2-hydroxy-5-(3-hydroxypropyl)phenyl]acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 75);
4-[[2-(5-Chlor-4-fluor-2-hydroxyphenyl)acetyl]amino]-N-(1-methylcyclobutyl)pyridin-2-carbonsäureamid (Verbindung 76);
4-[[2-(2,5-Difluorphenyl)acetyl]amino]-N-(1,1-dimethylprop-2-inyl)pyridin-2-carbonsäureamid (Verbindung 77);
4-[[2-(2,5-Difluorphenyl)acetyl]amino]-N-(4-fluor-1-bicyclo[2.1.1]hexanyl)pyridin-2-carbonsäureamid (Verbindung 77.1);
4-[[2-(4-Chlor-2-hydroxyphenyl)acetyl]amino]-N-(1,1-dimethylprop-2-inyl)pyridin-2-carbonsäureamid (Verbindung 78);
N-(1,1-Dimethylprop-2-inyl)-4-[[2-[2-hydroxy-4-(trifluormethyl)phenyl]acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 78.1);
N-(1,1-Dimethylprop-2-inyl)-4-[[2-[2-hydroxy-5-(trifluormethyl)phenyl]acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 78.2);
4-[(2-Chroman-4-ylacetyl)amino]-N-(1,1-dimethylprop-2-inyl)pyridin-2-carbonsäureamid (Verbindung 79);
N-(1,1-Dimethylprop-2-inyl)-4-[[2-(1-isopropyl-3,5-dimethylpyrazol-4-yl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 79.1);
N-(1,1-Dimethylprop-2-inyl)-4-[[2-(1H-indazol-4-yl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 79.2);
N-(1,1-Dimethylprop-2-inyl)-4-[[2-(1H-indol-7-yl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 79.3) ;
N-(1-Cyano-1-methylethyl)-4-[[2-(5-fluor-2-hydroxyphenyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 81);
N-(1-Cyano-2-hydroxy-1-methylethyl)-4-[[2-(5-fluor-2-hydroxyphenyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 81.1);
4-[[2-(5-Fluor-2-hydroxyphenyl)acetyl]amino]-N-isopropyl-pyridin-2-carbonsäureamid (Verbindung 81.2);
N-(1,1-Dimethylprop-2-inyl)-4-[[2-(5-fluor-2-hydroxyphenyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 81.3);
N-(4-Fluor-1-bicyclo[2.1.1]hexanyl)-4-[[2-(5-fluor-2-hydroxyphenyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 81.4);
4-[[2-(5-Fluor-2-hydroxyphenyl)acetyl]amino]-N-[1-(hydroxymethyl)cyclobutyl]pyridin-2-carbonsäureamid (Verbindung 81.5);
N-(1-Cyano-1-methylethyl)-4-(thiophen-3-carbonylamino)pyridin-2-carbonsäureamid (Verbindung 83);
N-(1-Cyano-1-methylethyl)-4-[(2-cyclohexylacetyl)amino]pyridin-2-carbonsäureamid (Verbindung 83.1);
N-(1-Cyano-1-methylethyl)-4-(cyclohexancarbonylamino)pyridin-2-carbonsäureamid (Verbindung 83.2);
N-(1-Cyano-1-methylethyl)-4-[(3,3-difluorcyclopentancarbonyl)amino]pyridin-2-carbonsäureamid (Verbindung 83.3);
N-(1-Cyano-1-methylethyl)-4-[(1-methylcyclopentancarbonyl)amino]pyridin-2-carbonsäureamid (Verbindung 83.4);
N-(1-Cyano-1-methylethyl)-4-(3-cyclohexylpropanoylamino)pyridin-2-carbonsäureamid (Verbindung 83.5);

4-(2-{Bicyclo[2.2.1]heptan-2-yl}acetamido)-N-(1-cyano-1-methylethyl)pyridin-2-carbonsäureamid (Verbindung 83.6) ;
N-(1-Cyano-1-methylethyl)-4-[[2-(1-methylcyclohexyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 83.7);
N-[2-[(1-Cyano-1-methylethyl)carbamoyl]-4-pyridyl]-2-cyclopropylpyrimidin-5-carbonsäureamid (Verbindung 83.8);
N-[2-[(1-Cyano-1-methylethyl)carbamoyl]-4-pyridyl]-3-isobutylisoxazol-5-carbonsäureamid (Verbindung 83.9);
N-(1-Cyano-1-methylethyl)-4-[[2-(4,4-difluorcyclohexyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 83.10);
4-[(1-Benzylcyclopropancarbonyl)amino]-N-(1-cyano-1-methylethyl)pyridin-2-carbonsäureamid (Verbindung 83.11);
N-(1-Cyano-1-methylethyl)-4-[3-(2-methoxy-4-pyridyl)propanoylamino]pyridin-2-carbonsäureamid (Verbindung 83.13);
4-[(5-tert.-Butyl-2-methylpyrazol-3-carbonyl)amino]-N-(1-cyano-1-methylethyl)pyridin-2-carbonsäureamid (Verbindung 83.14);
N-(1-Cyano-1-methylethyl)-4-[(2-pyrazol-1-ylbenzoyl)amino]pyridin-2-carbonsäureamid (Verbindung 83.15);
N-[2-[(1-Cyano-1-methylethyl)carbamoyl]-4-pyridyl]-6-(trifluormethyl)pyridin-2-carbonsäureamid (Verbindung 83.16) ;
N-[2-[(1-Cyano-1-methylethyl)carbamoyl]-4-pyridyl]-3-oxo-4H-1,4-benzoxazin-7-carbonsäureamid (Verbindung 83.17);
N-[2-[(1-Cyano-1-methylethyl)carbamoyl]-4-pyridyl]-1-ethylindol-2-carbonsäureamid (Verbindung 83.18);
N-(1-Cyano-1-methylethyl)-4-[[2-(2,2,2-trifluorethyl)pyrazol-3-carbonyl]amino]pyridin-2-carbonsäureamid (Verbindung 83.19);
N-[2-[(1-Cyano-1-methylethyl)carbamoyl]-4-pyridyl]-3-phenyl-isoxazol-4-carbonsäureamid (Verbindung 83.20);
4-[(1-Benzylpyrazol-4-carbonyl)amino]-N-(1-cyano-1-methylethyl)pyridin-2-carbonsäureamid (Verbindung 83.21);
N-(1-Cyano-1-methylethyl)-4-[(2-methyl-5-phenyl-pyrazol-3-carbonyl)amino]pyridin-2-carbonsäureamid (Verbindung 83.22);
N-(1-Cyano-1-methylethyl)-4-[[2-(3-methyl-1,2,4-oxadiazol-5-yl)benzoyl]amino]pyridin-2-carbonsäureamid (Verbindung 83.23);
N-(1-Cyano-1-methylethyl)-4-[(3-methyl-1-phenylpyrazol-4-carbonyl)amino]pyridin-2-carbonsäureamid (Verbindung 83.24);
N-[2-[(1-Cyano-1-methylethyl)carbamoyl]-4-pyridyl]-2-phenoxypyridin-3-carbonsäureamid (Verbindung 83.25);
N-(1-Cyano-1-methylethyl)-4-[[2,5-dimethyl-1-(2-thienylmethyl)pyrrol-3-carbonyl]amino]pyridin-2-carbonsäureamid (Verbindung 83.26);
N-[2-[(1-Cyano-1-methylethyl)carbamoyl]-4-pyridyl]-5-(2-methoxyphenyl)isoxazol-3-carbonsäureamid (Verbindung 83.27);
N-[2-[(1-Cyano-1-methylethyl)carbamoyl]-4-pyridyl]-4-methyl-2-phenylthiazol-5-carbonsäureamid (Verbindung 83.28);
4-[(4-Acetamidobenzoyl)amino]-N-(1-cyano-1-methylethyl)pyridin-2-carbonsäureamid (Verbindung 83.29);
N-[2-[(1-Cyano-1-methylethyl)carbamoyl]-4-pyridyl]-1,3-benzothiazol-7-carbonsäureamid (Verbindung 83.30);
N-(1-Cyano-1-methylethyl)-4-[3-(4-fluorphenyl) butanoylamino]pyridin-2-carbonsäureamid (Verbindung 83.31) ;
N-[2-[(1-Cyano-1-methylethyl)carbamoyl]-4-pyridyl]-1-methyl-2-oxochinolin-3-carbonsäureamid (Verbindung 83.32) ;
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-[1-cyano-2-methoxy-1-(methoxymethyl)ethyl]pyridin-2-carbonsäureamid (Verbindung 86);
4-[[2-(3-Amino-4-tert.-butylphenyl)acetyl]amino]-N-tert.-butyl-pyridin-2-carbonsäureamid (Verbindung 87);
4-[[2-(2-Amino-4-tert.-butylphenyl)acetyl]amino]-N-tert.-butylpyridin-2-carbonsäureamid (Verbindung 88);
N-tert.-Butyl-4-[[2-(4-tert.-butyl-3-hydroxyphenyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 89);
N-tert.-Butyl-4-[[2-(4-tert.-butyl-2-hydroxyphenyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 90);
N-tert.-Butyl-4-[[2-(4-tert.-butyl-2-fluor-5-hydroxyphenyl)acetyl]amino]pyridin-2-carbonsäureamid (Verbindung 91);
4-[[2-(4-Chlor-3-hydroxyphenyl)acetyl]amino]-N-(4-cyanotetrahydropyran-4-yl)pyridin-2-carbonsäureamid (Verbindung 92);
4-[[2-(4-Chlor-3-hydroxyphenyl)acetyl]amino]-N-(1-cyano-1-methylethyl)pyridin-2-carbonsäureamid (Verbindung 92.1);

4-[[2-(4-Chlor-3-hydroxyphenyl)acetyl]amino]-N-(1,1-dimethylprop-2-inyl)pyridin-2-carbonsäureamid (Verbindung 92.2);
4-[[2-(4-Chlor-3-hydroxyphenyl)acetyl]amino]-N-[(ls,2s)-2-hydroxycyclopentyl]pyridin-2-carbonsäureamid (Verbindung 92.3);
4-[[2-(4-tert.-Butyl-3-hydroxyphenyl)acetyl]amino]-N-[3-(hydroxymethyl)tetrahydrofuran-3-yl]pyridin-2-carbonsäureamid (Verbindung 93);
4-[[2-(4-tert.-Butyl-3-hydroxyphenyl)acetyl]amino]-N-[(2S)-2-hydroxycyclohexyl]pyridin-2-carbonsäureamid (Verbindung 93.1);
4-[[2-(4-tert.-Butyl-3-hydroxyphenyl)acetyl]amino]-N-[(2S)-2-hydroxycyclopentyl]pyridin-2-carbonsäureamid (Verbindung 93.2);
4-[[2-(4-tert.-Butyl-3-hydroxyphenyl)acetyl]amino]-N-(4-cyanotetrahydropyran-4-yl)pyridin-2-carbonsäureamid (Verbindung 93.3);
4-[[2-(4-tert.-Butyl-3-hydroxyphenyl)acetyl]amino]-N-(1-cyano-1-methylethyl)pyridin-2-carbonsäureamid (Verbindung 93.4);
4-[[2-(4-tert.-Butyl-3-hydroxyphenyl)acetyl]amino]-N-(1,1-dimethylprop-2-inyl)pyridin-2-carbonsäureamid (Verbindung 93.5); und
4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-(1-methyl-1-phenylethyl)pyridin-2-carbonsäureamid (Verbindung 94);
sowie Salzen und Solvaten der obengenannten Verbindungen.

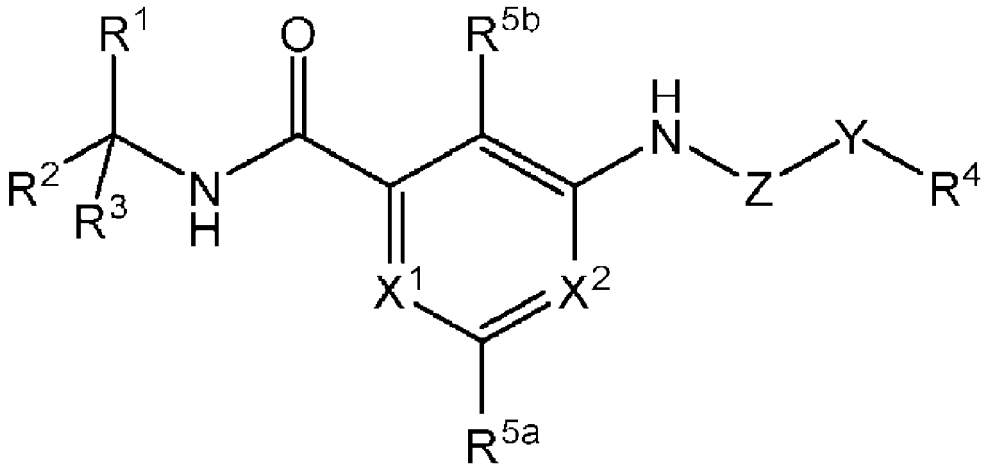
10. Verbindung nach Anspruch 1, bei der es sich um N-tert.-Butyl-4-[[2-(5-chlor-2-hydroxyphenyl)acetyl]-amino]pyridin-2-carbonsäureamid (Verbindung 3) oder ein Salz oder Solvat davon handelt.

11. Verbindung nach Anspruch 1, bei der es sich um 4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-[(3R)-3-(hydroxymethyl)tetrahydrofuran-3-yl]pyridin-2-carbonsäureamid oder 4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]-amino]-N-[(3S)-3-(hydroxymethyl)tetrahydrofuran-3-yl]-pyridin-2-carbonsäureamid (Verbindung 35a) oder ein Salz oder Solvat davon handelt.

12. Verbindung nach Anspruch 1, bei der es sich um 4-[[2-(5-Chlor-2-hydroxyphenyl)acetyl]amino]-N-(1,1-dimethylprop-2-inyl)pyridin-2-carbonsäureamid (Verbindung 36) oder ein Salz oder Solvat davon handelt.

13. Verbindung nach Anspruch 1, bei der es sich um N-(1,1-Dimethylprop-2-inyl)-4-[[2-[3-(trifluormethyl)-1H-pyrazol-4-yl] acetyl] amino]pyridin-2-carbonsäureamid (Verbindung 5.36) oder ein Salz oder Solvat davon handelt.

14. Verbindung der allgemeinen Formel (I) einschließlich aller tautomeren Formen, aller Enantiomere und Isotopenvarianten sowie Salze und Solvate davon:



(I)

wobei:

R^1 für H, CN, $C(O)OR^{12}$, C_{1-3}-Alkyl, C_{2-3}-Alkenyl oder C_{2-3}-Alkinyl steht, wobei die Alkyl-, Alkenyl- bzw. Alkinylgruppen jeweils gegebenenfalls durch einen oder mehrere Substituenten, geeigneterweise einen Substituenten, ausgewählt aus Fluor, OR^{12}, $N(R^{12})_2$, $C(O)OR^{12}$, $C(O)N(R^{12})_2$, $C(O)R^{12}$ und $N(R^{13})C(O)R^{12}$ substituiert sind;
wobei R^{12} und R^{13} jeweils unabhängig voneinander aus H, C_{1-6}-Alkyl und C_{1-6}-Fluoralkyl ausgewählt sind,
R^2 für H oder C_{1-6}-Alkyl, gegebenenfalls substituiert durch OR^{12}, steht;
R^3 für:

C_{1-10}-Alkyl, C_{2-10}-Alkenyl oder C_{2-10}-Alkinyl, jeweils gegebenenfalls substituiert durch einen oder mehrere Substituenten, geeigneterweise einen Substituenten, ausgewählt aus Fluor, CN, R^{14} OR^{14}, OR^{15}, $N(R^{15})_2$, $C(O)OR^{15}$, $C(O)N(R^{15})_2$, $N(R^{16})C(O)R^{15}$, $N(R^{15})S(O)_2R^{14}$, $N(R^{15})S(O)_2R^{16}$ und N $(R^{15})C(O)OR^{16}$; oder
ein 3- bis 7-gliedriges carbocyclisches oder heterocyclisches Ringsystem oder ein 6- bis 10-gliedriges Aryl- oder 5- bis 10-gliedriges Heteroarylringsystem, die jeweils gegebenenfalls durch einen oder mehrere Substituenten ausgewählt aus Halogen, CN, C_{1-4}-Alkyl, C_{1-4}-Halogenalkyl, OR^{17} und $N(R^{17})_2$ substituiert sind, steht;

wobei R^{14} für ein 6- bis 10-gliedriges Aryl- oder 5-bis 10-gliedriges Heteroarylringsystem oder ein 3- bis 7-gliedriges carbocyclisches oder heterocyclisches Ringsystem steht, die jeweils gegebenenfalls durch einen oder mehrere Substituenten ausgewählt aus Halogen, C_{1-4}-Alkyl, C_{1-4}-Halogenalkyl, OR^{17} und $N(R^{17})_2$ substituiert sind; wobei R^{17} jeweils unabhängig für H, C_{1-4}-Alkyl oder C_{1-4}-Halogenalkyl steht;
R^{15} und R^{16} jeweils unabhängig voneinander für H, C_{1-6}-Alkyl oder C_{1-6}-Halogenalkyl stehen; oder

R^2 und R^3 zusammen mit dem Kohlenstoffatom, an das sie gebunden sind, ein 3- bis 10-gliedriges carbocyclisches oder heterocyclisches Ringsystem bilden, gegebenenfalls substituiert durch einen oder mehrere Substituenten ausgewählt aus Halogen, CN, OR^9, $N(R^9)_2$, $C(O)OR^9$, $C(O)N(R^9)_2$, $C(O)R^9$, $N(R^9)C(O)R^9$ und gegebenenfalls durch Halogen, OR^9 oder $N(R^9)_2$ substituiertem C_{1-4}-Alkyl; oder
R^1, R^2 und R^3 zusammen mit dem Kohlenstoffatom, an das sie gebunden sind, ein verbrücktes 5- bis 10-gliedriges carbocyclisches oder heterocyclisches Ringsystem oder Phenyl bilden, jeweils gegebenenfalls substituiert durch einen oder mehrere Substituenten ausgewählt aus Halogen, CN, OR^9, $N(R^9)_2$, $C(O)OR^9$, $C(O)N(R^9)_2$, $C(O)R^9$, $N(R^9)C(O)R^9$ und gegebenenfalls durch Halogen, OR^9 oder $N(R^9)_2$ substituiertem C_{1-4}-Alkyl;
R^9 jeweils unabhängig aus H, C_{1-6}-Alkyl oder C_{1-6}-Halogenalkyl ausgewählt ist;
X^1 für N steht;
X^2 für CR^8 steht;
R^8 für H, Halogen, OH, O(C_{1-4}-Alkyl), CN oder NH_2 steht;
Y für eine Bindung oder eine geradkettige C_{1-6}-Alkylenkette steht, die gegebenenfalls durch einen oder mehrere R^{18}-Substituenten substituiert ist, wobei zwei R^{18}-Substituenten an die gleichen oder an verschiedene Kohlenstoffatome gebunden sein können;
wobei R^{18} jeweils unabhängig für C_{1-3}-Alkyl oder C_{1-3}-Halogenalkyl, in welchem ein $-CH_2-$ gegebenenfalls durch -NH- oder -O- ersetzt ist, steht und wobei zwei R^{18}-Gruppen zusammen mit dem Atom bzw. den Atomen, an das/die sie gebunden sind, ein 3- bis 6-gliedriges carbocyclisches oder heterocyclisches Ringsystem bilden können;
Z für -C(O)- oder -C(O)NH- steht;
R^4 für ein 6- bis 14-gliedriges Aryl-, 5- bis 14-gliedriges Heteroaryl- oder ein 5- bis 10-gliedriges carbocyclisches Ringsystem steht, jeweils gegebenenfalls substituiert durch einen oder mehrere Substituenten ausgewählt aus:

Halogen, CN, Nitro, R^{19}, OR^{19}, OR^6, SR^6, NR^6R^7, $C(O)R^6$, $C(O)R^{19}$, $C(O)OR^6$, $C(O)N(R^6)$ (R^7), $N(R^7)C(O)R^6$;
C_{1-6}-Alkyl oder O(C_{1-6}-Alkyl), jeweils gegebenenfalls substituiert durch einen oder mehrere Substituenten ausgewählt aus Halogen, CN, Nitro, R^{19}, OR^6, SR^6, NR^6R^7, $C(O)R^6$, $C(O)OR^6$, $C(O)N(R^6)(R^7)$ und $N(R^7)C(O)R^6$; und,
wenn R^4 keinen vollaromatischen Charakter hat, Oxo;

wobei R^{19} für ein 5- oder 6-gliedriges Aryl- oder Heteroarylringsystem oder ein 3- bis 7-gliedriges carbocyclisches oder heterocyclisches Ringsystem steht, jeweils gegebenenfalls substituiert durch einen oder mehrere Substituenten ausgewählt aus Halogen, C_{1-4}-Alkyl, C_{1-4}-Halogenalkyl,OH,

$O(C_{1-4}$-Alkyl), $O(C_{1-4}$-Halogenalkyl;
R^6 für H, C_{1-6}-Alkyl, C_{1-6}-Halogenalkyl, Benzyl, 3- bis 7-gliedriges Carbocyclyl oder 3- bis 7-gliedriges Heterocyclyl steht;
R^7 für H, C_{1-6}-Alkyl oder C_{1-6}-Halogenalkyl steht; oder
R^6 und R^7 zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen 4- bis 7-gliedrigen heterocyclischen Ring bilden können, gegebenenfalls mit einem oder mehreren weiteren Heteroatomen und gegebenenfalls substituiert durch einen oder mehrere Substituenten ausgewählt aus Oxo und Halogen; und

R^{5a} und R^{5b} jeweils unabhängig voneinander für H, C_{1-4}-Alkyl oder Halogen stehen; oder
Verbindung nach einem der Ansprüche 1 bis 13;
zur Verwendung in der Medizin, insbesondere bei der Behandlung oder Prophylaxe von durch die Modulation von TMEM16A zu beeinflussenden Krankheiten und Leiden, zum Beispiel Atemwegskrankheiten und -leiden, trockenem Mund (Xerostomie), intestinaler Hypermobilität, Cholestase und Augenleiden; und wobei die Verbindung der allgemeinen Formel (I) gegebenenfalls in Kombination mit einem zusätzlichen zur Behandlung oder Prävention von Atemwegsleiden geeigneten Wirkstoff verwendet wird.

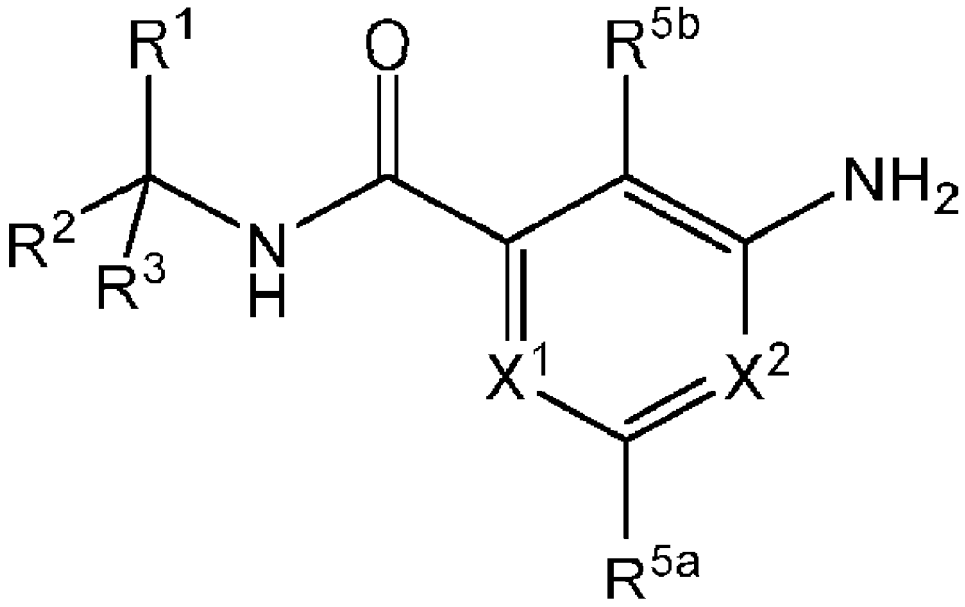
15. Verbindung zur Verwendung nach Anspruch 14, wobei die Atemwegskrankheiten und -leiden aus zystischer Fibrose, chronisch-obstruktiver Lungenkrankheit (Chronic Obstructive Pulmonary Disease, COPD), chronischer Bronchitis, Emphysem, Bronchiektase, einschließlich nicht durch zystische Fibrose verursachter Bonchiektase, Asthma und primärer ciliärer Dyskinesie ausgewählt sind; der trockene Mund (Xerostomie) die Folge von Sjögren-Syndrom, einer strahlentherapeutischen Behandlung oder xerogener Arzneimittel ist;

die intestinale Hypermobilität mit gastrischer Dyspepsie, Gastroparese, chronischer Verstopfung oder Reizdarmsyndrom assoziiert ist;
es sich bei der Augenkrankheit um Augentrockenheit handelt.

16. Verfahren zur Herstellung einer Verbindung nach einem der Ansprüche 1 bis 13, wobei das Verfahren Folgendes umfasst:

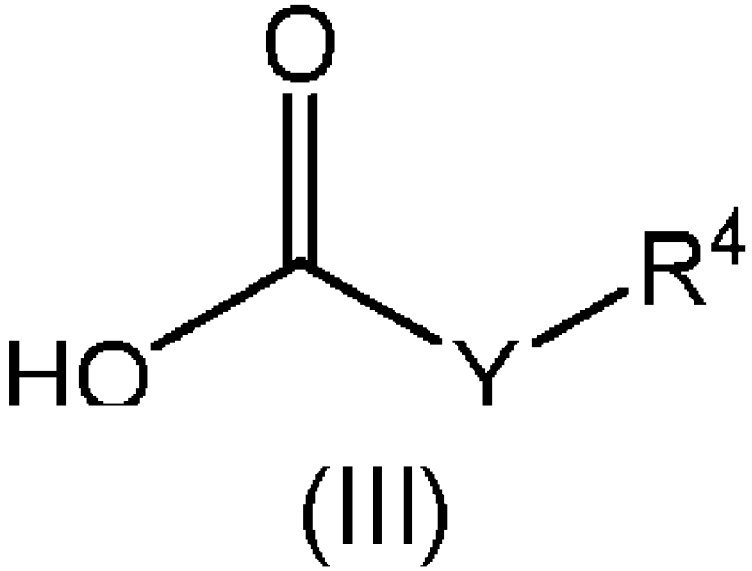
A. für eine Verbindung der allgemeinen Formel (I), in welcher Z für -C(O)- steht:

die Umsetzung einer Verbindung der allgemeinen Formel (II) :



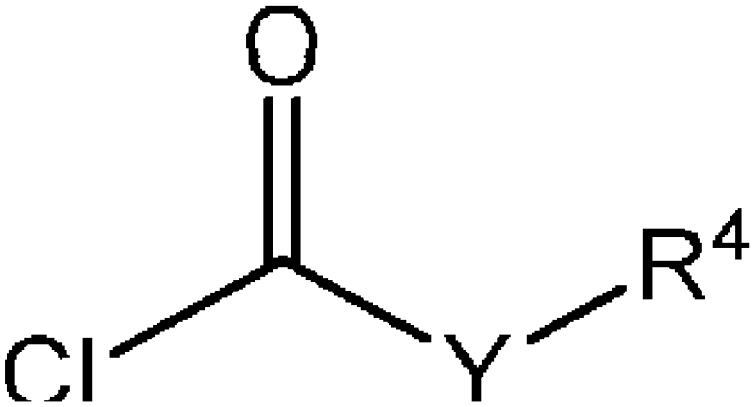
(II)

wobei R^1, R^2, R^3, R^{5a}, R^{5b}, X^1 und X^2 wie in Anspruch 1 definiert sind;
mit einer Verbindung der allgemeinen Formel (III):



(III)

wobei R^4 und Y wie in Anspruch 1 definiert sind;
in Gegenwart eines Kupplungsmittels; oder
die Umsetzung einer Verbindung der allgemeinen Formel (II) mit einem Säurechlorid der allgemeinen Formel (IV):

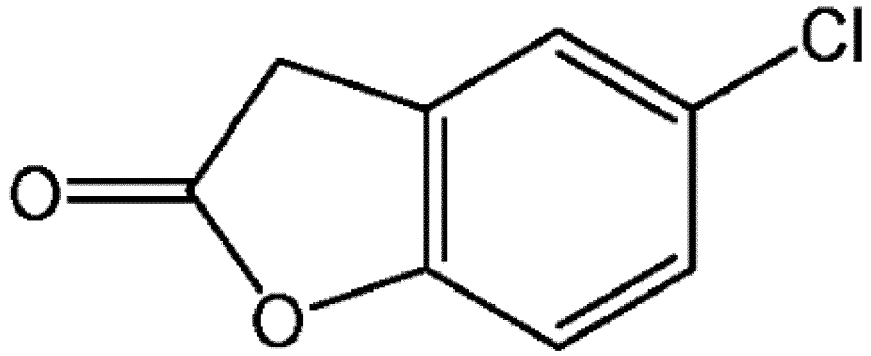


wobei R^4 und Y wie in Anspruch 1 definiert sind; oder

B. für Verbindungen der allgemeinen Formel (I), in denen Z für C(O)NH steht und Y für -C_{1-2}-Alkylen- steht: die Umsetzung einer Verbindung der allgemeinen Formel (II) mit einer Verbindung der allgemeinen Formel (XIV):

$$O=C=N-Y^1-R^4 \qquad \text{(XIV)}$$

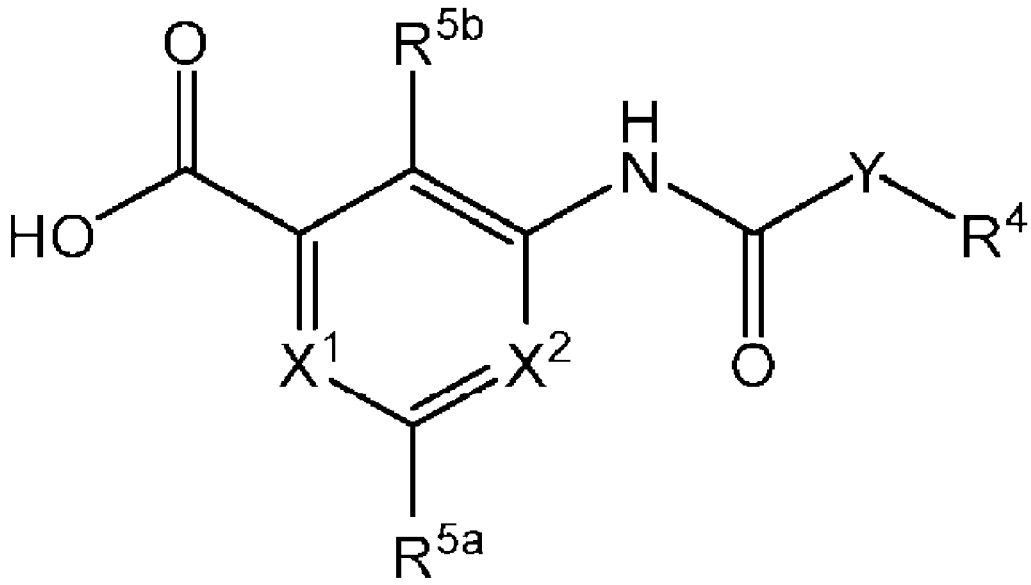
wobei R^4 wie in Anspruch 1 definiert ist und Y^1 für -CH_2- oder -CH_2CH_2- steht.
C. für Verbindungen der wie in Anspruch 8 definierten allgemeinen Formel (Id), in denen R^{11a} für Cl steht und R^{11b} für H steht:
die Umsetzung einer Verbindung der allgemeinen Formel (II) mit 5-Chlor-2(3H)-benzofuranon, das die folgende Struktur hat:



;

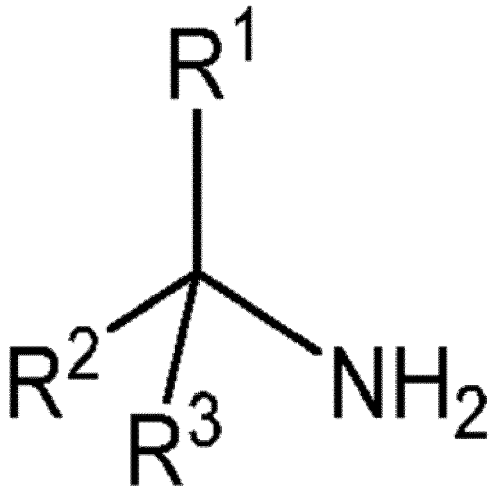
; oder

D. die Umsetzung einer Verbindung der allgemeinen Formel (X):



(X)

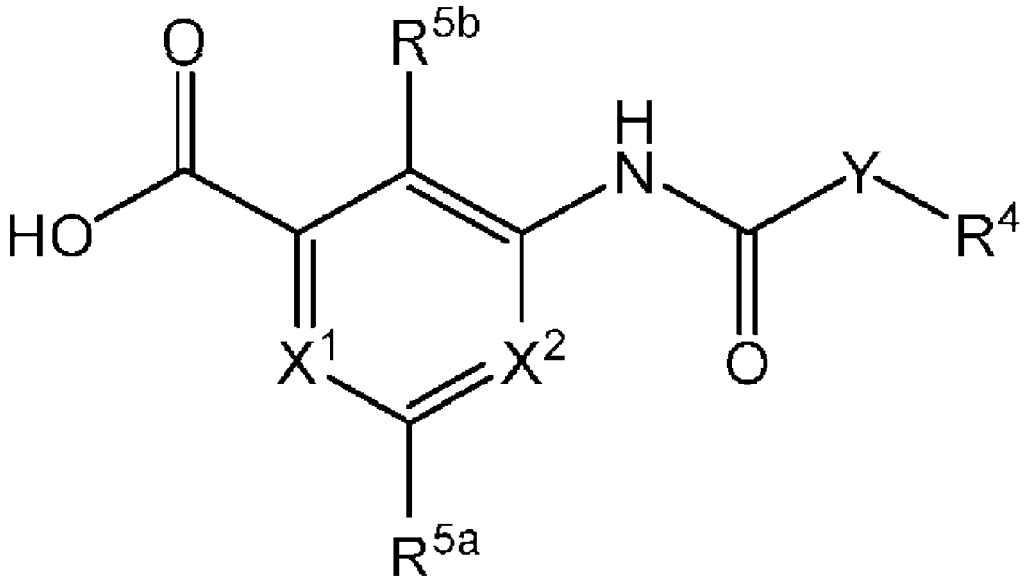
wobei X^1, X^2, Y, R^4, R^{5a} und R^{5b} wie in Anspruch 1 definiert sind; mit einer Verbindung der allgemeinen Formel (VII):



(VII)

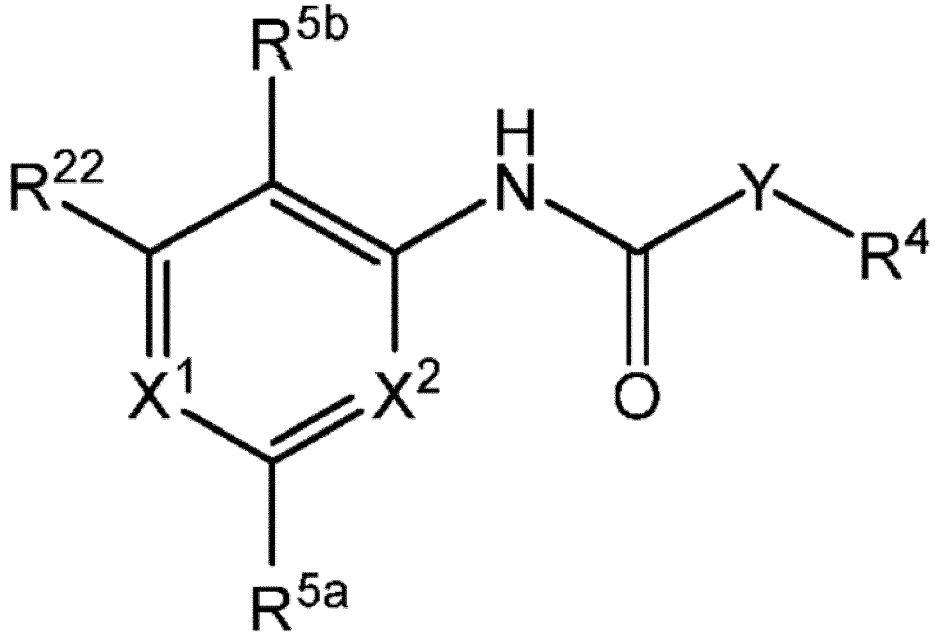
wobei R^1, R^2 und R^3 wie in Anspruch 1 definiert sind; oder

E. die Umsetzung einer Verbindung der allgemeinen Formel (X):



(X)

wobei X^1, X^2, Y, R^4, R^{5a} und R^{5b} wie in Anspruch 1 definiert sind, mit einer wie oben definierten Verbindung der allgemeinen Formel (VII); oder
F. die Umsetzung einer Verbindung der allgemeinen Formel (XV):



(XV)

wobei X^1, X^2, Y, R^4, R^{5a} und R^{5b} wie in Anspruch 1 definiert sind und R^{22} für Halogen steht;
mit einem Amin der wie oben definierten allgemeinen Formel (VII) und Kohlenstoffmonoxid in Gegenwart eines Phosphorliganden und eines Palladiumkatalysators; oder

G. die Umwandlung einer Verbindung der allgemeinen Formel (I) in eine andere Verbindung der allgemeinen Formel (I).

17. Pharmazeutische Zusammensetzung, umfassend eine Verbindung nach einem der Ansprüche 1 bis 13 zusammen mit einem pharmazeutisch unbedenklichen Exzipienten und gegebenenfalls weiterhin einschließlich eines zusätzlichen zur Behandlung oder Prävention von Atemwegsleiden geeigneten Wirkstoffs.

18. Produkt, umfassend eine Verbindung nach einem der Ansprüche 1 bis 13 und ein zusätzliches zur Behandlung oder Prävention von Atemwegsleiden geeignetes Mittel als Kombinationspräparat zur gleichzeitigen, aufeinanderfolgenden oder getrennten Anwendung bei der Behandlung einer durch die Modulation von TMEM16A zu beeinflussenden Krankheit bzw. eines solchen Leidens.

19. Verbindung zur Verwendung nach Anspruch 14 oder Anspruch 15, pharmazeutische Zusammensetzung nach Anspruch 17 oder Produkt nach Anspruch 18, wobei das zusätzliche zur Behandlung oder Prävention von Atemwegsleiden geeignete Mittel ausgewählt ist aus:

B2-Adrenorezeptoragonisten wie Metaproterenol, Isoproterenol, Isoprenalin, Albuterol, Salbutamol, Formoterol, Salmeterol, Indacaterol, Terbutalin, Orciprenalin, Bitolterolmesylat, Pirbuterol, Olodaterol, Vilanterol und Abediterol;
Antihistaminen, zum Beispiel Histamin-Hl-Rezeptorantagonisten wie Loratadin, Cetirizin, Desloratadin, Levocetirizin, Fexofenadin, Astemizol, Azelastin und Chlorpheniramin oder H_4-Rezeptorantagonisten;
Dornase alpha;
Corticosteroiden wie Prednison, Prednisolon, Flunisolid, Triamcinolonacetonid, Beclomethasondipropionat, Budesonid, Fluticasonpropionat, Mometasonfuroat und Fluticasonfuroat;
Leukotrienantagonisten wie Montelukast und Zafirlukast; Anticholinergika, insbesondere Muskarinantagonisten wie Ipratropium, Tiotropium, Glycopyrrolat, Aclidinium und Umeclidinium;
CFTR-Reparaturtherapien (z. B. CFTR potenzierenden, korrigierenden oder verstärkenden Mitteln) wie Ivacaftor, QBW251, VX659, VX445, VX561/CPT-656, VX152, VX440, GLP2737, GLP2222, GLP2451, PTI438, PTI801, PTI808, FDL-169 und FDL-176 und CFTR korrigierenden Mitteln wie Lumacaftor und Tezacaftor;

ENaC-Modulatoren, insbesondere ENaC-Inhibitoren wie:
Amilorid, VX-371, AZD5634, QBW276, SPX-101, BI443651, ETD001 und Verbindungen mit einem Kation ausgewählt aus:

2-[({3-Amino-5H-pyrrolo[2,3-b]pyrazin-2-yl}-formamido)ethyl]-6-(4-{bis[(2S,3R,4R,SR)-2,3,4,5,6-pentahydroxyhexyl]amino}piperidin-1-carbonyl)-1,3-diethyl-1H-1,3-benzodiazol-3-ium;
2-[({3-Amino-5H-pyrrolo[2,3-b]pyrazin-2-yl}-formamido)methyl]-6-{[2-(4-{bis[(2S,3R,4R,SR)-2,3,4,5,6-pentahydroxyhexyl]amino}piperidin-1-yl)ethyl]carbamoyl}-1,3-diethyl-1H-1,3-benzodiazol-3-ium;
2-[({3-Amino-5H-pyrrolo[2,3-b]pyrazin-2-yl}-formamido)methyl]-5-[4-({bis[(2S,3R,4R,5R)-2,3,4,5,6-pentahydroxyhexyl]amino}methyl)-piperidin-1-carbonyl]-1,3-diethyl-1H-1,3-benzodiazol-3-ium;
2-[({3-Amino-5H-pyrrolo[2,3-b]pyrazin-2-yl}-formamido)methyl]-6-[(3R)-3-{bis[(2S,3R,4R,5R)-2,3,4,5,6-pentahydroxyhexyl]amino}pyrrolidin-1-carbonyl]-1,3-diethyl-1H-1,3-benzodiazol-3-ium;
2-[({3-Amino-5H-pyrrolo[2,3-b]pyrazin-2-yl}-formamido)methyl]-6-[(3S)-3-{bis[(2S,3R,4R,5R)-2,3,4,5,6-pentahydroxyhexyl]amino}pyrrolidin-1-carbonyl]-1,3-diethyl-1H-1,3-benzodiazol-3-ium;
2-[({3-Amino-5H-pyrrolo[2,3-b]pyrazin-2-yl}-formamido)methyl]-1,3-diethyl-6-{ [(1r,4r)-4-{bis[(2S,3R,4R,5R)-2,3,4,5,6-pentahydroxyhexyl]amino}cyclohexyl]carbamoyl}-1H-1,3-benzodiazol-3-ium;
2-[({3-Amino-5H-pyrrolo[2,3-b]pyrazin-2-yl}-formamido)methyl]-1,3-diethyl-6-{[(1s,4s)-4-{bis[(2S,3R,4R,5R)-2,3,4,5,6-pentahydroxyhexyl]amino}cyclohexyl]carbamoyl}-1H-1,3-benzodiazol-3-ium;
und einem geeigneten Anion, zum Beispiel Halogenid, Sulfat, Nitrat, Phosphat, Formiat, Acetat, Trifluoracetat, Fumarat, Citrat, Tartrat, Oxalat, Succinat, Mandelat, Methansulfonat oder p-Toluolsulfonat;

Antibiotika;
die Luftwege hydratisierenden Mitteln (Osmolyten) wie hypertonischer Kochsalzlösung und Mannit (Bronchitol®); und
Mukolytika, z. B. N-Acetylcystein.

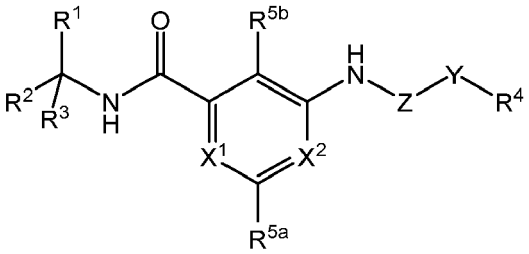
20. Verbindung nach Anspruch 2, wobei es sich bei der Verbindung um die Verbindung der Formel (Iz) handelt und wobei Y nicht für eine Bindung steht.

21. Verbindung nach Anspruch 1, wobei Y für gegebenenfalls durch einen oder mehrere R^{18}-Substituenten substituiertes geradkettiges C_{1-3}-Alkylen steht, wobei R^{18} wie oben definiert ist und wobei zwei R^{18}-Substituenten an das gleiche oder an verschiedene Kohlenstoffatome gebunden sein können.

22. Verbindung nach Anspruch 1, wobei R^4 für eine 6- bis 11-gliedrige Arylgruppe ausgewählt aus Phenyl, Naphthyl, Indanyl, 1,2,3,4-Tetrahydronaphthyl und Benzocycloheptanyl, die jeweils gegebenenfalls wie in Anspruch 1 definiert substituiert sind, steht.

Revendications

1. Composé de formule générale (I) y compris toutes les formes tautomères, tous les énantiomères et toutes les variantes isotopiques et tous les sels et les solvates correspondants :



(I)

R^1 étant H, CN, C(O)OR^{12}, C_{1-3} alkyle, C_{2-3} alcényle ou C_{2-3} alcynyle, l'un quelconque parmi lesquels groupes alkyle, alcényle ou alcynyle étant éventuellement substitué par un ou plusieurs substituants, de manière ap-

propriée un substituant, choisis parmi fluoro, OR^{12}, $N(R^{12})_2$, $C(O)OR^{12}$, $C(O)N(R^{12})_2$, $C(O)R^{12}$ et $N(R^{13})C(O)R^{12}$;
chaque R^{12} et R^{13} étant indépendamment choisi parmi H, C_{1-6} alkyle et C_{1-6} fluoroalkyle
R^2 étant H ou C_{1-6} alkyle éventuellement substitué par OR^{12} ;
R^3 étant :

C_{1-10} alkyle, C_{2-10} alcényle ou C_{2-10} alcynyle, l'un quelconque parmi lesquels étant éventuellement substitué par un ou plusieurs substituants, de manière appropriée un substituant, choisis parmi fluoro, CN, R^{14} OR^{14}, OR^{15}, $N(R^{15})_2$, $C(O)OR^{15}$, $C(O)N(R^{15})_2$, $N(R^{16})C(O)R^{15}$, $N(R^{15})S(O)_2R^{14}$, $N(R^{15})S(O)_2R^{16}$ et $N(R^{15})C(O)OR^{16}$; ou
un système cyclique carbocyclique ou hétérocyclique à 3 à 7 chaînons ou un système cyclique aryle à 6 à 10 chaînons ou hétéroaryle à 5 à 10 chaînons, l'un ou l'autre étant éventuellement substitué par un ou plusieurs substituants choisis parmi halogéno, CN, C_{1-4} alkyle, C_{1-4} halogénoalkyle, OR^{17} et $N(R^{17})_2$;
R^{14} étant un système cyclique aryle à 6 à 10 chaînons ou hétéroaryle à 5 à 10 chaînons ou un système cyclique carbocyclique ou hétérocyclique à 3 à 7 chaînons, l'un quelconque parmi lesquels étant éventuellement substitué par un ou plusieurs substituants choisis parmi halogéno, C_{1-4} alkyle, C_{1-4} halogénoalkyle, OR^{17} et $N(R^{17})_2$; chaque R^{17} étant indépendamment H, C_{1-4} alkyle ou C_{1-4} halogénoalkyle ; chaque R^{15} et R^{16} étant indépendamment H, C_{1-6} alkyle ou C_{1-6} halogénoalkyle ; ou
R^2 et R^3, conjointement avec l'atome de carbone auquel ils sont fixés, se combinant pour former un système cyclique carbocyclique ou hétérocyclique à 3 à 10 chaînons éventuellement substitué par un ou plusieurs substituants choisis parmi halogéno, CN, OR^9, $N(R^9)_2$, $C(O)OR^9$, $C(O)N(R^9)_2$, $C(O)R^9$, $N(R^9)C(O)R^9$ et C_{1-4} alkyle éventuellement substitué par halogéno, OR^9 ou $N(R^9)_2$; ou
R^1, R^2 et R^3, conjointement avec l'atome de carbone auquel ils sont fixés, se combinant pour former un système cyclique carbocyclique ou hétérocyclique à 5 à 10 chaînons ponté ou phényle, l'un quelconque parmi lesquels étant éventuellement substitué par un ou plusieurs substituants choisis parmi halogéno, CN, OR^9, $N(R^9)_2$, $C(O)OR^9$, $C(O)N(R^9)_2$, $C(O)R^9$, $N(R^9)C(O)R^9$ et C_{1-4} alkyle éventuellement substitué par halogéno, OR^9 ou $N(R^9)_2$;
chaque R^9 étant indépendamment choisi parmi H, C_{1-6} alkyle ou C_{1-6} halogénoalkyle ;
X^1 étant N ;
X^2 étant CR^8
R^8 étant H, halogéno, OH, $O(C_{1-4}$ alkyle), CN ou NH_2 ;
Y étant une liaison ou une chaîne C_{1-6} alkylène linéaire qui est éventuellement substituée par un ou plusieurs substituants R^{18}, deux substituants R^{18} pouvant être fixés au même atome de carbone ou à des atomes de carbone différents ;
chaque R^{18} étant indépendamment C_{1-3} alkyle ou C_{1-3} halogénoalkyle dans lequel un $-CH_2-$ est éventuellement remplacé par -NH- ou -O- et deux groupes R^{18} pouvant se combiner avec l'atome ou les atomes auquel/auxquels ils sont fixés pour former un système cyclique carbocyclique ou hétérocyclique à 3 à 6 chaînons ;
Z étant -C(O)- ou -C(O)NH- ;
R^4 étant un aryle à 6 à 14 chaînons, un hétéroaryle à 5 à 14 chaînons ou un système cyclique carbocyclique à 5 à 10 chaînons, l'un quelconque parmi lesquels étant éventuellement substitué par un ou plusieurs substituants choisis parmi :

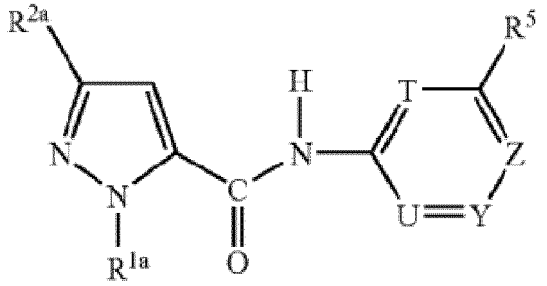
halogéno, CN, nitro, R^{19}, OR^{19}, OR^6, SR^6, NR^6R^7, $C(O)R^6$, $C(O)R^{19}$, $C(O)OR^6$, $C(O)N(R^6)(R^7)$, $N(R^7)C(O)R^6$;
C_{1-6} alkyle ou $O(C_{1-6}$ alkyle), l'un ou l'autre parmi lesquels étant éventuellement substitué par un ou plusieurs substituants choisis parmi halogéno, CN, nitro, R^{19}, OR^6, SR^6, NR^6R^7, $C(O)R^6C(O)OR^6$, $C(O)N(R^6)(R^7)$ et $N(R^7)C(O)R^6$; et
lorsque R^4 n'est pas de caractère totalement aromatique, oxo ;

R^{19} étant un système cyclique aryle ou hétéroaryle à 5 ou 6 chaînons ou un système cyclique carbocyclique ou hétérocyclique à 3 à 7 chaînons, l'un quelconque parmi lesquels étant éventuellement substitué par un ou plusieurs substituants choisis parmi halogéno, C_{1-4} alkyle, C_{1-4} halogénoalkyle, OH, $O(C_{1-4}$ alkyle), $O(C_{1-4}$ halogénoalkyle) ;
R^6 étant H, C_{1-6} alkyle, C_{1-6} halogénoalkyle, benzyle, carbocyclyle à 3 à 7 chaînons ou hétérocyclyle à 3 à 7 chaînons ;
R^7 étant H, C_{1-6} alkyle ou C_{1-6} halogénoalkyle ; ou R^6 et R^7, conjointement avec l'atome d'azote auquel ils sont fixés pouvant former un cycle hétérocyclique à 4 à 7 chaînons contenant éventuel-

lement un ou plusieurs hétéroatomes supplémentaires et éventuellement substitué par un ou plusieurs substituants choisis parmi oxo et halogéno ; et

chacun parmi R^{5a} et R^{5b} étant indépendamment H, C_{1-4} alkyle ou halogéno ;
étant entendu que :

lorsque X^2 est CH, Z est -C(0)- et Y est une liaison, R^4 n'est pas un cycle hétéroaryle à 5 à 10 chaînons lié à Y via un atome d'azote, et
les composés de formule (A) :

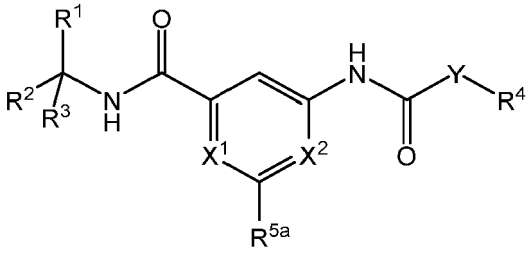


(A)

R^{1a} étant éthyle ; R^{2a} étant tert-butyle ; T, U et Y étant CH et Z étant N ; et R^5 étant C(O)NHEt, $C(O)NH(CH_2)_2CH_3$, $C(O)NH(CH_2)_2CH_2F$, $C(O)NH(CH_2)_3CH_3$, $C(O)NH(CH_2)_3CH_2F$, $C(O)NHCH_2C{=}CH$ ou $C(O)NHCH_2CH{=}CH_2$ étant exclus et toutes les formes tautomères, tous les énantiomères et toutes les variantes isotopiques et tous les sels et les solvates des composés de formule (A) n'étant pas exclus.

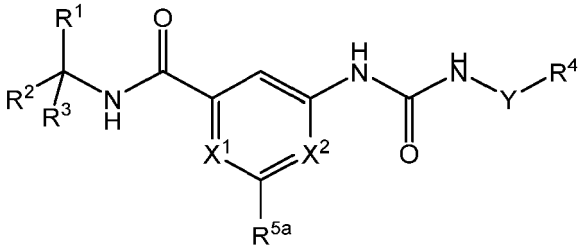
2. Composé selon la revendication 1,

Z étant -C(O)- et R^{5b} étant H, de sorte que le composé est de formule (Iz) :



(Iz)

R^1, R^2, R^3, R^4, R^{5a}, X^1, X^2 et Y étant tels que définis dans la revendication 1 ; ou
Z étant -C(0)NH-, et R^{5b} étant H de sorte que le composé est de formule générale (Iy) :



(Iy)

R^1, R^2, R^3, R^4, R^{5a}, X^1, X^2 et Y étant tels que définis dans la revendication 1.

3. Composé selon la revendication 1 ou la revendication 2, R^1 étant H, CN, éthynyle ou méthyle, l'un ou l'autre parmi lesquels étant non substitué ou étant substitué par OH.

4. Composé selon l'une quelconque des revendications 1 à 3,

R^2 étant méthyle ou éthyle ; et
R^3 étant C_{1-4} alkyle éventuellement substitué par un ou plusieurs substituants choisis parmi hydroxyle, méthoxy, éthoxy, -C(O)O-(C_{1-4} alkyle) et -N(H)C(O)O-(C_{1-4} alkyle) ; ou :

R^3 étant C_{1-10} alkyle ou C_{2-3} alcynyle, l'un ou l'autre parmi lesquels étant non substitué ou substitué par un unique substituant choisi parmi fluoro, R^{14} OR^{14}, OR^{15}, $C(O)OR^{15}$, $N(R^{16})S(O)_2R^{15}$ et $N(R^{16})C(O)OR^{15}$;
R^{14} étant choisi parmi phényle, pyridinyle et un cycle hétérocyclique à 5 ou 6 chaînons ;
R^{15} étant choisi parmi H, ou C_{1-4} alkyle ; et
R^{16} étant H ; ou
R^3 étant un système cyclique carbocyclique ou hétérocyclique à 3 à 7 chaînons, qui est non substitué ou substitué comme défini dans la revendication 1 ; ou
R^3 étant phényle ou pyridinyle, chacun desquels étant non substitué ou substitué par un ou plusieurs substituants choisis parmi OR^{17} et $N(R^{17})_2$, chaque R^{17} étant H ou méthyle.

5. Composé selon la revendication 4,

R^1 étant méthyle ou CN et R^2 et R^3 étant tous deux méthyle ; ou
R^2 et R^3 se combinant avec l'atome de carbone auquel ils sont fixés pour former un système cyclique carbocyclique ou hétérocyclique et R^1 étant H, méthyle, méthyle substitué par OH, CN, éthynyle ou $C(O)OR^{12}$, où R^{12} est comme défini dans la revendication 1.

6. Composé selon l'une quelconque des revendications 1 à 5, Y étant -CH_2-, -CH_2CH_2-, -$CH(CH_3)CH_2$-, -$CH_2CH(CH_3)$- ou -$CH_2CH_2CH_2$-, notamment -CH_2- ; et/ou

R^{5a} et R^{5b} étant tous deux H et/ou
X^2 étant CH ; et/ou :

R^4 étant un groupe aryle à 6 à 11 chaînons choisi parmi phényle, naphtyle, indanyle, 1,2,3,4-tétrahydronaphtyle et benzocycloheptanyle, l'un quelconque parmi lesquels étant éventuellement substitué comme défini dans la revendication 1 ; ou
R^4 étant un groupe hétéroaryle à 5 à 10 chaînons choisi parmi pyridinyle, quinoléinyle, quinoxalinyle, indazolyle, indolyle, benzoxazolyle, dihydrobenzofurannyle, furyle et thiényle, l'un quelconque parmi lesquels étant éventuellement substitué comme défini dans la revendication 1 ;
R^4 étant un groupe carbocyclyle choisi parmi cyclohexyle et adamantyle, l'un quelconque parmi lesquels étant éventuellement substitué comme défini dans la revendication 1 ; ou
R^4 étant phényle éventuellement substitué par un ou plusieurs substituants tels que définis dans la revendication 1 ; ou
R^4 étant un hétéroaryle à 5 à 10 chaînons choisi parmi pyridinyle, pyrrolyle, thiényle, furyle, benzoxazolyle, imidazolyle, indolyle ou indazolyle, l'un quelconque parmi lesquels étant éventuellement substitué comme défini dans la revendication 1.

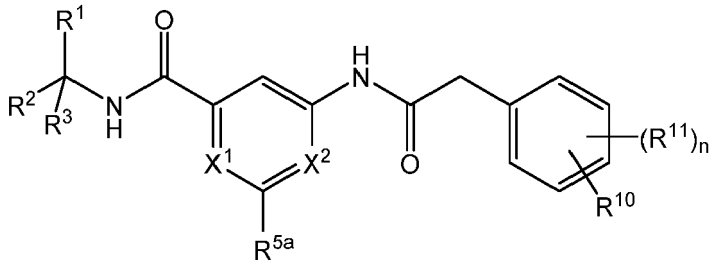
7. Composé selon la revendication 6, R^4 étant phényle qui est substitué par un groupe OH au niveau soit de la position 2, soit de la position 3 et éventuellement par un ou plusieurs substituants supplémentaires choisis parmi :

halogéno, CN, R^{19}, OR^{19};
OR^6, $C(O)OR^6$;
C_{1-4} alkyle ou O(C_{1-4} alkyle), l'un ou l'autre parmi lesquels étant éventuellement substitué par un ou plusieurs substituants choisis parmi halogéno, CN, R^{19}, OR^{19}, OR^6 et NR^6R^7 ;

R^6 étant H, C_{1-4} alkyle ou C_{1-4} halogénoalkyle ou, pour un groupement NR^6R^7, R^6 et R^7 se combinant avec l'atome d'azote auquel ils sont fixés pour former un cycle hétérocyclique à 5 ou 6 chaînons, contenant

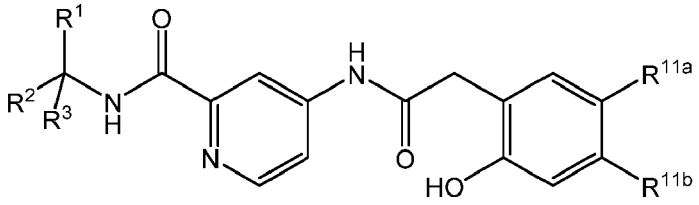
éventuellement un ou plusieurs hétéroatomes supplémentaires et éventuellement substitué par un ou plusieurs substituants halogéno ;
R^7 étant tel que défini dans la revendication 1 ; et R^{19} étant un groupe carbocyclyle à 3 à 6 chaînons ou phényle, chacun desquels étant éventuellement substitué par un ou plusieurs substituants choisis parmi halogéno, méthyle et méthoxy.

8. Composé selon l'une quelconque des revendications 1 à 7, Y étant $-CH_2-$, R^4 étant phényle et le composé étant un composé de formule générale (Ia) :

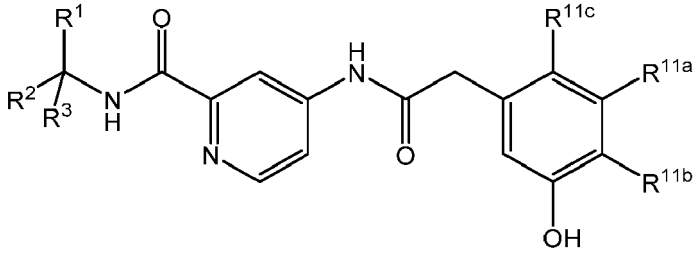


(Ia)

R^1, R^2, R^3, R^{5a}, X^1 et X^2 étant tels que définis dans la revendication 1 ;
R^{10} étant H, OH, halogéno, C_{1-6} alkyle, $-O(C_{1-6}$ alkyle) ;
chaque R^{11} étant indépendamment H, halogéno, OH, CN, C_{1-6} alkyle, C_{1-6} halogénoalkyle, $-O(C_{1-6}$ alkyle) ou $C(O)O-(C_{1-6}$ alkyle) ; et
n étant 1 ou 2 ; ou
un composé de formule générale (Id) ou (Ie) :



(Id)



(Ie)

R^1, R^2 et R^3 étant tels que définis dans la revendication 1 ;
R^{11a} étant H, halogéno, C_{1-4} alkyle, C_{1-4} halogénoalkyle ou $C(O)O(C_{1-4}$ alkyle) ;
R^{11b} étant H, halogéno, C_{1-4} alkyle ou C_{1-4} halogénoalkyle ; et
R^{11c} étant H, halogéno, CN, C_{1-4} alkyle ou C_{1-4} halogénoalkyle.

9. Composé selon la revendication 1 choisi parmi :

N-tert-Butyl-4-[[2-(2-hydroxyphényl)acétyl]amino]pyridine-2-carboxamide (Composé 1) ;
N-(1-Adamantyl)-4-[[2-(5-chloro-2-hydroxy-phényl)acétyl]amino]pyridine-2-carboxamide (Composé 1.3) ;

4-[[2-(5-Chloro-2-hydroxy-phényl)acétyl]amino]-N-(3-méthoxy-1,1-diméthyl-propyl)pyridine-2-carboxamide (Composé 1.4) ;
4-[[2-(5-Chloro-2-hydroxy-phényl)acétyl]amino]-N-(1-méthylcyclobutyl)pyridine-2-carboxamide (Composé 1.6) ;
4-[[2-(5-Chloro-2-hydroxy-phényl)acétyl]amino]-N-(1-méthylcyclohexyl)pyridine-2-carboxamide (Composé 1.7) ;
N-[3-[[4-[[2-(5-chloro-2-hydroxy-phényl)acétyl]amino]pyridine-2-carbonyl]amino]-3-méthyl-butyl]carbamate de tert-butyle (Composé 1.8) ;
4-[[2-(5-Chloro-2-hydroxy-phényl)acétyl]amino]-N-cyclohexyl-pyridine-2-carboxamide (Composé 1.10) ;
N-tert-Butyl-4-[[2-(5-chloro-2-hydroxy-phényl)acétyl]amino]pyridine-2-carboxamide (Composé 3) ;
N-(1,1-Diméthylpropyl)-4-[[2-(4-fluoro-2-hydroxy-phényl)acétyl]amino]pyridine-2-carboxamide (Composé 3.1a) ;
N-tert-Butyl-4-[[2-(4-fluoro-2-hydroxy-phényl)acétyl]amino]pyridine-2-carboxamide (Composé 3.2a) ;
N-tert-Butyl-4-[[2-(2-chloro-6-hydroxy-phényl)acétyl]amino]pyridine-2-carboxamide (Composé 3.3a) ;
4-[[2-(4-Bromo-5-chloro-2-hydroxy-phényl)acétyl]amino]-N-tert-butyl-pyridine-2-carboxamide (Composé 3.4a) ;
4-[[2-(5-tert-Butyl-2-hydroxy-phényl)acétyl]amino]-N-(1-cyanocyclobutyl)pyridine-2-carboxamide (Composé 3.5a) ;
4-[[2-(5-tert-Butyl-2-hydroxy-phényl)acétyl]amino]-N-(1-méthylcyclobutyl)pyridine-2-carboxamide (Composé 3.6a) ;
N-tert-butyl-4-[2-(2,5-dibromo-3-fluoro-6-hydroxyphényl)acétamido]pyridine-2-carboxamide (Composé 3.7a) ;
N-tert-Butyl-4-[[2-[2-hydroxy-5-(trifluorométhyl)phényl]acétyl]amino]pyridine-2-carboxamide (Composé 3.5b) ;
N-tert-Butyl-4-[[2-(4-chloro-2-hydroxy-phényl)acétyl]amino]pyridine-2-carboxamide (Composé 3.6b) ;
N-tert-Butyl-4-[[2-[2-hydroxy-4-(trifluorométhyl)phényl]acétyl]amino]pyridine-2-carboxamide (Composé 3.7b) ;
N-tert-Butyl-4-[[2-(2-hydroxy-5-méthoxy-phényl)acétyl]amino]pyridine-2-carboxamide (Composé 3.8b) ;
N-tert-Butyl-4-[(6-hydroxyindane-1-carbonyl)amino]pyridine-2-carboxamide (Composé 3.9b) ;
N-tert-Butyl-4-[(7-hydroxyindane-1-carbonyl)amino]pyridine-2-carboxamide (Composé 3.10b) ;
N-tert-Butyl-4-[[2-(2,5-dibromo-3-chloro-6-hydroxy-phényl)acétyl]amino]pyridine-2-carboxamide (Composé 3.11b);
N-tert-Butyl-4-[[2-(3-hydroxyphényle)acétyl]amino]pyridine-2-carboxamide (Composé 3.12b) ;
N-tert-Butyl-4-[[2-(2-fluoro-5-hydroxy-phényle)acétyl]amino]pyridine-2-carboxamide (Composé 3.13b) ;
N-tert-Butyl-4-[[2-(4-chloro-3-hydroxy-phényl)acétyl]amino]pyridine-2-carboxamide (Composé 3.14b) ;
N-tert-Butyl-4-[[2-(2-chloro-3-hydroxy-phényl)acétyl]amino]pyridine-2-carboxamide (Composé 3.15b) ;
N-tert-Butyl-4-[[2-(2-chloro-5-hydroxy-phényle)acétyl]amino]pyridine-2-carboxamide (Composé 3.16b) ;
N-tert-Butyl-4-[[2-(3-chloro-5-hydroxy-phényl)acétyl]amino]pyridine-2-carboxamide (Composé 3.17b) ;
N-tert-Butyl-4-[[2-(2-thiényl)acétyl]amino]pyridine-2-carboxamide (Composé 5) ;
4-[[2-(2-Adamantyl)acétyl]amino]-N-tert-butyl-pyridine-2-carboxamide (Composé 5.1) ;
N-tert-Butyl-4-[[2-(4-fluoro-2-méthoxy-phényl)acétyl]amino]pyridine-2-carboxamide (Composé 5.2) ;
N-tert-Butyl-4-[[2-(5-chloro-2-fluoro-phényl)acétyl]amino]pyridine-2-carboxamide (Composé 5.3) ;
N-tert-Butyl-4-[[2-(2-furyl)acétyl]amino]pyridine-2-carboxamide (Composé 5.4) ;
N-tert-Butyl-4-[[2-(3-chlorophényle)acétyl]amino]pyridine-2-carboxamide (Composé 5.5) ;
N-tert-Butyl-4-[[2-(1H-indol-3-yl)acétyl]amino]pyridine-2-carboxamide (Composé 5.6) ;
N-tert-Butyl-4-[[2-(o-tolyl)acétyl]amino]pyridine-2-carboxamide (Composé 5.7) ;
N-tert-Butyl-4-[[2-(3,4-dichlorophényle)acétyl]amino]pyridine-2-carboxamide (Composé 5.8) ;
N-tert-Butyl-4-[[2-(3-fluorophényl)acétyl]amino]pyridine-2-carboxamide (Composé 5.9) ;
N-tert-Butyl-4-[[2-(5-chloro-2-méthoxy-phényl)acétyl]amino]pyridine-2-carboxamide (Composé 5.10) ;
N-tert-Butyl-4-[[2-(p-tolyl)acétyl]amino]pyridine-2-carboxamide (Composé 5.11) ;
N-tert-Butyl-4-[[2-(2-fluorophényle)acétyl]amino]pyridine-2-carboxamide (Composé 5.12) ;
N-tert-Butyl-4-[[2-(4-fluorophényle)acétyl]amino]pyridine-2-carboxamide (Composé 5.13) ;
N-tert-Butyl-4-[[2-(m-tolyl)acétyl]amino]pyridine-2-carboxamide (Composé 5.14) ;
4-[[2-(1,3-Benzoxazol-6-yl)acétyl]amino]-N-tert-butyl-pyridine-2-carboxamide (Composé 5.15) ;
N-tert-Butyl-4-[[2-(2-chloro-3-pyridinyle)acétyl]amino]pyridine-2-carboxamide (Composé 5.16) ;
N-tert-Butyl-4-[[2-(2,6-dichlorophényle)acétyl]amino]pyridine-2-carboxamide (Composé 5.17) ;
N-tert-Butyl-4-[[2-(4-chloro-3-fluoro-phényl)acétyl]amino]pyridine-2-carboxamide (Composé 5.18) ;
N-tert-Butyl-4-[[2-(3,5-dichlorophényl)acétyl]amino]pyridine-2-carboxamide (Composé 5.19) ;
N-tert-Butyl-4-[[2-(2-chlorophényle)acétyl]amino]pyridine-2-carboxamide (Composé 5.20) ;
N-tert-Butyl-4-[[2-(3-chloro-4-hydroxy-phényl)acétyl]amino]pyridine-2-carboxamide (Composé 5.21) ;
N-tert-Butyl-4-(indane-1-carbonyle amino)pyridine-2-carboxamide (Composé 5.22) ;

N-tert-Butyl-4-[(2-quinoxalin-6-ylacétyle) amino]pyridine-2-carboxamide (Composé 5.23) ;
N-tert-Butyl-4-[[2-(2-naphtyle)acétyl]amino]pyridine-2-carboxamide (Composé 5.24) ;
N-tert-Butyl-4-(2,3-dihydrobenzofuran-3-carbonylamino)pyridine-2-carboxamide (Composé 5.25) ;
N-tert-Butyl-4-(6,7,8,9-tétrahydro-5H-benzo[7]annulène-5-carbonylamino) pyridine-2-carboxamide (Composé 5.26) ;
N-tert-Butyl-4-(tétralin-1-carbonylamino) pyridine-2-carboxamide (Composé 5.27) ;
N-tert-Butyl-4-[[2-(6-quinolyl)acétyl]amino]pyridine-2-carboxamide (Composé 5.29) ;
N-tert-butyl-4-[[1-(3-chlorophényle)cyclopropanecarbonyl]amino]pyridine-2-carboxamide (Composé 5.31) ;
N-tert-Butyl-4-[[2-(2,3-dihydro-1,4-benzodioxin-6-yl)acétyl]amino]pyridine-2-carboxamide (Composé 5.32) ;
N-(1,1-Diméthylprop-2-ynyl)-4-[(2-isochroman-1-ylacétyl)amino]pyridine-2-carboxamide (Composé 5.33) ;
4-[[2-(4,4-Difluorocyclohexyl)acétyl]amino]-N-(1,1-diméthylprop-2-ynyl)pyridine-2-carboxamide (Composé 5.34) ;
N-(1,1-Diméthylprop-2-ynyl)-4-[[2-[4-(trifluorométhyl)phényl]acétyl]amino]pyridine-2-carboxamide (Composé 5.35) ;
N-(1,1-Diméthylprop-2-ynyl)-4-[[2-[3-(trifluorométhyl)-1H-pyrazol-4-yl]acétyl]amino]pyridine-2-carboxamide (Composé 5.36) ;
N-(1,1-Diméthylprop-2-ynyl)-4-[[2-[3-(trifluorométhyl)phényl]acétyl]amino]pyridine-2-carboxamide (Composé 5.37) ;
N-(1,1-Diméthylprop-2-ynyl)-4-[[2-[2-(trifluorométhyl)phényl]acétyl]amino]pyridine-2-carboxamide (Composé 5.38) ;
4-[[2-(2,3-Dihydro-1,4-benzoxazin-4-yl)acétyl]amino]-N-(1,1-diméthylprop-2-ynyl)pyridine-2-carboxamide (Composé 5.39) ;
N-tert-Butyl-4-[[2-(5-cyano-2-hydroxy-phényl)acétyl]amino]pyridine-2-carboxamide (Composé 6) ;
4-[[2-(5-Chloro-2-hydroxy-phényl)acétyl]amino]-N-(1,1-diméthylbutyl)pyridine-2-carboxamide (Composé 7.2) ;
4-[[2-(5-Chloro-2-hydroxy-phényl)acétyl]amino]-N-(1,1,2-triméthylpropyl)pyridine-2-carboxamide (Composé 7.6) ;
4-[[2-(5-Chloro-2-hydroxy-phényl)acétyl]amino]-N-isopropyl-pyridine-2-carboxamide (Composé 7.7) ;
4-[[2-(5-Chloro-2-hydroxy-phényl)acétyl]amino]-N-(4-méthyltétrahydropyran-4-yl)pyridine-2-carboxamide (Composé 7.9) ;
4-[[2-(5-Chloro-2-hydroxy-phényl)acétyl]amino]-N-tétrahydropyran-4-yl-pyridine-2-carboxamide (Composé 7.11) ;
4-[2-(5-Chloro-2-hydroxyphényl)acétamido]-N-[(1s,4s)-4-hydroxycyclohexyl]pyridine-2-carboxamide (Composé 7.12) ;
4-[[2-(5-Chloro-2-hydroxy-phényl)acétyl]amino]-N-sec-butyl-pyridine-2-carboxamide (Composé 7.13) ;
4-[[2-(5-Chloro-2-hydroxy-phényl)acétyl]amino]-N-(2-hydroxy-1,1,2-triméthyl-propyl)pyridine-2-carboxamide (Composé 7.14) ;
N-(3-Bicyclo[1.1.1]pentanyl)-4-[[2-(5-chloro-2-hydroxy-phényl)acétyl]amino]pyridine-2-carboxamide (Composé 7.15) ;
4-[[2-(5-Chloro-2-hydroxy-phényl)acétyl]amino]-N-(1-cyanocyclobutyl)pyridine-2-carboxamide (Composé 7.16) ;
3-[[4-[[2-(5-chloro-2-hydroxy-phényl)acétyl]amino]pyridine-2-carbonyl]amino]pipéridine-1-carboxylate de tert-butyle (Composé 8.1) ;
(1r,5s,6s)-6-{4-[2-(5-chloro-2-hydroxyphényl)acétamido]pyridine-2-amido}-3-azabicyclo[3.1.0]hexane-3-carboxylate de tert-butyle (Composé 8.3) ;
4-[[2-(5-Chloro-2-hydroxy-phényl)acétyl]amino]-N-(1,1-diméthylpropyl)pyridine-2-carboxamide (Composé 9.2) ;
N-tert-Butyl-4-[[2-(5-tert-butyl-2-hydroxy-phényl)acétyl]amino]pyridine-2-carboxamide (Composé 10) ;
3-[2-[[2-(tert-butylcarbamoyl)-4-pyridinyl]amino]-2-oxo-éthyl]-4-hydroxy-benzoate de méthyle (Composé 13) ;
N-tert-Butyl-4-[[2-(2-hydroxy-5-méthyl-phényl)acétyl]amino]pyridine-2-carboxamide (Composé 15) ;
N-tert-Butyl-4-[[2-(3-hydroxy-2-pyridinyl)acétyl]amino]pyridine-2-carboxamide (Composé 19) ;
N-tert-Butyl-4-[[2-(5-fluoro-2-hydroxy-phényl)acétyl]amino]pyridine-2-carboxamide (Composé 20) ;
N-tert-Butyl-4-[[(1R) ou (1S)-indane-1-carbonyl]amino]pyridine-2-carboxamide (Composé 21a) ;
N-tert-Butyl-4-[[(1R) ou (1S)-indane-1-carbonyl]amino]pyridine-2-carboxamide (Composé 21b) ;
N-tert-Butyl-4-[(2-phénylacétyl)amino]pyridine-2-carboxamide (Composé 22) ;
4-(3,3-Diméthylbutanoylamino)-N-(1,1-diméthylprop-2-ynyl)pyridine-2-carboxamide (Composé 22.1) ;
4-[(2-Cyclopentylacétyl)amino]-N-(1,1-diméthylprop-2-ynyl)pyridine-2-carboxamide (Composé 22.2) ;
4-[[2-(3-Chloro-4-pyridinyl)acétyl]amino]-N-(1,1-diméthylprop-2-ynyl)pyridine-2-carboxamide (Composé 22.3) ;

4-[[2-(4-Chlorophényl)acétyl]amino]-N-(1-cyanocyclopropyl)pyridine-2-carboxamide (Composé 23) ;
4-[[2-(3-Chlorophényl)acétyl]amino]-N-(1-cyanocyclopropyl)pyridine-2-carboxamide (Composé 23.1) ;
4-[[2-(2-Chloro-5-fluoro-phényle)acétyl]amino]-N-(1-cyanocyclopropyl)pyridine-2-carboxamide (Composé 23.2) ;
N-tert-Butyl-4-(indane-2-carbonyle amino)pyridine-2-carboxamide (Composé 23.3) ;
N-tert-Butyl-4-[[2-[2-(difluorométhoxy)phényl]acétyl]amino]pyridine-2-carboxamide (Composé 23.4) ;
N-tert-Butyl-4-[[2-[2-(difluorométhyle)phényl]acétyl]amino]pyridine-2-carboxamide (Composé 23.5) ;
N-tert-Butyl-4-[[2-(3,4-difluorophényle)acétyl]amino]pyridine-2-carboxamide (Composé 23.6) ;
N-tert-Butyl-4-[[2-(3,5-difluorophényle)acétyl]amino]pyridine-2-carboxamide (Composé 23.7) ;
N-tert-Butyl-4-[[2-(2,3-difluorophényle)acétyl]amino]pyridine-2-carboxamide (Composé 23.8) ;
4-[[2-(2-Chlorophényl)acétyl]amino]-N-tétrahydropyran-4-yl-pyridine-2-carboxamide (Composé 23.9) ;
N-(1-Cyanocyclobutyl)-4-[[2-(6-quinolyle)acétyl]amino]pyridine-2-carboxamide (Composé 23.11) ;
N-tert-Butyl-4-[[2-[2-(trifluorométhyle)phényl]acétyl]amino]pyridine-2-carboxamide (Composé 23.12) ;
4-[[2-(2-Bromophényl)acétyl]amino]-N-tert-butyl-pyridine-2-carboxamide (Composé 23.13) ;
N-tert-Butyl-4-[[2-(2-cyanophényle)acétyl]amino]pyridine-2-carboxamide (Composé 23.14) ;
4-[[2-(2-Chlorophényl)acétyl]amino]-N-(4-cyanotétrahydropyran-4-yl)pyridine-2-carboxamide (Composé 23.15) ;
N-(4-Cyanotétrahydropyran-4-yl)-4-[[2-(6-quinolyl)acétyl]amino]pyridine-2-carboxamide (Composé 23.16) ;
4-[[2-(2-Chloro-5-méthoxy-phényl)acétyl]amino]-N-(1-cyanocyclopropyl)pyridine-2-carboxamide (Composé 24) ;
N-(3-Bicyclo[1.1.1]pentanyl)-4-[[2-(5-tert-butyl-2-hydroxy-phényl)acétyl]amino]pyridine-2-carboxamide (Composé 25) ;
-[[2-(5-tert-Butyl-2-hydroxy-phényl)acétyl]amino]-N-(4-cyanotétrahydropyran-4-yl)pyridine-2-carboxamide (Composé 25.1) ;
N-tert-Butyl-4-[[2-(2-hydroxy-5-phényl-phényl)acétyl]amino]pyridine-2-carboxamide (Composé 26) ;
N-tert-Butyl-4-[[2-[5-chloro-2-hydroxy-4-(pyrrolidin-1-ylméthyl)phényl]acétyl]amino]pyridine-2-carboxamide (Composé 27) ;
N-tert-Butyl-4-[[2-[4-[(tert-butylamino)méthyl]-5-chloro-2-hydroxy-phényl]acétyl]amino]pyridine-2-carboxamide (Composé 27.1) ;
N-tert-Butyl-4-[[2-[5-chloro-2-hydroxy-4-(morpholinométhyl)phényl]acétyl]amino]pyridine-2-carboxamide (Composé 27.2) ;
N-tert-Butyl-4-[[2-[5-chloro-4-[(3,3-difluoropyrrolidin-1-yl)méthyl]-2-hydroxy-phényl]acétyl]amino]pyridine-2-carboxamide (Composé 27.3) ;
N-tert-butyl-4-[[2-(5-chloro-2-hydroxy-phényl)acétyl]amino]-5-fluoro-pyridine-2-carboxamide (Composé 28) ;
N-tert-Butyl-4-[[2-(5-chloro-2-hydroxy-phényl)acétyl]amino]-3-fluoro-pyridine-2-carboxamide (Composé 28.1) ;
4-[[2-(2-Chlorophényl)acétyl]amino]-N-(1-cyanocyclobutyl)pyridine-2-carboxamide (Composé 30) ;
4-[[2-(2-Chlorophényl)acétyl]amino]-N-(1,1-diméthylprop-2-ynyl)pyridine-2-carboxamide (Composé 30.1) ;
4-[[2-(2-Chlorophényl)acétyl]amino]-N-(4-fluoro-1-bicyclo[2.1.1]hexanyl)pyridine-2-carboxamide (Composé 30.2) ;
4-[[2-(2-Chlorophényl)acétyl]amino]-N-(1-cyclopropyl-1-méthyl-éthyl)pyridine-2-carboxamide (Composé 30.3) ;
4-[[2-(2-Chlorophényl)acétyl]amino]-N-(1-cyano-1-méthyl-éthyl)pyridine-2-carboxamide (Composé 30.3a) ;
4-[[2-(2-Chlorophényl)acétyl]amino]-N-(1-méthyl-3-bicyclo[1.1.1]pentanyl)pyridine-2-carboxamide (Composé 30.4) ;
4-[[2-(2-Chlorophényl)acétyl]amino]-N-(1-cyano-3-bicyclo[1.1.1]pentanyle) pyridine-2-carboxamide (Composé 30.5) ;
4-[[2-(2-Chlorophényl)acétyl]amino]-N-(2,2-difluorocyclopropyl)pyridine-2-carboxamide (Composé 30.6) ;
4-[[2-(2-Chlorophényl)acétyl]amino]-N-(1-cyanocyclopropyl)pyridine-2-carboxamide (Composé 30.7) ;
4-[[2-(2-Chlorophényl)acétyl]amino]-N-(1-méthylcyclopropyl)pyridine-2-carboxamide (Composé 30.8) ;
4-[[2-(2-Chlorophényl)acétyl]amino]-N-(3-fluoro-1-bicyclo[1.1.1]pentanyl)pyridine-2-carboxamide (Composé 30.9) ;
4-[[2-(2-Chlorophényl)acétyl]amino]-N-(2-fluoro-1,1-diméthyl-éthyl)pyridine-2-carboxamide (Composé 30.10) ;
4-[[2-(2-Chlorophényl)acétyl]amino]-N-(4-éthynyltétrahydropyran-4-yl)pyridine-2-carboxamide (Composé 30.11) ;
4-[[2-(2-Chlorophényl)acétyl]amino]-N-(1-cyanocyclopentyl)pyridine-2-carboxamide (Composé 30.12) ;
4-[[2-(2-Chlorophényl)acétyl]amino]-N-(2,2-difluoro-1,1-diméthyl-éthyl)pyridine-2-carboxamide (Composé 30.13) ;
4-[[2-(5-Chloro-2-hydroxy-phényl)acétyl]amino]-N-(4-cyanotétrahydropyran-4-yl)pyridine-2-carboxamide

(Composé 31) ;
4-[[2-(5-Chloro-2-hydroxy-phényl)acétyl]amino]-N-(1-éthynylcyclopentyl)pyridine-2-carboxamide (Composé 31.2) ;
4-[2-(5-Chloro-2-hydroxyphényl)acétamido]-N-[(ls,2s)-2-hydroxycyclohexyl]pyridine-2-carboxamide (Composé 31.3) ;
4-[[2-(5-Chloro-2-hydroxy-phényl)acétyl]amino]-N-[(1S,2S)-2-hydroxycyclohexyl]pyridine-2-carboxamide ou 4-[[2-(5-Chloro-2-hydroxy-phényl)acétyl]amino]-N-[(1R,2R)-2-hydroxycyclohexyl]pyridine-2-carboxamide (Composé 31.3a) ;
4-[[2-(5-Chloro-2-hydroxy-phényl)acétyl]amino]-N-(4-éthynyltétrahydropyran-4-yl)pyridine-2-carboxamide (Composé 31.4) ;
N-[(6-Amino-2-pyridinyl)méthyl]-4-[[2-(5-chloro-2-hydroxy-phényl)acétyl]amino]pyridine-2-carboxamide (Composé 32) ;
acide 12-[[4-[[2-(5-Chloro-2-hydroxy-phényl)acétyl]amino]pyridine-2-carbonyl]amino] dodécanoïque (Composé 32.1) ;
4-[[2-(5-Chloro-2-hydroxy-phényle)acétyl]amino]-N-(3-pyridinylméthyl)pyridine-2-carboxamide (Composé 32.2) ;
4-[[2-(5-Chloro-2-hydroxy-phényl)acétyl]amino]-N-(2-pyridinylméthyl)pyridine-2-carboxamide (Composé 32.3) ;
4-[[2-(5-Chloro-2-hydroxy-phényle)acétyl]amino]-N-(4-pyridinylméthyl)pyridine-2-carboxamide (Composé 32.4) ;
4-[[2-(5-Chloro-2-hydroxy-phényle)acétyl]amino]-N-[(2-hydroxyphényle) méthyl]pyridine-2-carboxamide (Composé 32.5) ;
4-[[2-(5-Chloro-2-hydroxy-phényl)acétyl]amino]-N-(1,1-diméthyl-2-morpholino-éthyl)pyridine-2-carboxamide (Composé 32.6) ;
4-[[2-(5-Chloro-2-hydroxy-phényle)acétyl]amino]-N-(2-hydroxy-1,1-diméthyl-éthyl)pyridine-2-carboxamide (Composé 32.7) ;
4-[[2-(5-Chloro-2-hydroxy-phényle)acétyl]amino]-N-(3,3-difluoro-4-pipéridyl)pyridine-2-carboxamide (Composé 32.8) ;
4-[[2-(5-Chloro-2-hydroxy-phényle)acétyl]amino]-N-(1H-imidazol-2-yl)pyridine-2-carboxamide (Composé 32.9) ;
4-[[2-(5-Chloro-2-hydroxy-phényl)acétyl]amino]-N-[(1R,2R)-2-hydroxycyclopentyl]pyridine-2-carboxamide (Composé 33) ;
4-[[2-(5-Chloro-2-hydroxy-phényl)acétyl]amino]-N-(1-cyano-1-méthyl-éthyl)pyridine-2-carboxamide (Composé 34) ;
4-[[2-(5-Chloro-2-hydroxy-phényl)acétyl]amino]-N-[3-(hydroxyméthyle) tétrahydrofuran-3-yl]pyridine-2-carboxamide (Composé 35) ;
4-[[2-(5-Chloro-2-hydroxy-phényl)acétyl]amino]-N-[(3R)-3-(hydroxyméthyl)tétrahydro furan-3-yl]pyridine-2-carboxamide ou 4-[[2-(5-chloro-2-hydroxy-phényl)acétyl]amino]-N-[(3S)-3-(hydroxyméthyl)tétrahydrofuran-3-yl]pyridine-2-carboxamide (Composé 35a) ;
4-[[2-(5-Chloro-2-hydroxy-phényl)acétyl]amino]-N-[(3R)-3-(hydroxyméthyl)tétrahydro furan-3-yl]pyridine-2-carboxamide ou 4-[[2-(5-chloro-2-hydroxy-phényl)acétyl]amino]-N-[(3S)-3-(hydroxyméthyl)tétrahydrofuran-3-yl]pyridine-2-carboxamide (Composé 35b) ;
4-[[2-(5-Chloro-2-hydroxy-phényl)acétyl]amino]-N-(4-hydroxy-4-méthyl-cyclohexyle) pyridine-2-carboxamide en tant que mélange 6 : 4 de stéréoisomères (Composé 35.1) ;
4-[[2-(5-Chloro-2-hydroxy-phényle)acétyl]amino]-N-[(1s,2r)-2-(hydroxyméthyl)cyclohexyl]pyridine-2-carboxamide (Composé 35.2) ;
4-[[2-(5-Chloro-2-hydroxy-phényl)acétyl]amino]-N-[(1s,3r)-3-hydroxycyclopentyl]pyridine-2-carboxamide (Composé 35.3) ;
4-[[2-(5-Chloro-2-hydroxy-phényl)acétyl]amino]-N-[2-hydroxy-1-(hydroxy méthyl)-1-méthyl-éthyl]pyridine-2-carboxamide (Composé 35.4) ;
4-[[2-(5-Chloro-2-hydroxy-phényl)acétyl]amino]-N-(3-hydroxycyclohexyl)pyridine-2-carboxamide en tant que mélange de stéréoisomères (Composé 35.6) ;
4-[[2-(5-Chloro-2-hydroxy-phényl)acétyl]amino]-N-(3-phénoxypropyl)pyridine-2-carboxamide (Composé 35.7) ;
4-[[2-(5-Chloro-2-hydroxy-phényl)acétyl]amino]-N-(1-méthylcyclopropyl)pyridine-2-carboxamide (Composé 35.8) ;
4-[[2-(5-Chloro-2-hydroxy-phényl)acétyl]amino]-N-[1-méthyl-1-(2-pyridinyle) éthyl]pyridine-2-carboxamide (Composé 35.9) ;

4-[[2-(5-Chloro-2-hydroxy-phényl)acétyl]amino]-N-(3-phénylpropyl)pyridine-2-carboxamide (Composé 35.10) ;
4-[[2-(5-Chloro-2-hydroxy-phényl)acétyl]amino]-N-[2-hydroxy-1-(2-pyridinyl)éthyl]pyridine-2-carboxamide (Composé 35.11) ;
4-[[2-(5-Chloro-2-hydroxy-phényle)acétyl]amino]-N-[(5-méthoxy-2-pyridinyl)méthyl]pyridine-2-carboxamide (Composé 35.12) ;
3-[[4-[[2-(5-chloro-2-hydroxy-phényle)acétyl]amino]pyridine-2-carbonyl]amino]-3-méthyl-butanoate d'éthyle (Composé 35.13) ;
4-[[2-(5-Chloro-2-hydroxy-phényle)acétyl]amino]-N-(3-hydroxy-1,1-diméthyl-propyl)pyridine-2-carboxamide (Composé 35.14) ;
N-Benzyl-4-[[2-(5-chloro-2-hydroxy-phényle)acétyl]amino]pyridine-2-carboxamide (Composé 35.15) ;
4-[[2-(5-Chloro-2-hydroxy-phényle)acétyl]amino]-N-phényl-pyridine-2-carboxamide (Composé 35.16) ;
4-[[2-(5-Chloro-2-hydroxy-phényl)acétyl]amino]-N-[(1S,2S)-2-hydroxycyclopentyl]pyridine-2-carboxamide (Composé 35.17) ;
4-[[2-(5-Chloro-2-hydroxy-phényle)acétyl]amino]-N-[(1R,2S)-2-hydroxycyclopentyl]pyridine-2-carboxamide (Composé 35.18) ;
4-[[2-(5-Chloro-2-hydroxy-phényl)acétyl]amino]-N-[(1S,2R)-2-hydroxycyclopentyl]pyridine-2-carboxamide (Composé 35.19) ;
4-[[2-(5-Chloro-2-hydroxy-phényl)acétyl]amino]-N-(1-éthynylcyclohexyl)pyridine-2-carboxamide (Composé 35.24) ;
4-[[2-(5-Chloro-2-hydroxy-phényl)acétyl]amino]-N-[1-(hydroxyméthyl)cyclobutyl]pyridine-2-carboxamide (Composé 35.25) ;
4-[[2-(5-Chloro-2-hydroxy-phényl)acétyl]amino]-N-[3-(hydroxyméthyl)oxétan-3-yl]pyridine-2-carboxamide (Composé 35.26) ;
4-[[2-(5-Chloro-2-hydroxy-phényl)acétyl]amino]-N-(1-cyano-2-méthoxy-1-méthyl-éthyl)pyridine-2-carboxamide (Composé 35.27) ;
4-[[2-(5-Chloro-2-hydroxy-phényl)acétyl]amino]-N-[(1-hydroxycyclobutyl)méthyl]pyridine-2-carboxamide (Composé 35.28) ;
4-[[2-(5-Chloro-2-hydroxy-phényl)acétyl]amino]-N-(1,1-diméthylprop-2-ynyl)pyridine-2-carboxamide (Composé 36) ;
4-[[2-(5-Chloro-2-hydroxy-phényl)acétyl]amino]-N-(1-cyano-1,2-diméthyl-propyl)pyridine-2-carboxamide (Composé 37) ;
4-[[2-(5-Chloro-2-hydroxy-phényl)acétyl]amino]-N-(1-méthylcyclopentyl)pyridine-2-carboxamide (Composé 38) ;
N-(4-tert-Butylcyclohexyl)-4-[[2-(5-chloro-2-hydroxy-phényl)acétyl]amino]pyridine-2-carboxamide (Composé 39) ;
N-tert-Butyl-4-[[2-(2-chloro-3-fluoro-phényl)acétyl]amino]pyridine-2-carboxamide (Composé 40) ;
N-tert-Butyl-4-[[2-(2-chloro-5-fluoro-phényl)acétyl]amino]pyridine-2-carboxamide (Composé 40.1) ;
4-[[2-(5-Chloro-2-hydroxy-phényl)acétyl]amino]-N-[4-(2-hydroxyéthyle) tétrahydropyran-4-yl]pyridine-2-carboxamide (Composé 42) ;
4-[[2-(5-Chloro-2-hydroxy-phényl)acétyl]amino]-N-[1,1-diméthyl-3-(2,2,2-trifluoroéthylamino)propyl]pyridine-2-carboxamide (Composé 43) ;
4-[[2-(5-Chloro-2-hydroxy-phényl)acétyl]amino]-N-(4-fluoro-1-bicyclo[2.1.1]hexanyl)pyridine-2-carboxamide (Composé 44) ;
4-[[2-(5-Chloro-2-hydroxy-phényl)acétyl]amino]-N-[3-(2,2-diméthylpropanoylamino)-1,1-diméthyl-propyl]pyridine-2-carboxamide (Composé 45) ;
4-[[2-(5-Chloro-2-hydroxy-phényl)acétyl]amino]-N-(1-cyano-2-hydroxy-1-méthyl-éthyl)pyridine-2-carboxamide (Composé 46) ;
4-[[2-(5-Chloro-2-hydroxy-phényl)acétyl]amino]-N-[(1S)-1-cyano-2-hydroxy-1-méthyl-éthyl]pyridine-2-carboxamide ou 4-[[2-(5-chloro-2-hydroxy-phényl)acétyl]amino]-N-[(1R)-1-cyano-2-hydroxy-1-méthyl-éthyl]pyridine-2-carboxamide (Composé 46a) ;
4-[[2-(5-Chloro-2-hydroxy-phényl)acétyl]amino]-N-[(1S)-1-cyano-2-hydroxy-1-méthyl-éthyl]pyridine-2-carboxamide ou 4-[[2-(5-chloro-2-hydroxy-phényl)acétyl]amino]-N-[(1R)-1-cyano-2-hydroxy-1-méthyl-éthyl]pyridine-2-carboxamide (Composé 46b) ;
4-[[2-(5-Chloro-2-hydroxy-phényl)acétyl]amino]-N-(3-cyanotétrahydrofuran-3-yl)pyridine-2-carboxamide (Composé 47) ;
2-[4-[[4-[[2-(5-chloro-2-hydroxy-phényle)acétyl]amino]pyridine-2-carbonyl]amino]tétrahydropyran-4-yl]acétate de méthyle (Composé 47.1) ;
4-[[4-[[2-(5-chloro-2-hydroxy-phényl)acétyl]amino]pyridine-2-carbonyl]amino]tétrahydropyran-4-carboxylate

de méthyle (Composé 47.2) ;
4-[[2-(5-Chloro-2-hydroxy-phényl)acétyl]amino]-N-(3-cyanooxétan-3-yl)pyridine-2-carboxamide (Composé 47.3) ;
4-[[2-(5-Fluoro-2-hydroxy-phényl)acétyl]amino]-N-(1-méthylcyclobutyl)pyridine-2-carboxamide (Composé 48) ;
N-(4-Cyanotétrahydropyran-4-yl)-4-[[2-(5-fluoro-2-hydroxy-phényl)acétyl]amino]pyridine-2-carboxamide (Composé 48.1) ;
N-[3-(tert-Butylamino)-1,1-diméthyl-3-oxo-propyl]-4-[[2-(5-chloro-2-hydroxy-phényle)acétyl]amino]pyridine-2-carboxamide (Composé 49) ;
4-[[2-(5-Chloro-2-hydroxy-phényl)acétyl]amino]-N-[3-(méthanesulfonamido)-1,1-diméthyl-propyl]pyridine-2-carboxamide (Composé 50) ;
N-(3-Acétamido-1,1-diméthyl-propyl)-4-[[2-(5-chloro-2-hydroxy-phényl)acétyl]amino]pyridine-2-carboxamide (Composé 51) ;
4-[[2-(5-Chloro-2-hydroxy-phényl)acétyl]amino]-N-[4-(hydroxyméthyl)tétrahydro pyran-4-yl]pyridine-2-carboxamide (Composé 53) ;
N-tert-Butyl-4-[[2-[3-(1-hydroxyéthyl)phényl]acétyl]amino]pyridine-2-carboxamide (Composé 54) ;
N-tert-Butyl-5-chloro-4-[[2-(5-chloro-2-hydroxy-phényl)acétyl]amino]pyridine-2-carboxamide (Composé 55) ;
N-tert-Butyl-4-[[2-[5-chloro-2-[(4-méthoxyphényl)méthoxy]phényl]acétyl]amino]pyridine-2-carboxamide (Composé 56) ;
N-tert-butyl-4-[[(1S) ou (1R)-4-chloro-7-hydroxy-indane-1-carbonyl]amino]pyridine-2-carboxamide (Composé 57a) ;
N-tert-butyl-4-[[(1S) ou (1R)-4-chloro-7-hydroxy-indane-1-carbonyl]amino]pyridine-2-carboxamide (Composé 57b) ;
N-tert-Butyl-4-[[2-(2-cyclopropylphényl)acétyl]amino]pyridine-2-carboxamide (Composé 58) ;
4-[[2-(3-Bromo-5-chloro-2-hydroxy-phényl)acétyl]amino]-N-tert-butyl-pyridine-2-carboxamide (Composé 59) ;
N-(4-Fluoro-1-bicyclo[2.1.1]hexanyl)-4-[[2-(2-fluorophényl)acétyl]amino]pyridine-2-carboxamide (Composé 60) ;
N-(1-Cyano-2-hydroxy-1-méthyl-éthyl)-4-[[2-(2-fluorophényl)acétyl]amino]pyridine-2-carboxamide (Composé 60.1) ;
N-(1,1-Diméthylprop-2-ynyl)-4-[[2-(2-fluorophényl)acétyl]amino]pyridine-2-carboxamide (Composé 60.2) ;
N-tert-Butyl-4-[[2-(5-chloro-2-hydroxy-3-isopropyl-phényl)acétyl]amino]pyridine-2-carboxamide (Composé 61) ;
N-tert-Butyl-4-[[2-[5-chloro-2-hydroxy-3-(1-méthoxyéthyl)phényl]acétyl]amino]pyridine-2-carboxamide (Composé 62) ;
4-[[2-(6-Quinolyl)acétyl]amino]-N-tétrahydropyran-4-yl-pyridine-2-carboxamide (Composé 63) ;
4-(Benzylcarbamoylamino)-N-tert-butyl-pyridine-2-carboxamide (Composé 64) ;
N-tert-Butyl-4-(cyclohexylméthylcarbamoylamino)pyridine-2-carboxamide (Composé 64.1) ;
N-tert-Butyl-4-(2-phényléthylcarbamoylamino)pyridine-2-carboxamide (Composé 64.2) ;
N-tert-Butyl-4-[[(1R)-1-phényléthyl]carbamoylamino]pyridine-2-carboxamide (Composé 64.3) ;
N-tert-Butyl-4-[[(1S)-1-phényléthyl]carbamoylamino]pyridine-2-carboxamide (Composé 64.4) ;
N-tert-Butyl-4-[(2-chlorophényle)méthylcarbamoylamino]pyridine-2-carboxamide (Composé 64.5) ;
N-tert-butyl-4-(1H-indol-3-ylcarbamoylamino)pyridine-2-carboxamide (Composé 64.6) ;
N-tert-Butyl-4-[(3-chlorophényl)méthylcarbamoylamino]pyridine-2-carboxamide (Composé 64.7) ;
N-tert-butyl-4-[(4-chlorophényl)méthylcarbamoylamino]pyridine-2-carboxamide (Composé 64.8) ;
N-tert-Butyl-4-[(2-hydroxyphényl)carbamoylamino]pyridine-2-carboxamide (Composé 65) ;
N-tert-Butyl-4-[(2-méthoxyphényl)méthylcarbamoylamino]pyridine-2-carboxamide (Composé 65.1) ;
N-tert-Butyl-4-[(2-hydroxyphényl)méthylcarbamoylamino]pyridine-2-carboxamide (Composé 65.2) ;
N-tert-Butyl-4-[(3-hydroxyphényl)méthylcarbamoylamino]pyridine-2-carboxamide (Composé 65.3) ;
N-tert-Butyl-4-[(4-hydroxyphényl)méthylcarbamoylamino]pyridine-2-carboxamide (Composé 65.4) ;
N-tert-Butyl-4-[[2-[2-hydroxy-5-(1-hydroxyéthyl)phényl]acétyl]amino]pyridine-2-carboxamide (Composé 66) ;
N-tert-Butyl-4-[[2-[2-hydroxy-5-[1-(2,2,2-trifluoroéthylamino)éthyl]phényl]acétyl]amino]pyridine-2-carboxamide (Composé 67) ;
N-tert-Butyl-4-[[2-[3-(cyanométhyl)phényl]acétyl]amino]pyridine-2-carboxamide (Composé 68) ;
N-tert-Butyl-4-[[2-[3-(méthoxyméthyl)phényl]acétyl]amino]pyridine-2-carboxamide (Composé 69) ;
N-tert-Butyl-4-[[2-[2-hydroxy-5-(morpholinométhyl)phényl]acétyl]amino]pyridine-2-carboxamide (Composé 70) ;
4-[[2-(5-Fluoro-2-hydroxy-phényl)acétyl]amino]-N-[3-(hydroxyméthyl)tétrahydro furan-3-yl]pyridine-2-carboxamide (Composé 72) ;
4-[[2-(5-Chloro-2-hydroxy-phényl)acétyl]amino]-N-[1-(hydroxyméthyl)-2-méthoxy-1-méthyl-éthyl]pyridine-2-

carboxamide (Composé 73) ;
4-[[2-(5-Chloro-2-hydroxy-phényl)acétyl]amino]-N-(1,1-diméthylbut-2-ynyle) pyridine-2-carboxamide (Composé 73.1) ;
N-tert-Butyl-4-[[2-[2-hydroxy-5-(3-hydroxypropyl)phényl]acétyl]amino]pyridine-2-carboxamide (Composé 75) ;
4-[[2-(5-Chloro-4-fluoro-2-hydroxy-phényl)acétyl]amino]-N-(1-méthylcyclobutyl)pyridine-2-carboxamide (Composé 76) ;
4-[[2-(2,5-Difluorophényl)acétyl]amino]-N-(1,1-diméthylprop-2-ynyl)pyridine-2-carboxamide (Composé 77) ;
4-[[2-(2,5-Difluorophényl)acétyl]amino]-N-(4-fluoro-1-bicyclo[2.1.1]hexanyle) pyridine-2-carboxamide (Composé 77.1) ;
4-[[2-(4-Chloro-2-hydroxy-phényl)acétyl]amino]-N-(1,1-diméthylprop-2-ynyl)pyridine-2-carboxamide (Composé 78) ;
N-(1,1-Diméthylprop-2-ynyl)-4-[[2-[2-hydroxy-4-(trifluorométhyl)phényl]acétyl]amino]pyridine-2-carboxamide (Composé 78.1) ;
N-(1,1-Diméthylprop-2-ynyl)-4-[[2-[2-hydroxy-5-(trifluorométhyl)phényl]acétyl]amino]pyridine-2-carboxamide (Composé 78.2) ;
4-[(2-Chroman-4-ylacétyl)amino]-N-(1,1-diméthylprop-2-ynyl)pyridine-2-carboxamide (Composé 79) ;
N-(1,1-Diméthylprop-2-ynyl)-4-[[2-(1-isopropyl-3,5-diméthyl-pyrazol-4-yl)acétyl]amino]pyridine-2-carboxamide (Composé 79.1) ;
N-(1,1-Diméthylprop-2-ynyl)-4-[[2-(1H-indazol-4-yl)acétyl]amino]pyridine-2-carboxamide (Composé 79.2) ;
N-(1,1-Diméthylprop-2-ynyl)-4-[[2-(1H-indol-7-yl)acétyl]amino]pyridine-2-carboxamide (Composé 79.3) ;
N-(1-Cyano-1-méthyl-éthyl)-4-[[2-(5-fluoro-2-hydroxy-phényl)acétyl]amino]pyridine-2-carboxamide (Composé 81) ;
N-(1-Cyano-2-hydroxy-1-méthyl-éthyl)-4-[[2-(5-fluoro-2-hydroxy-phényl)acétyl]amino]pyridine-2-carboxamide (Composé 81.1) ;
4-[[2-(5-Fluoro-2-hydroxy-phényl)acétyl]amino]-N-isopropyl-pyridine-2-carboxamide (Composé 81.2) ;
N-(1,1-Diméthylprop-2-ynyl)-4-[[2-(5-fluoro-2-hydroxy-phényl)acétyl]amino]pyridine-2-carboxamide (Composé 81.3) ;
N-(4-Fluoro-1-bicyclo[2.1.1]hexanyl)-4-[[2-(5-fluoro-2-hydroxy-phényl)acétyl]amino]pyridine-2-carboxamide (Composé 81.4) ;
4-[[2-(5-Fluoro-2-hydroxy-phényl)acétyl]amino]-N-[1-(hydroxyméthyl)cyclobutyl]pyridine-2-carboxamide (Composé 81.5) ;
N-(1-Cyano-1-méthyl-éthyl)-4-(thiophéne-3-carbonylamino)pyridine-2-carboxamide (Composé 83) ;
N-(1-Cyano-1-méthyl-éthyl)-4-[(2-cyclohexylacétyle) amino]pyridine-2-carboxamide (Composé 83.1) ;
N-(1-Cyano-1-méthyl-éthyl)-4-(cyclohexanecarbonylamino)pyridine-2-carboxamide (Composé 83.2) ;
N-(1-Cyano-1-méthyl-éthyl)-4-[(3,3-difluorocyclopentanecarbonyl)amino]pyridine-2-carboxamide (Composé 83.3) ;
N-(1-Cyano-1-méthyl-éthyl)-4-[(1-méthylcyclopentanecarbonyl)amino]pyridine-2-carboxamide (Composé 83.4) ;
N-(1-Cyano-1-méthyl-éthyl)-4-(3-cyclohexylpropanoylamino)pyridine-2-carboxamide (Composé 83.5) ;
4-(2-{Bicyclo[2.2.1]heptan-2-yl}acétamido)-N-(1-cyano-1-méthyléthyl)pyridine-2-carboxamide (Composé 83.6) ;
N-(1-Cyano-1-méthyl-éthyl)-4-[[2-(1-méthylcyclohexyl)acétyl]amino]pyridine-2-carboxamide (Composé 83.7) ;
N-[2-[(1-Cyano-1-méthyl-éthyl)carbamoyl]-4-pyridinyl]-2-cyclopropyl-pyrimidine-5-carboxamide (Composé 83.8) ;
N-[2-[(1-Cyano-1-méthyl-éthyl)carbamoyl]-4-pyridinyl]-3-isobutyl-isoxazole-5-carboxamide (Composé 83.9) ;
N-(1-Cyano-1-méthyl-éthyl)-4-[[2-(4,4-difluorocyclohexyl)acétyl]amino]pyridine-2-carboxamide (Composé 83.10) ;
4-[(1-Benzylcyclopropanecarbonyl)amino]-N-(1-cyano-1-méthyl-éthyl)pyridine-2-carboxamide (Composé 83.11) ;
N-(1-Cyano-1-méthyl-éthyl)-4-[3-(2-méthoxy-4-pyridinyl)propanoylamino]pyridine-2-carboxamide (Composé 83.13) ;
4-[(5-tert-Butyl-2-méthyl-pyrazole-3-carbonyl)amino]-N-(1-cyano-1-méthyl-éthyl)pyridine-2-carboxamide (Composé 83.14) ;
N-(1-Cyano-1-méthyl-éthyl)-4-[(2-pyrazol-1-ylbenzoyl)amino]pyridine-2-carboxamide (Composé 83.15) ;
N-[2-[(1-Cyano-1-méthyl-éthyl)carbamoyl]-4-pyridinyl]-6-(trifluorométhyl)pyridine-2-carboxamide (Composé 83.16) ;
N-[2-[(1-Cyano-1-méthyl-éthyl)carbamoyl]-4-pyridinyl]-3-oxo-4H-1,4-benzoxazine-7-carboxamide (Composé 83.17) ;

N-[2-[(1-Cyano-1-méthyl-éthyl)carbamoyl]-4-pyridinyl]-1-éthyl-indole-2-carboxamide (Composé 83.18) ;
N-(1-Cyano-1-méthyl-éthyl)-4-[[2-(2,2,2-trifluoroéthyl)pyrazole-3-carbonyl]amino]pyridine-2-carboxamide (Composé 83.19) ;
N-[2-[(1-Cyano-1-méthyl-éthyl)carbamoyl]-4-pyridinyl]-3-phényl-isoxazole-4-carboxamide (Composé 83.20) ;
4-[(1-Benzylpyrazole-4-carbonyl)amino]-N-(1-cyano-1-méthyl-éthyl)pyridine-2-carboxamide (Composé 83.21) ;
N-(1-Cyano-1-méthyl-éthyl)-4-[(2-méthyl-5-phényl-pyrazole-3-carbonyl)amino]pyridine-2-carboxamide (Composé 83.22) ;
N-(1-Cyano-1-méthyl-éthyl)-4-[[2-(3-méthyl-1,2,4-oxadiazol-5-yl)benzoyl]amino]pyridine-2-carboxamide (Composé 83.23) ;
N-(1-Cyano-1-méthyl-éthyl)-4-[(3-méthyl-1-phényl-pyrazole-4-carbonyl)amino]pyridine-2-carboxamide (Composé 83.24) ;
N-[2-[(1-Cyano-1-méthyl-éthyl)carbamoyl]-4-pyridinyl]-2-phénoxy-pyridine-3-carboxamide (Composé 83.25) ;
N-(1-Cyano-1-méthyl-éthyl)-4-[[2,5-diméthyl-1-(2-thiénylméthyl)pyrrole-3-carbonyl]amino]pyridine-2-carboxamide (Composé 83.26) ;
N-[2-[(1-Cyano-1-méthyl-éthyl)carbamoyl]-4-pyridinyl]-5-(2-méthoxyphényl)isoxazole-3-carboxamide (Composé 83.27) ;
N-[2-[(1-Cyano-1-méthyl-éthyl)carbamoyl]-4-pyridinyl]-4-méthyl-2-phényl-thiazole-5-carboxamide (Composé 83.28) ;
4-[(4-Acétamidobenzoyl)amino]-N-(1-cyano-1-méthyl-éthyl)pyridine-2-carboxamide (Composé 83.29) ;
N-[2-[(1-Cyano-1-méthyl-éthyl)carbamoyl]-4-pyridinyl]-1,3-benzothiazole-7-carboxamide (Composé 83.30) ;
N-(1-Cyano-1-méthyl-éthyl)-4-[3-(4-fluorophényle)butanoylamino]pyridine-2-carboxamide (Composé 83.31) ;
N-[2-[(1-Cyano-1-méthyl-éthyl)carbamoyl]-4-pyridinyl]-1-méthyl-2-oxo-quinoléine-3-carboxamide (Composé 83.32) ;
4-[[2-(5-Chloro-2-hydroxy-phényl)acétyl]amino]-N-[1-cyano-2-méthoxy-1-(méthoxy méthyl)éthyl]pyridine-2-carboxamide (Composé 86) ;
4-[[2-(3-Amino-4-tert-butyl-phényl)acétyl]amino]-N-tert-butyl-pyridine-2-carboxamide (Composé 87) ;
4-[[2-(2-Amino-4-tert-butyl-phényl)acétyl]amino]-N-tert-butyl-pyridine-2-carboxamide (Composé 88) ;
N-tert-Butyl-4-[[2-(4-tert-butyl-3-hydroxy-phényl)acétyl]amino]pyridine-2-carboxamide (Composé 89) ;
N-tert-Butyl-4-[[2-(4-tert-butyl-2-hydroxy-phényl)acétyl]amino]pyridine-2-carboxamide (Composé 90) ;
N-tert-Butyl-4-[[2-(4-tert-butyl-2-fluoro-5-hydroxy-phényl)acétyl]amino]pyridine-2-carboxamide (Composé 91) ;
4-[[2-(4-Chloro-3-hydroxy-phényl)acétyl]amino]-N-(4-cyanotétrahydropyran-4-yl)pyridine-2-carboxamide (Composé 92) ;
4-[[2-(4-Chloro-3-hydroxy-phényl)acétyl]amino]-N-(1-cyano-1-méthyl-éthyl)pyridine-2-carboxamide (Composé 92.1) ;
4-[[2-(4-Chloro-3-hydroxy-phényl)acétyl]amino]-N-(1,1-diméthylprop-2-ynyl)pyridine-2-carboxamide (Composé 92.2) ;
4-[[2-(4-Chloro-3-hydroxy-phényl)acétyl]amino]-N-[(1s,2s)-2-hydroxycyclopentyl]pyridine-2-carboxamide (Composé 92.3) ;
4-[[2-(4-tert-Butyl-3-hydroxy-phényl)acétyl]amino]-N-[3-(hydroxyméthyle) tétrahydrofuran-3-yl]pyridine-2-carboxamide (Composé 93) ;
4-[[2-(4-tert-Butyl-3-hydroxy-phényl)acétyl]amino]-N-[(2S)-2-hydroxycyclohexyl]pyridine-2-carboxamide (Composé 93.1) ;
4-[[2-(4-tert-Butyl-3-hydroxy-phényl)acétyl]amino]-N-[(2S)-2-hydroxycyclopentyl]pyridine-2-carboxamide (Composé 93.2) ;
4-[[2-(4-tert-Butyl-3-hydroxy-phényl)acétyl]amino]-N-(4-cyanotétrahydropyran-4-yl)pyridine-2-carboxamide (Composé 93.3) ;
4-[[2-(4-tert-Butyl-3-hydroxy-phényl)acétyl]amino]-N-(1-cyano-1-méthyl-éthyl)pyridine-2-carboxamide (Composé 93.4) ;
4-[[2-(4-tert-Butyl-3-hydroxy-phényl)acétyl]amino]-N-(1,1-diméthylprop-2-ynyl)pyridine-2-carboxamide (Composé 93.5) ; et
4-[[2-(5-Chloro-2-hydroxy-phényl)acétyl]amino]-N-(1-méthyl-1-phényl-éthyle) pyridine-2-carboxamide (Composé 94) ;
et sels et solvates de l'un quelconque parmi les composés ci-dessus.

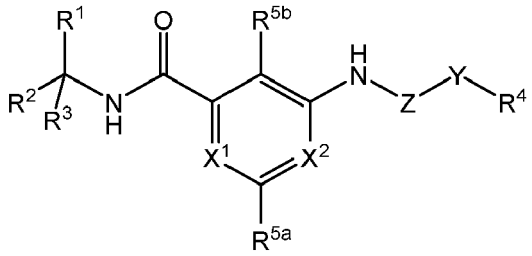
10. Composé selon la revendication 1 qui est N-tert-Butyl-4-[[2-(5-chloro-2-hydroxy-phényl)acétyl]amino]pyridine-2-carboxamide (Composé 3) ou un sel ou un solvate correspondant.

11. Composé selon la revendication 1 qui est 4-[[2-(5-Chloro-2-hydroxy-phényl)acétyl]amino]-N-[(3R)-3-(hydroxyméthyl)tétrahydrofuran-3-yl]pyridine-2-carboxamide ou 4-[[2-(5-chloro-2-hydroxy-phényl)acétyl]amino]-N-[(3S)-3-(hydroxyméthyl)tétrahydrofuran-3-yl]pyridine-2-carboxamide (Composé 35a) ou un sel ou un solvate correspondant.

12. Composé selon la revendication 1 qui est 4-[[2-(5-Chloro-2-hydroxy-phényl)acétyl]amino]-N-(1,1-diméthylprop-2-ynyl)pyridine-2-carboxamide (Composé 36) ou un sel ou un solvate correspondant.

13. Composé selon la revendication 1 qui est N-(1,1-Diméthylprop-2-ynyl)-4-[[2-[3-(trifluorométhyl)-1H-pyrazol-4-yl]acétyl]amino]pyridine-2-carboxamide (Composé 5.36) ou un sel ou un solvate correspondant.

14. Composé de formule générale (I) y compris toutes les formes tautomères, tous les énantiomères et toutes les variantes isotopiques et tous les sels et les solvates correspondants :



(I)

R^1 étant H, CN, $C(O)OR^{12}$, C_{1-3} alkyle, C_{2-3} alcényle ou C_{2-3} alcynyle, l'un quelconque parmi lesquels groupes alkyle, alcényle ou alcynyle étant éventuellement substitué par un ou plusieurs substituants, de manière appropriée un substituant, choisis parmi fluoro, OR^{12}, $N(R^{12})_2$, $C(O)OR^{12}$, $C(O)N(R^{12})_2$, $C(O)R^{12}$ et $N(R^{13})C(O)R^{12}$; chaque R^{12} et R^{13} étant indépendamment choisi parmi H, C_{1-6} alkyle et C_{1-6} fluoroalkyle
R^2 étant H ou C_{1-6} alkyle éventuellement substitué par OR^{12};
R^3 étant :

C_{1-10} alkyle, C_{2-10} alcényle ou C_{2-10} alcynyle, l'un quelconque parmi lesquels étant éventuellement substitué par un ou plusieurs substituants, de manière appropriée un substituant, choisis parmi fluoro, CN, R^{14} OR^{14}, OR^{15}, $N(R^{15})_2$, $C(O)OR^{15}$, $C(O)N(R^{15})_2$, $N(R^{16})C(O)R^{15}$, $N(R^{15})S(O)_2R^{14}$, $N(R^{15})S(O)_2R^{16}$ et $N(R^{15})C(O)OR^{16}$; ou
un système cyclique carbocyclique ou hétérocyclique à 3 à 7 chaînons ou un système cyclique aryle à 6 à 10 chaînons ou hétéroaryle à 5 à 10 chaînons, l'un ou l'autre parmi lesquels étant éventuellement substitué par un ou plusieurs substituants choisis parmi halogéno, CN, C_{1-4} alkyle, C_{1-4} halogénoalkyle, OR^{17} et $N(R^{17})_2$;
R^{14} étant un système cyclique aryle à 6 à 10 chaînons ou hétéroaryle à 5 à 10 chaînons ou un système cyclique carbocyclique ou hétérocyclique à 3 à 7 chaînons, l'un quelconque parmi lesquels étant éventuellement substitué par un ou plusieurs substituants choisis parmi halogéno, C_{1-4} alkyle, C_{1-4} halogénoalkyle, OR^{17} et $N(R^{17})_2$; chaque R^{17} étant indépendamment H, C_{1-4} alkyle ou C_{1-4} halogénoalkyle ;
chaque R^{15} et R^{16} étant indépendamment H, C_{1-6} alkyle ou C_{1-6} halogénoalkyle ; ou
R^2 et R^3, conjointement avec l'atome de carbone auquel ils sont fixés, se combinant pour former un système cyclique carbocyclique ou hétérocyclique à 3 à 10 chaînons éventuellement substitué par un ou plusieurs substituants choisis parmi halogéno, CN, OR^9, $N(R^9)_2$, $C(O)OR^9$, $C(O)N(R^9)_2$, $C(O)R^9$, $N(R^9)C(O)R^9$ et C_{1-4} alkyle éventuellement substitué par halogéno, OR^9 ou $N(R^9)_2$; ou R^1, R^2 et R^3, conjointement avec l'atome de carbone auquel ils sont fixés, se combinant pour former un système cyclique carbocyclique ou hétérocyclique à 5 à 10 chaînons ponté ou phényle, l'un quelconque parmi lesquels étant éventuellement substitué par un ou plusieurs substituants choisis parmi halogéno, CN, OR^9, $N(R^9)_2$, $C(O)OR^9$, $C(O)N(R^9)_2$, $C(O)R^9$, $N(R^9)C(O)R^9$ et C_{1-4} alkyle éventuellement substitué par halogéno, OR^9 ou $N(R^9)_2$;
chaque R^9 étant indépendamment choisi parmi H, C_{1-6} alkyle ou C_{1-6} halogénoalkyle ;
X^1 étant N ;
X^2 étant CR^8
R^8 étant H, halogéno, OH, O (C_{1-4} alkyle), CN ou NH_2 ;
Y étant une liaison ou une chaîne C_{1-6} alkylène linéaire qui est éventuellement substituée par un ou plusieurs

substituants R^{18}, deux substituants R^{18} pouvant être fixés au même atome de carbone ou à des atomes de carbone différents ;
chaque R^{18} étant indépendamment C_{1-3} alkyle ou C_{1-3} halogénoalkyle dans lequel un $-CH_2-$ est éventuellement remplacé par -NH- ou -O- et deux groupes R^{18} pouvant se combiner avec l'atome ou les atomes auquel/auxquels ils sont fixés pour former un système cyclique carbocyclique ou hétérocyclique à 3 à 6 chaînons ;
Z étant -C(O)- ou -C(O)NH- ;
R^4 étant un aryle à 6 à 14 chaînons, un hétéroaryle à 5 à 14 chaînons ou un système cyclique carbocyclique à 5 à 10 chaînons, l'un quelconque parmi lesquels étant éventuellement substitué par un ou plusieurs substituants choisis parmi :

halogéno, CN, nitro, R^{19}, OR^{19}, OR^6, SR^6, NR^6R^7, $C(O)R^6$, $C(O)R^{19}$, $C(O)OR^6$, $C(O)N(R^6)(R^7)$, $N(R^7)C(O)R^6$;
C_{1-6} alkyle ou $O(C_{1-6}$ alkyle), l'un ou l'autre parmi lesquels étant éventuellement substitué par un ou plusieurs substituants choisis parmi halogéno, CN, nitro, R^{19}, OR^6, SR^6, NR^6R^7, $C(O)R^6C(O)OR^6$, $C(O)N(R^6)(R^7)$ et $N(R^7)C(O)R^6$; et
lorsque R^4 n'est pas de caractère totalement aromatique, oxo ;
R^{19} étant un système cyclique aryle ou hétéroaryle à 5 ou 6 chaînons ou un système cyclique carbocyclique ou hétérocyclique à 3 à 7 chaînons, l'un quelconque parmi lesquels étant éventuellement substitué par un ou plusieurs substituants choisis parmi halogéno, C_{1-4} alkyle, C_{1-4} halogénoalkyle, OH, $O(C_{1-4}$ alkyle), $O(C_{1-4}$ halogénoalkyle) ;
R^6 étant H, C_{1-6} alkyle, C_{1-6} halogénoalkyle, benzyle, carbocyclyle à 3 à 7 chaînons ou hétérocyclyle à 3 à 7 chaînons ;
R^7 étant H, C_{1-6} alkyle ou C_{1-6} halogénoalkyle ; ou
R^6 et R^7, conjointement avec l'atome d'azote auquel ils sont fixés, pouvant former un cycle hétérocyclique à 4 à 7 chaînons contenant éventuellement un ou plusieurs hétéroatomes supplémentaires et éventuellement substitué par un ou plusieurs substituants choisis parmi oxo et halogéno ; et
chacun parmi R^{5a} et R^{5b} étant indépendamment H, C_{1-4} alkyle ou halogéno ; ou
composé selon l'une quelconque des revendications 1 à 13 ;
pour une utilisation en médecine, notamment dans le traitement ou la prophylaxie de maladies et d'affections affectées par la modulation de TMEM16A, par exemple des maladies et des affections respiratoires, la sécheresse de la bouche (xérostomie), l'hypermobilité intestinale, la cholestase et les affections oculaires ; et éventuellement, le composé de formule générale (I) étant utilisé en combinaison avec un agent actif supplémentaire utile dans le traitement ou la prévention d'affections respiratoires.

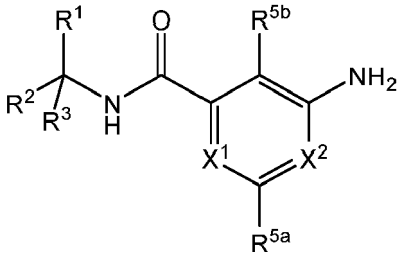
15. Composé pour une utilisation selon la revendication 14, les maladies et affections respiratoires étant choisies parmi la mucoviscidose, la bronchopneumopathie chronique obstructive (COPD), la bronchite chronique, l'emphysème, la bronchiectasie, y compris la bronchiectasie sans mucoviscidose, l'asthme et la dyskinésie ciliaire primaire ;

la bouche sèche (xérostomie) résultant du syndrome de Sjorgens, d'un traitement par radiothérapie ou de médicaments xérogènes ;
l'hypermobilité intestinale étant associée à une dyspepsie gastrique, une gastroparésie, une constipation chronique ou un syndrome du côlon irritable ;
la maladie oculaire étant une maladie de l'œil sec.

16. Procédé pour la préparation d'un composé selon l'une quelconque des revendications 1 à 13, le procédé comprenant :

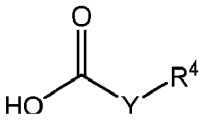
A. pour un composé de formule générale (I) dans laquelle Z est -C(O)- :

la mise en réaction d'un composé de formule générale (II) :



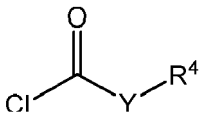
(II)

R^1, R^2, R^3, R^{5a}, R^{5b}, X^1 et X^2 étant tels que définis dans la revendication 1 ;
avec un composé de formule générale (III) :



(III)

R^4 et Y étant tels que définis dans la revendication 1 ; en la présence d'un agent de couplage ; ou
la mise en réaction d'un composé de formule générale (II) avec un chlorure d'acide de formule générale (IV) :

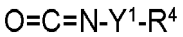


(IV)

R^4 et Y étant tels que définis dans la revendication 1 ; ou

B. pour des composés de formule générale (I) dans laquelle Z est C(O)NH et Y est -C_{1-2} alkylène- :

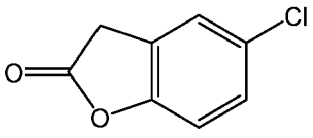
la mise en réaction d'un composé de formule générale (II) avec un composé de formule générale (XIV) :



(XIV)

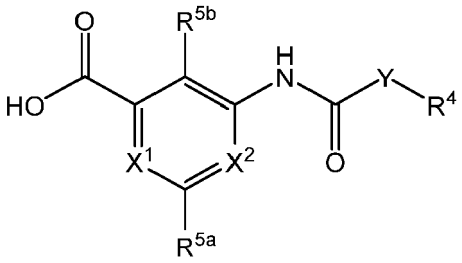
R^4 étant tel que défini dans la revendication 1 et Y^1 étant -CH_2- ou -CH_2CH_2-.

C. pour des composés de formule générale (Id) tels que définis dans la revendication 8 dans laquelle R^{11a} est Cl et R^{11b} est H :
la mise en réaction d'un composé de formule générale (II) avec de la 5-chloro-2(3*H*)-benzofuranone, qui possède la structure :



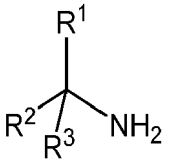
; ou

D. la mise en réaction d'un composé de formule générale (X) :



(X)

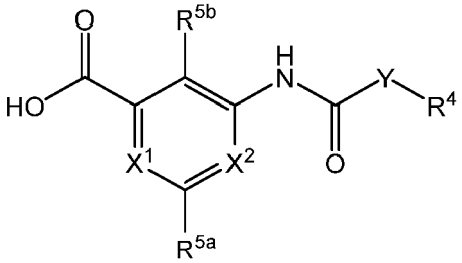
X^1, X^2, Y, R^4, R^{5a} et R^{5b} étant tels que définis dans la revendication 1 ;
avec un composé de formule générale (VII) :



(VII)

R^1, R^2 et R^3 étant tels que définis dans la revendication 1 ; ou

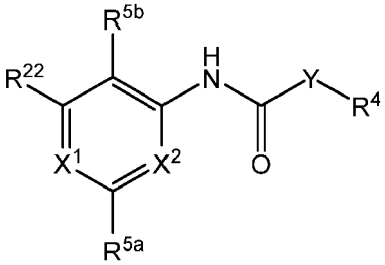
E. la mise en réaction d'un composé de formule générale (X) :



(X)

X^1, X^2, Y, R^4, R^{5a} et R^{5b} étant tels que définis dans la revendication 1 ;
avec un composé de formule générale (VII) tel que défini ci-dessus ; ou

F. la mise en réaction d'un composé de formule générale (XV) :



(XV)

X^1, X^2, Y, R^4, R^{5a} et R^{5b} étant tels que définis dans la revendication 1 et R^{22} étant halogéno ;
avec une amine de formule générale (VII) telle que définie ci-dessus et du monoxyde de carbone en la

présence d'un ligand au phosphore et d'un catalyseur au palladium ; ou

G. la conversion d'un composé de formule générale (I) en un autre composé de formule générale (I).

17. Composition pharmaceutique comprenant un composé selon l'une quelconque des revendications 1 à 13 conjointement avec un excipient pharmaceutiquement acceptable et éventuellement en outre comprenant un agent actif supplémentaire utile dans le traitement ou la prévention d'affections respiratoires.

18. Produit comprenant un composé selon l'une quelconque des revendications 1 à 13 et un agent supplémentaire utile dans le traitement ou la prévention d'affections respiratoires en tant que préparation combinée pour une utilisation simultanée, séquentielle ou séparée dans le traitement d'une maladie ou d'une affection affectée par la modulation de TMEM16A.

19. Composé pour une utilisation selon la revendication 14 ou la revendication 15, composition pharmaceutique selon la revendication 17 ou produit selon la revendication 18, l'agent supplémentaire utile dans le traitement ou la prévention d'affections respiratoires étant choisi parmi :

des agonistes des adrénorécepteurs β2 tels que le métaprotérénol, l'isoprotérénol, l'isoprénaline, l'albutérol, le salbutamol, le formotérol, le salmétérol, l'indacatérol, la terbutaline, l'orciprénaline, le mésylate de bitoltérol, le pirbutérol, l'olodatérol, le vilantérol et l'abéditérol ;
des antihistaminiques, par exemple les antagonistes des récepteurs H1 de l'histamine tels que la loratadine, la cétirizine, la desloratadine, la lévocétirizine, la fexofénadine, l'astémizole, l'azélastine et la chlorphéniramine ou les antagonistes des récepteurs H4 ; la dornase alpha ;
des corticostéroïdes tels que la prednisone, la prednisolone, le flunisolide, l'acétonide de triamcinolone, le dipropionate de béclométhasone, le budésonide, le propionate de fluticasone, le furoate de mométasone et le furoate de fluticasone ;
des antagonistes des leucotriènes tels que le montelukast et le zafirlukast ;
des composés anticholinergiques, notamment les antagonistes muscariniques tels que l'ipratropium, le tiotropium, le glycopyrrolate, l'aclidinium et l'umeclidinium ;
des thérapies de réparation de la CFTR (par exemple, des potentialisateurs, des correcteurs ou des amplificateurs de la CFTR) telles que l'Ivacaftor, QBW251, VX659, VX445, VX561/CPT-656, VX152, VX440, GLP2737, GLP2222, GLP2451, PTI438, PTI801, PTI808, FDL-169 et FDL-176 et des correcteurs de la CFTR tels que le Lumacaftor et le Tezacaftor ;
des modulateurs d'ENaC, particulièrement des inhibiteurs d'ENaC tels que :
amiloride, VX-371, AZD5634, QBW276, SPX-101, BI443651, ETD001 et des composés possédant un cation choisi parmi :

2-[({3-amino-5H-pyrrolo[2,3-b]pyrazin-2-yl}formamido)éthyl]-6-(4-{bis[(2*S*,3*R*,4*R*,5*R*)-2,3,4,5,6-pentahydroxyhexyl]amino}pipéridine-1-carbonyl)-1,3-diéthyl-1*H*-1,3-benzodiazol-3-ium ;
2-[({3-amino-5H-pyrrolo[2,3-b]pyrazin-2-yl}formamido)méthyl]-6-{[2-(4-{bis[(2S,3R,4R,5R)-2,3,4,5,6-pentahydroxyhexyl]amino}pipéridin-1-yl)éthyl]carbamoyl}-1,3-diéthyl-1*H*-1,3-benzodiazol-3-ium ;
2-[({3-amino-5*H*-pyrrolo[2,3-b]pyrazin-2-yl}formamido)méthyl]-5-[4-({bis[(2*S*,3*R*,4*R*,5*R*)-2,3,4,5,6-pentahydroxyhexyl]amino}méthyl)pipéridine-1-carbonyl]-1,3-diéthyl-1*H*-1,3-benzodiazol-3-ium ;
2-[({3-amino-5*H*-pyrrolo[2,3-b]pyrazin-2-yl}formamido)méthyl]-6-[(3*R*)-3-{bis[(2*S*,3*R*,4*R*,5*R*)-2,3,4,5,6-pentahydroxyhexyl]amino}pyrrolidine-1-carbonyl]-1,3-diéthyl-1*H*-1,3-benzodiazol-3-ium ;
2-[({3-amino-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl}formamido)méthyl]-6-[(3*S*)-3-{bis[(2*S*,3*R*,4*R*,5*R*)-2,3,4,5,6-pentahydroxyhexyl]amino}pyrrolidine-1-carbonyl]-1,3-diéthyl-1*H*-1,3-benzodiazol-3-ium ;
2-[({3-amino-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl}formamido)méthyl]-1,3-diéthyl-6-{[(1*r*,4*r*)-4-{bis[(2*S*,3*R*,4*R*,5*R*)-2,3,4,5,6-pentahydroxyhexyl]amino}cyclohexyl]carbamoyl}-1*H*-1,3-benzodiazol-3-ium ;
2-[({3-amino-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl}formamido)méthyl]-1,3-diéthyl-6-{[(1*s*,4*s*)-4-{bis[(2*S*,3*R*,4*R*,5*R*)-2,3,4,5,6-pentahydroxyhexyl]amino}cyclohexyl]carbamoyl}-1*H*-1,3-benzodiazol-3-ium ;
et un anion approprié, par exemple halogénure, sulfate, nitrate, phosphate, formiate, acétate, trifluoroacétate, fumarate, citrate, tartrate, oxalate, succinate, mandélate, méthane sulfonate ou p-toluènesulfonate ;
des antibiotiques ;
des agents d'hydratation des voies respiratoires (osmolytes) tels qu'une solution saline hypertonique et le mannitol (Bronchitol®) ; et

des agents mucolytiques par ex. la N-acétylcystéine.

20. Composé selon la revendication 2, le composé étant un composé de formule (Iz) et Y n'étant pas une liaison.

21. Composé selon la revendication 1, Y étant un C_{1-3} alkylène linéaire éventuellement substitué par un ou plusieurs substituants R^{18}, R^{18} étant tel que défini ci-dessus et deux substituants R^{18} pouvant être fixés au même atome de carbone ou à des atomes de carbone différents.

22. Composé selon la revendication 1, R^4 étant un groupe aryle à 6 à 11 chaînons choisi parmi phényle, naphtyle, indanyle, 1,2,3,4-tétrahydronaphtyle et benzocycloheptanyle, l'un quelconque parmi lesquels étant éventuellement substitué comme défini dans la revendication 1.

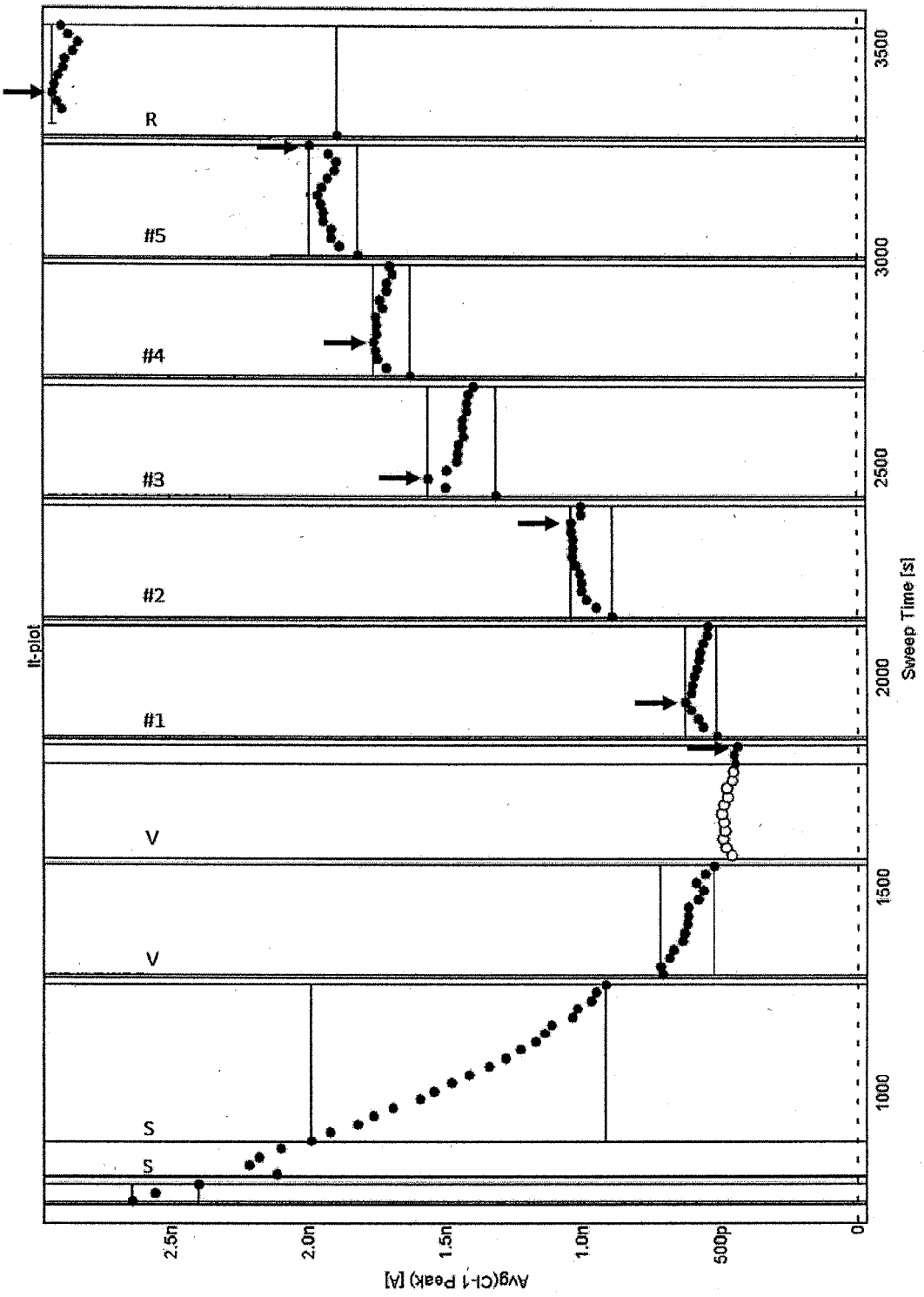

It-plot
R
#5
#4
#3
#2
#1
V
V
S
S
Avg(Ch-1 Peak) [A]
2.5n
2.0n
1.5n
1.0n
500p
0
Sweep Time [s]
3500
3000
2500
2000
1500
1000

Figure 1

REFERENCES CITED IN THE DESCRIPTION

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