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(54) **6-(PYRIDINYL)-4-PYRIMIDONE DERIVATES AS TAU PROTEIN KINASE 1 INHIBITORS**

6-(PYRIDINYL)-4-PYRIMIDONDERIVATE ALS INHIBITOREN DER TAU-PROTEINKINASE-1

DÉRIVÉS DE 6-(PYRIDINYL)-4-PYRIMIDONE COMME INHIBITEURS DE LA PROTÉINE KINASE TAU 1

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(73) Proprietors:
- **Mitsubishi Tanabe Pharma Corporation**
  Osaka 541-8505 (JP)
- **SANOFI**
  75013 Paris (FR)

(72) Inventors:
- **WATANABE, Kazutoshi,**
  Mitsubishi Pharma Corporation
  Chuo-ku, Tokyo 103-8405 (JP)
- **FUKUNAGA, Kenji,**
  Mitsubishi Pharma Corporation
  Chuo-ku, Tokyo 103-8405 (JP)
- **KOHARA, Toshiyuki,**
  Mitsubishi Pharma Corporation
  Chuo-ku, Tokyo 103-8405 (JP)
- **UEHARA, Fumiaki,**
  Mitsubishi Pharma Corporation
  Chuo-ku, Tokyo 103-8405 (JP)
- **HIKI, Shinsuke,**
  Mitsubishi Pharma Corporation
  Chuo-ku, Tokyo 103-8405 (JP)
- **YOKOSHIMA, Satoshi**
  Tokyo 1200006 (JP)

(74) Representative: **Polypatent**
Postfach 40 02 43
51410 Bergisch Gladbach (DE)

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EP-A- 1 136 483 **EP-A- 1 454 908**
WO-A-00/18758 **WO-A-01/70729**
WO-A-03/037888 **WO-A-2004/085408**

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Description

Technical Field

[0001] The present invention relates to compounds that are useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of diseases mainly caused by abnormal activity of tau protein kinase 1, such as neurodegenerative diseases (e.g. Alzheimer disease).

Background Art

[0002] Alzheimer disease is progressive senile dementia, in which marked cerebral cortical atrophy is observed due to degeneration of nerve cells and decrease of nerve cell number. Pathologically, numerous senile plaques and neurofibrillary tangles are observed in brain. The number of patients has been increased with the increment of aged population, and the disease arises a serious social problem. Although various theories have been proposed, a cause of the disease has not yet been elucidated. Early resolution of the cause has been desired.

[0003] It has been known that the degree of appearance of two characteristic pathological changes of Alzheimer disease well correlates to the degree of intellectual dysfunction. Therefore, researches have been conducted from early 1980's to reveal the cause of the disease through molecular level investigations of components of the two pathological changes. Senile plaques accumulate extracellularly, and β amyloid protein has been elucidated as their main component (abbreviated as "A β " hereinafter in the specification: Biochem. Biophys. Res. Commun., 120, 885 (1984); EMBO J., 4, 2757 (1985); Proc. Natl. Acad. Sci. USA, 82, 4245 (1985)). In the other pathological change, i.e., the neurofibrillary tangles, a double-helical filamentous substance called paired helical filament (abbreviated as "PHF" hereinafter in the specification) accumulate intracellularly, and tau protein, which is a kind of microtubule-associated protein specific for brain, has been revealed as its main component (Proc. Natl. Acad. Sci. USA, 85, 4506 (1988); Neuron, 1, 827 (1988)).

[0004] Furthermore, on the basis of genetic investigations, presenilins 1 and 2 were found as causative genes of familial Alzheimer disease (Nature, 375, 754 (1995); Science, 269, 973 (1995); Nature. 376, 775 (1995)), and it has been revealed that presence of mutants of presenilins 1 and 2 promotes the secretion of A β (Neuron, 17, 1005 (1996); Proc. Natl. Acad. Sci. USA, 94, 2025 (1997)). From these results, it is considered that, in Alzheimer disease, A β abnormally accumulates and agglomerates due to a certain reason, which engages with the formation of PHF to cause death of nerve cells. It is also expected that extracellular outflow of glutamic acid and activation of glutamate receptor responding to the outflow may possibly be important factors in an early process of the nerve cell death caused by ischemic cerebrovascular accidents.

[0005] It has been reported that kainic acid treatment that stimulates the AMPA receptor, one of glutamate receptor, increases mRNA of the amyloid precursor protein (abbreviated as "APP" hereinafter in the specification) as a precursor of A β (Society for Neuroscience Abstracts, 17, 1445 (1991)), and also promotes metabolism ofAPP (The Journal of Neuroscience, 10, 2400 (1990)). Therefore, it has been strongly suggested that the accumulation of A β is involved in cellular death due to ischemic cerebrovascular disorders. Other diseases in which abnormal accumulation and agglomeration of A β are observed include, for example, Down syndrome, cerebral bleeding due to solitary cerebral amyloid angiopathy, Lewy body disease. Furthermore, as diseases showing neurofibrillary tangles due to the PHF accumulation, examples include progressive supranuclear palsy, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, Guam parkinsonism-dementia complex, Lewy body disease.

[0006] The tau protein is generally composed of a group of related proteins that forms several bands at molecular weights of 48-65 kDa in SDS-polyacrylamide gel electrophoresis, and it promotes the formation of microtubules. It has been verified that tau protein incorporated in the PHF in the brain suffering from Alzheimer disease is abnormally phosphorylated compared with usual tau protein (J. Biochem., 99, 1807 (1986); Proc. Natl. Acad. Sci. USA, 83, 4913 (1986)). An enzyme catalyzing the abnormal phosphorylation has been isolated. The protein was named as tau protein kinase 1 (abbreviated as "TPK1" hereinafter in the specification), and its physicochemical properties have been elucidated (J. Biol. Chem., 267, 10897 (1992)). Moreover, cDNA of rat TPK1 was cloned from a rat cerebral cortex cDNA library based on a partial amino acid sequence of TPK1, and its nucleotide sequence was determined and an amino acid sequence was deduced. As a result, it has been revealed that the primary structure of the rat TPK1 corresponds to that of the enzyme known as rat GSK-3 β (glycogen synthase kinase 3 β , FEBS Lett., 325, 167 (1993)).

[0007] It has been reported that A β , the main component of senile plaques, is neurotoxic (Science, 250, 279 (1990)). However, various theories have been proposed as for the reason why A β causes the cell death, and any authentic theory has not yet been established. Takashima et al. observed that the cell death was caused by A β treatment of fetal rat hippocampus primary culture system, and then found that the TPK1 activity was increased by A β treatment and the cell death by A β was inhibited by antisense of TPK1 (Proc. Natl. Acad. Sci. USA, 90, 7789 (1993); EP616032).

[0008] In view of the foregoing, compounds which inhibit the TPK1 activity may possibly suppress the neurotoxicity of A β and the formation of PHF and inhibit the nerve cell death in the Alzheimer disease, thereby cease or defer the

progress of the disease. The compounds may also be possibly used as a medicament for therapeutic treatment of ischemic cerebrovascular disorder, Down syndrome, cerebral amyloid angiopathy, cerebral bleeding due to Lewy body disease by suppressing the cytotoxicity of A β. Furthermore, the compounds may possibly be used as a medicament for therapeutic treatment of neurodegenerative diseases such as progressive supranuclear palsy, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, Guam parkinsonism-dementia complex, Lewy body disease, Pick's disease, corticobasal degeneration and frontotemporal dementia, vascular dementia, traumatic injuries, brain and spinal cord trauma, peripheral neuropathies, retinopathies and glaucoma, as well as other diseases such as non-insulin dependent diabetes, obesity, manic depressive illness, schizophrenia, alopecia, breast cancer, non-small cell lung carcinoma, thyroid cancer, T or B-cell leukemia, and several virus-induced tumors.

[0009] As structurally similar compounds to the compounds of the present invention represented by formula (I) described later, the compounds disclosed in the International Publication Nos. WO01/70729, WO03/037888 and WO03/027080 are known. However, these compounds are not enough as medicament in the pharmacokinetics .

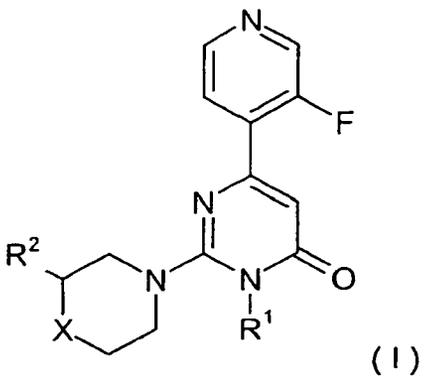
Disclosure of the Invention

[0010] An object of the present invention is to provide compounds useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of diseases such as Alzheimer disease. More specifically, the object is to provide novel compounds useful as an active ingredient of a medicament that enables radical prevention and/or treatment of the neurodegenerative diseases such as Alzheimer disease by inhibiting the TPK1 activity to suppress the neurotoxicity of A β and the formation of the PHF and by inhibiting the death of nerve cells.

[0011] In order to achieve the foregoing object, the inventors of the present invention conducted screenings of various compounds having inhibitory activity against the phosphorylation of TPK1. As a result, they found that compounds represented by the following formula (I) had the desired activity and were useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of the aforementioned diseases. The present invention was achieved on the basis of these findings.

[0012] The present invention thus provides;

1. A compound represented by the formula (I), an optically active isomer thereof, or a pharmaceutically acceptable salt thereof:



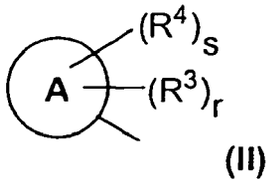
(I)

wherein each symbol is as defined below.

R^1 represents a C_1-C_{12} alkyl;

R^2 represents

a group represented by the following formula (II):



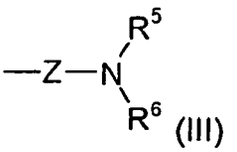
(II)

wherein A represents a C_6-C_{10} aryl or a heterocycle selected from the group consisting of benzofuran, dihydrobenzofuran, isobenzofuran, chromene, indole, indoline, isoindole, benzoxazolinone, tetrahydroisoquinoline, chroman, isochroman, benzothiophen, isoindoline, indazole, benzimidazole, benzotriazole,benzothiazolinone, quinoline, phthalazine, quinoxaline, quinazoline, cinnoline, benzothiazole, benzodioxole, benzodioxane, phthalimide;

R^3 may be the same or different and represents hydrogen atom,
hydroxyl,
a halogen,
nitro,
cyano
a C_1-C_6 alkyl which may be substituted,
a C_2-C_6 alkenyl which may be substituted,
a C_2-C_6 alkynyl which may be substituted,
a C_3-C_7 cycloalkyl which may be substituted,
a C_3-C_7 cycloalkenyl which may be substituted,
a C_6-C_{10} aryl which may be substituted,
a heterocycle which may be substituted,
a C_1-C_6 alkyloxy which may be substituted,
a C_3-C_6 alkenyloxy which may be substituted,
a C_3-C_6 alkynyloxy which may be substituted,
a C_3-C_7 cycloalkyloxy which may be substituted,
a C_3-C_7 cycloalkenyloxy which may be substituted,
a C_6-C_{10} aryloxy which may be substituted,
a heterocycle-oxy group which may be substituted, mercapto,
a C_1-C_6 alkylthio which may be substituted,
a C_3-C_6 alkenylthio which may be substituted,
a C_3-C_6 alkynylthio which may be substituted,
a C_3-C_7 cycloalkylthio which may be substituted,
a C_3-C_7 cycloalkenylthio which may be substituted,
a C_6-C_{10} arylthio which may be substituted,
a heterocycle-thio group which may be substituted, amino,
a C_1-C_6 alkylamino which may be substituted,
a C_3-C_6 alkenylamino which may be substituted,
a C_3-C_6 alkynylamino which may be substituted,
a C_3-C_7 cycloalkylamino which may be substituted,
a C_3-C_7 cycloalkenylamino which may be substituted,
a C_6-C_{10} arylamino which may be substituted,
a heterocycle-amino which may be substituted,
a N,N-di-C_1-C_6 alkylamino which may be substituted,
a N-C_1-C_6 alkyl-N-C_3-C_6 alkenylamino which may be substituted,
a N-C_1-C_6 alkyl-N-C_3-C_6 alkynylamino which may be substituted,
a N-C_1-C_6 alkyl-N-C_3-C_7 cycloalkylamino which may be substituted,
a N-C_1-C_6 alkyl-N-C_3-C_7 cycloalkenylamino which may be substituted,
a N-C_1-C_6 alkyl-N-C_6-C_{10} arylamino which may be substituted,
a N-C_1-C_6 alkyl-N-heterocycle-amino which may be substituted,
a N,N-di-C_3-C_6 alkenylamino which may be substituted,
a N-C_3-C_6 alkenyl-N-C_3-C_6 alkynylamino which may be substituted,
a N-C_3-C_6 alkenyl-N-C_3-C_7 cycloalkylamino which may be substituted,
a N-C_3-C_6 alkenyl-N-C_3-C_7 cycloalkenylamino which may be substituted,
a N-C_3-C_6 alkenyl-N-C_6-C_{10} arylamino which may be substituted,
a N-C_3-C_6 alkenyl-N-heterocycle-amino which may be substituted,
a N,N-di-C_3-C_6 alkynylamino which may be substituted,
a N-C_3-C_6 alkynyl-N-C_3-C_7 cycloalkylamino which may be substituted,
a N-C_3-C_6 alkynyl-N-C_3-C_7 cycloalkenylamino which may be substituted,
a N-C_3-C_6 alkynyl-N-C_6-C_{10} arylamino which may be substituted,
a N-C_3-C_6 alkynyl-N-heterocycle-amino which may be substituted,
a N,N-di-C_3-C_7 cycloalkylamino which may be substituted,
a N-C_3-C_7 cycloalkyl-N-C_3-C_7 cycloalkenylamino which may be substituted,
a N-C_3-C_7 cycloalkyl-N-C_6-C_{10} arylamino which may be substituted,

a N-C_3-C_7 cycloalkyl-N-heterocycle-amino which may be substituted,
a N,N-di-C_3-C_7 cycloalkenylamino which may be substituted,
a N-C_3-C_7 cycloalkenyl-N-C_6-C_{10} arylamino which may be substituted,
a N-C_3-C_7 cycloalkenyl-N-heterocycle-amino which may be substituted,
a N,N-di-C_6-C_{10} arylamino which may be substituted,
a N-C_6-C_{10} aryl-N-heterocycle-amino which may be substituted,
a N,N-diheterocycle-amino which may be substituted,
a C_1-C_6 alkylcarbonyl which may be substituted,
a C_2-C_6 alkenylcarbonyl which may be substituted,
a C_2-C_6 alkynylcarbonyl which may be substituted,
a C_3-C_7 cycloalkylcarbonyl which may be substituted,
a C_3-C_7 cycloalkenylcarbonyl which may be substituted,
a C_6-C_{10} arylcarbonyl which may be substituted,
a heterocycle-carbonyl which may be substituted,
a C_1-C_6 alkylsulfonyl which may be substituted,
a C_3-C_6 alkenylsulfonyl which may be substituted,
a C_3-C_6 alkynylsulfonyl which may be substituted,
a C_3-C_7 cycloalkylsulfonyl which may be substituted,
a C_3-C_7 cycloalkenylsulfonyl which may be substituted,
a C_6-C_{10} arylsulfonyl which may be substituted,
a heterocycle-sulfonyl which may be substituted, carboxyl,
a C_1-C_6 alkyloxycarbonyl which may be substituted,
a C_3-C_6 alkenyloxycarbonyl which may be substituted,
a C_3-C_6 alkynyloxycarbonyl which may be substituted,
a C_3-C_7 cycloalkyloxycarbonyl which may be substituted,
a C_3-C_7 cycloalkenyloxycarbonyl which may be substituted,
a C_6-C_{10} aryloxycarbonyl which may be substituted,
a heterocycle-oxycarbonyl which may be substituted, aminocarbonyl,
a C_1-C_6 alkylaminocarbonyl which may be substituted,
a C_3-C_6 alkenylaminocarbonyl which may be substituted,
a C_3-C_6 alkynylaminocarbonyl which may be substituted,
a C_3-C_7 cycloalkylaminocarbonyl which may be substituted,
a C_3-C_7 cycloalkenylaminocarbonyl which may be substituted,
a C_6-C_{10} arylaminocarbonyl which may be substituted,
a heterocycle-aminocarbonyl which may be substituted,
a N,N-di-C_1-C_6 alkylaminocarbonyl which may be substituted,
a N-C_1-C_6 alkyl-N-C_3-C_7 alkenylaminocarbonyl which may be substituted,
a N-C_1-C_6 alkyl-N-C_3-C_7 alkynylaminocarbonyl which may be substituted,
a N-C_1-C_6 alkyl-N-C_3-C_7 cycloalkylaminocarbonyl which may be substituted,
a N-C_1-C_6 alkyl-N-C_3-C_7 cycloalkenylaminocarbonyl which may be substituted,
a N-C_1-C_6 alkyl-N-C_6-C_{10} arylaminocarbonyl which may be substituted,
a N-C_1-C_6 alkyl-N-heterocycle-aminocarbonyl which may be substituted,
a N,N-di-C_3-C_6 alkenylaminocarbonyl which may be substituted,
a N-C_3-C_6 alkenyl-N-C_3-C_6 alkynylaminocarbonyl which may be substituted,
a N-C_3-C_6 alkenyl-N-C_3-C_7 cycloalkylaminocarbonyl which may be substituted,
a N-C_3-C_6 alkenyl-N-C_3-C_7 cycloalkenylaminocarbonyl which may be substituted,
a N-C_3-C_6 alkenyl-N-C_6-C_{10} arylaminocarbonyl which may be substituted,
a N-C_3-C_6 alkenyl-N-heterocycle-aminocarbonyl which may be substituted,
a N,N-di-C_3-C_6 alkynylaminocarbonyl which may be substituted,
a N-C_3-C_6 alkynyl-N-C_3-C_7 cycloalkylaminocarbonyl which may be substituted,
a N-C_3-C_6 alkynyl-N-C_3-C_7 cycloalkenylaminocarbonyl which may be substituted,
a N-C_3-C_6 alkynyl-N-C_6-C_{10} arylaminocarbonyl which may be substituted,
a N-C_3-C_6 alkynyl-N-heterocycle-aminocarbonyl which may be substituted,
a N,N-di-C_3-C_7 cycloalkylaminocarbonyl which may be substituted,
a N-C_3-C_7 cycloalkyl-N-C_3-C_7 cycloalkenylaminocarbonyl which may be substituted,
a N-C_3-C_7 cycloalkyl-N-C_6-C_{10} arylaminocarbonyl which may be substituted,
a N-C_3-C_7 cycloalkyl-N-heterocycle-aminocarbonyl which may be substituted,
a N,N-di-C_3-C_7 cycloalkenylaminocarbonyl which may be substituted,

a N-C_3-C_7 cycloalkenyl-N-C_6-C_{10} arylaminocarbonyl which may be substituted,
a N-C_3-C_7 cycloalkenyl-N-heterocycle-aminocarbonyl which may be substituted,
a N,N-di-C_6-C_{10} arylaminocarbonyl which may be substituted,
a N-C_6-C_{10} aryl-N-heterocycle-aminocarbonyl which may be substituted, or
a N,N-di-heterocycle-aminocarbonyl which may be substituted, aminothiocarbonyl,
a C_1-C_6 alkylaminothiocarbonyl which may be substituted,
a C_3-C_6 alkenylaminothiocarbonyl which may be substituted,
a C_3-C_6 alkynylaminothiocarbonyl which may be substituted,
a C_3-C_7 cycloalkylaminothiocarbonyl which may be substituted,
a C_3-C_7 cycloalkenylaminothiocarbonyl which may be substituted,
a C_6-C_{10} arylaminothiocarbonyl which may be substituted,
a heterocycle-aminothiocarbonyl which may be substituted,
a N,N-di-C_1-C_6 alkylaminothiocarbonyl which may be substituted,
a N-C_1-C_6 alkyl-N-C_3-C_7 alkenylaminothiocarbonyl which may be substituted,
a N-C_1-C_6 alkyl-N-C_3-C_7 alkynylaminothiocarbonyl which may be substituted,
a N-C_1-C_6 alkyl-N-C_3-C_7 cycloalkylaminothiocarbonyl which may be substituted,
a N-C_1-C_6 alkyl-N-C_3-C_7 cycloalkenylaminothiocarbonyl which may be substituted,
a N-C_1-C_6 alkyl-N-C_6-C_{10} arylaminothiocarbonyl which may be substituted,
a N-C_1-C_6 alkyl-N-heterocycle-aminothiocarbonyl which may be substituted,
a N,N-di-C_3-C_6 alkenylaminothiocarbonyl which may be substituted,
a N-C_3-C_6 alkenyl-N-C_3-C_6 alkynylaminothiocarbonyl which may be substituted,
a N-C_3-C_6 alkenyl-N-C_3-C_7 cycloalkylaminothiocarbonyl which may be substituted,
a N-C_3-C_6 alkenyl-N-C_3-C_7 cycloalkenylaminothiocarbonyl which may be substituted,
a N-C_3-C_6 alkenyl-N-C_6-C_{10} arylaminothiocarbonyl which may be substituted,
a N-C_3-C_6 alkenyl- N-heterocycle-aminothiocarbonyl which may be substituted,
a N,N-di-C_3-C_6 alkynylaminothiocarbonyl which may be substituted,
a N-C_3-C_6 alkynyl-N-C_3-C_7 cycloalkylaminothiocarbonyl which may be substituted,
a N-C_3-C_6 alkynyl-N-C_3-C_7 cycloalkenylaminothiocarbonyl which may be substituted,
a N-C_3-C_6 alkynyl-N-C_6-C_{10} arylaminothiocarbonyl which may be substituted,
a N-C_3-C_6 alkynyl-N-heterocycle-aminothiocarbonyl which may be substituted,
a N,N-di-C_3-C_7 cycloalkylaminothiocarbonyl which may be substituted,
a N-C_3-C_7 cycloalkyl-N-C_3-C_7 cycloalkenylaminothiocarbonyl which may be substituted,
a N-C_3-C_7 cycloalkyl-N-C_6-C_{10} arylaminothiocarbonyl which may be substituted,
a N-C_3-C_7 cycloalkyl-N-heterocycle-aminothiocarbonyl which may be substituted,
a N,N-di-C_3-C_7 cycloalkenylaminothiocarbonyl which may be substituted,
a N-C_3-C_7 cycloalkenyl-N-C_6-C_{10} arylaminothiocarbonyl which may be substituted,
a N-C_3-C_7 cycloalkenyl-N-heterocycle-aminothiocarbonyl which may be substituted,
a N,N-di-C_6-C_{10} arylaminothiocarbonyl which may be substituted,
a N-C_6-C_{10} aryl-N-heterocycle-aminothiocarbonyl which may be substituted, or
a N,N-di-heterocycle-aminothiocarbonyl which may be substituted,
R^4 represents hydrogen atom, or
a group represented by the following formula (III):

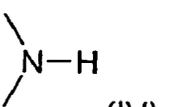


(III)

wherein Z represents a bond, carbonyl or sulfonyl,
R^5 and R^6 each independently represents hydrogen atom,
a C_1-C_6 alkyl which may be substituted,
a C_2-C_6 alkenyl which may be substituted,
a C_2-C_6 alkynyl which may be substituted,
a C_3-C_7 cycloalkyl which may be substituted,
a C_3-C_7 cycloalkenyl which may be substituted,
a C_6-C_{10} aryl which may be substituted,

a heterocycle which may be substituted,
a C_1-C_6 alkylcarbonyl which may be substituted,
a C_2-C_6 alkenylcarbonyl which may be substituted,
a C_2-C_6 alkynylcarbonyl which may be substituted,
a C_3-C_7 cycloalkylcarbonyl which may be substituted,
a C_3-C_7 cycloalkenylcarbonyl which may be substituted,
a C_6-C_{10} arylcarbonyl which may be substituted,
a heterocycle-carbonyl which may be substituted,
a C_1-C_6 alkylsulfonyl which may be substituted,
a C_3-C_6 alkenylsulfonyl which may be substituted,
a C_3-C_6 alkynylsulfonyl which may be substituted,
a C_3-C_7 cycloalkylsulfonyl which may be substituted,
a C_3-C_7 cycloalkenylsulfonyl which may be substituted,
a C_6-C_{10} arylsulfonyl which may be substituted,
a heterocycle-sulfonyl which may be substituted, carboxyl,
a C_1-C_6 alkyloxycarbonyl which may be substituted,
a C_3-C_6 alkenyloxycarbonyl which may be substituted,
a C_3-C_6 alkynyloxycarbonyl which may be substituted,
a C_3-C_7 cycloalkyloxycarbonyl which may be substituted,
a C_3-C_7 cycloalkenyloxycarbonyl which may be substituted,
a C_6-C_{10} aryloxycarbonyl which may be substituted,
a heterocycle-oxycarbonyl which may be substituted, aminocarbonyl,
a C_1-C_6 alkylaminocarbonyl which may be substituted,
a C_3-C_6 alkenylaminocarbonyl which may be substituted,
a C_3-C_6 alkynylaminocarbonyl which may be substituted,
a C_3-C_7 cycloalkylaminocarbonyl which may be substituted,
a C_3-C_7 cycloalkenylaminocarbonyl which may be substituted,
a C_6-C_{10} arylaminocarbonyl which may be substituted,
a heterocycle-aminocarbonyl which may be substituted,
a N,N-di-C_1-C_6 alkylaminocarbonyl which may be substituted,
a N-C_1-C_6 alkyl-N-C_3-C_7 alkenylaminocarbonyl which may be substituted,
a N-C_1-C_6 alkyl-N-C_3-C_7 alkynylaminocarbonyl which may be substituted,
a N-C_1-C_6 alkyl-N-C_3-C_7 cycloalkylaminocarbonyl which may be substituted,
a N-C_1-C_6 alkyl-N-C_3-C_7 cycloalkenylaminocarbonyl which may be substituted,
a N-C_1-C_6 alkyl-N-C_6-C_{10} arylaminocarbonyl which may be substituted,
a N-C_1-C_6 alkyl-N-heterocycle-aminocarbonyl which may be substituted,
a N,N-di-C_3-C_6 alkenylaminocarbonyl which may be substituted,
a N-C_3-C_6 alkenyl-N-C_3-C_6 alkynylaminocarbonyl which may be substituted,
a N-C_3-C_6 alkenyl-N-C_3-C_7 cycloalkylaminocarbonyl which may be substituted,
a N-C_3-C_6 alkenyl-N-C_3-C_7 cycloalkenylaminocarbonyl which may be substituted,
a N-C_3-C_6 alkenyl-N-C_6-C_{10} arylaminocarbonyl which may be substituted,
a N-C_3-C_6 alkenyl-N-heterocycle-aminocarbonyl which may be substituted,
a N,N-di-C_3-C_6 alkynylaminocarbonyl which may be substituted,
a N-C_3-C_6 alkynyl-N-C_3-C_7 cycloalkylaminocarbonyl which may be substituted,
a N-C_3-C_6 alkynyl-N-C_3-C_7 cycloalkenylaminocarbonyl which may be substituted,
a N-C_3-C_6 alkynyl-N-C_6-C_{10} arylaminocarbonyl which may be substituted,
a N-C_3-C_6 alkynyl-N-heterocycle-aminocarbonyl which may be substituted,
a N,N-di-C_3-C_7 cycloalkylaminocarbonyl which may be substituted,
a N-C_3-C_7 cycloalkyl-N-C_3-C_7 cycloalkenylaminocarbonyl which may be substituted,
a N-C_3-C_7 cycloalkyl-N-C_6-C_{10} arylaminocarbonyl which may be substituted,
a N-C_3-C_7 cycloalkyl-N-heterocycle-aminocarbonyl which may be substituted,
a N,N-di-C_3-C_7 cycloalkenylaminocarbonyl which may be substituted,
a N-C_3-C_7 cycloalkenyl-N-C_6-C_{10} arylaminocarbonyl which may be substituted,
a N-C_3-C_7 cycloalkenyl-N-heterocycle-aminocarbonyl which may be substituted,
a N,N-di-C_6-C_{10} arylaminocarbonyl which may be substituted,
a N-C_6-C_{10} aryl-N-heterocycle-aminocarbonyl which may be substituted, or
a N,N-di-heterocycle-aminocarbonyl which may be substituted, aminothiocarbonyl,
a C_1-C_6 alkylaminothiocarbonyl which may be substituted,

a C_3-C_6 alkenylaminothiocarbonyl which may be substituted,
a C_3-C_6 alkynylaminothiocarbonyl which may be substituted,
a C_3-C_7 cycloalkylaminothiocarbonyl which may be substituted,
a C_3-C_7 cycloalkenylaminothiocarbonyl which may be substituted,
a C_6-C_{10} arylaminothiocarbonyl which may be substituted,
a heterocycle-aminothiocarbonyl which may be substituted,
a N,N-di-C_1-C_6 alkylaminothiocarbonyl which may be substituted,
a N-C_1-C_6 alkyl-N-C_3-C_7 alkenylaminothiocarbonyl which may be substituted,
a N-C_1-C_6 alkyl-N-C_3-C_7 alkynylaminothiocarbonyl which may be substituted,
a N-C_1-C_6 alkyl-N-C_3-C_7 cycloalkylaminothiocarbonyl which may be substituted,
a N-C_1-C_6 alkyl-N-C_3-C_7 cycloalkenylaminothiocarbonyl which may be substituted,
a N-C_1-C_6 alkyl-N-C_6-C_{10} arylaminothiocarbonyl which may be substituted,
a N-C_1-C_6 alkyl-N-heterocycle-aminothiocarbonyl which may be substituted,
a N,N-di-C_3-C_6 alkenylaminothiocarbonyl which may be substituted,
a N-C_3-C_6 alkenyl-N-C_3-C_6 alkynylaminothiocarbonyl which may be substituted,
a N-C_3-C_6 alkenyl-N-C_3-C_7 cycloalkylaminothiocarbonyl which may be substituted,
a N-C_3-C_6 alkenyl-N-C_3-C_7 cycloalkenylaminothiocarbonyl which may be substituted,
a N-C_3-C_6 alkenyl-N-C_6-C_{10} arylaminothiocarbonyl which may be substituted,
a N-C_3-C_6 alkenyl-N-heterocycle-aminothiocarbonyl which may be substituted,
a N,N-di-C_3-C_6 alkynylaminothiocarbonyl which may be substituted,
a N-C_3-C_6 alkynyl-N-C_3-C_7 cycloalkylaminothiocarbonyl which may be substituted,
a N-C_3-C_6 alkynyl-N-C_3-C_7 cycloalkenylaminothiocarbonyl which may be substituted,
a N-C_3-C_6 alkynyl-N-C_6-C_{10} arylaminothiocarbonyl which may be substituted,
a N-C_3-C_6 alkynyl-N-heterocycle-aminothiocarbonyl which may be substituted,
a N,N-di-C_3-C_7 cycloalkylaminothiocarbonyl which may be substituted,
a N-C_3-C_7 cycloalkyl-N-C_3-C_7 cycloalkenylaminothiocarbonyl which may be substituted,
a N-C_3-C_7 cycloalkyl-N-C_6-C_{10} arylaminothiocarbonyl which may be substituted,
a N-C_3-C_7 cycloalkyl-N-heterocycle-aminothiocarbonyl which may be substituted,
a N,N-di-C_3-C_7 cycloalkenylaminothiocarbonyl which may be substituted,
a N-C_3-C_7 cycloalkenyl-N-C_6-C_{10} arylaminothiocarbonyl which may be substituted,
a N-C_3-C_7 cycloalkenyl-N-heterocycle-aminothiocarbonyl which may be substituted,
a N,N-di-C_6-C_{10} arylaminothiocarbonyl which may be substituted,
a N-C_6-C_{10} aryl-N-heterocycle-aminothiocarbonyl which may be substituted, or a N,N-di-heterocycle-aminothiocarbonyl which may be substituted, or R^5 and R^6 may combine to each other to form a 3 to 7-membered nitrogen-containing heterocyclic ring which may further contain oxygen and/or sulfur atom and may be substituted, or
R^5 and R^3 may combine to each other to form a 5 to 7-membered nitrogen-containing heterocyclic ring which may further contain oxygen and/or sulfur atom and may be substituted,
each of r and s represents 0 or an integer of 1 to 5, provided that sum of r and s is 5 or less;
X represents oxygen atom, or
a group represented by the following formula (IV):



(IV)

2. The compound, an optically active isomer thereof, or a pharmaceutically acceptable salt thereof according to claim 1, wherein R^1 is a C_1-C_6 alkyl.
3. The compound, an optically active isomer thereof, or a pharmaceutically acceptable salt thereof according to claim 1, wherein R^1 is methyl group.
4. The compound, an optically active isomer thereof, or a pharmaceutically acceptable salt thereof according to any one of the claims 1 to 3, wherein A is phenyl group.
5. The compound, an optically active isomer thereof, or a pharmaceutically acceptable salt thereof according to any one of the claims 1 to 4, wherein X is oxygen atom.
6. The compound, an optically active isomer thereof, or a pharmaceutically acceptable salt thereof according to any one of the claims 1 to 4, wherein X is a group represented by the formula (IV).
7. A compound according to claim 1 selected from the group consisting of:

6-(3-Fluoro-pyridin-4-yl)-3-methyl-2-((3S)-3-(4-morpholin-4-yl-phenyl)-piperazin-1-yl)-3H-pyrimidin-4-one;
2-((2S)-2-(4-((3R)-3-Dimethylamino-pyrrolidin-1-yl)-phenyl)-morpholin-4-yl)-6-(3-fluoro-pyridin-4-yl)-3-methyl-3H-pyrimidin-4-one;
6-(3-Fluoro-pyridin-4-yl)-3-methyl-2-((3S)-3-(4-piperidin-1-yl-phenyl)-piperazin-1-yl)- 3H-pyrimidin-4-one;
6-(3-Fluoro-pyridin-4-yl)-3-methyl-2-((2S)-2-(4-(4-pyrrolidin-1-yl-piperidin-1-yl)-phenyl(-morpholin-4-yl)-3H-pyrimidin-4-one;
2-((2S)-2-(4-(4-Dimethylamino-piperidin-1-yl)-phenyl)-morpholin-4-yl)-6-(3-fluoro-pyridin-4-yl)-3-methyl-3H-pyrimidin-4-one;
6-(3-Fluoro-pyridin-4-yl)-3-methyl-2-((3S)-3-(4-(4-methyl-piperazin-1-yl)-phenyl)-piperazin-1-yl)-3H-pyrimidin-4-one;
6-(3-Fluoro-pyridin-4-yl)-2-(3S)-3-(4-(4-hydroxy-piperidin-1-yl)-phenyl)-piperazin-1-yl)-3-methyl-3H-pyrimidin-4-one;
6-(3-Fluoro-pyridin-4-yl)-2-((3S)-3-(4-((3R)-3-hydroxy-pyrrolidin-1-yl)-phenyl)-piperazin-1-yl)-3-methyl-3H-pyrimidin-4-one;
2-((2S)-2-(4-((3S,5R)-3,5-Dimethyl-piperazin-1-yl)-phenyl)-morpholin-4-yl)-6-(3-fluoro-pyridin-4-yl)-3-methyl-3H-pyrimidin-4-one;
6-(3-Fluoro-pyridin-4-yl)-3-methyl-2-((2S)-2-(4-(4-methyl-piperazin-1-yl)-phenyl)-morpholin-4-yl)-3H-pyrimidin-4-one;
2-((2S)-2-(4-((3S)-3-Dimethylamino-pyrrolidin-1-yl)-phenyl)-morpholin-4-yl)-6-(3-fluoro-pyridin-4-yl)-3-methyl-3H-pyrimidin-4-one;
6-(3-Fluoro-pyridin-4-yl)-2-((2S)-2-(4-(4-isopropyl-piperazin-1-yl)-phenyl)-morpholin-4-yl)-3-methyl-3H-pyrimidin-4-one;
6-(3-Fluoro-pyridin-4-yl)-2-((2S)-2-(4-(4-(2-hydroxyethyl)-piperazin-1-yl)-phenyl)-morpholin-4-yl)-3-methyl-3H-pyrimidin-4-one;
6-(3-fluoro-pyridin-4-yl)-3-methyl-2-((3S)-3-(4-((3S)-3-(pyrrolidin-1-yl)-pyrrolidin-1-yl)-phenyl)-piperazin-1-yl)-3H-pyrimidin-4-one;
6-(3-Fluoro-pyridin-4-yl)-3-methyl-2-((3S)-3-(4-(5-methyl-(1,2,4)oxadiazol-3-yl)-phenyl)-piperazin-1-yl)-3H-pyrimidin-4-one;
2-((2S)-2-(4-Cyclopentylamino-phenyl)-morpholin-4-yl)-6-(3-fluoro-pyridin-4-yl)-3-methyl-3H-pyrimidin-4-one;
6-(3-Fluoro-pyridin-4-yl)-2-((2S)-2-(4-(3-hydroxy-azetidin-1-yl)-phenyl)-morphol in-4-yl)-3-methyl-3H-pyrimidin-4-one;
N-(4-((2S)-4-((4-(3-Fluoro-pyridin-4-yl)-1-methyl-6-oxo-1,6-dihydro-pyrimidin-2-yl)-morpholin-2-yl)-phenyl)-acetamide;
2-((2S)-2-(4-Cyclopentyloxy-phenyl)-morpholin-4-yl)-6-(3-fluoro-pyridin-4-yl)-3-methyl-3H-pyrimidin-4-one;
2-((2S)-2-(4-Cyclopropylmethoxy-phenyl)-morpholin-4-yl)-6-(3-fluoro-pyridin-4-yl)-3- methyl-3H-pyrimidin-4-one;
2-((2S)-2-(4-(2-Dimethylamino-ethoxy)-phenyl)-morpholin-4-yl)-6-(3-fluoro-pyridin-4- yl)-3-methyl-3H-pyrimidin-4-one;
2-((2S)-2-(4-Amino-phenyl)-morpholin-4-yl)-6-(3-fluoro-pyridin-4-yl)-3-methyl-3H-pyrimidin-4-one;
Cyclopropanecarboxylic acid (4-((2S)-4-(4-(3-fluoro-pyridin-4-yl)-1-methyl-6-oxo-1,6- dihydro-pyrimidin-2-yl)-morpholin-2-yl)-phenyl)-amide;
N-(4-((2S)-4-(4-(3-Fluoro-pyridin-4-yl)-1-methyl-6-oxo-1,6-dihydro-pyrimidin-2-yl)-morpholin-2-yl)-phenyl)-2,2-dimethyl-propionamide;
6-(3-Fluoro-pyridin-4-yl)-3-methyl-2-((2S)-2-(4-(methyl-((3R)-tetrahydro-furan-3-yl)- amino)-phenyl)-morpholin-4-yl)-3H-pyrimidin-4-one;
6-(3-Fluoro-pyridin-4-yl)-3-methyl-2-((2S)-2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-morpholin-4-yl)-3H-pyrimidin-4-one;
6-(3-Fluoro-pyridin-4-yl)-2-((2S)-2-(4-hydroxy-phenyl)-morpholin-4-yl)-3-methyl-3H- pyrimidin-4-one;
2-((2S)-2-(4-(2-Diethylamino-ethoxy)-phenyl)-morpholin-4-yl)-6-(3-fluoro-pyridin-4-yl)-3-methyl-3H-pyrimidin-4-one;
6-(3-Fluoro-pyridin-4-yl)-3-methyl-2-((2S)-2-(4-(2-piperidin-1-yl-ethoxy)-phenyl)-morpholin-4-yl)-3H-pyrimidin-4-one;
6-(3-Fluoro-pyridin-4-yl)-3-methyl-2-((2S)-2-(4-(2-(4-methyl-piperazin-1-yl)-ethoxy)- phenyl)-morpholin-4-yl)-3H-pyrimidin-4-one;
N^2,N^2-Dimethyl-N^1-(4-((2S)-4-(3-methyl-4-oxo-3,4-dihydro-6-(3-fluoropyridin-4-yl)pyrimidin-2-yl)morpholin-2-yl)phenyl)glycinamide;
Methyl (4-((2S)-4-(6-(3-fluoropyridin-4-yl)-3-methyl-4-oxo-3H-pyrimidin-2-yl)morpholin-2-yl)phenyl)carbamate;
N'-(4-((2S)-4-(6-(3-Fluoropyridin-4-yl)-3-methyl-4-oxo-3H-pyrimidin-2-yl)morpholin-2-yl)phenyl)-N,N-dimethylu-

rea;
6-{4-[4-(3-Fluoropyridin-4-yl)-1-methyl-6-oxo-1,6-dihydropyrimidin-2-yl]morpholin-2-yl}-3,4-dihydroquinolin-2(1H)-one;
6-(3-Fluoro-pyridin-4-yl)-3-methyl-2-{(2S)-2-[4-morpholine-4-carbonyl]-phenyl}-morpholin-4-yl}-3H-pyrimidin-4-one;
N-(3-{(2S)-4-[4-(3-Fluoropyridin-4-yl)-1-methyl-6-oxo-1,6-dihydropyrimidin-2-yl]-morpholin-2-yl}-4-methoxyphenyl)acetamide;
N-(3-{(2S)-4-[4-(3-Fluoropyridin-4-yl)-1-methyl-6-oxo-1,6-dihydropyrimidin-2-yl]-morpholin-2-yl}phenyl)acetamide; and
6-(3-Fluoropyridin-4-yl)-3-methyl-2-((3S)-3-(4-([1,2,4]oxadiazol-3-yl)phenyl)piperazin- 1-yl)-3H-pyrimidin-4-one,

an optically active isomer thereof, or a pharmaceutically acceptable salt thereof.

8. A medicament comprising as an active ingredient a substance selected from the group consisting of the compound represented by the formula (I) and an optically active isomer thereof, or a pharmaceutically acceptable salt thereof according to claim 1.

9. The medicament according to claim 8 which is used for preventive and/or therapeutic treatment of a disease caused by tau protein kinase 1 hyperactivity to suppress the neurotoxicity of beta amyloid protein and the formation of the paired helical filament and to inhibit the death of nerve cells..

10. The medicament according to claim 8 which is used for preventive and/or therapeutic treatment of a neurodegenerative disease

11. The medicament according to claim 10, wherein the disease is selected from the group consisting of Alzheimer disease, ischemic cerebrovascular accidents, Down syndrome, cerebral bleeding due to cerebral amyloid angiopathy, progressive supranuclear palsy, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, Guam parkinsonism-dementia complex, Lewy body disease, Pick's disease, corticobasal degeneration, frontotemporal dementia, vascular dementia, traumatic injuries, brain and spinal cord trauma, peripheral neuropathies, retinopathies and glaucoma.

12. The medicament according to claim 8, which is used for preventive and/or therapeutic treatment of a disease selected from the group consisting of non-insulin dependent diabetes, obesity, manic depressive illness, schizophrenia, alopecia, breast cancer, non-small cell lung carcinoma, thyroid cancer, T or B-cell leukemia, and a virus-induced tumor.

Mode for Carrying Out the Invention

[0013] Unless otherwise indicated, the following definitions are set forth to illustrate and defined the meaning and scope of the various terms used to describe the invention herein.

[0014] The term "C_1-C_{12} alkyl" means alkyl group having 1 to 12 carbon atoms which may be either linear or branched, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, 1,1-dimethylpropyl, n-hexyl, isohexyl, heptyl, octyl, nonyl, decyl, undecyl or dodecyl.

[0015] The term "C_1-C_6 alkyl" means alkyl group having 1 to 6 carbon atoms which may be either linear or branched, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, 1,1-dimethylpropyl, n-hexyl, isohexyl (a C_1-C_6 alkyl moiety of substituents containing a C_1-C_6 alkyl moiety mentioned in the specification has the same meaning).

[0016] The term "C_2-C_6 alkenyl" means alkenyl group having 2 to 6 carbon atoms, for example, vinyl, propenyl, butenyl, pentenyl, hexenyl (a C_2-C_6 alkenyl moiety of substituents containing a C_2-C_6 alkenyl moiety mentioned in the specification has the same meaning).

[0017] The term "C_3-C_6 alkenyl" means alkenyl group having 3 to 6 carbon atoms, for example, propenyl, butenyl, pentenyl, hexenyl (a C_3-C_6, alkenyl moiety of substituents containing a C_3-C_6 alkenyl moiety mentioned in the specification has the same meaning).

[0018] The term "C_2-C_6 alkynyl" means alkynyl group having 2 to 6 carbon atoms, for example, ethynyl, propynyl, butynyl, pentynyl, hexynyl (a C_2-C_6 alkynyl moiety of substituents containing a C_2-C_6 alkynyl moiety mentioned in the specification has the same meaning).

[0019] The term "C_3-C_6 alkynyl" means alkynyl group having 3 to 6 carbon atoms, for example, propynyl, butynyl, pentynyl, hexynyl (a C_3-C_6 alkynyl moiety of substituents containing a C_3-C_6 alkynyl moiety mentioned in the specification has the same meaning).

[0020] The term "C_3-C_7 cycloalkyl" means cycloalkyl having 3 to 7 carbon atoms, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl (a C_3-C_7 cycloalkyl moiety of substituents containing a C_3-C_7 cycloalkyl moiety mentioned in the specification has the same meaning).

[0021] The term "C_3-C_7 cycloalkenyl" means cycloalkenyl group having 3 to 7 carbon atoms, for example, cyclopropenyl cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl (a C_3-C_7 cycloalkenyl moiety of substituents containing a C_3-C_7 cycloalkenyl moiety mentioned in the specification has the same meaning).

[0022] The term "C_6-C_{10} aryl" means a group having 6 to 10 carbon atoms derived from, for example, benzene, naphthalene, indane, indene, tetrahydronaphthalene (a C_6-C_{10} aryl moiety of substituents containing a C_6-C_{10} aryl moiety mentioned in the specification has the same meaning). The bond position in the cycle is not limited.

[0023] The term "heterocycle" means cyclic group derived from, for example, furan, dihydrofuran, tetrahydrofuran, pyran, dihydropyran, tetrahydropyran, benzofuran, dihydrobenzofuran, isobenzofuran, chromene, chroman, isochroman, thiophene, benzothiophene, pyrrole, pyrroline, pyrrolidine, imidazole, imidazoline, imidazolidine, pyrazole, pyrazoline, pyrazolidine, triazole, tetrazole, pyridine, pyridine oxide, piperidine, pyrazine, piperazine, pyrimidine, pyridazine, indole, indoline, isoindole, isoindoline, indazole, benzimidazole, benzotriazole, tetrahydroisoquinoline, benzothiazolinone, benzoxazolinone, purine, quinolizine, quinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, pteridine, oxazole, oxazolidine, isoxazole, isoxazolidine, oxadiazole, thiazole, benzothiazole, thiazylidine, isothiazole, isothiazolidine, benzodioxole, dioxane, benzodioxane, dithian, morpholine, thiomorpholine, phthalimide homopiperidinyl, homopiperazinyl(a heterocycle moiety of substituents containing a heterocycle moiety mentioned in the specification has the same meaning). The bond position in the cycle is not limited.

[0024] The term "halogen" means chlorine, bromine, fluorine, or iodine.

[0025] In the specification, when a functional group is defined as "which may be substituted", the number of substituents as well as their types and substituting positions are not particularly limited, and when two or more substituents are present, they may be the same or different. Examples of the substituent include, for example, a C_1-C_6 alkyl, a C_2-C_6 alkenyl, a C_2-C_6 alkynyl, a C_3-C_7 cycloalkyl, a C_3-C_7 cycloalkenyl, a C_6-C_{10} aryl, a heterocycle, a C_1-C_6 alkyloxy, a C_3-C_6 alkenyloxy, a C_3-C_6 alkynyloxy, a C_3-C_7 cycloalkyloxy, a C_3-C_7 cycloalkenyloxy, a C_6-C_{10} aryloxy, a heterocycloxy, a halogen, nitro, cyano, hydroxyl, oxo group, a C_1-C_6 alkylcarbonyl, a C_2-C_6 alkenylcarbonyl, a C_2-C_6 alkynylcarbonyl, a C_3-C_7 cycloalkylcarbonyl, a C_3-C_7 cycloalkenylcarbonyl, a C_6-C_{10} arylcarbonyl, a heterocyclecarbonyl, a C_1-C_6 alkylsulfonyl, a C_2-C_6 alkenylsulfonyl, a C_2-C_6, alkynylsulfonyl, a C_3-C_7 cycloalkylsulfonyl, a C_3-C_7 cycloalkenylsulfonyl, a C_6-C_{10} arylsulfonyl, a heterocyclesulfonyl, a C_1-C_6 alkyloxycarbonyl, a C_3-C_6 alkenyloxycarbonyl, a C_3-C_6 alkynyloxycarbonyl, a C_3-C_7 cycloalkyloxycarbonyl, a C_3-C_7 cycloalkenyloxycarbonyl, a C_6-C_{10} aryloxycarbonyl, a heterocycleoxycarbonyl, amino, a C_1-C_6 alkylamino, a C_2-C_6 alkenylamino, a C_2-C_6 alkynylamino, a C_3-C_7 cycloalkylamino, a C_3-C_7 cycloalkenylamino, a C_6-C_{10} arylamino, a heterocycle-amino, a N,N-di-C_1-C_6 alkylamino, aminocarbonyl, a C_1-C_6 alkylaminocarbonyl, a C_3-C_6 alkenylaminocarbonyl, a C_3-C_6 alkynylaminocarbonyl, a C_3-C_7 cycloalkylaminocarbonyl, a C_3-C_7 cycloalkenylaminocarbonyl, a C_6-C_{10} arylaminocarbonyl, a heterocycle-aminocarbonyl, a N,N-di-C_1-C_6 alkylaminocarbonyl. In the above substituents, every term expressed by "C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 alkynyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkenyl, C_6-C_{10} aryl, heterocycle" represents the same meaning as defined above. These substituents are also substituted by the substituents described above.

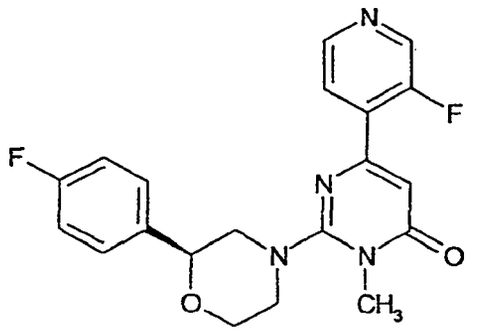
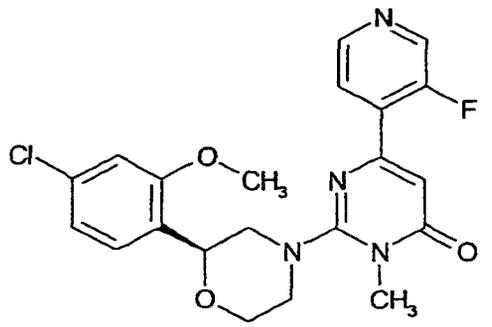
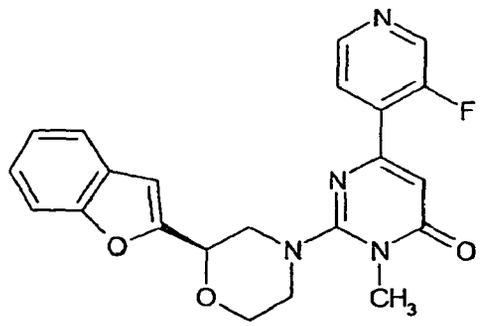
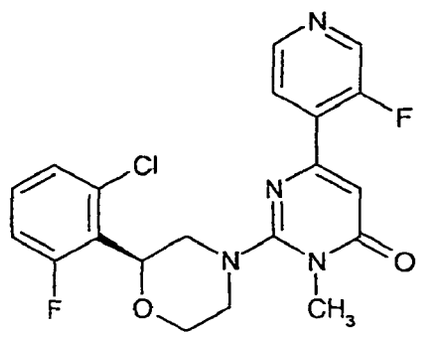
[0026] The pharmaceutically acceptable salt of the compound represented by the aforementioned formula (I) may include the salt with inorganic acid such as hydrochloric acid, hydrobromic acid and the salt with organic acid such as acetic acid, propionic acid, tartaric acid, fumaric acid, maleic acid, malic acid, oxalic acid, succinic acid, citric acid, benzoic acid .

[0027] In addition to the compound represented by the aforementioned formula (I), an optically active isomer thereof, or a pharmaceutically acceptable salt thereof, their solvates and hydrates also fall within the scope of the present invention. The compound represented by the formula (I) may have one or more asymmetric carbon atoms. As for the stereochemistry of such asymmetric carbon atoms, they may independently be in either of (R) and (S) configuration, and the pyrimidone derivative may exist as stereoisomers such as optical isomers, or diastereoisomers. Any stereoisomers of pure form, any mixtures of stereoisomers, racemates fall within the scope of the present invention

[0028] Examples of preferred compounds of the present invention are shown in the tables set out below.

[0029] Compound N□ 2, 39, 53, 54, 56, 59, 60-63, 65, 72, 74, 76, 83, 94-97, 104-109, 114, 117, 122-132, 140-142, 152-154, 164-196, 203, 2,07, 208, 247-279, 281, 282, 293, 303, 308, 309 323-330, 333, 351 and 358-364 were removed in tables 1 and 2.

Table 1

Compound No.	STRUCTURE
1	
3	
4	
5	

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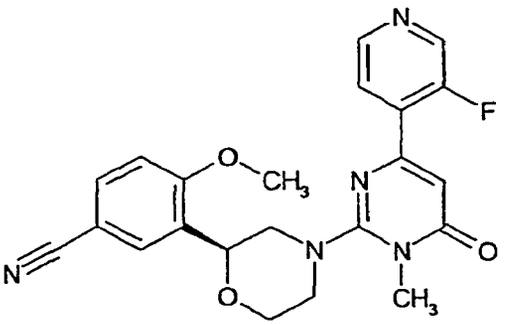
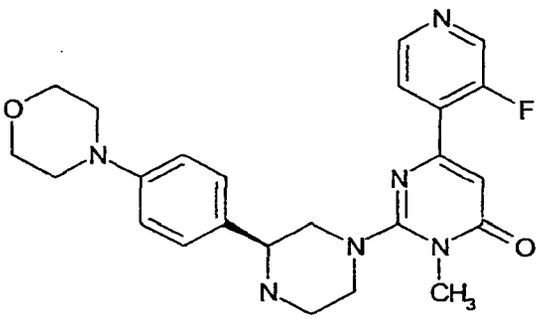
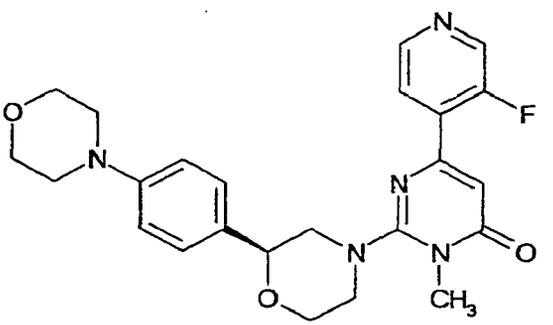
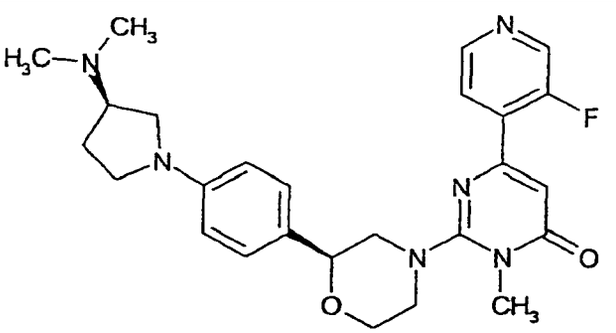
6	
7	
8	
9	

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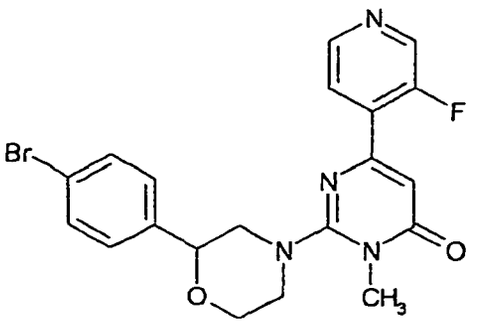
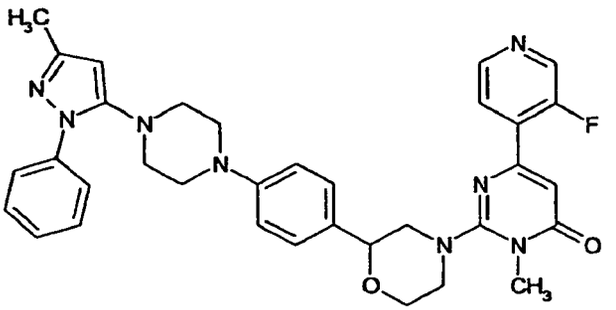
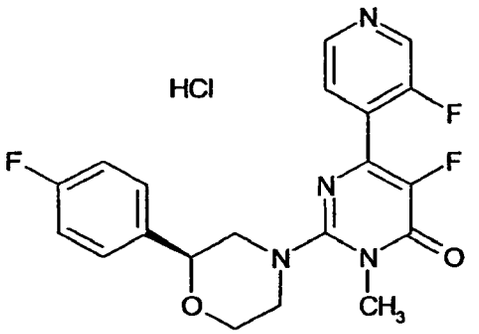
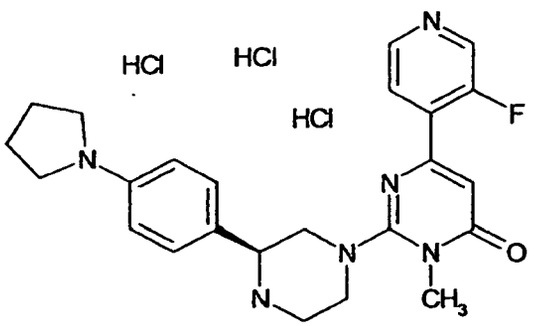
10	
11	
12	
13	

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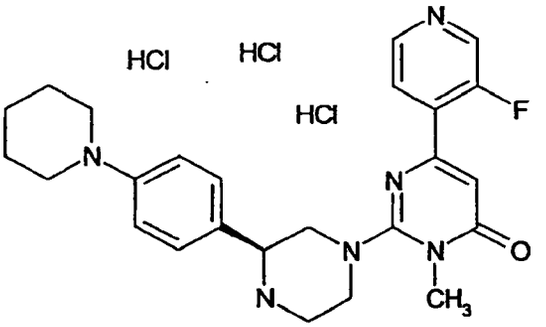
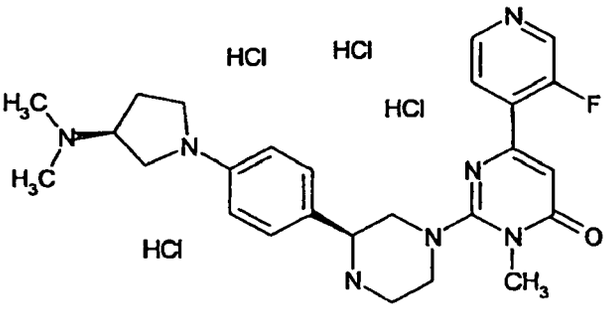
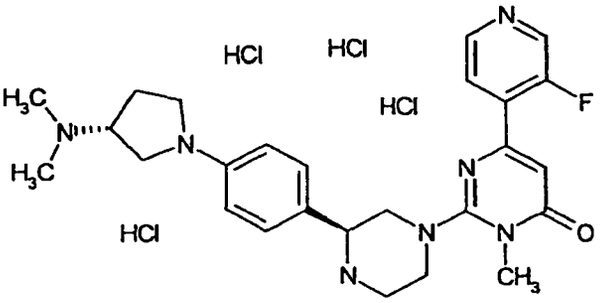
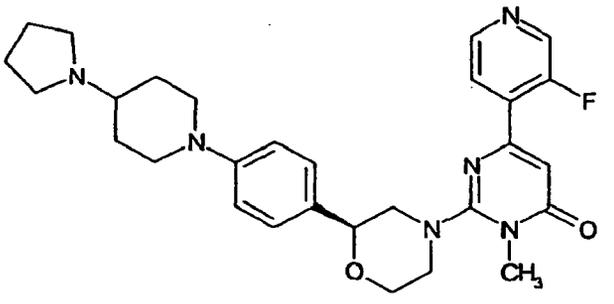
14	
15	
16	
17	

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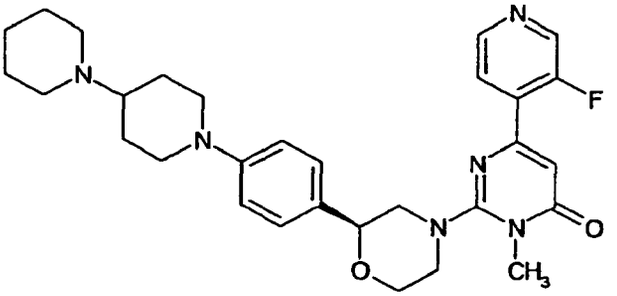
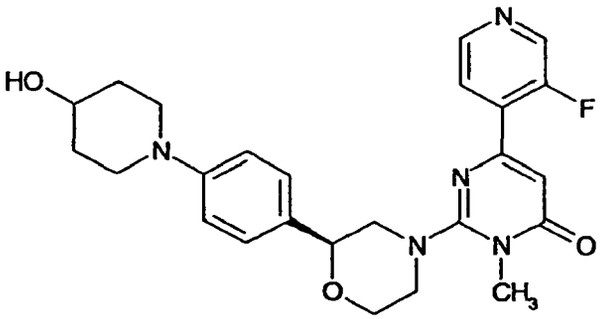
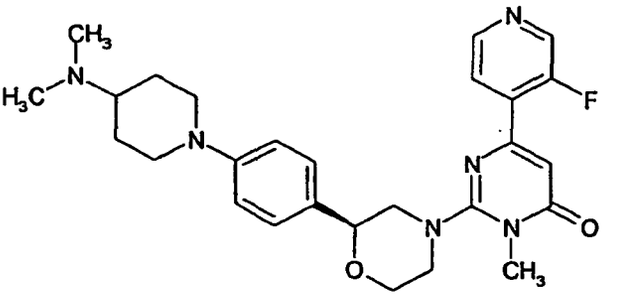
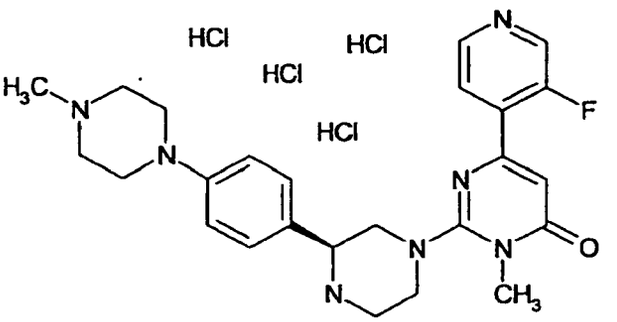
18	
19	
20	
21	

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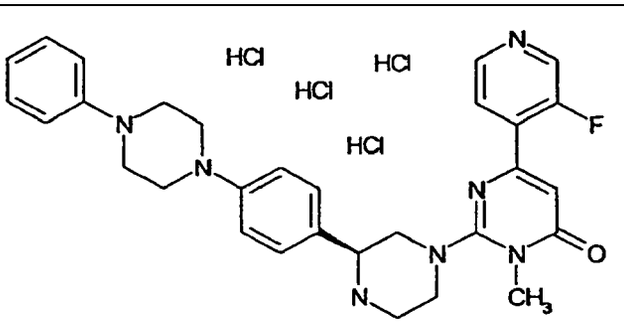
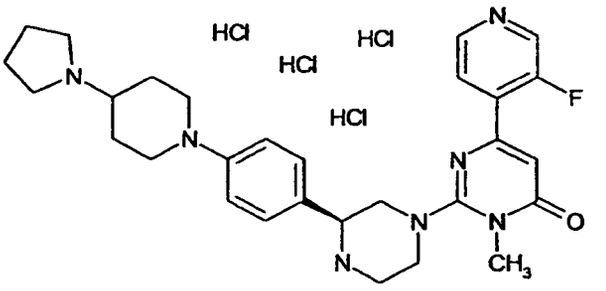
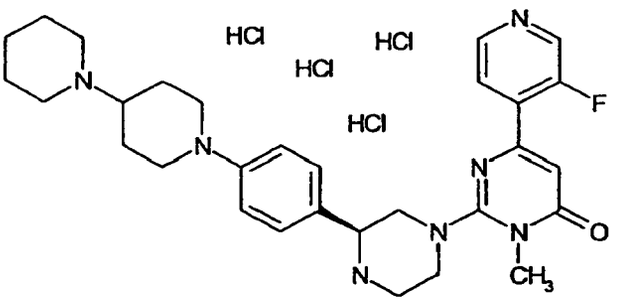
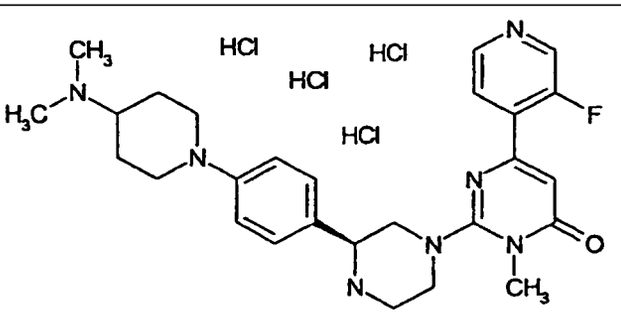
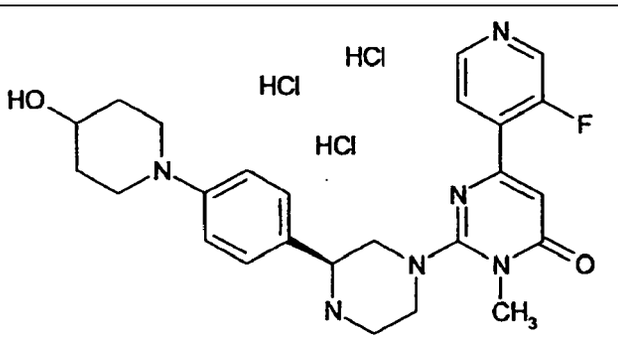
Compound No.	STRUCTURE
22	
23	
24	
25	
26	

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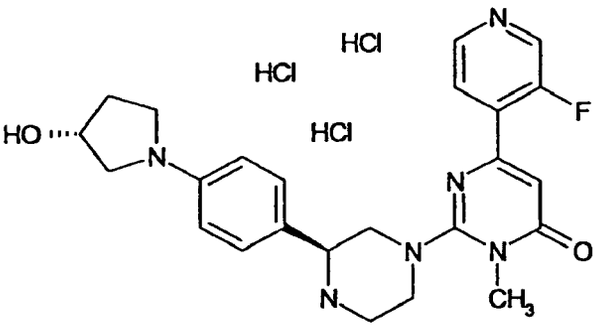
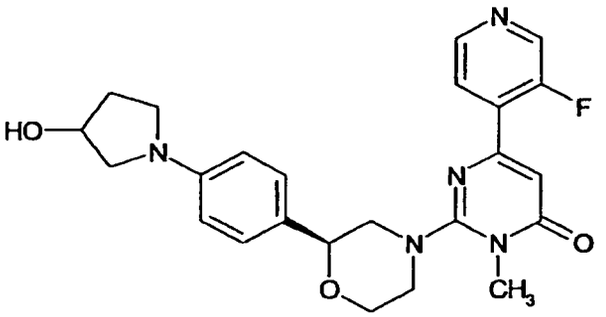
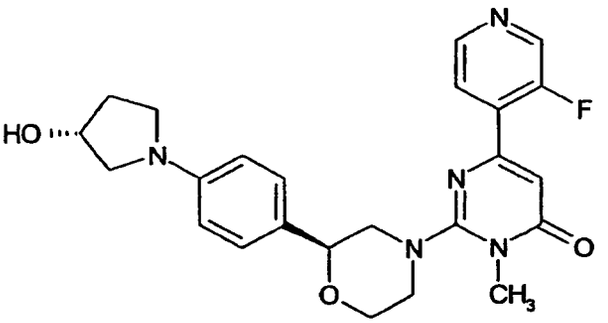
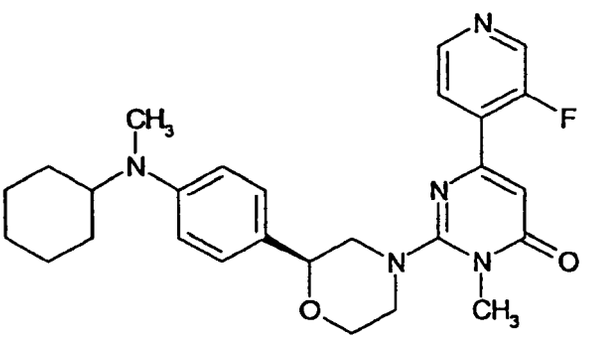
Compound No.	STRUCTURE
27	
28	
29	
30	

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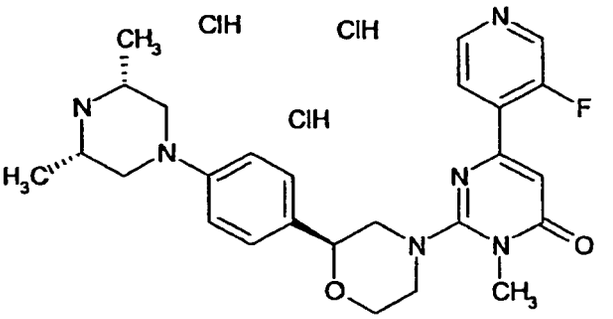
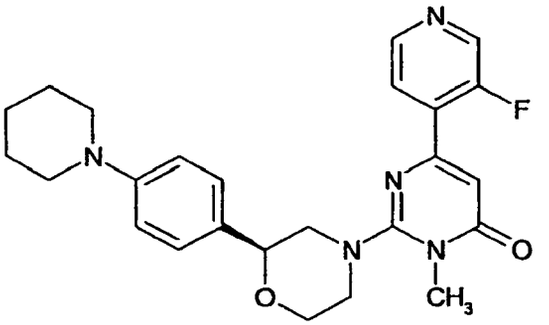
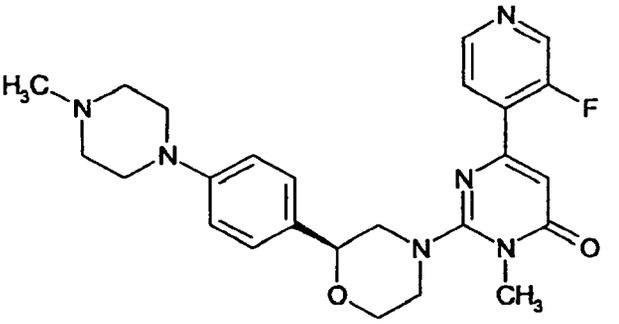
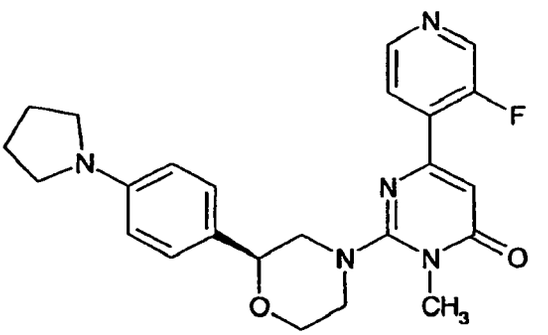
Compound No.	STRUCTURE
31	
32	
33	
34	

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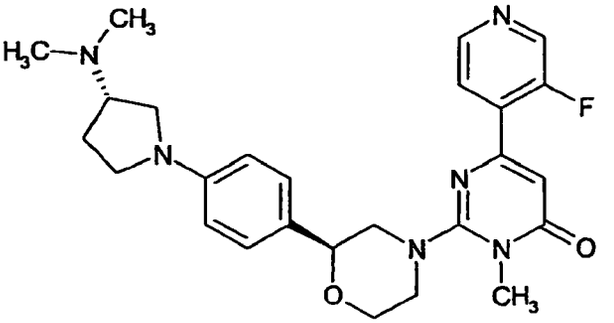
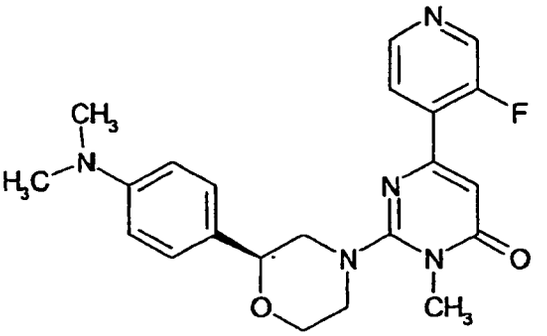
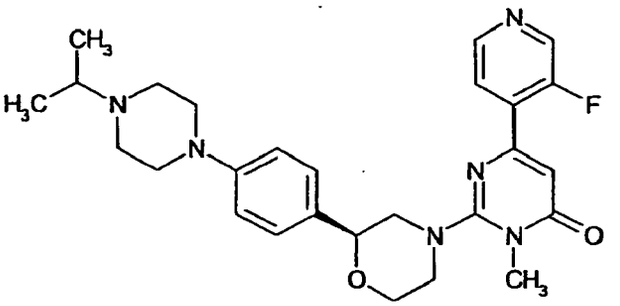
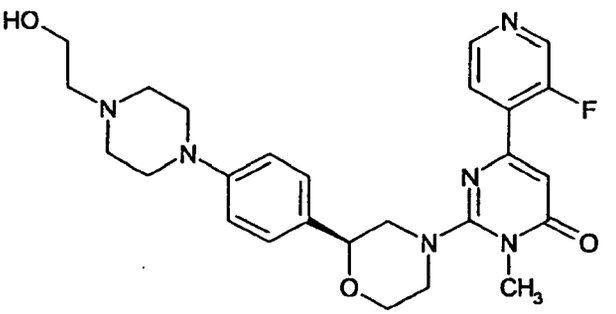
Compound No.	STRUCTURE
35	
36	
37	
38	

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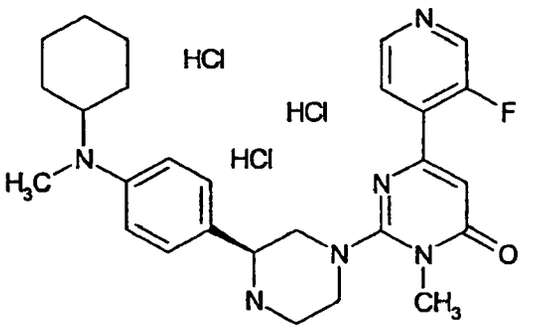
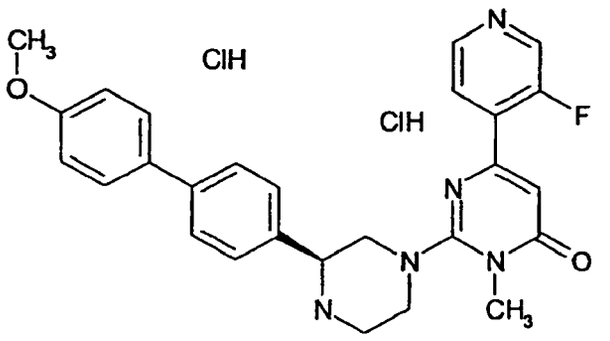
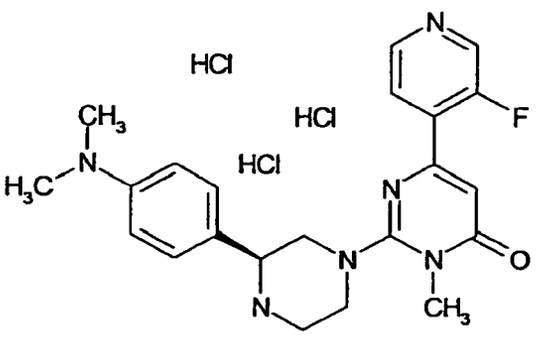
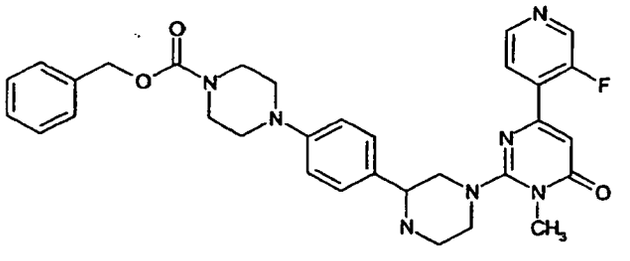
Compound No.	STRUCTURE
40	
41	
42	
43	

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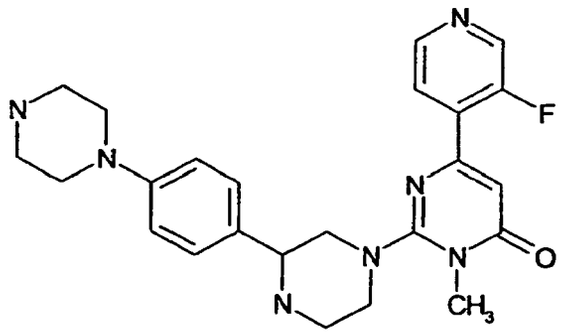
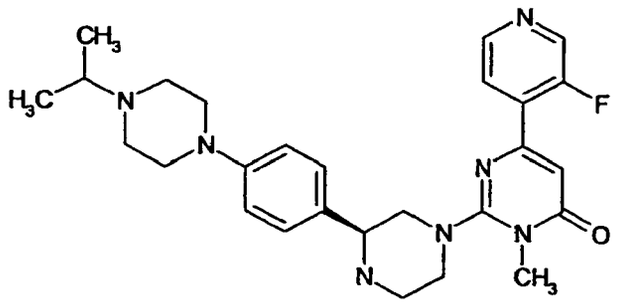
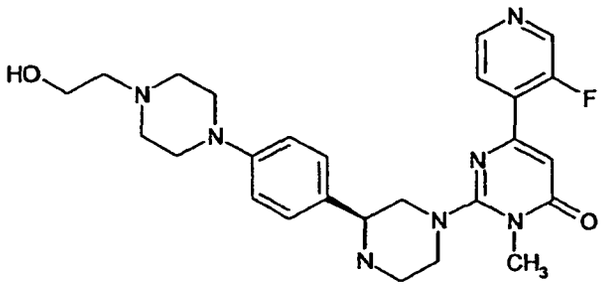
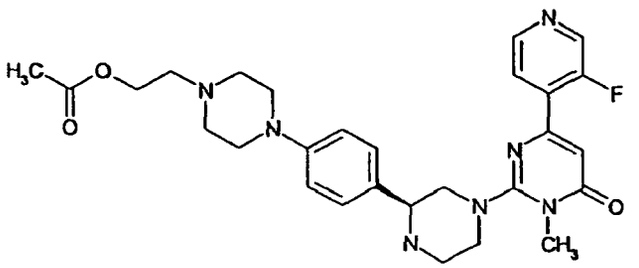
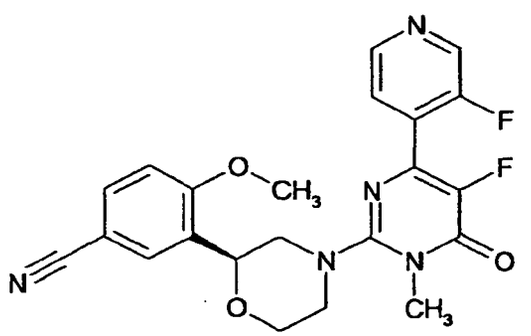
Compound No.	STRUCTURE
44	
45	
46	
47	
48	

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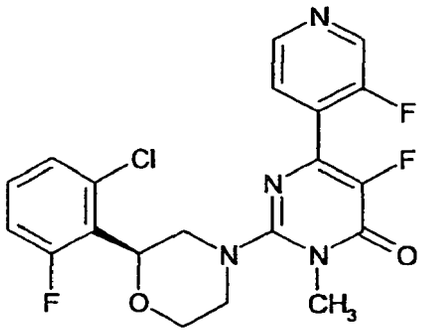
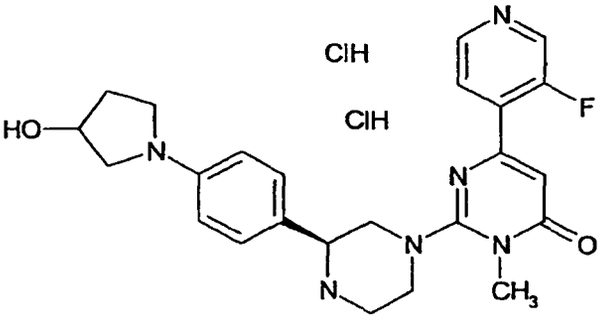
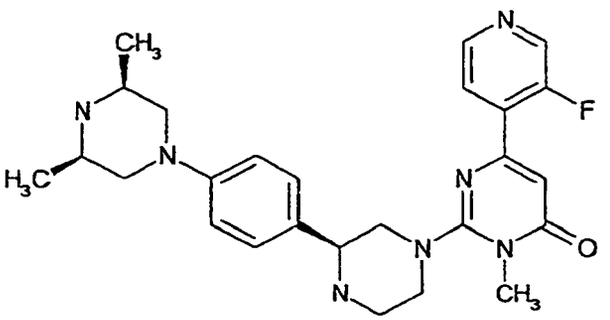
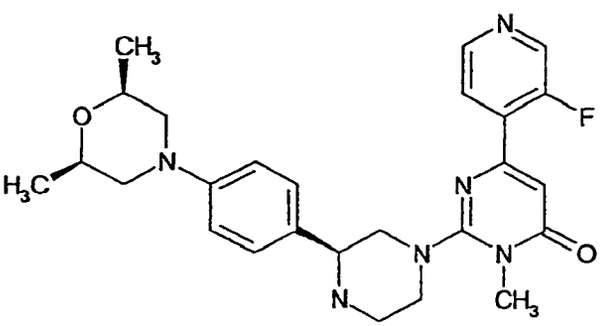
Compound No.	STRUCTURE
49	
50	
51	
52	

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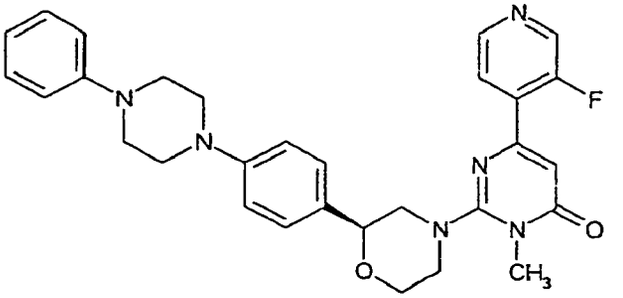
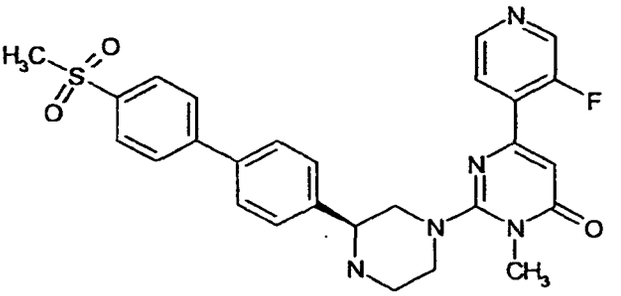
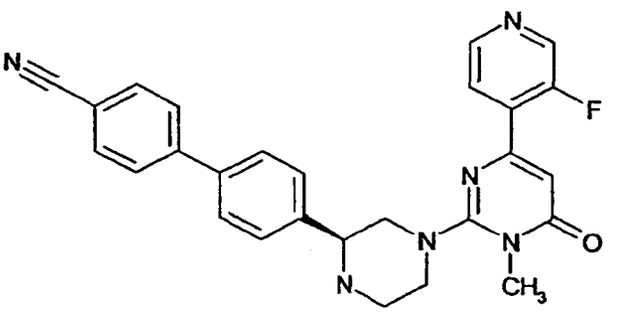
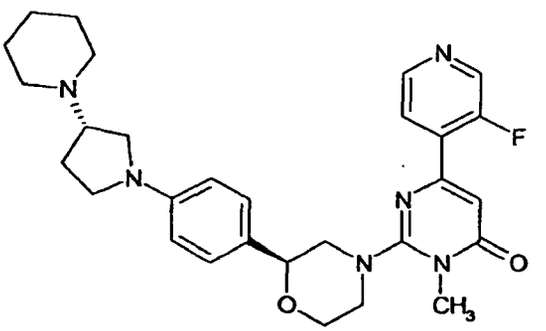
Compound No.	STRUCTURE
55	
57	
58	
64	

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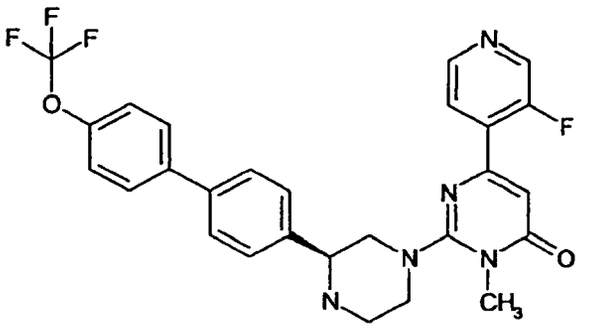
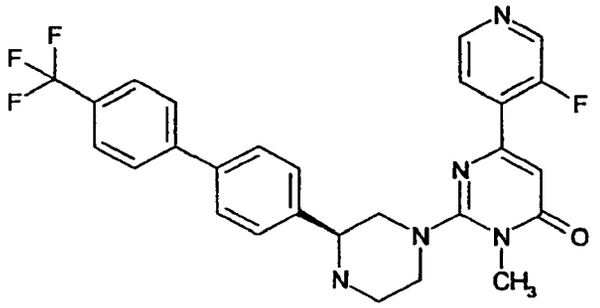
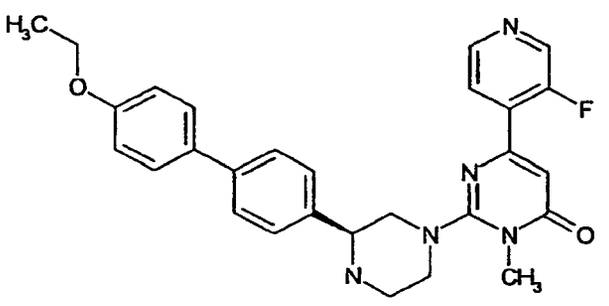
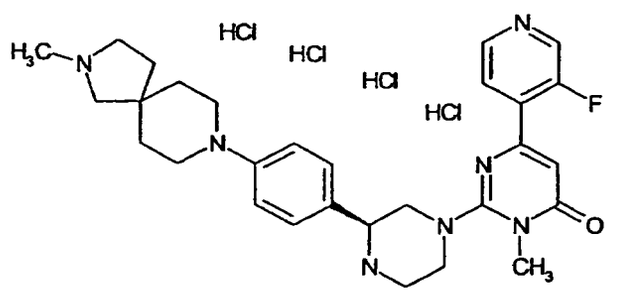
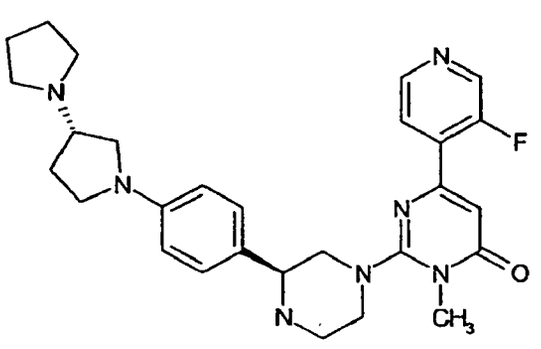
Compound No.	STRUCTURE
66	
67	
68	
69	
70	

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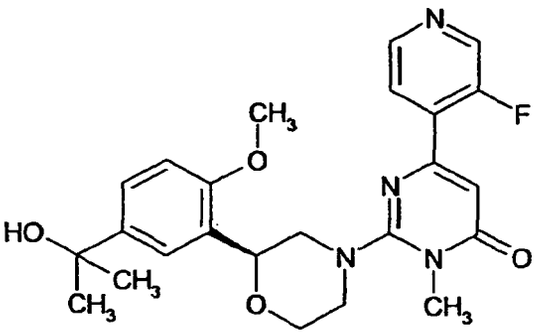
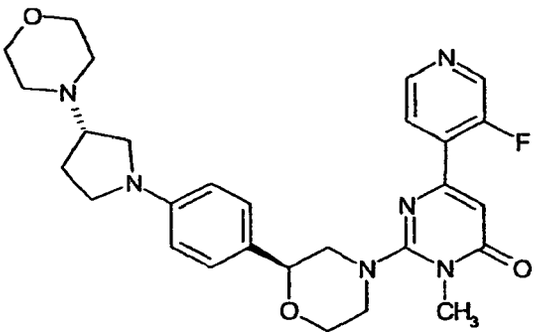
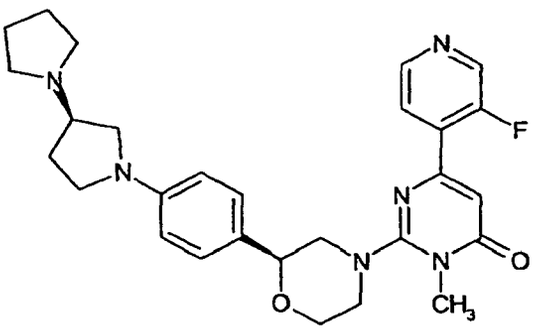
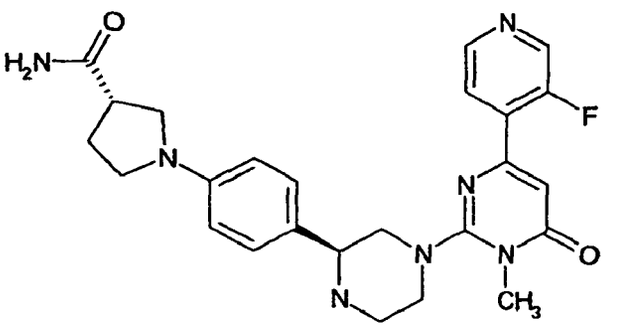
Compound No.	STRUCTURE
71	
73	
75	
77	

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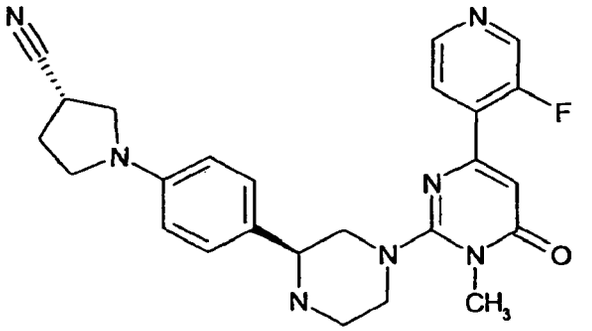
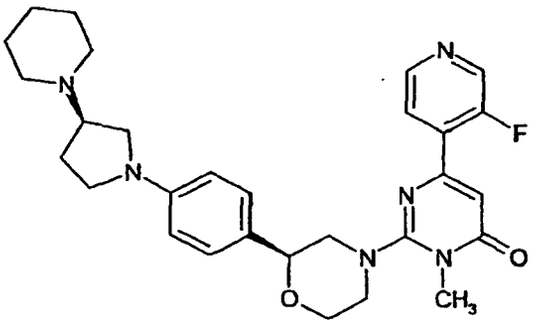
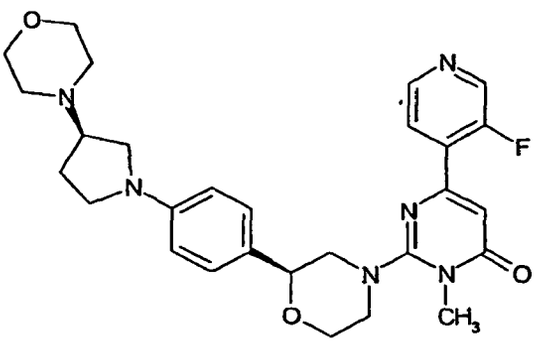
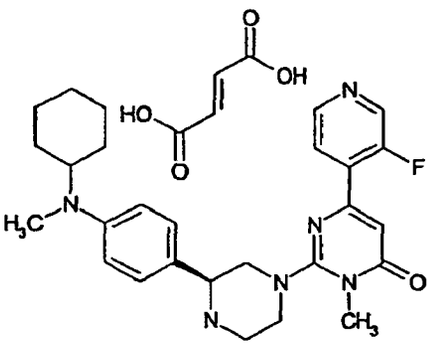
Compound No.	STRUCTURE
78	
79	
80	
81	

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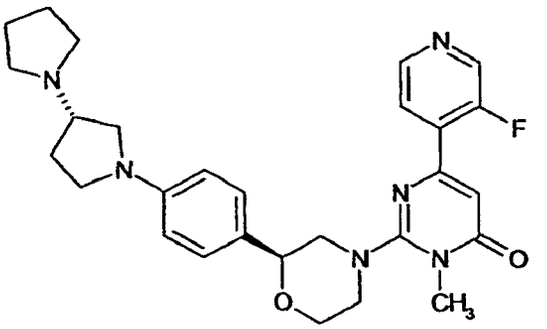
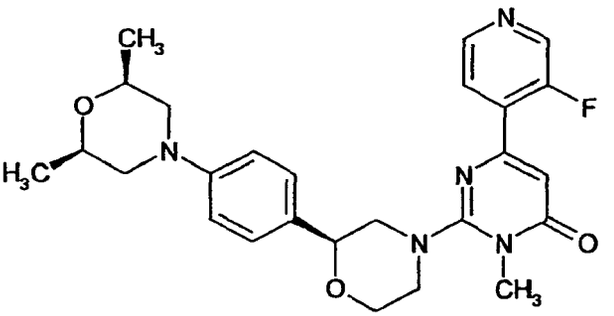
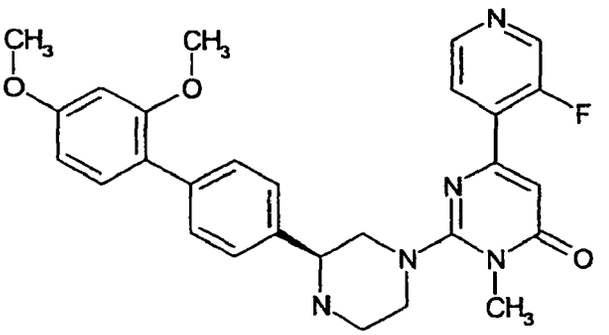
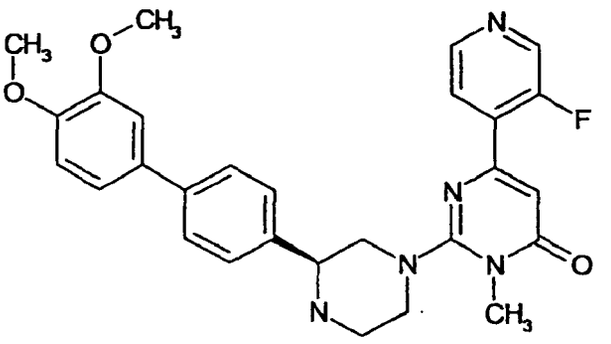
Compound No.	STRUCTURE
82	
84	
85	
86	

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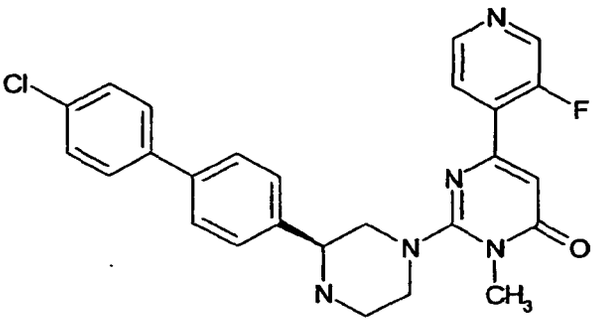
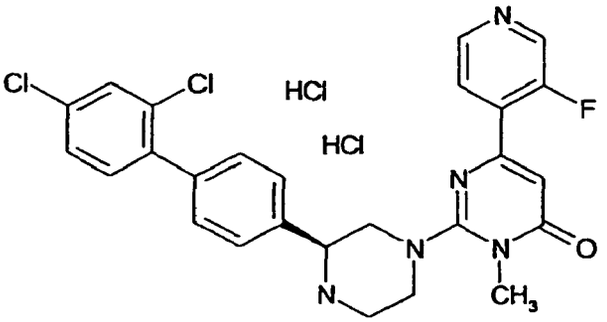
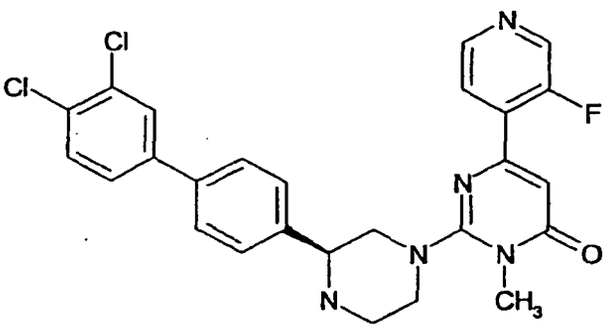
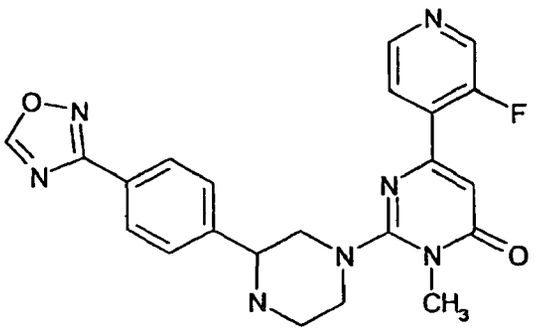
Compound No.	STRUCTURE
87	
88	
89	
90	

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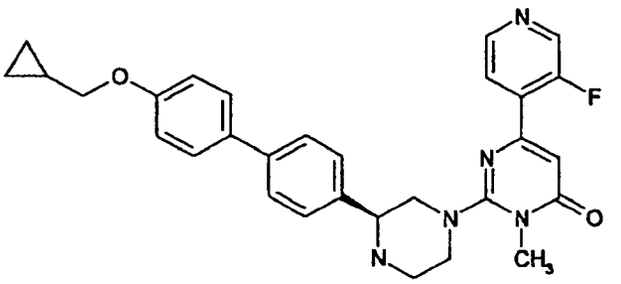
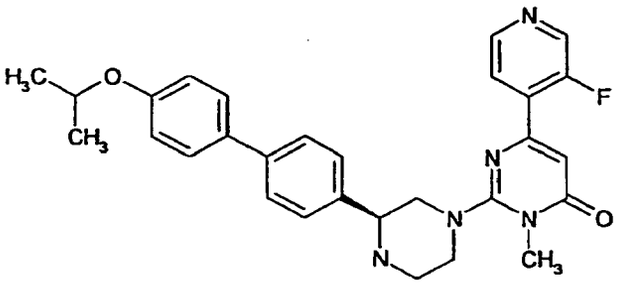
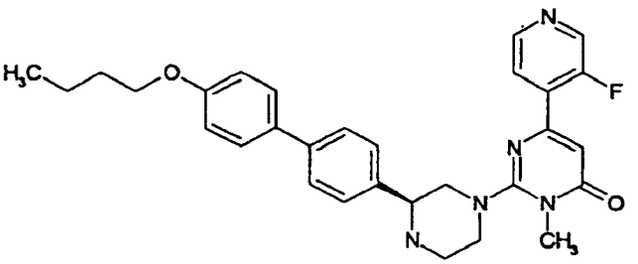
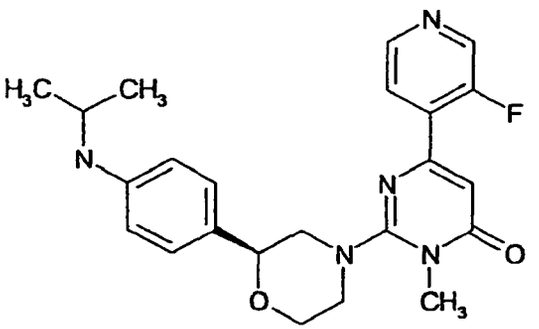
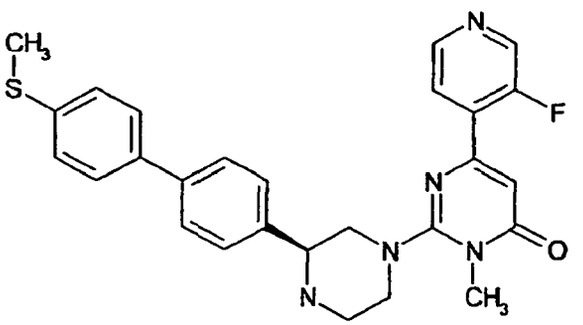
91	
92	
93	
98	
99	

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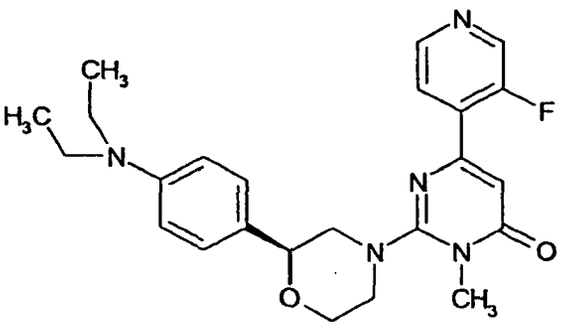
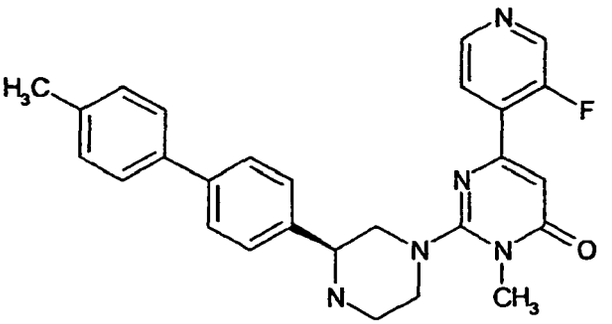
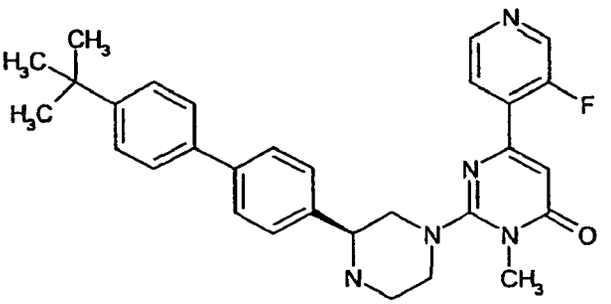
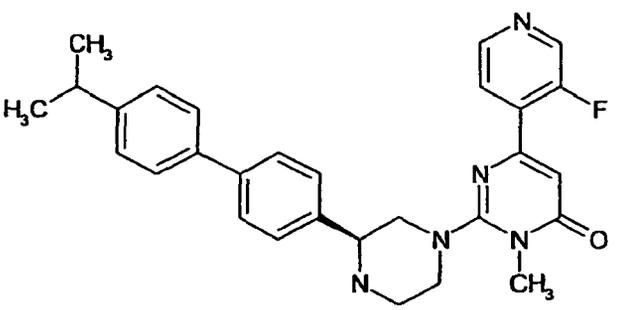
100	
101	
102	
103	

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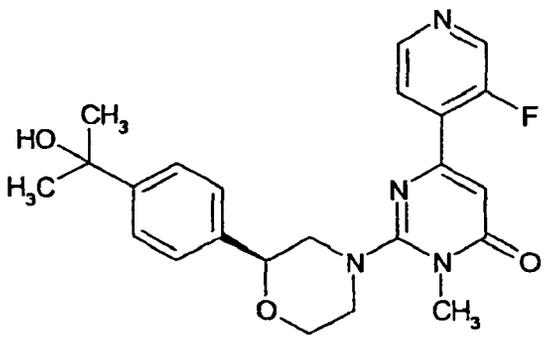
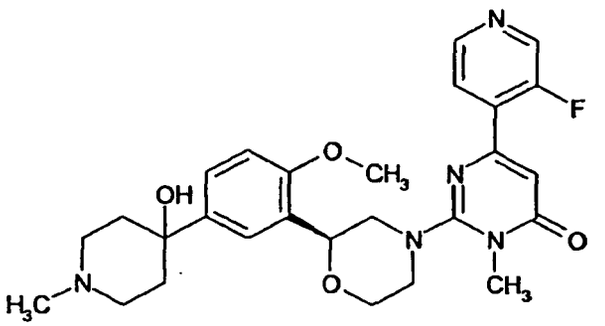
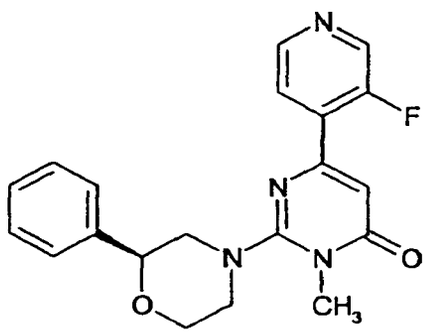
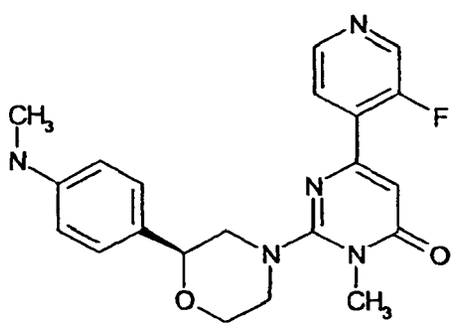
Compound No.	STRUCTURE
110	
111	
112	
113	

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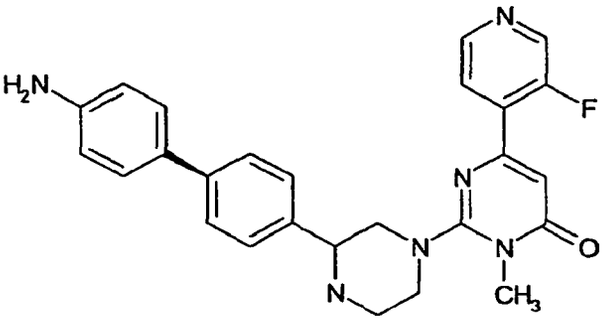
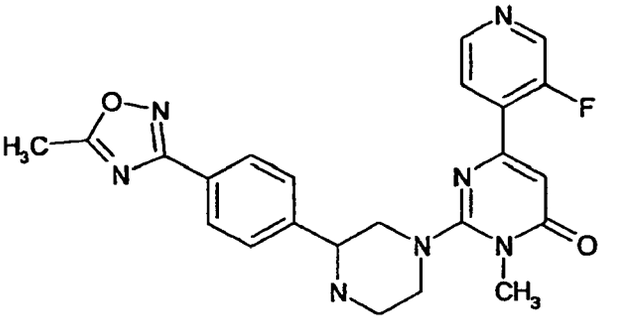
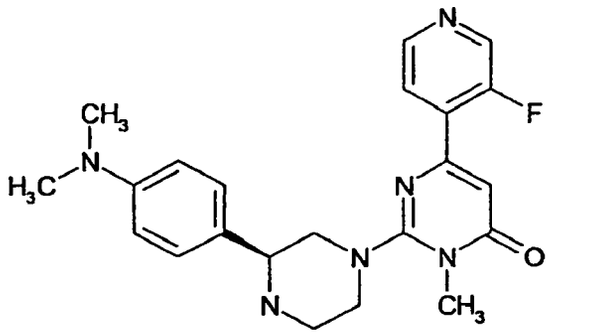
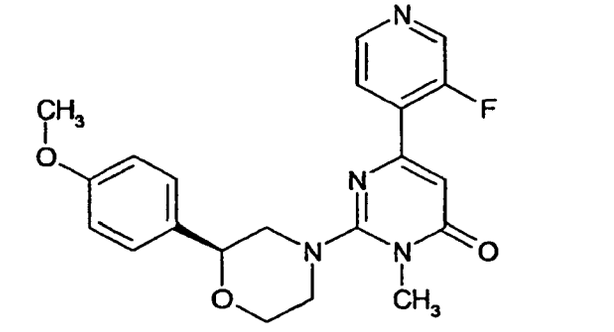
Compound No.	STRUCTURE
115	
116	
118	
119	

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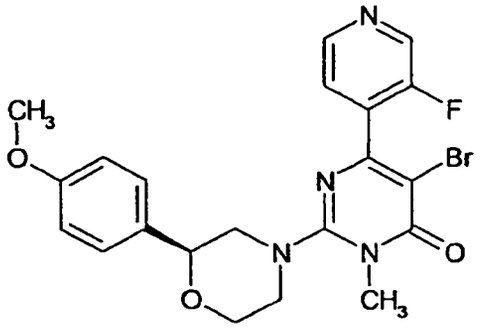
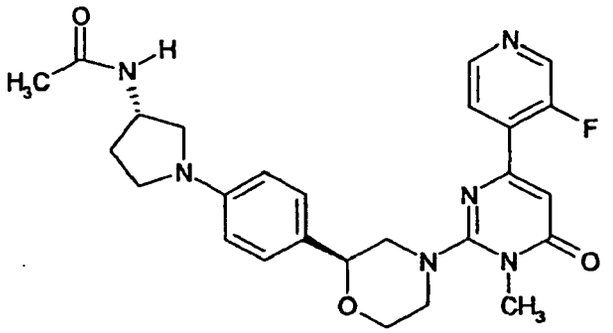
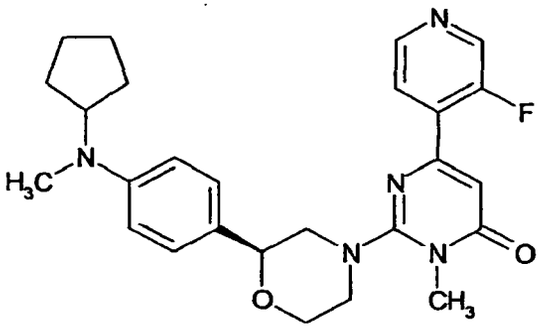
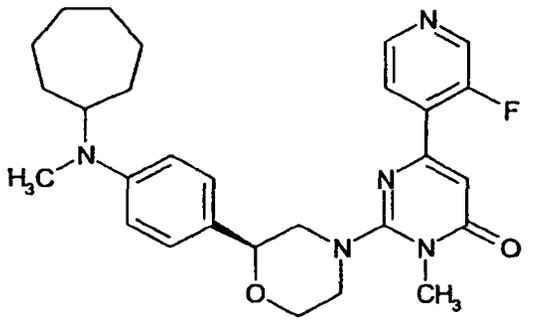
Compound No.	STRUCTURE
120	
121	
133	
134	

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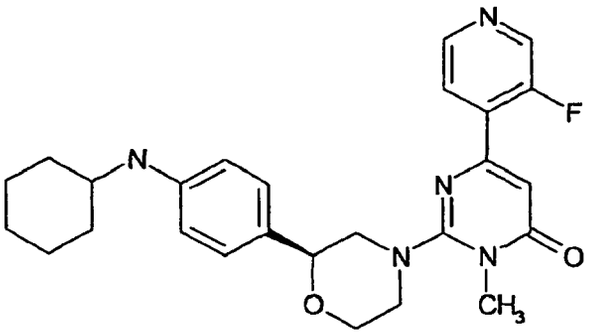
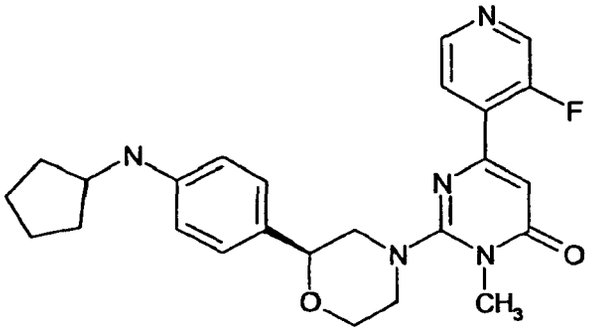
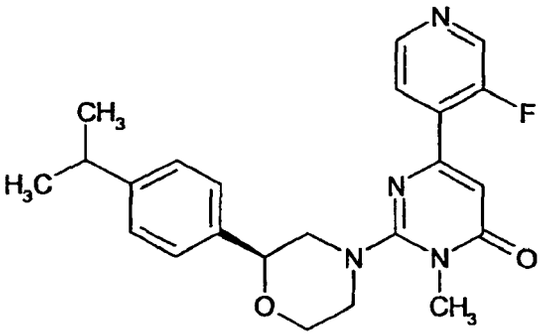
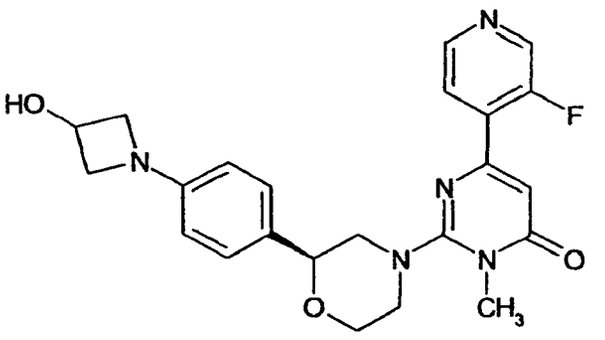
Compound No.	STRUCTURE
135	
136	
137	
138	

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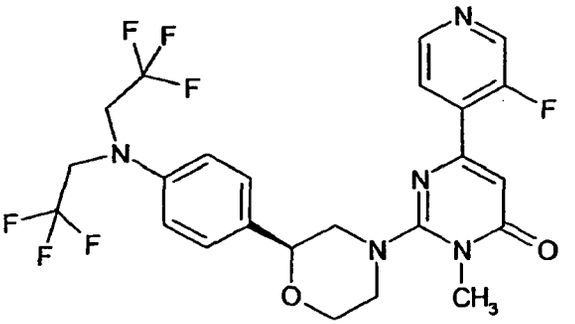
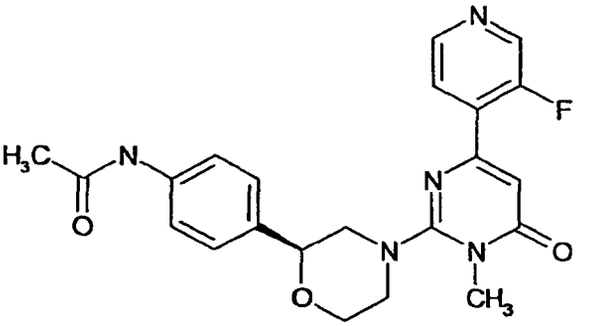
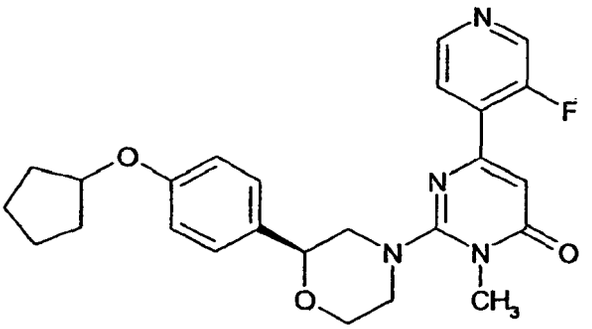
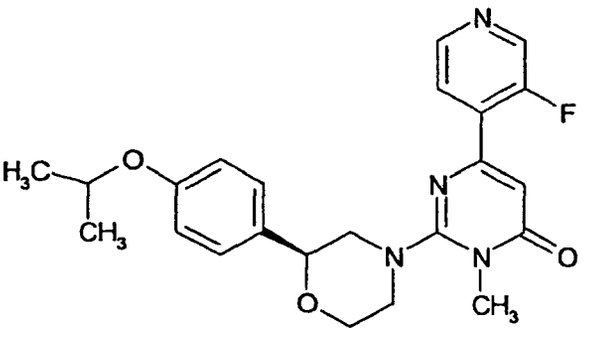
Compound No.	STRUCTURE
139	
143	
144	
145	

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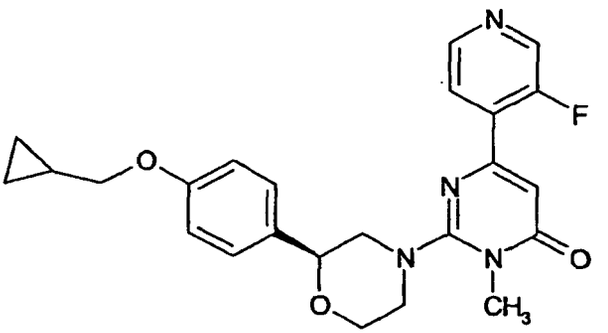
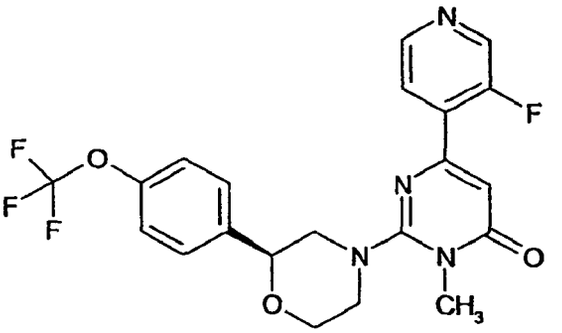
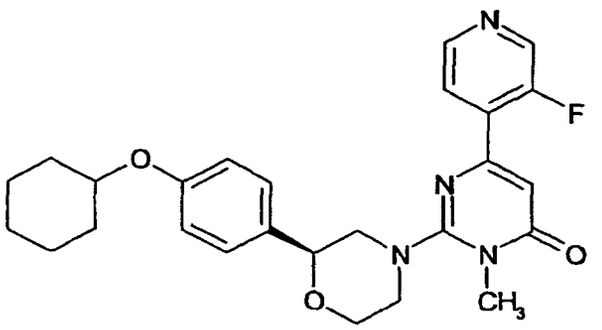
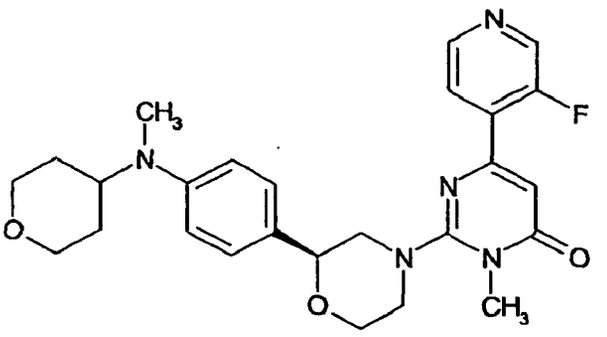
Compound No.	STRUCTURE
146	
147	
148	
149	

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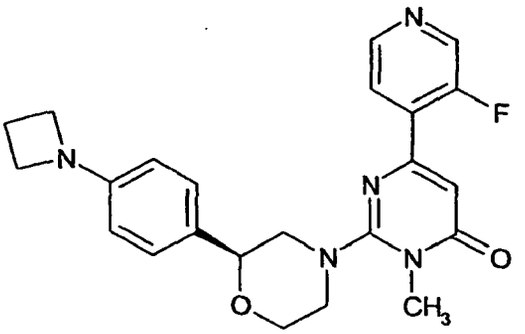
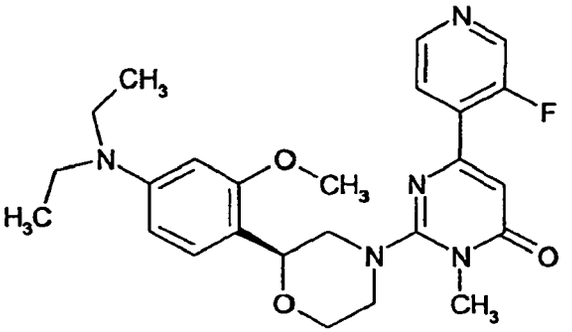
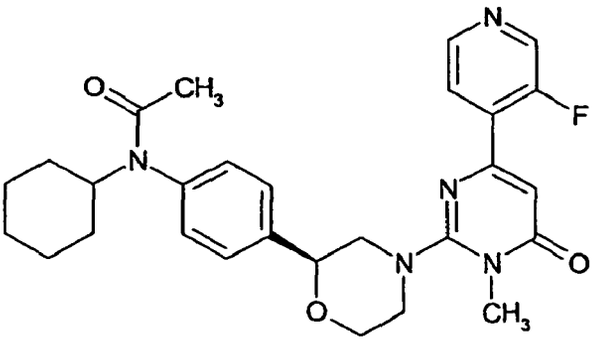
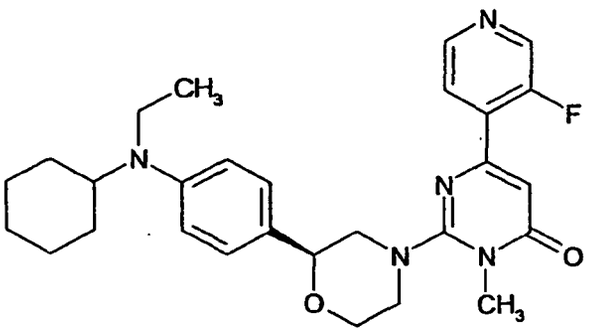
Compound No.	STRUCTURE
150	
151	
155	
156	

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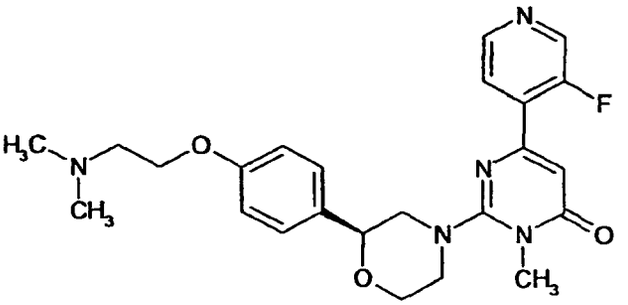
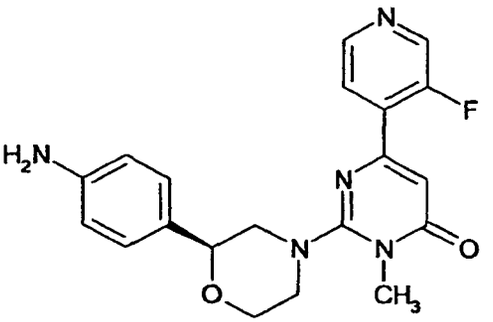
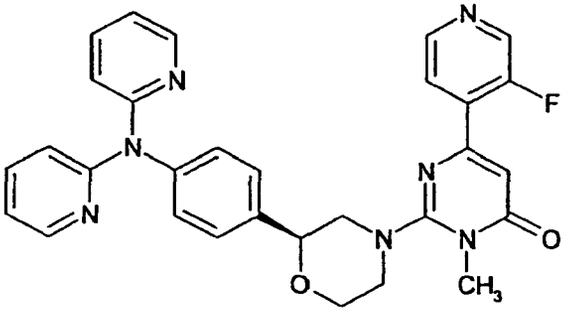
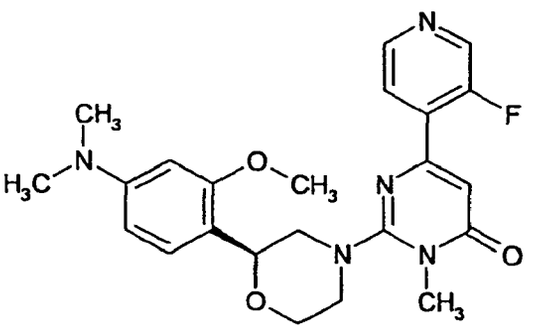
Compound No.	STRUCTURE
157	
158	
159	
160	

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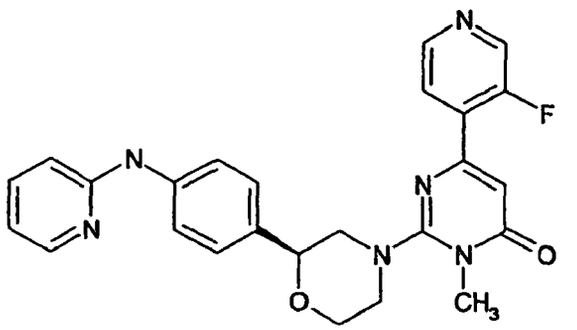
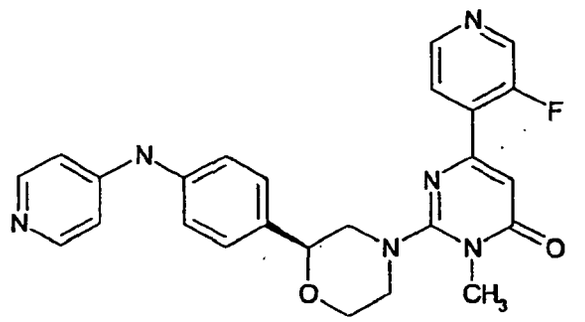
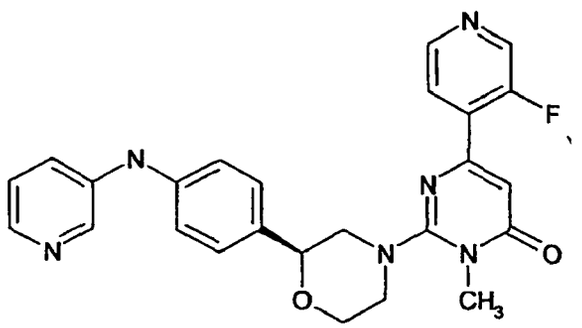
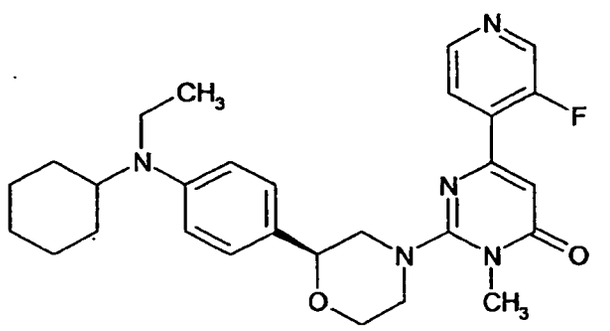
Compound No.	STRUCTURE
161	
162	
163	
197	

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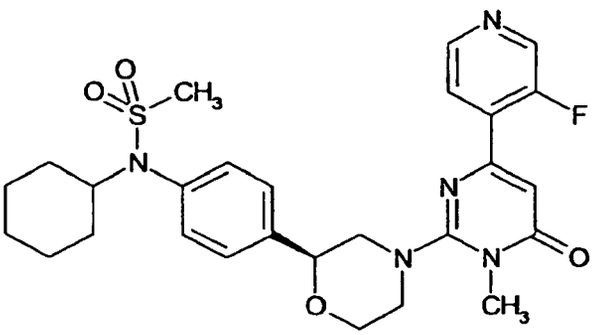
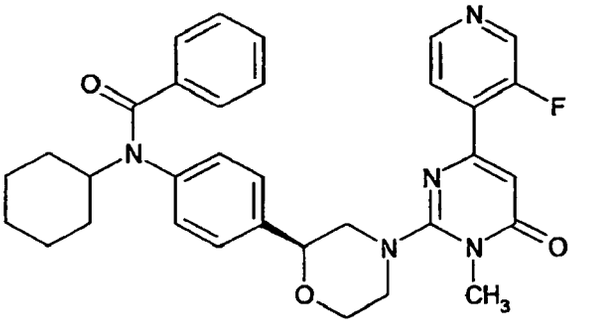
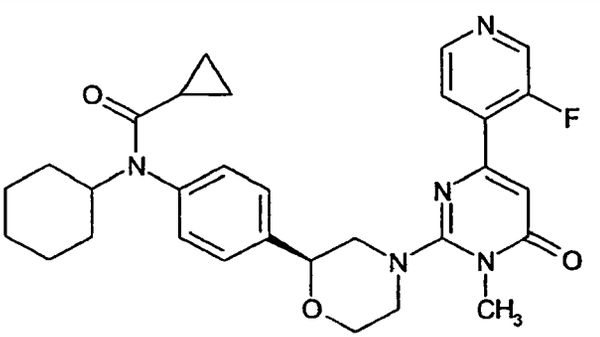
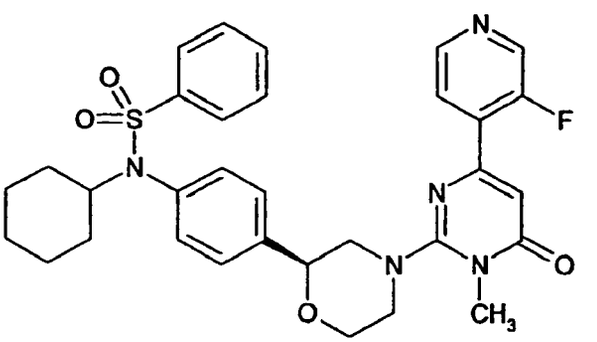
198	
199	
200	
201	

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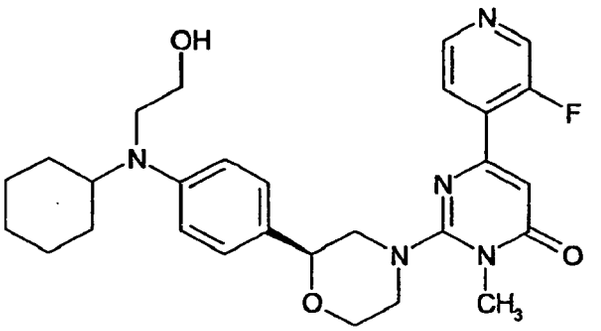
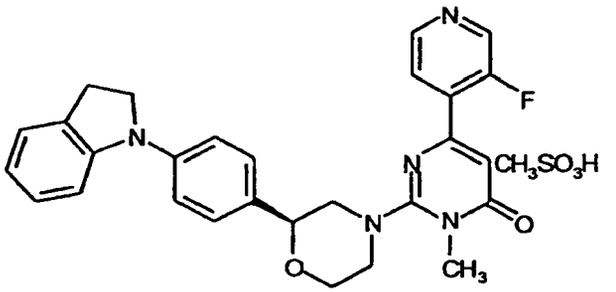
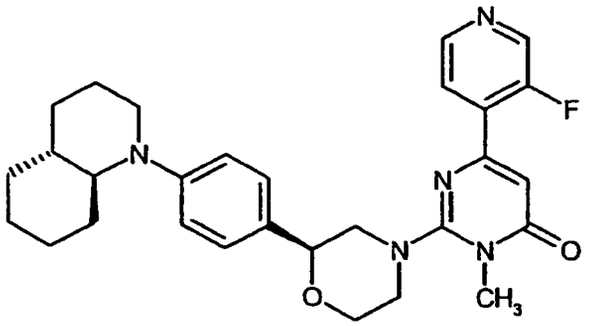
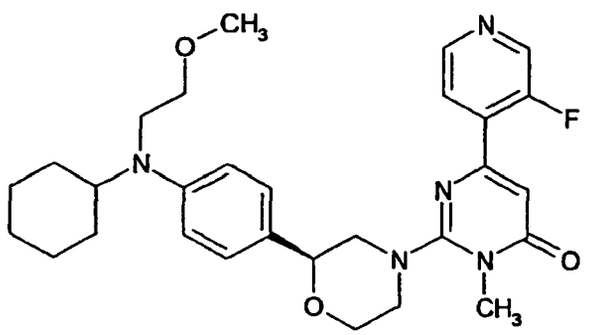
202	
204	
205	
206	

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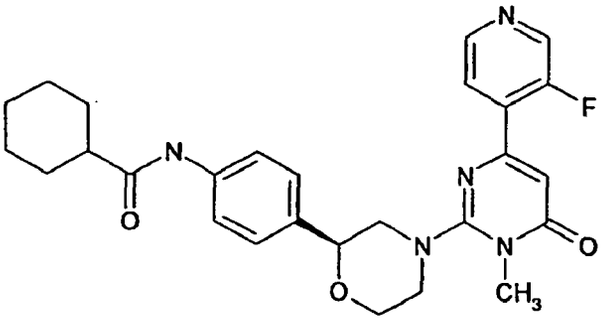
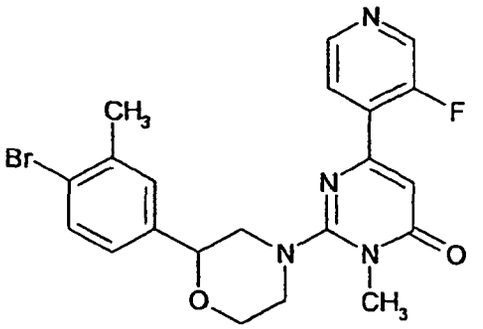
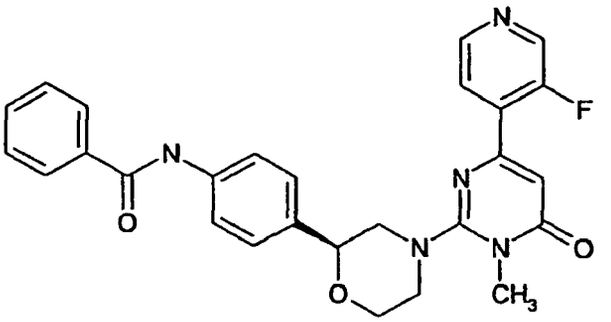
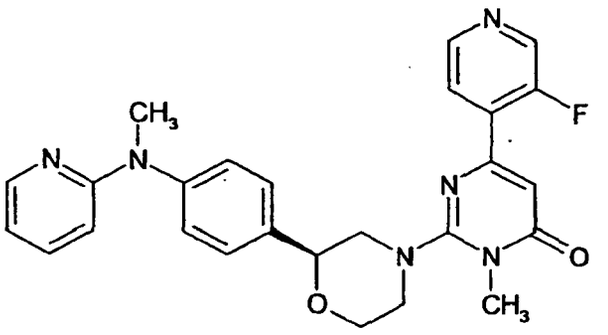
Compound No.	STRUCTURE
209	
210	
211	
212	

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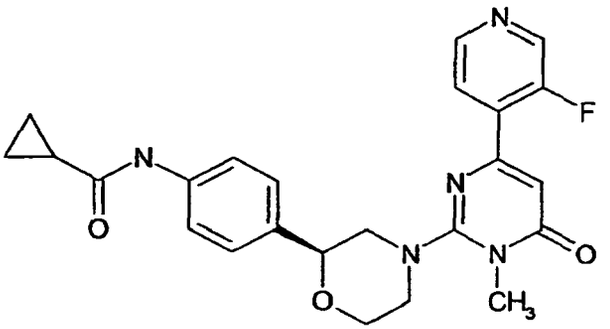
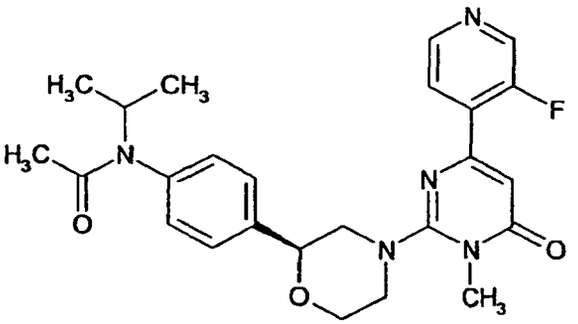
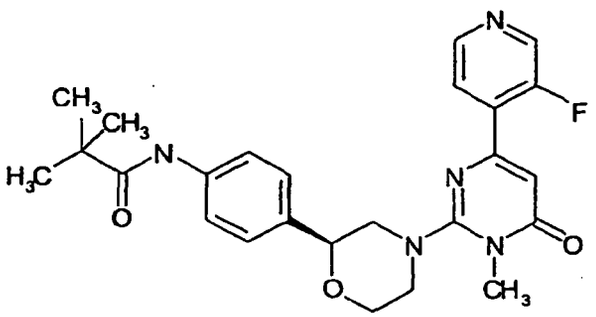
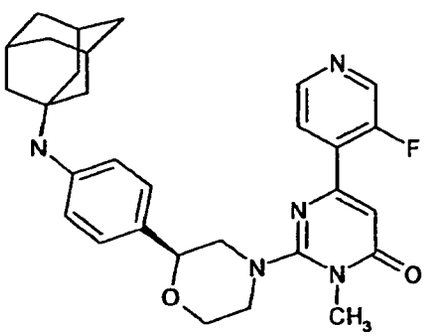
213	
214	
215	
216	

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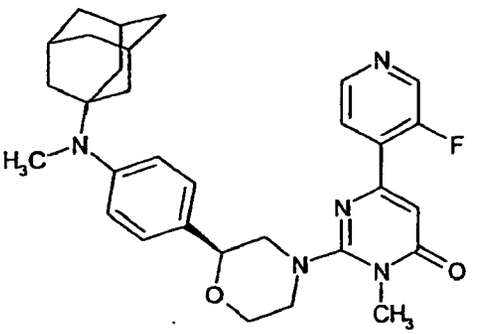
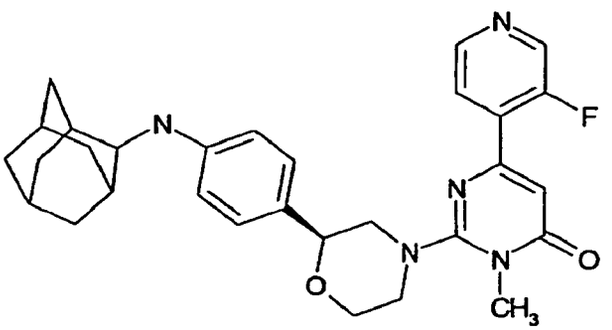
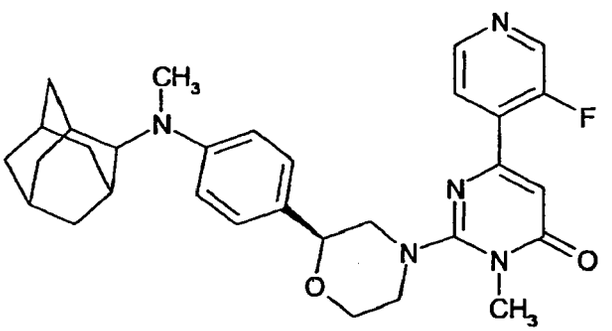
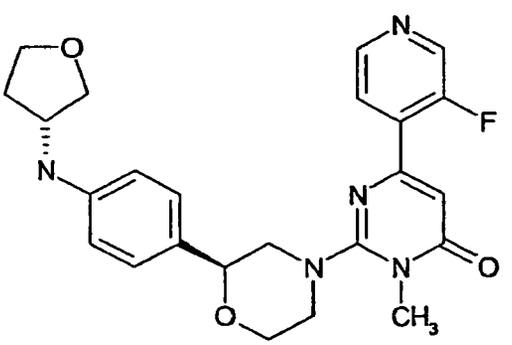
Compound No.	STRUCTURE
217	
218	
219	
220	

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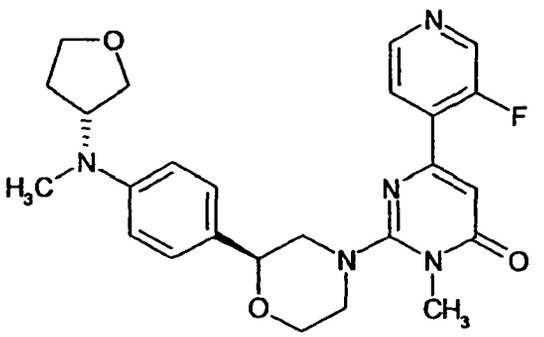
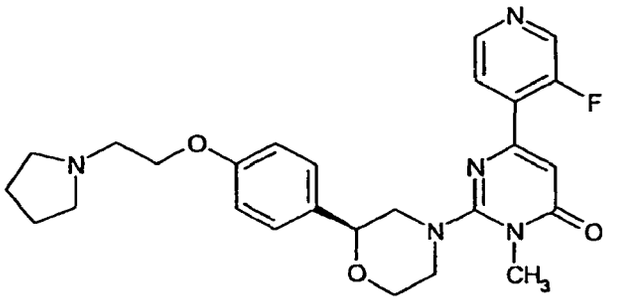
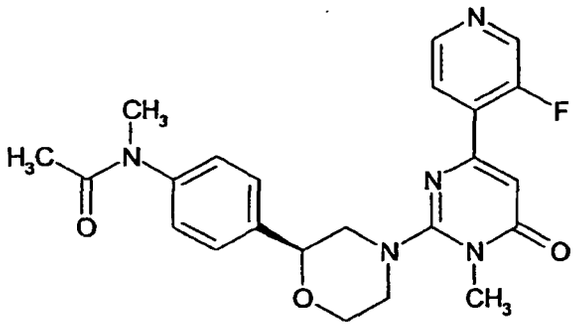
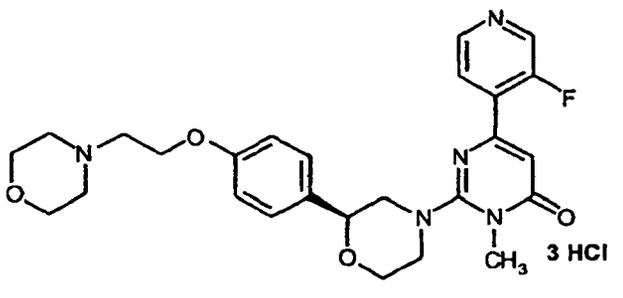
Compound No.	STRUCTURE
221	
222	
223	
224	

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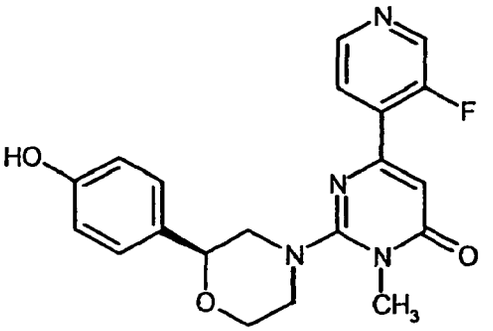
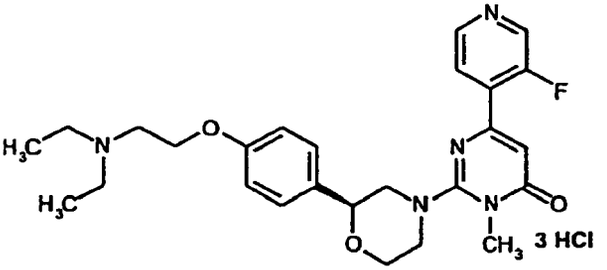
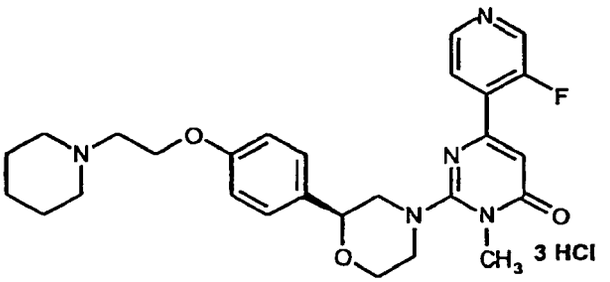
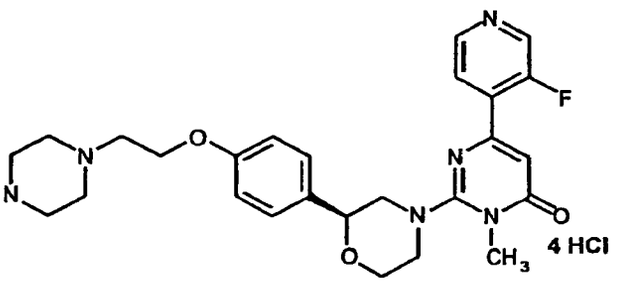
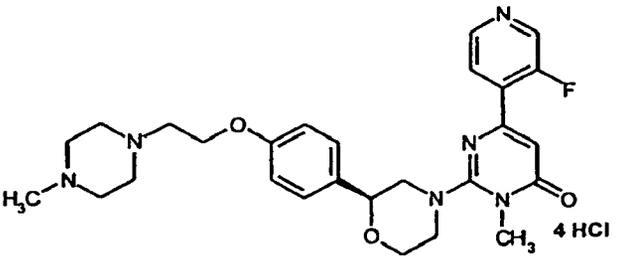
Compound No.	STRUCTURE
225	
226	
227	
228	
229	

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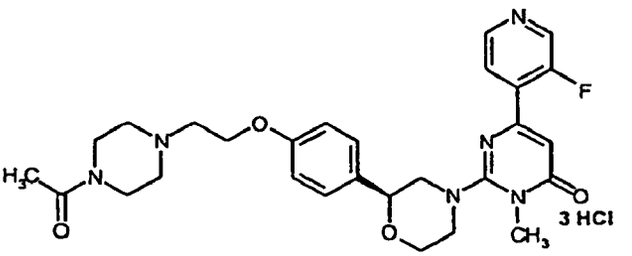
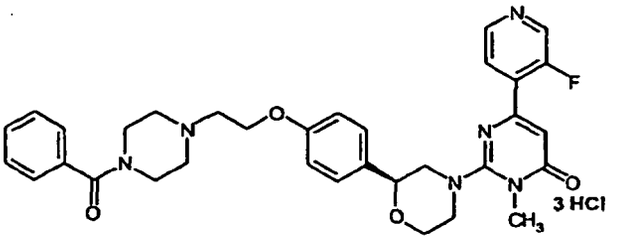
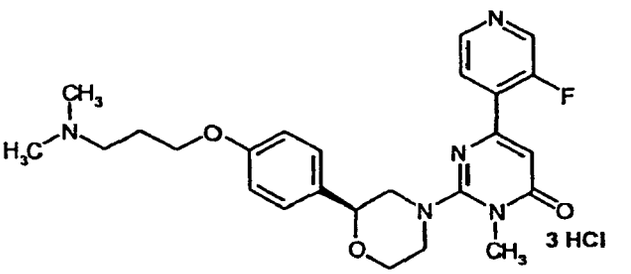
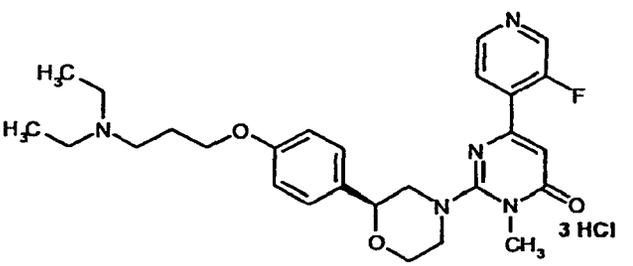
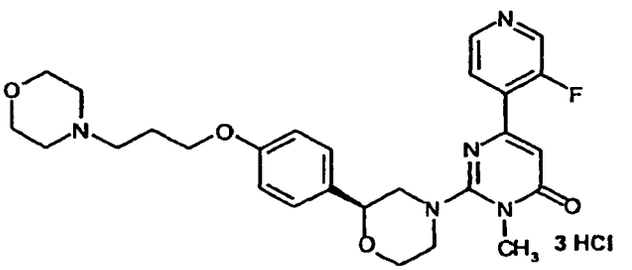
Compound No.	STRUCTURE
230	
231	
232	
233	
234	

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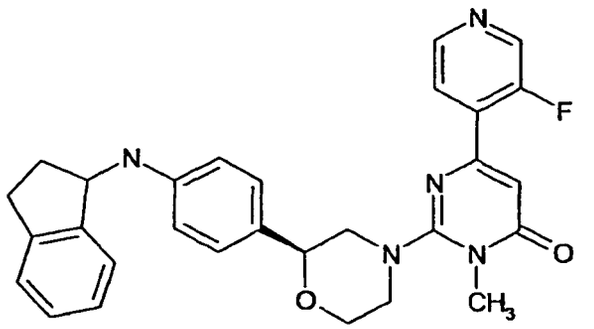
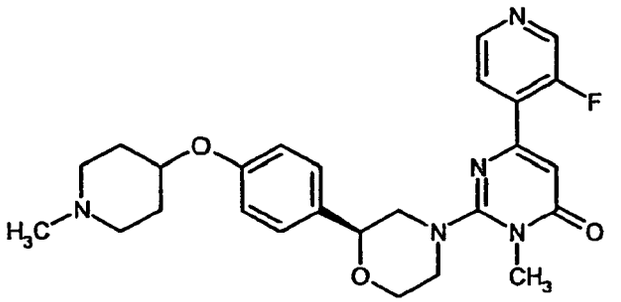
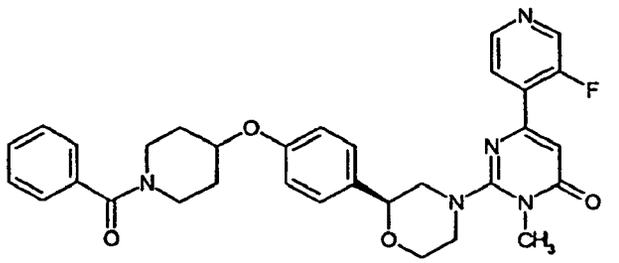
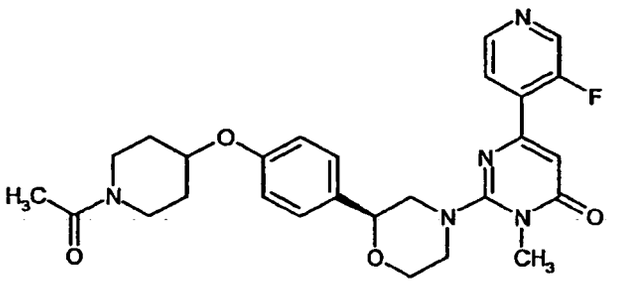
Compound No.	STRUCTURE
235	
236	
237	
238	

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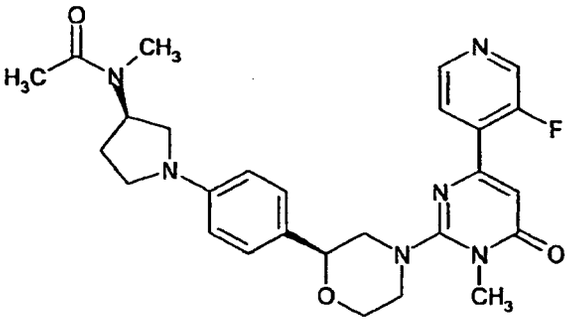
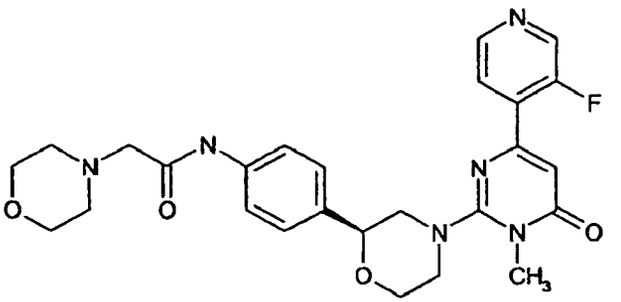
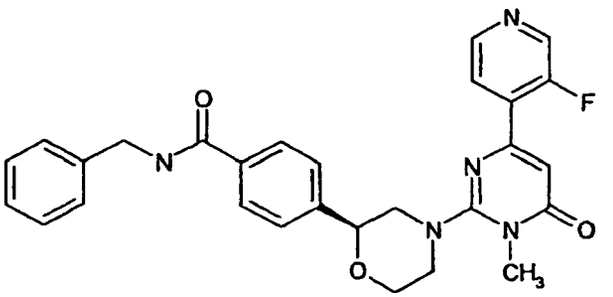
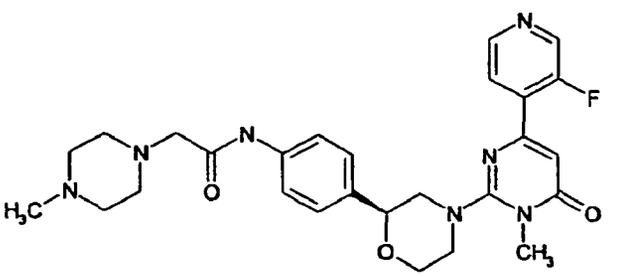
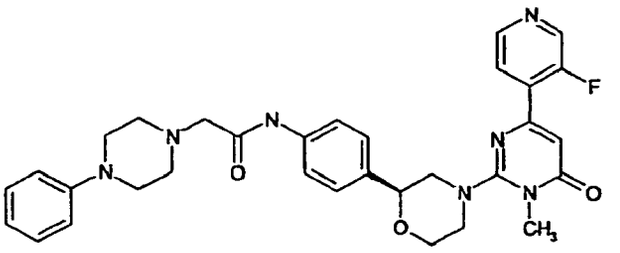
Compound No.	STRUCTURE
239	
240	
241	
242	
243	

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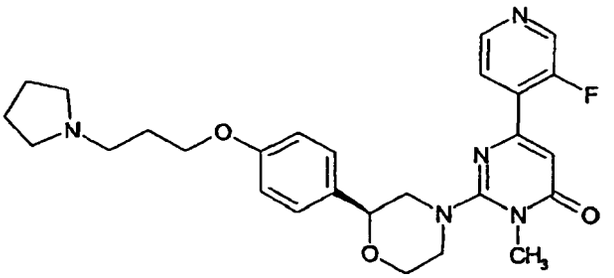
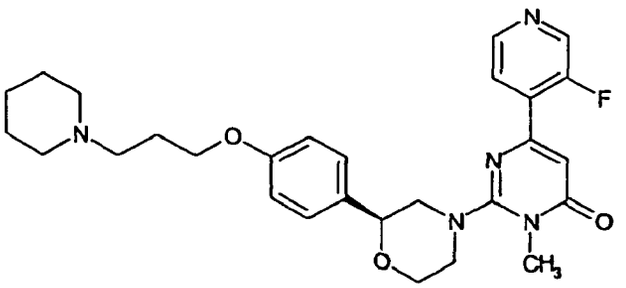
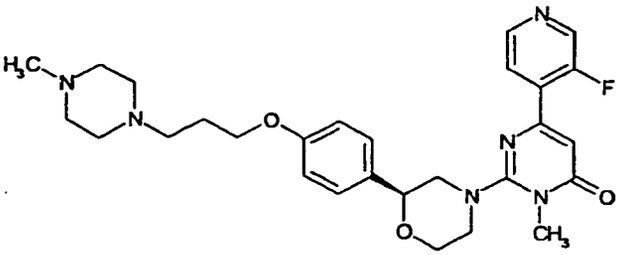
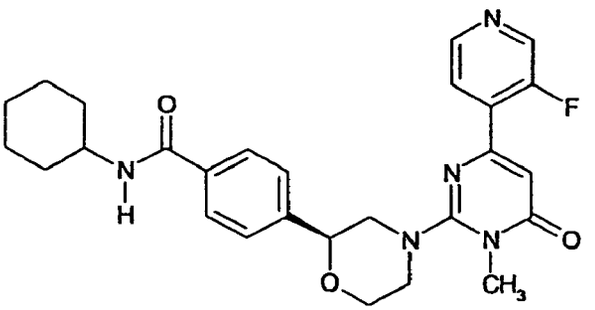
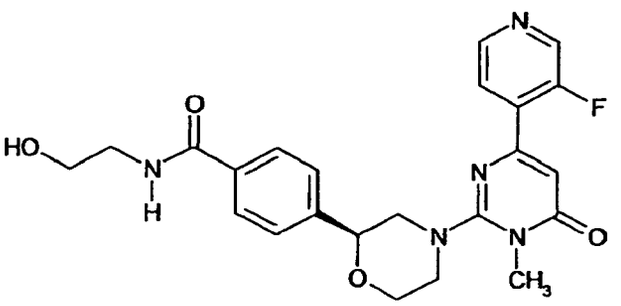
Compound No.	STRUCTURE
244	
245	
246	
280	
283	

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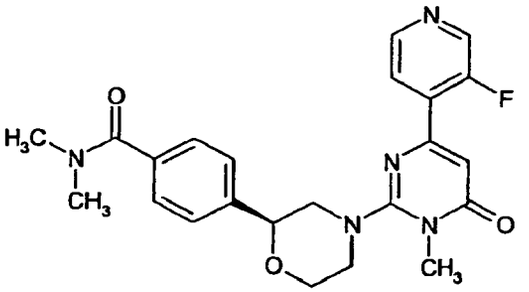
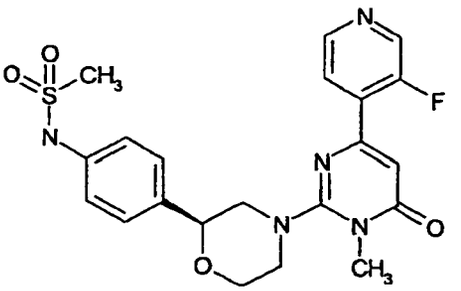
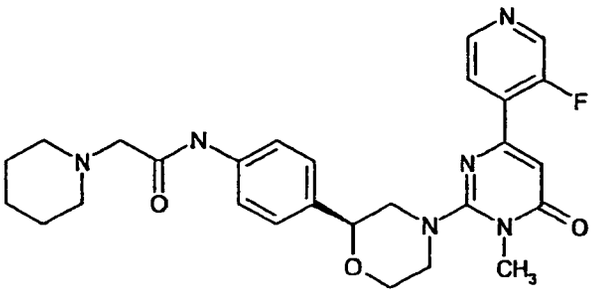
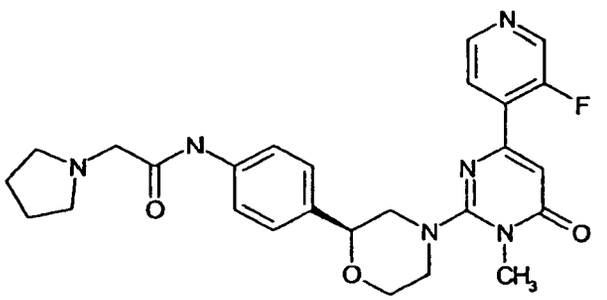
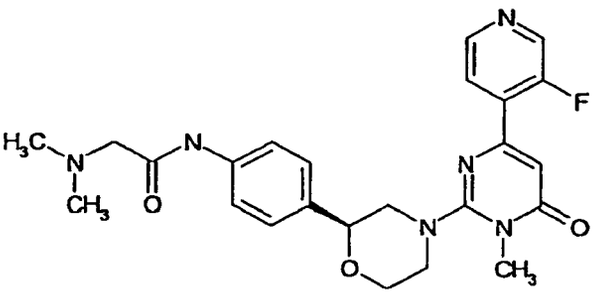
Compound No.	STRUCTURE
284	
285	
286	
287	
288	

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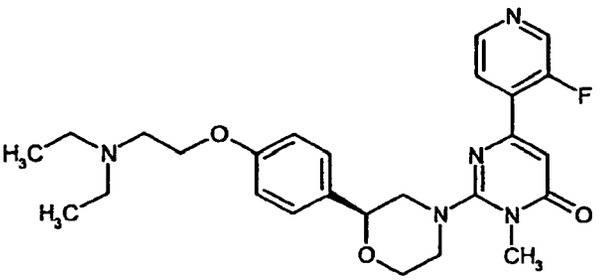
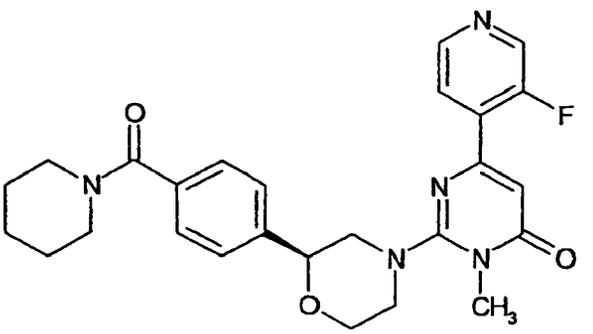
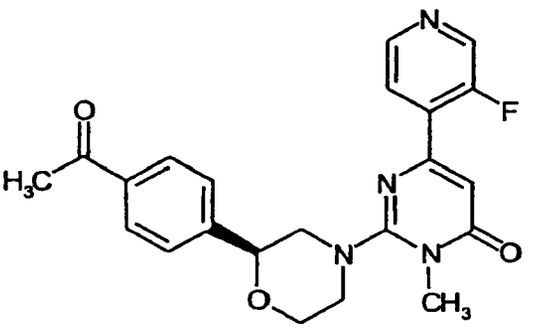
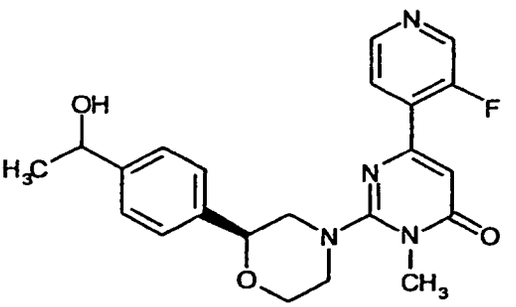
Compound No.	STRUCTURE
289	
290	
291	
292	

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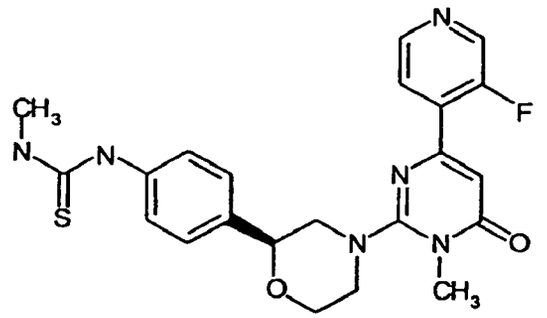
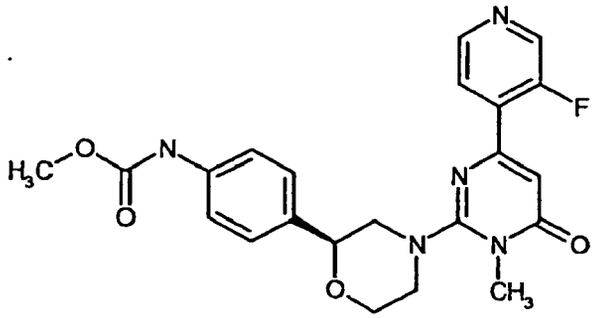
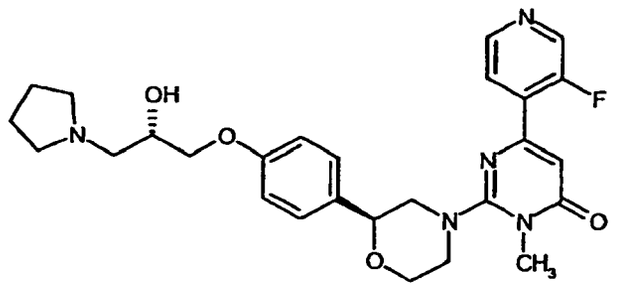
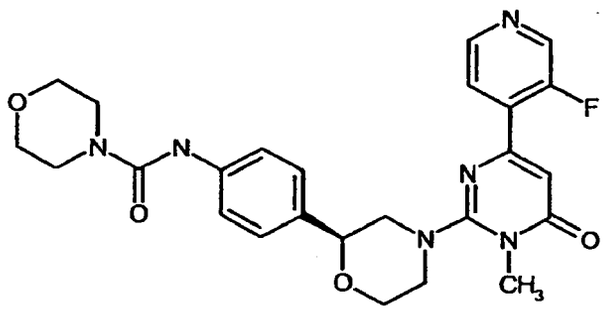
294	
295	
296	
297	

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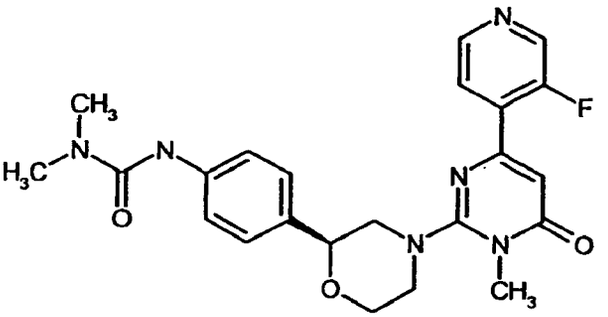
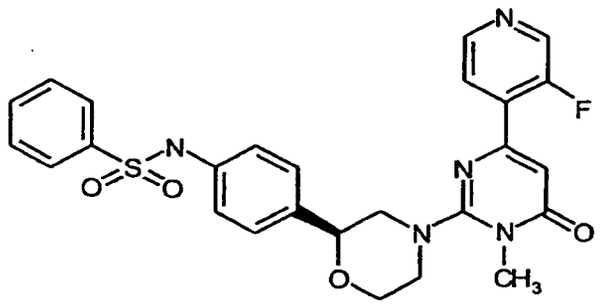
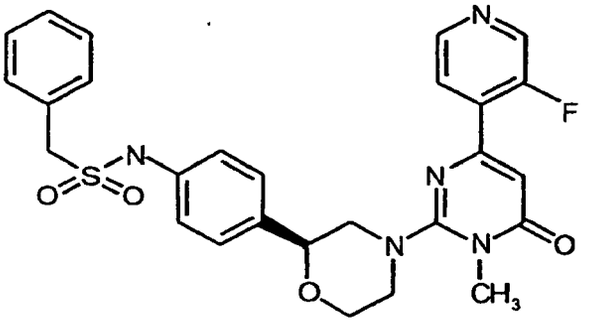
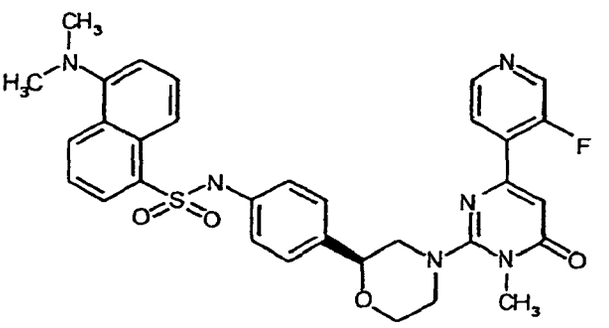
298	
299	
300	
301	

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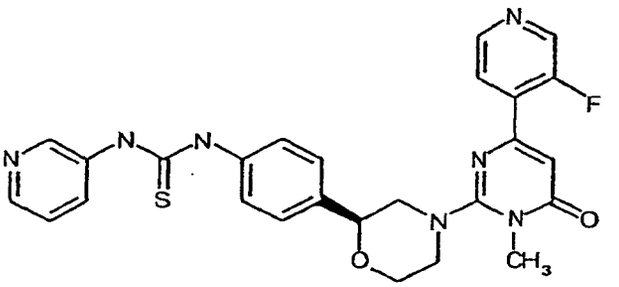
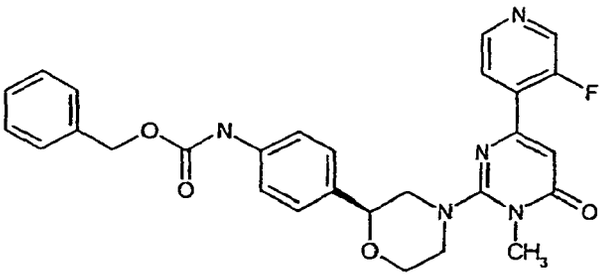
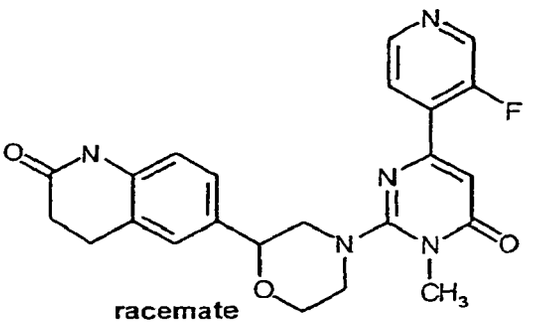
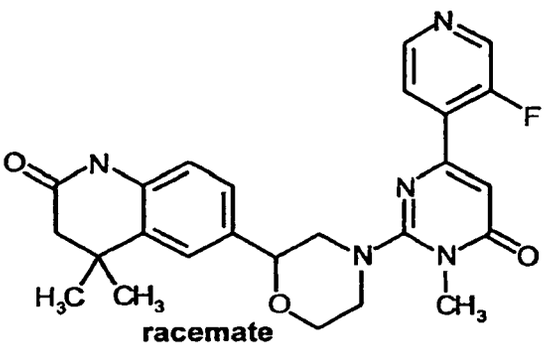
302	
304	
305	 racemate
306	 racemate

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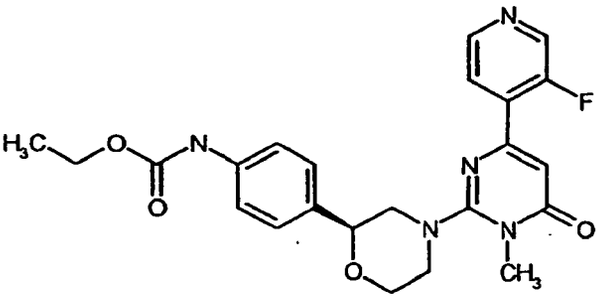
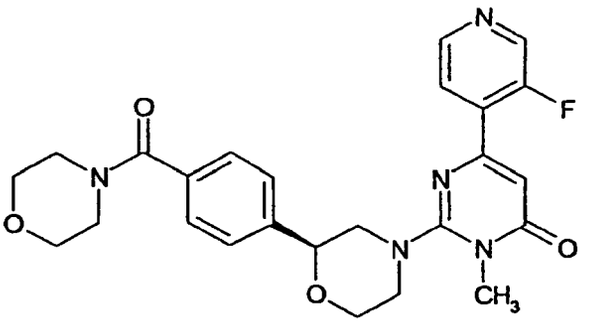
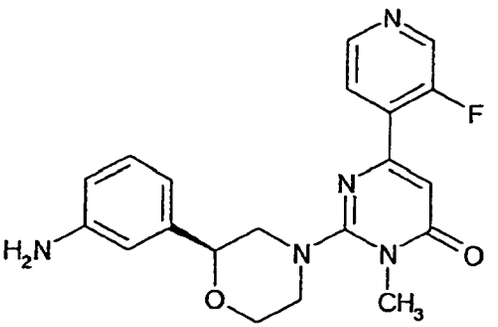
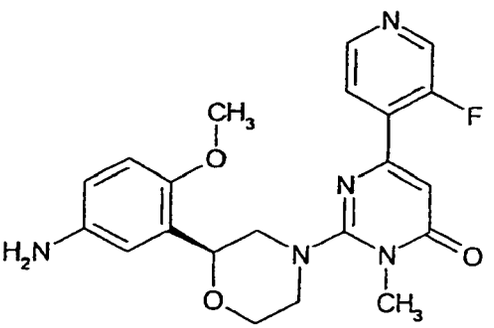
Compound No.	STRUCTURE
307	
310	
311	
312	

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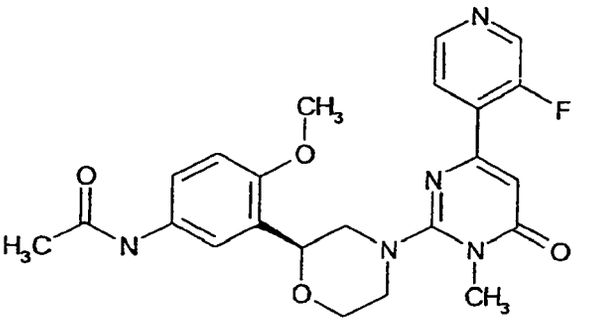
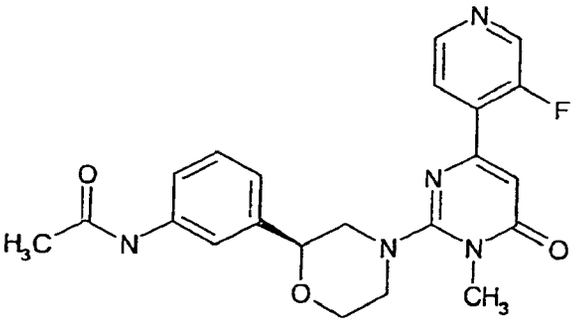
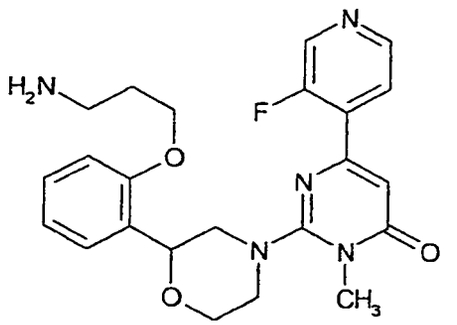
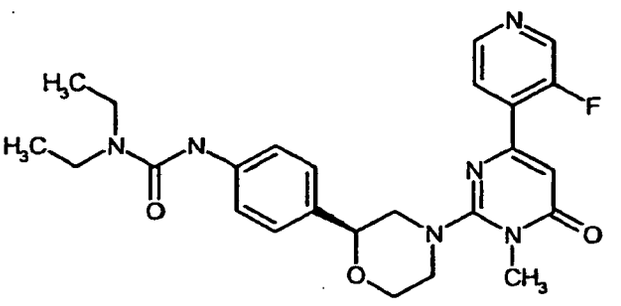
Compound No.	STRUCTURE
313	
314	
315	
316	

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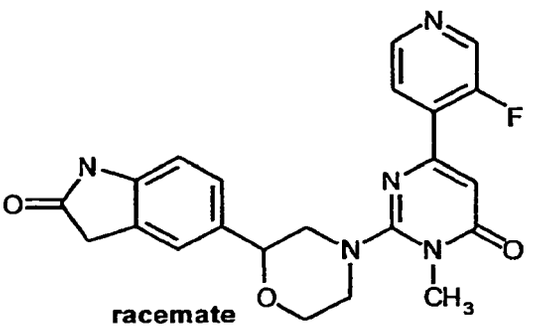
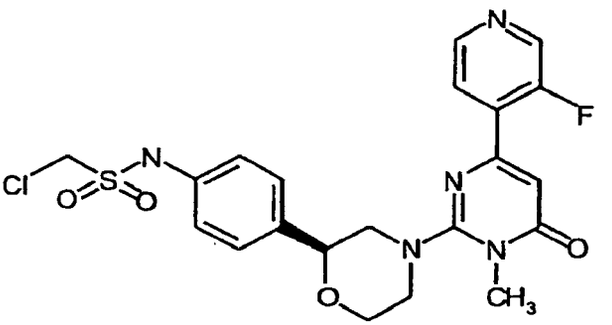
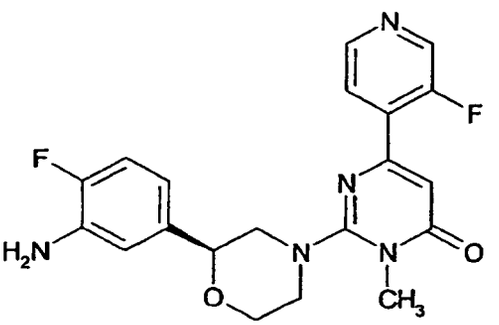
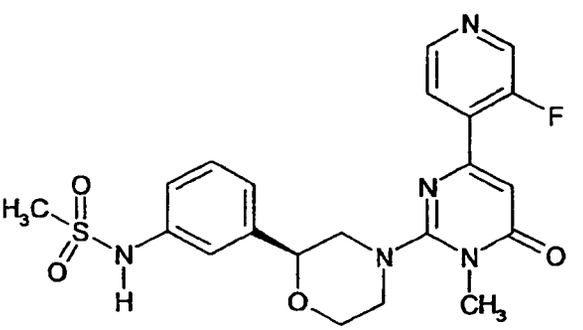
Compound No.	STRUCTURE
317	 racemate
318	
319	
320	

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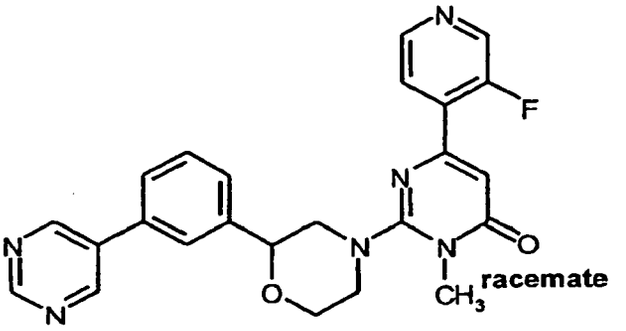
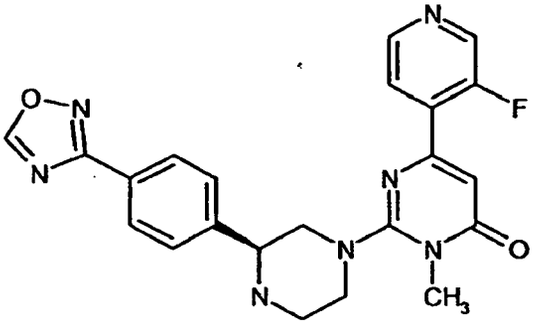
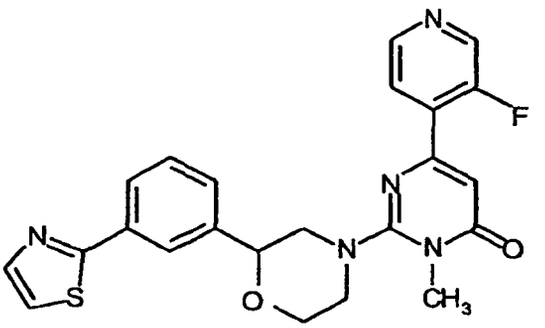
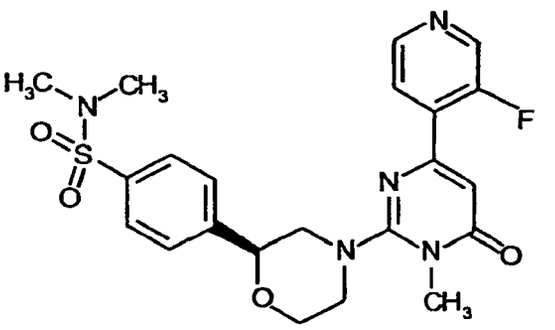
Compound No.	STRUCTURE
321	
322	
331	
332	

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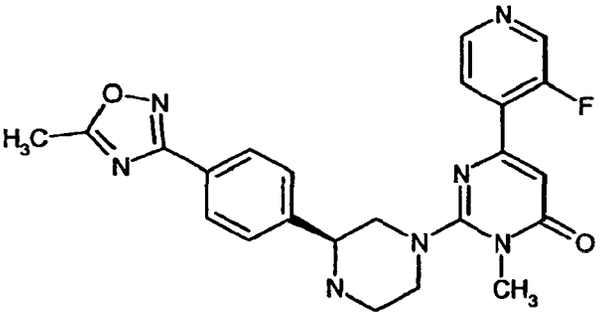
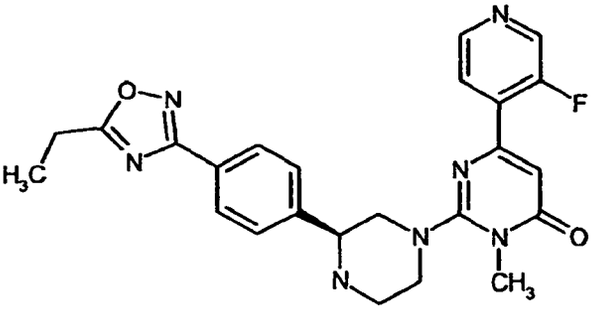
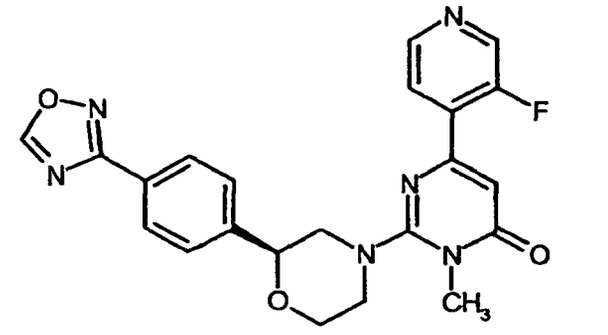
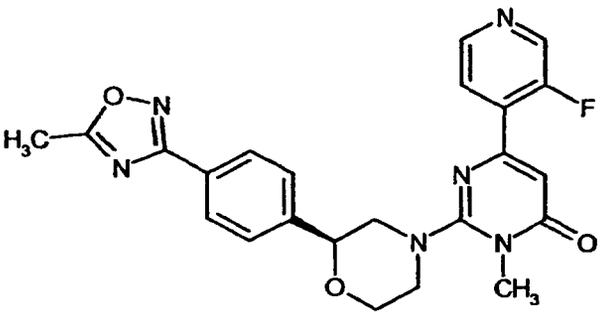
Compound No.	STRUCTURE
334	
335	
336	
337	

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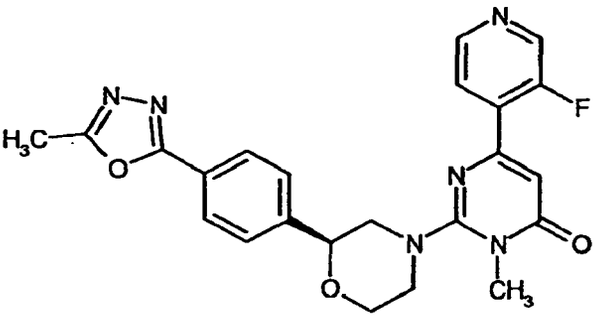
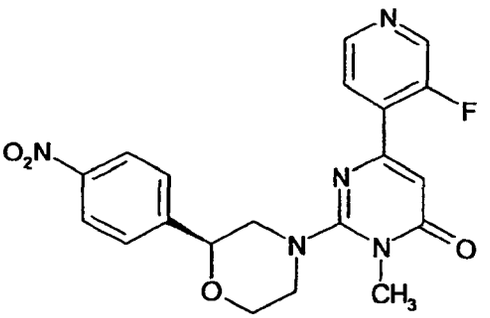
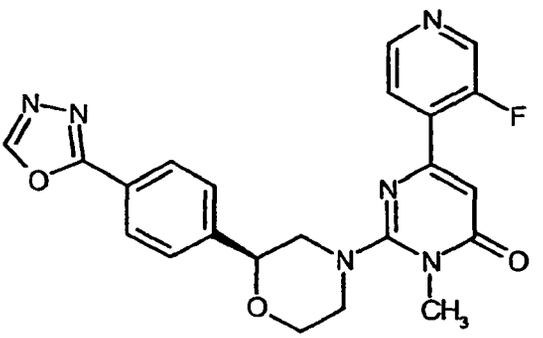
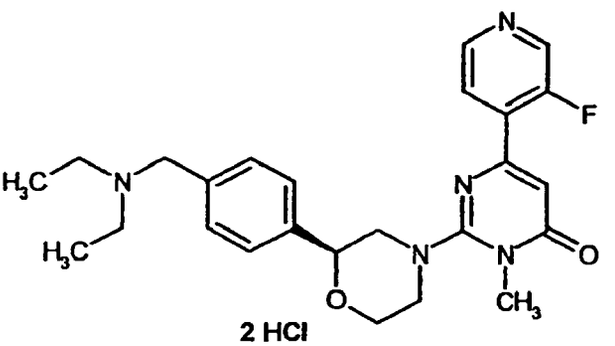
Compound No.	STRUCTURE
338	
339	
340	
341	 2 HCl

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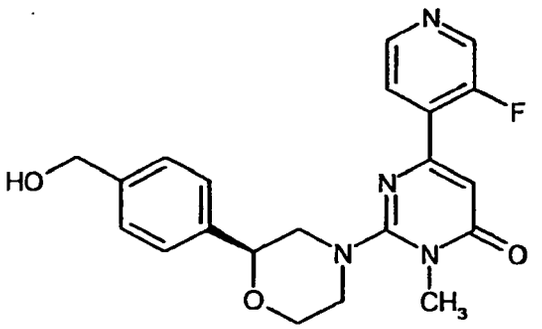
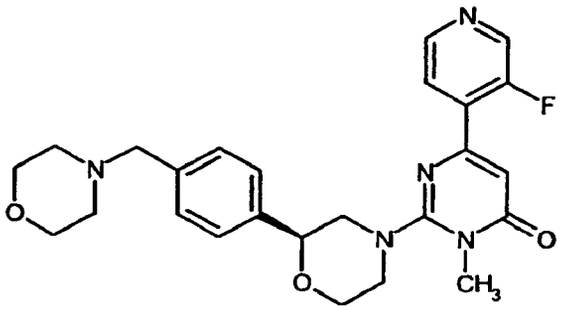
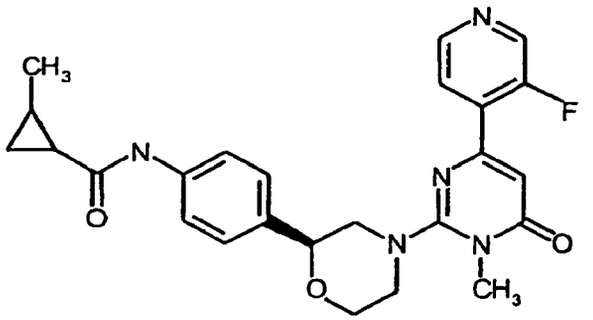
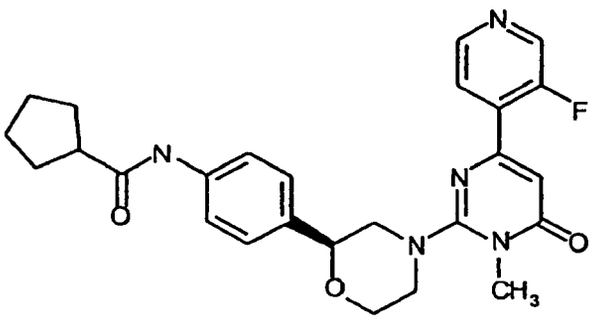
Compound No.	STRUCTURE
342	
343	
344	
345	

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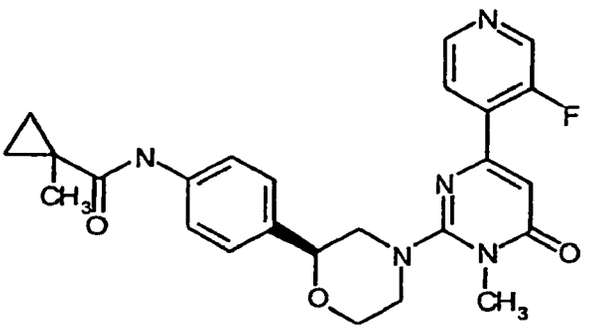
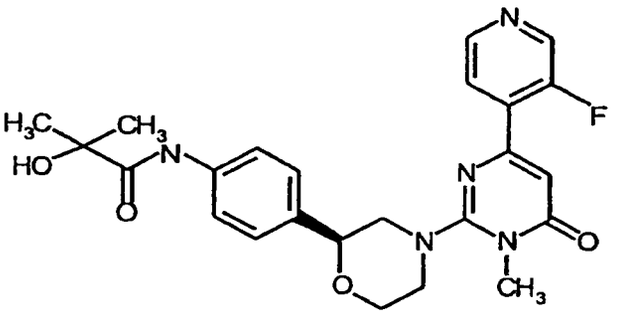
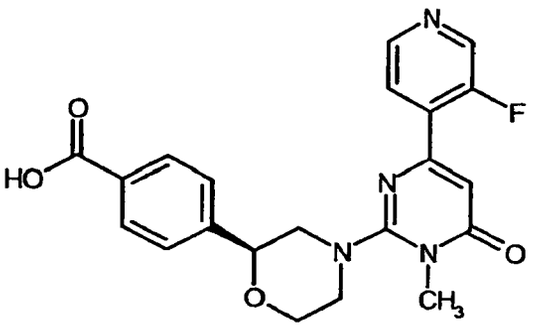
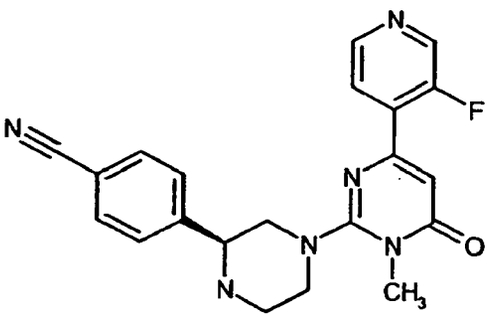
Compound No.	STRUCTURE
346	
347	
348	
349	

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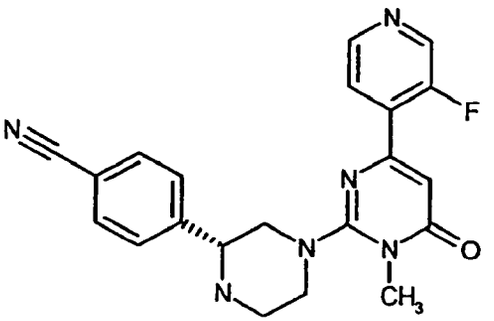
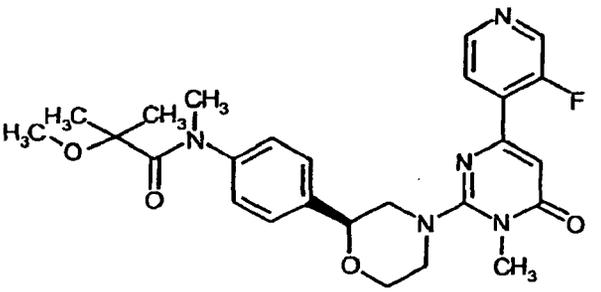
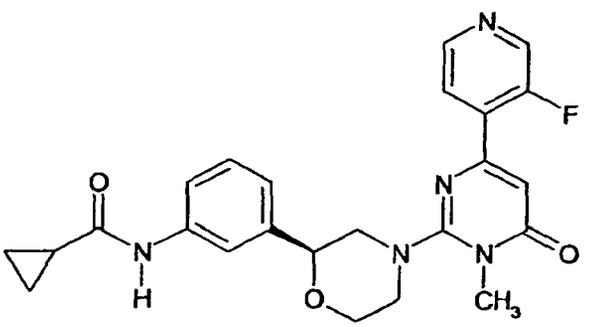
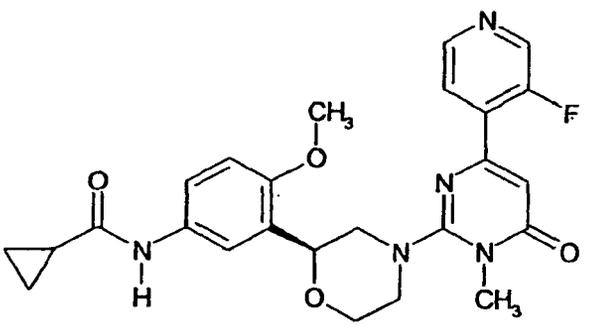
Compound No.	STRUCTURE
350	
352	
353	
354	

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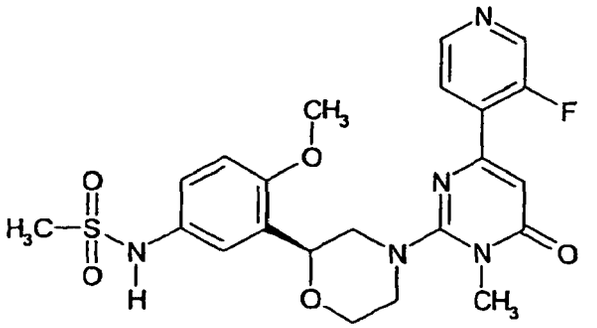
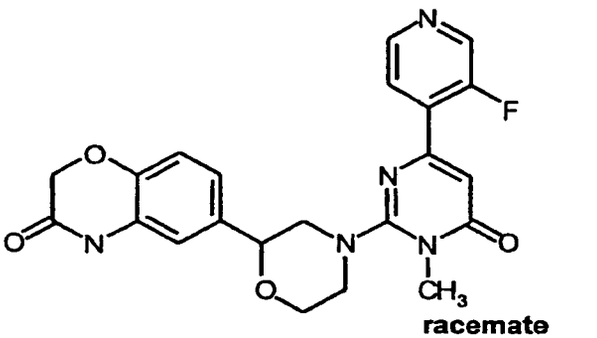
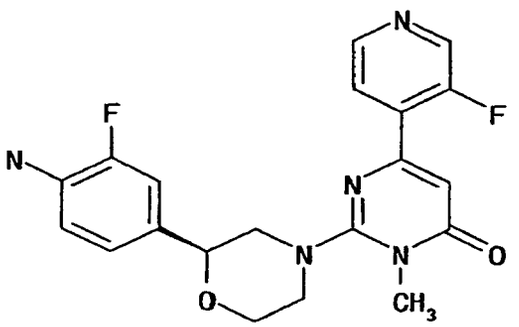
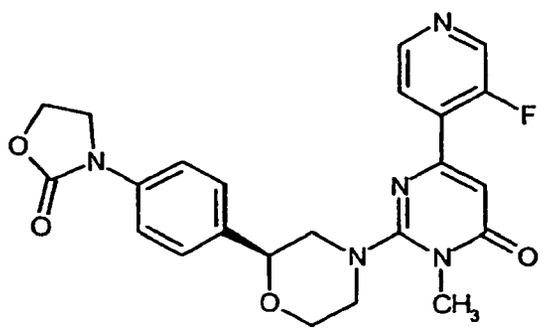
Compound No.	STRUCTURE
355	
356	 racemate
357	
365	

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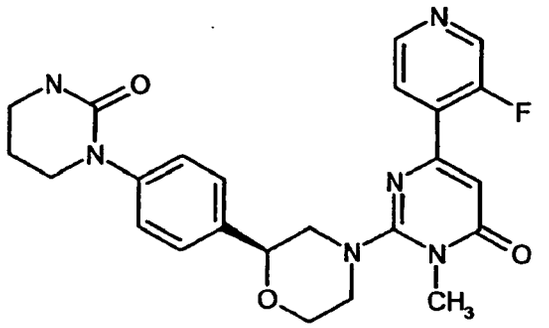
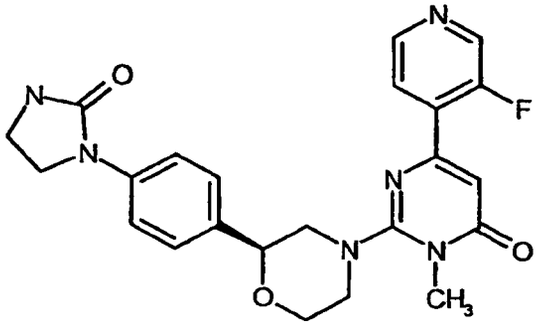
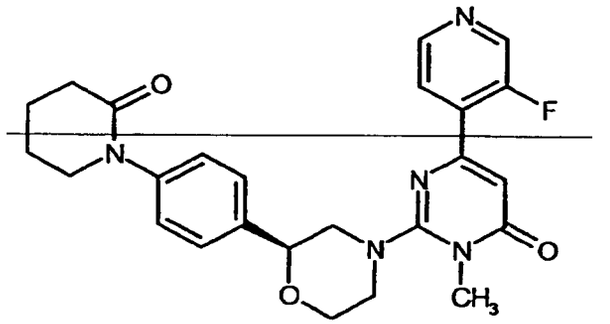
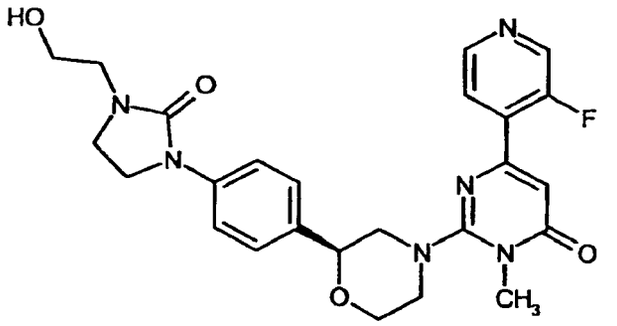
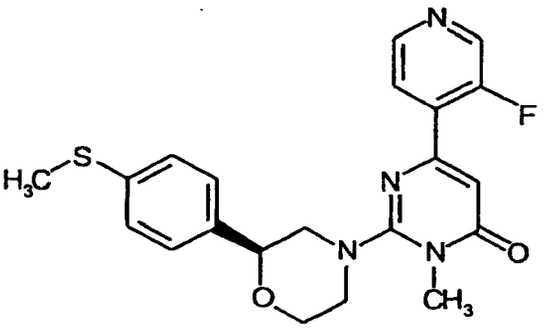
Compound No.	STRUCTURE
366	
367	
368	
369	

(continued)

Compound No.	STRUCTURE
370	

[0030] Particularly preferred compounds of the present invention represented by formula (I) include:

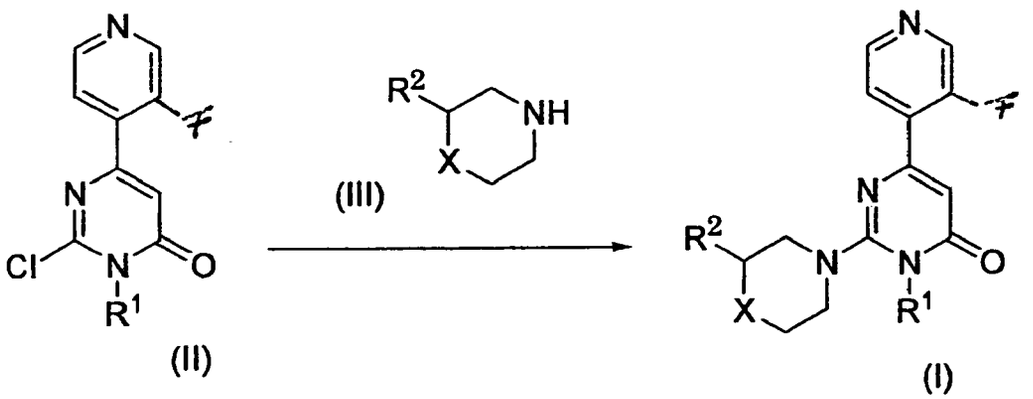
6-(3-Fluoro-pyridin-4-yl)-3-methyl-2-((3S)-3-(4-morpholin-4-yl-phenyl)-piperazin-1-yl)-3H-pyrimidin-4-one;
2-((2S)-2-(4-((3R)-3-Dimethylamino-pyrrolidin-1-yl)-phenyl)-morpholin-4-yl)-6-(3-fluoro-pyridin-4-yl)-3-methyl-3H-pyrimidin-4-one:
6-(3-Fluoro-pyridin-4-yl)-3-methyl-2-((3S)-3-(4-piperidin-1-yl-phenyl)-piperazin-1-yl)-3H-pyrimidin-4-one;
6-(3-Fluoro-pyridin-4-yl)-3-methyl-2-((2S)-2-(4-(4-pyrrolidin-1-yl-piperidin-1-yl)-phenyl(-morpholin-4-yl)-3H-pyrimidin-4-one;
2-((2S)-2-(4-(4-Dimethylamino-piperidin-1-yl)-phenyl)-morpholin-4-yl)-6-(3-fluoro-pyridin-4-yl)-3-methyl-3H-pyrimidin-4-one;
6-(3-Fluoro-pyridin-4-yl)-3-methyl-2-((3S)-3-(4-(4-methyl-piperazin-1-yl)-phenyl)-piperazin-1-yl)-3H-pyrimidin-4-one;
6-(3-Fluoro-pyridin-4-yl)-2-(3S)-3-(4-(4-hydroxy-piperidin-1-yl)-phenyl)-piperazin-1-yl)-3-methyl-3H-pyrimidin-4-one;
6-(3-Fluoro-pyridin-4-yl)-2-((3S)-3-(4-((3R)-3-hydroxy-pyrrolidin-1-yl)-phenyl)-piperazin-1-yl)-3-methyl-3H-pyrimidin-4-one;
2-((2S)-2-(4-((3S,5R)-3,5-Dimethyl-piperazin-1-yl)-phenyl)-morpholin-4-yl)-6-(3-fluoro-pyridin-4-yl)-3-methyl-3H-pyrimidin-4-one;
6-(3-Fluoro-pyridin-4-yl)-3-methyl-2-((2S)-2-(4-(4-methyl-piperazin-1-yl)-phenyl)-morpholin-4-yl)-3H-pyrimidin-4-one;
2-((2S)-2-(4-((3S)-3-Dimethylamino-pyrrolidin-1-yl)-phenyl)-morpholin-4-yl)-6-(3-fluoro-pyridin-4-yl)-3-methyl-3H-pyrimidin-4-one;
6-(3-Fluoro-pyridin-4-yl)-2-((2S)-2-(4-(4-isopropyl-piperazin-1-yl)-phenyl)-morpholin-4-yl)-3-methyl-3H-pyrimidin-4-one;
6-(3-Fluoro-pyridin-4-yl)-2-((2S)-2-(4-(4-(2-hydroxyethyl)-piperazin-1-yl)-phenyl)-morpholin-4-yl)-3-methyl-3H-pyrimidin-4-one;
6-(3-fluoro-pyridin-4-yl)-3-methyl-2-((3S)-3-(4-((3S)-3-(pyrrolidin-1-yl)-pyrrolidin-1-yl)-phenyl)-piperazin-1-yl)-3H-pyrimidin-4-one;
6-(3-Fluoro-pyridin-4-yl)-3-methyl-2-((3S)-3-(4-(5-methyl-(1,2,4)oxadiazol-3-yl)-phenyl)-piperazin-1-yl)-3H-pyrimidin-4-one;
6-(3-Fluoro-pyridin-4-yl)-3-methyl-2-[3-(4-morpholin-4-yl-phenyl)-piperidin-1-yl]-3H-pyrimidin-4-one;
2-((2S)-2-(4-Cyclopentylamino-phenyl)-morpholin-4-yl)-6-(3-fluoro-pyridin-4-yl)-3-methyl-3H-pyrimidin-4-one;
6-(3-Fluoro-pyridin-4-yl)-2-((2S)-2-(4-(3-hydroxy-azetidin-1-yl)-phenyl)-morpholin-4-yl)-3-methyl-3H-pyrimidin-4-one;
N-(4-((2S)-4-((4-(3-Fluoro-pyridin-4-yl)-1-methyl-6-oxo-1,6-dihydro-pyrimidin-2-yl)-morpholin-2-yl)-phenyl)-acetamide
2-((2S)-2-(4-Cyclopentyloxy-phenyl)-morpholin-4-yl)-6-(3-fluoro-pyridin-4-yl)-3-methyl-3H-pyrimidin-4-one;
2-((2S)-2-(4-Cyclopropylmethoxy-phenyl)-morpholin-4-yl)-6-(3-fluoro-pyridin-4-yl)-3-methyl-3H-pyrimidin-4-one;
2-((2S)-2-(4-(2-Dimethylamino-ethoxy)-phenyl)-morpholin-4-yl)-6-(3-fluoro-pyridin-4-yl)-3-methyl-3H-pyrimidin-4-one;
2-((2S)-2-(4-Amino-phenyl)-morpholin-4-yl)-6-(3-fluoro-pyridin-4-yl)-3-methyl-3H-pyrimidin-4-one;
Cyclopropanecarboxylicacid(4-((2S)-4-(4-(3-fluoro-pyridin-4-yl)-1-methyl-6-oxo-1,6-dihydro-pyrimidin-2-yl)-morpho-

lin-2-yl)-phenyl)-amide;
N-(4-((2S)-4-(4-(3-Fluoro-pyridin-4-yl)-1-methyl-6-oxo-1,6-dihydro-pyrimidin-2-yl)-morpholin-2-yl)-phenyl)-2,2-dimethyl-propionamide;
6-(3-Fluoro-pyridin-4-yl)-3-inethyl-2-((2S)-2-(4-(methyl-((3R)-tetrahydro-furan-3-yl)-amino)-phenyl)-morpholin-4-yl)-3H-pyrimidin-4-one;
6-(3-Fluoro-pyridin-4-yl)-3-methyl-2-((2S)-2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-morpholin-4-yl)-3H-pyrimidin-4-one;
6-(3-Fluoro-pyridin-4-yl)-2-((2S)-2-(4-hydroxy-phenyl)-morpholin-4-yl)-3-methyl-3H-pyrimidin-4-one;
2-((2S)-2-(4-(2-Diethylamino-ethoxy)-phenyl)-morpholin-4-yl)-6-(3-ffuoro-pyridin-4-yl)-3-methyl-3H-pyrimidin-4-one;
6-(3-Fluoro-pyridin-4-yl)-3-methyl-2-((2S)-2-(4-(2-piperidin-1-yl-ethoxy)-phenyl)-morpholin-4-yl)-3H-pyrimidin-4-one;
6-(3-Fluoro-pyridin-4-yl)-3-methyl-2-((2S)-2-(4-(2-(4-methyl-piperazin-1-yl)ethoxy)-phenyl)-morpholin-4-yl)-3H-pyrimidin-4-one;
N^2,N^2-Dimethyl-N^1-(4-((2S)-4-(3-methyl-4-oxo-3,4-dihydro-6-(3-fluoropyriclin-4-yl)pyrimidin-2-yl) morpholin-2-yl) phenyl)glycinamide;
Methyl (4-((2S)-4-(6-(3-ffuoropyridin-4-yl)-3-methyl-4-oxo-3H-pyrimidin-2-yl)morpholin-2-yl)phenyl)carbamate;
N'-(4-((2S)-4-(6-(3-Fluoropyridin-4-yl)-3-methyl-4-oxo-3H-pyrimidin-2-yl)morpholin-2-yl)phenyl)-N,N-dimethylurea;
6-{4-(4-(3-Fluoropyridin-4-yl)-1-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)morpholin-2-yl}-3,4-dihydroquinolin-2(1H)-one;
6-(3-Fluoro-pyridin-4-yl)-3-methyl-2-{(2S)-2-[4-morpholine-4-carbonyl]-phenyl}-morpholin-4-yl}-3H-pyrimidin-4-one;
N-(3-{(2S)-4-[4-(3-Fluoropyridin-4-yl)-1-methyl-6-oxo-1,6-dihydropyrimidin-2-yl]-morpholin-2-yl}-4-methoxyphenyl)acetamide;
N-(3-{(2S)-4-[4-(3-Fluoropyridin-4-yl)-1-methyl-6-oxo-1,6-dihydropyrimidin-2-yl]-niorpholin-2-yl}phenyl)acetamide; and
6-(3-Fluoropyridin-4-yl)-3-methyl-2-((3S)-3-(4-([1,2,4]oxadiazol-3-yl)phenyl)piperazin-1-yl)-3H-pyrimidin-4-one,

an optically active isomer thereof, or a pharmaceutically acceptable salt thereof.

[0031] Salts of the aforementioned preferred compound, and solvates or hydrates of the aforementioned compounds and salts thereof are also preferred.

[0032] The compounds represented by the aforementioned formula (I) can be prepared, for example, according to the method explained below.



(In the above scheme, definitions of each symbol are the same as those already described.)

[0033] The 2-chloropyrimidone represented by the above formula (II) is prepared easily by the method described in the specification of W02003/027080 and WO2003/037888.

[0034] Then the chloride derivative (II) is allowed to react with the amine (III) or salts thereof in the presence of a base such as sodium hydroxide, potassium hydroxide, sodium methoxide, sodium ethoxide, sodium carbonate, sodium hydrogencarbonate, potassium carbonate, triethylamine, diisopropylethylamine, and 1,8-diazabicyclo[5,4,0]undec-7-en for 1 to 100 hours at a suitable temperature ranging from 0 ˚C to 200 ˚C under nitrogen or argon atmosphere or under

ordinary air to afford the desired compound (I).

[0035] Examples of a solvent for the reactions include, for example, alcoholic solvent such as methanol, ethanol, 1-propanol, isopropanol, tert-butanol, ethylene glycol, propylene glycol; etheric solvents such as diethyl ether, tert-butyl methyl ether, tetrahydrofuran, isopropyl ether; hydrocarbonic solvents such as benzene, toluene, xylene; halogenated hydrocarbonic solvents such as dichloromethane, chloroform, dichloroethane; aprotic polar solvents such as formamide, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone, dimethyl sulfoxide, sulfolane, hexamethylphosphoric triamide, water. Generally, a single solvent or a mixture of two or more solvents may be used so as to be suitable to a base used.

[0036] The compounds of the present invention have inhibitory activity against TPK1, and they inhibit TPK1 activity in neurodegenerative diseases such as Alzheimer disease, thereby suppress the neurotoxicity of Aβ and the formation of PHF and inhibit the nerve cell death. Accordingly, the compounds of the present invention are useful as an active ingredient of a medicament which radically enables preventive and/or therapeutic treatment of Alzheimer disease. In addition, the compounds of the present invention are also useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of ischemic cerebrovascular accidents, Down syndrome, cerebral bleeding due to solitary cerebral amyloid angiopathy, progressive supranuclear palsy, subacute sclerosing panencephalitis, postencephalitic parkinsonism, pugilistic encephalosis, Guam parkinsonism-dementia complex, Lewy body disease, Pick's disease, corticobasal degeneration frontotemporal dementia, vascular dementia, traumatic injuries, brain and spinal cord trauma, peripheral neuropathies, retinopathies and glaucoma, non-insulin dependent diabetes, obesity, manic depressive illness, schizophrenia, alopecia, breast cancer, non-small cell lung carcinoma, thyroid cancer, T or B-cell leukemia, and several virus-induced tumors. As the compound of the present invention has good pharmacological activities, good safety and good pharmacokinetics, the compound has preferable characteristics as a medicament.

[0037] As the active ingredient of the medicament of the present invention, a substance may be used which is selected from the group consisting of the compound represented by the aforementioned formula (I) and pharmacologically acceptable salts thereof, and solvates thereof and hydrates thereof. The substance, per se, may be administered as the medicament of the present invention, however, it is desirable to administer the medicament in a form of a pharmaceutical composition which comprises the aforementioned substance as an active ingredient and one or more of pharmaceutical additives. As the active ingredient of the medicament of the present invention, two or more of the aforementioned substance may be used in combination.

[0038] A type of the pharmaceutical composition is not particularly limited, and the composition may be provided as any formulation for oral or parenteral administration. For example, the pharmaceutical composition may be formulated, for example, in the form of pharmaceutical compositions for oral administration such as granules, fine granules, powders, hard capsules, soft capsules, syrups, emulsions, suspensions, solutions, or in the form of pharmaceutical compositions for parenteral administrations such as injections for intravenous, intramuscular, or subcutaneous administration, drip infusions, transdermal preparations, transmucosal preparations, nasal drops, inhalants, suppositories.

[0039] Dose and frequency of administration of the medicament of the present invention are not particularly limited, and they may be appropriately chosen depending on conditions such as a purpose of preventive and/or therapeutic treatment, a type of a disease, the body weight or age of a patient, severity of a disease . Generally, a daily dose for oral administration to an adult may be 0.01 to 1,000 mg (the weight of an active ingredient), and the dose may be administered once a day or several times a day as divided portions, or once in several days. When the medicament is used as an injection, administrations may preferably be performed continuously or intermittently in a daily dose of 0.001 to 3000 mg (the weight of an active ingredient) to an adult.

Examples

[0040] The present invention will be explained more specifically with reference to examples. However, the scope of the present invention is not limited to the following examples. The compound numbers in the examples correspond to those in the table above.

Reference Example 1:

Synthesis of 2-chloro-6-(3-fluoropyridin-4-yl)-3-methyl-3H-pyrimidin-4-one

3-Fluoroisonicotinic acid

[0041] 3-Fluoropyridine (25 g, 257mmol) was added to a solution of butyllithium (270 mmol) and diisopropylamine (27.4 g, 271 mmol) in tetrahydrofuran (600 mL) at -78˚C. After stirring for one hour, crushed dry ice was added to the solution and the solution was warmed to room temperature during one hour. Aqueous hydrogen chloride was added to the solution to acidify the solution to pH 5. The resulting precipitate was filtered and dried. The title compound (25.2 g,

179 mmol, 70%) was obtained as colorless crystal.

3-(3-Fluoro-pyridin-4-yl)-3-oxo-propionic acid ethyl ester

[0042] Carbonyl diimidazole (30.5 g, 188 mmol) was added to a solution of 3-fluoroisonicotinic acid (25.2 g, 179 mmol) in tetrahydrofuran, and the mixture was refluxed for 1 hour. After cooled to room temperature, the solution was added with potassium monoethylmalonate (33.6 g, 197 mmol) and magnesium chloride (20.5 g, 215 mmol), and the mixture was heated at 60 ˚C. After cooled to room temperature, the solution was added with aqueous hydrogen chloride for acidification to pH 5, and then extracted with ethyl acetate. The extract was dried over magnesium sulfate and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (eluent; ethyl acetate / hexane = 1/2) to give desired keto-ester (25.0g, 118mmol, 66%) as colorless crystal.

6-(3-Fluoropyridin-4-yl)-2-mercapto-3-methyl-3H-pyrimidin-4-one

[0043] A suspension of 3-(3-fluoropyridin-4-yl)-3-oxo-propionic acid ethyl ester (60.3 g, 286 mmol), N-methylthiourea (88 g, 976 mmol) and 1,8-diazabicyclo[5,4,0] undec-7-ene (48 g, 315 mmol) in toluene (600 ml) was heated at 100 ˚C for 5 hour. After addition of water (2000 ml) and methanesulfonic acid (30.3 g, 315 mmol) at room temperature and stirring for one hour, resulting precipitate was collected by filtration and dried to afford 6-(3-fluoropyridin-4-yl)-2-mercapto-3-methyl-3H-pyrimidin-4-one (46.3 g, 195 mmol, 68%) as white crystals.

2-Chloro-6-(3-fluoropyridin-4-yl)-3-methyl-3H-pyrimidin-4-one

[0044] After one hour stirring of a solution of phosphorus oxychloride (45 g, 293 mmol) in dimethylformamide (450 ml) at room temperature, 6-(3-fluoropyridin-4-yl)-2-mercapto-3-methyl-3H-pyrimidin-4-one (46.3 g, 195 mmol) was added and heated at 60 ˚C for 2 hours. The resulting suspension was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The aqueous layer was extracted with ethyl acetate and the combined organic layer was washed with brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was washed by hexane to furnish 2-chloro-6-(3-fluoropyridin-4-yl)-3-methyl-3H-pyrimidin-4-one (34.2 g, 143 mmol, 73%) as white crystals.

Reference Example 2:

Synthesis of 2-Chloro-6-(2,3-dichloropyridin-4-yl)-3-methyl- 3H-pyrimidin-4-one

2,3-Dichloroisonicotinic acid

[0045] To a solution of diisopropylamine (21.6g, 213 mmol) and n-butyllithium in hexane (137 ml, 214 mmol) in tetrahydrofuran (600 ml) was added 2,3-dichloropyridine (30.0 g, 203 mmol) in tetrahydrofuran at -78 ˚C. After 2 hour stirring, dry ice (100 g) was added and the solution was further stirred for one hour. Resulting white precipitate formed by acidification to pH 1 with 6N hydrochloric acid was collected by filtration and dried to afford 2,3-dichloroisonicotinic acid (32.5 g, 169 mmol, 83%) as white crystals.

3-((2,3-Dichloropyridin)-4-yl)-3-oxo-propionic acid ethyl ester

[0046] A solution of 2,3-dichloroisonicotinic acid (25.3 g, 132 mmol) and 1,1'-carbonyldiimidazole (22.5 g, 139 mmol) in tetrahydrofuran (500 ml) was heated at 90 ˚C for 2 hours. Malonic acid monoethyl ester potassium salt (24.7 g, 145 mmol) and magnesium chloride (15.1 g, 159 mmol) was added and heated at 60 ˚C for 3 hours. The resulting suspension was acidified and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel chromatography eluting 20-50% of ethyl acetate in hexane to afford 3-((2,3-dichloropyridin)-4-yl)-3-oxo-propionic acid ethyl ester (22.0 g, 83.9 mmol, 64%) as white crystals.

6-(2,3-Dichloropyridirt-4-yl)-2-mercapto-3-methyl-3H-pyrimidin-4-one

[0047] A suspension of 3-((2,3-dichloropyridin)-4-yl)-3-oxo-propionic acid ethyl ester (22.0 g, 83.9 mmol), N-methylthiourea (25.8 g, 286 mmol) and 1,8-diazabicyclo[5,4,0] undec-7-ene (14.1 g, 92.6 mmol) in toluene (450 ml) was heated at 100 ˚C for 5 hours. After the suspension was added with water (1000 ml) and methanesulfonic acid (8.9 g, 92.0 mmol) at room temperature and stirred for one hour, the precipitate was collected by filtration and dried to afford 6-(2,3-dichloropyridin-4-yl)-2-mercapto-3-methyl-3H-pyrimidin-4-one (3.58 g, 12.4 mmol, 15%) as white crystal.

2-Chloro-6-(2,3-dichloropyridin-4-yl)-3-methyl-3H-pyrimidin-4-one

[0048] After one hour stirring of a solution of phosphorus oxychloride (2.9 g, 18.9 mmol) in dimethylformamide (30 ml) at room temperature, 6-(2,3-dichloropyridin-4-yl)-2-mercapto-3-methyl-3H-pyrimidin-4-one (3.58 g, 12.4 mmol) was added and heated at 60 ˚C for 2 hours. The resulting suspension was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was washed by hexane to furnish 2-chloro-6-(2,3-dichloropyridin-4-yl)-3-methyl-3H-pyrimidin-4-one (2.6 g, 8.95 mmol, 72%) as white crystals.

Reference Example 3:

Synthesis of (2S)-2-(4-Piperidin-1-yl-phenyl)-piperazine trihydrochloride

(2S)-2-(4-Bromophenyl)-piperazine-1,4-dicarboxylic acid di-tert-butyl ester

[0049] (2S)-2-(4-Bromophenyl)-piperazine-1,4-dicarboxylic acid di-tert-butyl ester was prepared from 4-bromophenacyl bromide by the same route as (2S)-2-(4-chlorophenyl)-piperazine-1,4-dicarboxylic acid di-tert-butyl ester in WO2004/085408.

(2S)-2-(4-Piperidin-1-yl-phenyl)-piperazine-1,4-dicarboxylic acid di-tert-butyl ester

[0050] A solution of (2S)-2-(4-bromophenyl)-piperazine-1,4-dicarboxylic acid di-tert-butyl ester (1.06 g, 2.40 mmol), piperidine (0.29 ml, 2.88 mmol), palladium acetate (22.0 mg , 0.096 mmol), sodium tert-butoxide (323 mg, 3.36 mmol) and 2-(di-t-butylphosphino)biphenyl (57.0 mg, 0.192 mmol) in toluene (16 ml) was stirred at 80 ˚C for 6 hours. Water and ethyl acetate were added to the solution and the solution was passed through Celite column. The whole was extracted with ethyl acetate and the organic lawyer was washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give (2S)-2-(4-piperidin-1-yl-phenyl)-piperazine-1,4-dicarboxylic acid di-tert-butyl ester (455 mg, 43%) as white crystals.

(2S)-2-(4-Piperidin-1-yl-phenyl)-piperazine trihydrochloride

[0051] Hydrogen chloride (4N, 1.5 ml) in ethyl acetate was added to a solution of (2S)-2-(4-piperidin-1-yl-phenyl)-piperazine-1,4-dicarboxylic acid di-tert-butyl ester (455 g, 1.02 mmol) in dichloromethane (10 ml) and the solution was stirred for 2 hours. Filtration and washing with ethyl acetate of the precipitant gave (2S)-2-(4-piperidin-1-yl-phenyl)-piperazine trihydrochloride (353 mg, 98%) as white crystals. ^{1}H-NMR(DMSO-d6) δ : 1.65(2H,m), 1.81-1.91(4H, m), 3.39-3.53(10H,m), 4.68(1H, m), 7.71(4H,m), 10.0(3H,m), 10.68(1H,m).

Reference Example 4:

Synthesis of N-(4-((2S)-morpholin-2-yl)phenyl)acetamide

2-Bromo-(1S)-1-(4-bromophenyl)ethanol

[0052] A borane-tetrahydrofuran complex (1.0 M solution in tetrahydrofuran, 270 ml, 270 mmol) was added to the solution of (S)-CBS ((S)-2-methyl-CBS-oxazaborolidine, 50 ml, 1.0M solution in toluene) at -30 ˚C over 15 minutes and the solution was stirred for 15 minutes. 4-Bromophenacyl bromide (75.0g, 270 mmol) in dichloromethane (350 ml) was dropped over 70 minutes keeping the temperature -32 to -28 ˚C. After one hour stirring, the solution was warmed to room temperature, and methanol (10 ml) was added slowly and then 0.5 M hydrochloric acid (300 ml) was dropped over 10 minutes. The solution was filtered after 40 minutes stirring and filtrate was extracted with dichloromethane. The combined organic layer was washed with 0.5 M hydrochloric acid, 0.1M aqueous sodium hydroxide and brine and dried over anhydrous sodium sulfate. Concentration of the organic layer yielded 2-bromo-(1S)-1-(4-bromophenyl)ethanol (77 g) as a pale brown oil.

(2S)-2-(4-Bromophenyl) oxirane

[0053] Aqueous sodium hydroxide (1M, 400 ml) was added to 2-bromo-(1S)-1-(4-bromophenyl)ethanol (77.0 g) in diethyl ether (400 ml) and stirred at room temperature for 5 hours. The organic layer was separated and aqueous layer

was extracted with ether. The combined organic layer was washed with brine and dried over anhydrous sodium sulfate. Removal of the solvent yielded (2S)-2-(4-bromophenyl) oxirane (55.0 g) as a pale brown oil.

(1S)-1-(4-Bromophenyl)-2-((1R)-1-phenylethylamino)ethanol

[0054] A mixture of (2S)-2-(4-bromophenyl)oxirane (55.0 g) and (R)-1-phenylethylamine (98.2g, 810 mmol) was heated at 80 ˚C for 6 hours. Addition of isopropyl ether (200 ml) to the residue after distillation of excess phenethylamine and successive filtration yielded (1S)-1-(4-bromophenyl)-2-((1R)-1-phenylethylamino) ethanol (57.0 g) as white crystals. Further crystallization was performed by the concentration of the filtrate in vacuo and cooling the residue in refrigerator. Filtration of the crystal with isopropyl ether (30 ml) yielded additional title compound (5.60 g) as crystals (72.4% yield, 3 steps).

(6S)-6-(4-Bromophenyl)-4-((1R)-1-phenyethyl)morpholin-3-one

[0055] A solution of chloroacetyl chloride (24.3g, 215 mmol) in dichloromethane (100 ml) was dropped into the ice-cooled solution of (1S)-1-(4-bromophenyl)-2-((1R)-1-phenylethylamino)ethanol (62.6 g, 215 mmol) and triethylamine (21.8g, 215 mmol) in dichloromethane (600 ml) over 30 minutes and the mixture was stirred for one hour at the same temperature. Resulting solution was washed with 0.5 M hydrochloric acid, saturated sodium hydrogen carbonate, brine and dried over anhydrous magnesium sulfate. The solvents were removed under reduced pressure and potassium hydroxide (85%, 16.1g, 244 mmol) was added to a solution of resulting pale brown oil in isopropyl alcohol (600 ml) and stirred for 16 hours. The solvent was removed in vacuo and the residue was partitioned between water and ethyl acetate. The organic layer was washed with 0.5 M hydrochloric acid, saturated sodium hydrogen carbonate, brine and dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure furnished (6S)-6-(4-bromophenyl)-4-((1R)-1-phenyethyl)morpholin-3-one (70.2 g) as a brown oil.

(2S)-2-(4-Bromophenyl)-4-((1R)-1-phenylethyl)morpholine

[0056] A borane-tetrahydrofuran complex (1.0M solution in tetrahydrofuran, 510 ml, 510 mm) was added to the ice-cooled solution of (6S)-6-(4-bromophenyl)-4-((1R)-1-phenyethyl)-morpholin-3-one (70.2 g) in tetrahydrofuran (500 ml) over 45 minutes and the solution was stirred at the same temperature for one hour and room temperature for 30 minutes. After careful addition of methanol (60 ml) to the ice-cooled solution, the solvent was removed under reduced pressure and the residue in methanol (750 ml) and 1M aqueous sodium hydroxide (280 ml) was stirred at 80 ˚C for one hour with addition of 1M aqueous sodium hydroxide (70 ml) in every 15 minutes. The solvent was removed under reduced pressure and the residue was partitioned between water and ethyl acetate. The organic layer was washed with water and brine and dried over anhydrous magnesium sulfate. Removal of the solvent yielded (2S)-2-(4-bromophenyl)-4-((1R)-1-phenylethyl)morpholine (65.0 g, 96.3% yield, 2 steps) as white crystals.
Melting point; 85-87˚C
IR : 1487, 1449, 1117, 1098, 809, 758, 699, 550 cm^{-1}
^{1}H-NMR($CDCl_3$) δ : 1.35(3H,d), 2.10(2H,m), 2.60(1H,m), 3.05(1H,m), 3.35(1H,q), 3.75(1H,m), 3.89(1H,m), 4.55(1H,m), 7.25(7H,m), 7.46(2H,d)

(2S)-2-(4-Aminophenyl)-4-((1R)-1-phenylethyl)morpholine

[0057] A solution of (2S)-2-(4-bromophenyl)-4-((1R)-1-phenylethyl)morpholine (15.6 g, 45 mmol), benzophenone imine (9 g, 50 mmol), tris(dibenzylideneacetone)-dipalladium(0)-chloroform adduct (0.93 g, 0.9 mmol), sodium tert-butoxide (6.0 g, 63 mmol) and 2-(di-t-butylphosphino)biphenyl (0.53 g, 1.8 mmol) in toluene (135 ml) was stirred at 95 ˚C for 4 hours. The solvent was removed in vacuo and the residue was partitioned between water and ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. To a solution of the resulting residue in tetrahydrofuran (180 ml) was added 6N hydrochloric acid (180 ml) and the mixture was stirred at room temperature for one hour. The solvent was removed in vacuo and the residue was partitioned between water and ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and the solvent was evaporated. The resulting residue was purified by column chromatography on silica gel (hexane-AcOEt, 2:1) to give (2S)-2-(4-aminophenyl)-4-((1R)-1-phenylethyl)morpholine (12.2 g, 96%) as an oil.

N-(4-((2S)-4-((1R)-1-Phenylethyl)morpholin-2-yl)phenyl)acetamide

[0058] To a solution of (2S)-2-(4-aminophenyl)-4-((1R)-1-phenylethyl)morpholine (7.9 g, 28 mmol) and triethylamine (8.5 g, 84 mmol) in tetrahydrofuran (180 ml) was added acetyl chloride (4.4 g, 56 mmol). The mixture was stirred at

room temperature for 2 hours and partitioned between water and chloroform. The organic extract was washed with brine and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the precipitated crystals were collected by filtration, washed with isopropyl ether to give N-(4-((2S)-4-((1R)-1-phenylethyl)morpholin-2-yl)phenyl)-acetamide (6.47 g, 71%) as yellow crystals.

N-(4-((2S)-Morpholin-2-yl)phenyl)acetamide

[0059] To a solution of N-(4-((2S)-4-((1R)-1-phenylethyl)morpholin-2-yl)phenyl) acetamide (6.47 g, 20 mmol) and ammonium formate (6.3 g, 100 mmol) in mixture of tetrahydrofuran (136 ml), methanol (270 ml) and water (70 ml) was added 10% palladium on carbon (wet, 270 mg) and the solution was stirred at 95˚C for 3 hours. After filtration, the solvent was removed in vacuo and the residue was partitioned between water and dichloromethane. The organic layer was dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure to give N-(4-((2S)- morpholin-2-yl)phenyl)acetamide (5.78 g, quant.) as an yellow oil.

Reference Example 5:

Synthesis of (2S)-2-(5-Cyano-2-methoxyphenyl)-morpholine hydrochloride

(2S)-2-Bromo-1-(5-bromo-2-methoxyphenyl) ethanol

[0060] To a solution of (S)-2-methyl-CBS-oxazaborolidine (39.5 ml, 1.0 M solution in toluene, 39.5 mmol) was added borane-tetrahydrofuran complex (237 ml, 1.0 M solution in tetrahydrofuran, 237 mmol) at -40 ˚C. To the resulting solution was added a solution of 5'-bromo-2'-methoxyphenacyl bromide (60.8 g, 197.4 mmol) in tetrahydrofuran (400 ml) through dropping funnel over one hour. After stirring for 3 hours below 0 ˚C, methanol (ca. 50 ml) was added dropwise. After stirring the resulting solution for another 30 minutes at room temperature, the solvents were removed in vacuo. The residue was partitioned between ethyl acetate and 1N hydrochloric acid. The organic layer was washed with hydrochloric acid and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was used for the next reaction without further purification.

(2S)-2-(5-Bromo-2-methoxyphenyl)-oxirane

[0061] A mixture of (2S)-2-bromo-1-(5-bromo-2-methoxyphenyl)-ethanol in diethyl ether (250 ml) and potassium hydroxide (26.3 g, 395 mmol) in water (250 ml) was stirred vigorously until the consumption of the starting material. The organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was used for the next reaction without further purification.

(2S)-2-Benzylamino-1-(5-bromo-2-methoxyphenyl)-ethanol

[0062] A mixture of (2S)-2-(5-bromo-2-methoxyphenyl)-oxirane and benzylamine (147 ml, 1.34 mol) was heated at 80 ˚C for 4.5 hours. The excess benzylamine was distilled off under reduced pressure. Washing of the residue with diethyl ether/hexane afforded (2S)-2-benzylamino-1-(5-bromo-2-methoxyphenyl)-ethanol (104.5 g, 70%, 3steps) as white crystals.

(6S)-4-Benzyl-6-(5-bromo-2-methoxyphenyl)-morpholin-3-one

[0063] A solution of chloroacetyl chloride (24.3 g, 215 mmol) in dichloromethane (100 ml) was dropped into a mixture of (2S)-2-benzylamino-1-(5-bromo-2-methoxyphenyl)-ethanol (101.8 g, 302.7 mmol) in dichloromethane (600 ml) and 1N aqueous sodium hydroxide at 0 ˚C and stirred for one hour. The resulting solution was partitioned between water and dichloromethane. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. Potassium hydroxide (34.0 g, 605 mmol) was added to a solution of the residue in 2-propanol (600 ml) and the solution was stirred for 16 hours. The solvent was removed in vacuo and the residue was partitioned between water and ethyl acetate. The organic layer was washed with brine and dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure gave (6S)-4-benzyl-6-(5-bromo-2-methoxyphenyl)-morpholin-3-one (108.7 g, 95%, 2 steps) as a pale yellow oil.

(2S)-4-Benzyl-2-(5-bromo-2-methoxyphenyl)-morpholine

[0064] A solution of (6S)-4-benzyl-6-(5-bromo-2-methoxyphenyl)-morpholin-3-one (67.2 g, 179 mmol) in tetrahydro-

furan (200 ml) was added to an ice-cooled mixture of lithium borohydride (8.55 g, 393 mmol) and chlorotrimethylsilane (99.7 ml, 785 mmol) in tetrahydrofuran (500 ml) over 45 minutes and the solution was stirred at same temperature for one hour and then at room temperature for 5 hours. After careful addition of methanol (60 ml) to the ice-cooled solution, solvent was removed under reduced pressure and the residue in 10% aqueous sodium hydroxide (280 ml) was stirred at 90 ˚C for 3 hours. The solvents were removed under reduced pressure and the residue was partitioned between water and diethyl ether. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate and concentrated in vacuo. Purification of the residue by silica gel column chromatography (hexane/ethyl acetate) gave (2S)-4-benzyl-2-(5-bromo-2-methoxyphenyl)-morpholine (46.1g, 71%, 2 steps) as a yellow oil.

(2S)-4-Benzyl-2-(5-cyano-2-methoxyphenyl)-morpholine

[0065] A solution of (2S)-4-benzyl-2-(5-bromo-2-methoxyphenyl)-morpholine (17.1 g, 47.2 mmol) and copper cyanide (6.35 g, 70.9 mmol) in 1-methyl-2-pyrrolidinone (140 ml) was stirred at 160 ˚C for 9 hours. Diethyl ether and 1N aqueous sodium hydroxide were added to the reaction mixture, and the solution was passed through Celite column. The whole was extracted with diethyl ether. The organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate) to give (2S)-4-benzyl-2-(5-cyano-2-methoxyphenyl)-morpholine (10.1 mg, 69%) as a yellow oil.

(2S)-2-(5-Cyano-2-methoxyphenyl)-morpholine hydrochloride

[0066] To a solution of (2S)-4-benzyl-2-(5-cyano-2-methoxyphenyl)-morpholine (10.8 g, 35.0 mmol) in 1,2-dichloroethane (80 ml) was added 1-chloroethyl chloroformate (5.73 ml, 52.5 mmol) at room temperature. Upon disappearance of the starting material, the reaction mixture was concentrated under reduced pressure. The residue was then dissolved in methanol (100 ml) and refluxed for 30 minutes. The solvents were removed in vacuo and the residue was filtered and washed with ethyl acetate to afford (2S)-2-(5-cyano-2-methoxyphenyl)-morpholine hydrochloride (8.08 g, 91%) as white solids.
^{1}H-NMR(DMSO-d6) δ : 2.91-3.36(4H,m), 3.91(3H; s), 3.95(1H, m), 4.13(1H, dd, J = 12.3, 3.3 Hz), 5.06(1H, dd, J = 11.1, 2.1 Hz), 7.25(1H, d, J = 5.7 Hz), 7.77(1H, d, J = 2.1 Hz), 7.86 (1H, dd, J = 5.7, 2.1 Hz), 9.57(2H, m).

Reference Example 6 :

Synthesis of (2S)-2-(4-(N-methyl-N-((3R)-tetrahydrofuran-3-yl)amino)phenyl)-morpholine hydrochloride

4-((1R)-1-phenylethyl)-(2S)-2-(4-(N-((3R)-tetrahydrofuran-3-yl)amino)phenyl)-morpholine

[0067] (R)-(+)-3-Aminotetrahydrofuran toluene-4-sulfonate (2.0 g, 7.7 mmol) was added to a suspension of (2S)-2-(4-bromophenyl-4-((R)-1-phenylethyl)morpholine (2.4 g, 6.9 mmol), palladium acetate (65 mg, 0.29 mmol), 2-(di-t-butylphosphino)biphenyl (170 mg, 0.57 mmol), and sodium tert-butoxide (3.4 g, 35.4 mmol) in tert-butanol (50 ml) at room temperature. After heating at 90 ˚C for 6 hours, the resulting suspension was passed through a Celite column. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel chromatography eluting 5-10%methanolinchloroformtoafford4-((1R)-1-phenylethyl)-(2S)-2-(4-(N-((3R)-tetrahydrofuran-3-yl)amino)phenyl)morpholine (1.3 g, 53%) as white crystals. ^{1}H-NMR($CDCl_3$) δ : 1.35 (3H, d, J=6.8 Hz), 2.04-2.16 (4H, m), 2.55-2.62 (1H, m), 3.08-3.12 (1H, m), 3.33-3.38 (1H, m), 3.67-3.93 (5H, m) ,3.98-4.02 (1H ,m) ,4.46-4.58 (2H ,m) ,6.57 (2H , d, J=7.2 Hz), 6.83 (1H, d, J=9.0 Hz), 7.21-7.33 (7H, m)

(25)-2-(4-(N-methyl-N-((3R)-tetrahydrofuran-3-yl)amino)phenyl)-4-((1R)-1-phenylethyl)morpholine

[0068] Sodium triacetoxyborohydride (2.4 g, 11.3 mmol) was added to a solution of 4-((1R)-1-phenylethyl)-(2S)-2-(4-(N-((3R)-tetrahydrofuran-3yl)amino)phenyl)-morpholine (1.3 g, 3.69 mmol) and formalin (35%, 1.6 g, 18.6 mmol) in dichloroethane (50 mL) at room temperature. After stirring for 2 hours, the resulting suspension was partitioned between ethyl acetate and 1 N sodium hydroxide. The aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel chromatography eluting 5-10% methanol in chloroform to furnish (2S)-2-(4-(N-methyl-N-((3R)-tetrahydrofuran-3-yl)amino)phenyl)-4-((1R)-1-phenylethyl)morpholine (1.35 g, 100%) as a pale yellow oil.
^{1}H-NMR($CDCl_3$) δ : 1.33 (3H, d, J=6.8 Hz), 2.02-2.13(4H,m), 2.53-2.60 (1H, m), 3.00(3H, s),3.08-3.12 (1H, m), 3.30-3.34 (1H, m), 3.70-3.98 (5H, m), 4.00-4.06 (1H, m), 4.46-4.58 (2H, m), 6.60 (2H, d, J=7.2 Hz), 7.28-7.37 (7H, m)

(2S)-2-(4-(N-methyl-N-((3R)-tetrahydrofuran-3-yl)amino)phenyl)morpholine hydrochloride

[0069] A solution of 10% palladium on carbon (1.0 g) and ((2S)-2-(4-(N-methyl-N-((3R)-tetrahydrofuran-3yl)amino)phenyl)-4-((1R)-1-phenylethyl)morpholine (3.69 mmol) in methanol (10 ml) was stirred under hydrogen atmosphere vigorously at 50 ˚C for 10 hours. The catalyst was filtered off with a Celite pad, and the filtrate was concentrated under reduced pressure. The residue was treated by 4N hydrogen chloride in ethyl acetate and concentrated under reduced pressure to give a pale yellow solid, which was recrystallized from ethanol to afford (2S)-2-(4-(N-methyl-N-((3R)-tetrahydrofuran-3yl)amino)phenyl)morpholine hydrochloride (0.9 g, 73%) as white crystals.
^{1}H-NMR($CDCl_3$) δ : 2.99 (3H, s), 3.00-3.12 (2H, m), 3.23-3.28 (1H, m), 3.61-4.02 (9H, m), 4.51-4.53 (1H, m), 4.79 (1H, d, J=10.1 Hz), 7.42-7.48 (4H ,m), 9.63 (2H, br)

Reference Example 7:

Synthesis of (2S)-2-(4-(N-((3R)-tetrahydrofuran-3-yl)amino)phenyl)morpholine

[0070] To a solution of 4-((1R)-1-phenylethyl)-(2S)-2-(4-[N-{(3R)-tetrahydrofuran-3-yl} amino]phenyl)morpholine (0.40 g, 1.09 mmol) and ammonium formate (0.69 g, 10.9 mmol) in mixture of tetrahydrofuran (50 ml), methanol (100 ml) and water (16 ml) was added 10% palladium on carbon (wet, 150 mg) and stirred at 95˚C for one hour. After filtration, the solvent was removed *in vacuo* and the residue was partitioned between water and dichloromethane. The organic layer was dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure to give (2S)-2-[4-{N-((3R)-tetrahydrofuran-3-yl)amino}phenyl]morpholine (0.28 g, quant.) as a colorless oil.
^{1}H-NMR($CDCl_3$) δ : 1.90 (1H, m), 2,21 (1H, m), 2.80-2.98 (4H, m), 3.67-4.20 (9H, m), 4.36 (1H, d, J = 10.2 Hz), 6.56 (2H, d, J = 3.4 Hz), 7.18 (2H, d, J = 3.4 Hz)

Reference Example 8:

Synthesis of (2S)-2-(4-(1-acetylpiperidin-4-yloxy)phenyl)morpholine hydrochloride

2-Bromo-1-(4-hydroxypheny)-ethan-1-one

[0071] Phenyltrimethylammonium tribromide (276 g, 734 mmol) was added to a suspension of 4-hydroxyacetophenone (100 g, 734 mmol) in tetrahydrofuran (1000 ml) at room temperature. After stirring for 3 hours, the resulting suspension was filtered, and the filtrate was concentrated under reduced pressure. The residue was washed with diisopropyl ether to afford 2-bromo-1-(4-hydroxyphenyl)-ethan-1-one (85 g, 54%) as white crystals.
^{1}H-NMR($CDCl_3$) δ : 3.84 (1H, br), 4.40 (2H, s), 6.98 (2H, d, J=7.2 Hz), 7.91 (2H, d, J=7.2 Hz)

4-(2-Bromoacety)phenyl methanesulfonate

[0072] Methanesulfonyl chloride (50 g, 436 mmol) was added to a solution of 2-bromo-1-(4-hydroxyphenyl)-ethan-1-one (85 g, 395 mmol) and triethylamine (48g, 474 mmol) in tetrahydrofuran (1000 ml) at 0 ˚C and the mixture was stirred for 30 minutes at room temperature. The mixture was partitioned between water and ethyl acetate, and the organic layer was washed with brine, dried over magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was washed with diisopropyl ether to afford 4-(2-bromoacetyl)phenyl methanesulfonate (96 g, 83%) as white crystals.
^{1}H-NMR($CDCl_3$) δ = 3.22 (3H, s), 4.41 (2H, s), 7.41 (2H, d, J=7.2 Hz), 8.06 (2H, d, J=7.2 Hz)

4-((2S)-2-Bromo-1-hydroxyethyl)phenyl methanesulfonate

[0073] Borane-tetrahydrofuran complex (1.0 M solution in tetrahydrofuran, 330 ml) was added to a solution of (S)-CBS ((S)-2-methyl-CBS-oxazaborolidine, 50 ml, 1.0 M solution in toluene) at -30 ˚C over 15 minutes and stirred for 30 minutes. 4-(2-Bromoacetyl)phenyl methanesulfonate (96 g, 328 mmol) in tetrahydrofuran (500 ml) was dropped over 70 minutes keeping the temperature -32 to -28 ˚C. After one hour stirring, the solution was warmed to room temperature, and methanol (10 ml) was added slowly and then 0.5 M hydrochloric acid (300 ml) was dropped over 10 minutes. The solution was filtered after 40 minutes stirring and filtrate was extracted with ethyl acetate. The combined organic layer was washed with 0.5 M hydrochloric acid, 0.1M aqueous sodium hydroxide and brine and dried over anhydrous sodium sulfate. Concentration of the organic layer yielded 4-((2S)-2-bromo-1-hydroxyethyl)phenyl methanesulfonate as a pale brown oil.
^{1}H-NMR($CDCl_3$) δ : 2.72 (1H, d, J=1.2 Hz), 3.10 (3H, s), 3.44-3.58 (2H, m), 4.93-4.97 (1H, m), 7.30 (2H, d, J=7.2 Hz), 7.46 (2H, d, J=7.2 Hz)

4-((S)-Oxiranyl)phenyl methanesulfonate

[0074] Aqueous sodium hydroxide (1M, 600 mi) was added to 4-((2S)-2-bromo-1-hydroxyethyl)phenyl methanesulfonate (328 mmol) in diethyl ether (400 ml) and stirred at room temperature for 5 hours. The organic layer was separated and aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the residue was washed with diisopropyl ether to afford 4-((S)-oxiranyl)phenyl methanesulfonate (69 g, 98%) as white crystals. ^{1}H-NMR($CDCl_3$) δ : 2.75 (1H, dd, J=1.2 Hz, 6.8 Hz), 3.14-3.16 (4H, m), 3.88 (1H, dd, J=1.2 Hz, 7.2 Hz), 7.28 (2H, d, J=7.2 Hz), 7.42 (2H, d, J=7.2 Hz)

4-((1S)-2-benzylamino-1-hydroxyethyl)phenyl methanesulfonate

[0075] A mixture of 4-((S)-oxiranyl)phenyl methanesulfonate (69 g, 322 mmol) and benzylamine (104 g, 971 mmol) was heated at 80˚C for 3 hours. An excess benzylamine was evaporated under reduced pressure and the residue was washed with diisopropyl ether to afford 4-((1S)-2-benzylamino-1-hydroxyethyl)phenyl methanesulfonate (71.0 g, 69%) as white crystals.
^{1}H-NMR($CDCl_3$) δ : 2.68-2.72 (1H, m), 2.96 (1H, dd, J=4.8 Hz, 10.2 Hz), 3.12 (3H, s), 3.84 (2H, d, J=1.2 Hz), 4.72 (1H, dd, J=1.2 Hz, 10.2Hz), 7.23-7.43 (9H, m)

4-((2S)-4-Benzpl-5-oxo-morpholin-2-yl)phenyl methanesulfonate

[0076] Chloroacetyl chloride (27.5 g, 243 mmol) was dropped to a solution of 4-((1S)-2-benzylamino-1-hydroxyethyl)phenyl methanesulfonate (71 g, 221 mmol) in 1N aqueous sodium hydroxide (330 ml) and stirred for one hour at room temperature. Resulting solution was extracted with chloroform, and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and potassium hydroxide (85%, 17.5 g, 265 mmol) was added to a solution of resulting pale brown oil in 2-propanol (600 ml) and stirred for 10 hours. The solvent was removed in vacuo and the residue was partitioned between water and chloroform. The organic layer was washed with 0.5 M hydrochloric acid, saturated sodium hydrogen carbonate, brine and dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure furnished 4-((2S)-4-benzyl-5-oxo-morpholin-2-yl)phenyl methanesulfonate (79.8 g, 100%) as a brown oil.
^{1}H-NMR($CDCl_3$) δ = 3.13 (3H, s), 3.29-3.36 (2H, m), 4.36-4.46 (4H, m), 4.81 (1H, dd, J=1.2 Hz, 10 Hz), 7.24-7.42 (9H, m)

(2S)-4-Benzyl-2-(4-hydroxyphenyl)moxoholine

[0077] Chlorotrimethylsilane (96 g, 884 mmol) was added to a solution of lithium borohydride (9.6 g, 441 mmol) in tetrahydrofuran (500 ml) and the solution was stirred for one hour at room temperature. A solution of 4-((2S)-4-benzyl-5-oxo-morpholin-2-yl)phenyl methanesulfonate (79.8 g, 221 mmol) in tetrahydrofuran (200 ml) was added to the solution and stirred at room temperature for one hour. After careful addition of methanol (60 ml) under ice-cooling, the solvent was removed under reduced pressure. Potassium hydroxide (145 g, 2.2 mol) was added to a solution of the residue in ethanol (300 ml) and water (300 ml) and the solution was stirred at 80˚C for 2 hours. The solvents were removed under reduced pressure and the residue was extracted with ethyl acetate and dried over anhydrous magnesium sulfate. Removal of the solvent yielded (2S)-4-benzyl-2-(4-hydroxyphenyl)morpholine (39.8 g, 67 %) as white crystals. ^{1}H-NMR($CDCl_3$) δ : 2.05-2.31 (2H, m), 2.72-2.89 (2H, m), 3.54 (2H, s), 3.81-3.86 (1H, m), 3.96-4.00 (1H, m), 4.50 (1H, dd, J=1.2 Hz, 10.2 Hz), 5.12 (1H, br), 6.75 (2H, d, J=7.2 Hz), 7.19-1.32 (7H, m)

(2S)- 2-(4-(1-Acetylpiperidin-4-yloxy)phenyl)-4-benzylmorpholine

[0078] Diisopropylazodicarboxylate (40% in toluene, 5.7 g, 11.3 mmol) was added to a solution of (2S)- 2-(4-hydroxyphenyl)-4-benzylmorpholine (2.0g, 7.43 mmol), triphenylphosphine (3.0g, 11.4 mmol) and 1-acetyl-4-hydroxypiperidin (1.6 g, 11.2 mmol) in tetrahydrofuran (40 ml) at room temperature and the mixture stirred for 10 hours. The mixture was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated in vacuo. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography eluting 10-50% ethyl acetate in hexane to furnish (2S)-2-(4-(1-acetylpiperidin-4-yloxy)phenyl)-4-benzylmorpholine (1.68 g, 57%) as colorless oil.
^{1}H-NMR($CDCl_3$) δ : 1.68-1.89 (4H, m), 2.11 (9H, s), 2.11-2.15 (1H, m), 2.24-2.31 (1H, m), 2.73-2.89 (2H, m), 3.33-3.40 (1H, m), 3.54 (2H, s), 3.65-3.85 (4H, m), 3.97-4.01 (1H, m), 4.89-4.53 (2H, m), 6.85 (2H, d, J=6.8 Hz), 7.24-7.33 (7H, m) ($CDCl_3$)

(2S)-2-(4-(1-acetylpiperidin-4-yloxy)phenyl)morpholine hydrochloride

[0079] 1-Chloroethyl chloroformate (0.92 g, 6.43 mmol) was added to a solution of (2S)-2-(4-(1-acetylpiperidin-4-yloxy)phenyl)-4-benzylmorpholine (1.68 g, 4.26 mmol) in dichloroethane (30 ml). The reaction mixture was stirred vigorously at room temperature for 10 hours. The solvent was evaporated under reduced pressure and methanol (40 ml) was added to the residue. The mixture was heated at 80 ˚C for one hour, and then the solvent was evaporated under reduced pressure to give a white solid, which was recrystallized from ethanol to afford (2S)-2-(4-(1-acetylpiperidin-4-yloxy)phenyl)morpholine hydrochloride (1.3 g, 100 %) as white crystals. ^{1}H-NMR($CDCl_3$) δ : 1.45-1.61 (2H, m), 11.80-1.95 (2H, m), 2.01 (3H, s), 2.84-3.42 (6H, m), 3.67-3.92 (4H, m), 4.61-4.63 (1H, m), 4.72 (1H, dd, J=1.2Hz 10.2Hz), 7.00 (2H, d, J=6.8Hz), 7.23 (2H, d, J=6.8Hz), 9.78 (2H, br) (DMSO-d_6)

Reference Example 9:

Synthesis of 4-((2S)-morpholin-2-yl)phenylamine

[0080] To a solution of (2S)-2-(4-aminophenyl)-4-((1R)-1-phenylethyl)morpholine (17.45 g, 61.8 mmol) and ammonium formate (11.7 g, 185.4 mmol) in a mixture of tetrahydrofuran (180 ml), methanol (180 ml) and water (45 ml) was added 10% palladium on carbon (wet, 1.8 g) and the solution was stirred at 95 ˚C for 3 hours. After filtration, the solvent was removed *in vacuo* and the residue was partitioned between water and dichloromethane. The organic layer was dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure to give 4-((2S)-morpholin-2-yl)phenylamine (10.45 g, 95 %) as pale yellow crystals. ^{1}H-NMR($CDCl_3$) δ : 2.46-2.50 (2H, m), 2.68 (2H, d, J=5.8 Hz), 2.76 (1H, d, J=12.2 Hz), 3.52 (1H, m), 3.79 (1H, d, J=10.9 Hz), 4.13 (1H, d, J=9.7 Hz), 4.95 (2H, br.s), 6.49 (2H, d, J=8.1 Hz), 6.94 (2H, d, J=8.1 Hz).

Reference Example 10:

Synthesis of (2S)-2-(4-([1,2,4]oxadiazol-3-yl)phenyl)piperazine dihydrochloride

(2S)-1,4-Dibenzyl-2-(4-bromophenyl)piperazine

[0081] Hydrogen chloride in ethyl acetate solution (4N) was added to a solution of di-tert-butyl (2S)-2-(4-bromophenyl)piperazine-1,4-dicarboxylate (10 g, 22.7 mmol) in methanol (50 ml). The mixture was stirred for one hour at room temperature and the solvent was evaporated under reduced pressure to give white solid. The mixture was partitioned between saturated aqueous sodium bicarbonate and chloroform. The organic layer was washed with brine, dried over magnesium sulfate and concentrated *in vacuo* to afford (2S)-2-(4-bromophenyl)piperazine as white crystals. Benzylbromide (9.7 g, 56.7 mmol) was added to a solution of sodium hydride (60% in oil, 2.0 g, 50 mmol) and (2S)-2-(4-bromophenyl)piperazine in tetrahydrofuran (50 ml) at room temperature and the mixture was stirred for one hour. The mixture was partitioned between water and chloroform. The organic layer was washed with brine, dried over magnesium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography eluting 5-10% methanol in chloroform to furnish (2S)-1,4-Dibenzyl-2-(4-bromophenyl)piperazine (6.1 g, 64%) as a colorless oil. ^{1}H-NMR($CDCl_3$) δ : 2.48-2.70 (6H, m), 3.48 (2H, s), 3.60 (2H, s), 4.24 (1H, d, J = 10.0Hz), 7.05-7.20 (10H, m), 7.28 (2H, d, J = 7.2Hz), 7.43(2H, d, J = 7.2Hz).

4-((2S)-1,4-Dibenzylpiperazin-2-yl)benzaldehyde

[0082] n-Butyllithium (1.56M in hexane, 14 ml, 21.8 mmol) was added to a solution of (2S)-1,4-dibenzyl-2-(4-bromophenyl)piperazine (6.1 g, 14.5 mmol) in tetrahydrofuran (60 ml) at -78 ˚C. After one hour stirring, dimethylformamide (1.6 g, 21.9 mmol) was added and the solution was stirred for one hour. The mixture was partitioned between water and chloroform. The organic layer was washed with brine, dried over magnesium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography eluting 5-10% methanol in chloroform to furnish 4-((2S)-1,4-dibenzylpiperazin-2-yl)benzaldehyde (1.6 g, 41 %) as a colorless oil. ^{1}H-NMR($CDCl_3$) δ : 2.48-2.72 (6H, m), 3.58 (2H, s), 3.68 (2H, s), 4.32 (1H, d, J = 10.0
Hz), 7.10-7.24 (10H, m), 7.28 (2H, d, J = 7.2 Hz), 7.46(2H, d, J = 7.2 Hz), 9.98 (1H, s).

4-((2S)-1,4-Dibenzylpiperazin-2-yl)benzonitrile

[0083] Hydroxylamine hydrochloride (0.5 g, 7.75 mmol) was added to a solution of 4-((2S)-1,4-dibenzylpiperazin-2-yl)benzaldehyde (2.2 g, 5.94 mmol) in 1N aqueous sodium hydroxide (10 ml) and ethanol (10 ml) at room tem-

perature and stirred for 2 hours. The mixture was partitioned between water and chloroform. The organic layer was washed with brine, dried over magnesium sulfate and concentrated in vacuo. The residue was dissolved in acetic acid (10 ml) and was stirred at 80 ˚C for 6 hours. The solvent was removed under reduced pressure and the residue was partitioned between saturated aqueous sodium bicarbonate and chloroform. The organic layer was washed with brine, dried over magnesium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography eluting 5-10% methanol in chloroform to furnish 4-((2S)-1,4-dibenzylpiperazin-2-yl)benzonitrile (1.4 g, 64 %) as a colorless oil.

^{1}H-NMR($CDCl_3$) δ : 2.45-2.68 (6he m), 3.54 (2H, s), 3.62 (2H, s), 4.26 (1H, d, J = 10.0 Hz), 7.07-7.14 (10H, m), 7.30 (2H, d, J = 7.2 Hz), 7.46(2H, d, J = 7.2 Hz).

Di-tert-butyl (2S)-2-(4-cpanophenyl)piperazine-1,4-dicarboxylate

[0084] 1-Chloroethyl chloroformate (2.7 g, 18.9 mmol) was added to a solution of 4-((2S)-1,4-dibenzylpiperazin-2-yl)benzonitrile (1.4 g, 3.81 mmol) in dichloroethane (30 ml). The reaction mixture was vigorously stirred at room temperature for 10 hours. The solvent was evaporated under reduced pressure and methanol (40 ml) was added to the residue. The mixture was heated at 80 ˚C for one hour and the solvent was evaporated under reduced pressure to afford (2S)-2-(4-cyanophenyl)piperazine as white crystals. Di-tert-butyl di-carbonate (1.9 g, 8.71 mmol) was added to a solution of triethylamine (1.2 g, 11.9 mmol) and (2S)-2-(4-eyanophenyl)piperazine in tetrahydrofuran (50 ml) at room temperature and the mixture was stirred at 50 ˚C for one hour. The mixture was partitioned between water and ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography eluting 10-20% ethyl acetate in hexane to furnish di-tert-butyl (2S)-2-(4-cyanophenyl)piperazine-1,4-dicarboxylate (1.2 g, 81%) as white crystals. ^{1}H-NMR($CDCl_3$) δ : 1.41 (9H, s), 1.45 (9H, s), 2.91-2.98 (2H, m), 3.34-3.40 (1H, m), 3.86-3.98 (2H, m), 4.39-4.44 (1H, m), 5.52 (1H, br), 7.42 (2H, d, J = 7.2 Hz), 7.66 (2H, d, J = 7.2Hz).

(2S)-2-(4-([1,2,4]Oxadiazol-3-yl)phenyl)piperazine dihydrochloride

[0085] Hydroxylamine hydrochloride (1.3 g, 20.2 mmol) and sodium carbonate (3.4 g, 32.1 mmol) were added to a solution of di-tert-butyl (2S)-2-(4-cyanophenyl)piperazine-1,4-dicarboxylate (2.5 g, 6.45 mmol) in ethanol (15 ml) and water (15 ml) at the room temperature and the solution was stirred at 80 ˚C for 2 hours. The mixture was partitioned between water and chloroform. The organic layer was washed with brine, dried over magnesium sulfate and concentrated in vacuo. Triethyl orthoformate (9.6 g, 64.8 mmol) and p-toluenesulfonic acid monohydrate (0.12 g, 0.63 mmol) were added to a solution of the residue in toluene (25 ml) and stirred at 90 ˚C for 2 hours. The mixture was partitioned between water and ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography eluting 10-20% ethyl acetate in hexane to furnish di-tert-butyl (2S)-2-(4-([1,2,4]oxadiazol-3-yl)phenyl)-piperazine-1,4-dicarboxylate (1.94 g, 70%) as a colorless oil. Hydrogen chloride in ethyl acetate(4N) was added to a solution of di-tert-butyl (2S)-2-(4-([1,2,4]oxadiazol-3-yl)phenyl)piperazine-1,4-dicarboxylate (1.94 g, 4.51 mmol) in methanol and the mixture was stirred at room temperature for one hour. The solvent was evaporated under reduced pressure to give white solid, which was washed with ethyl acetate to afford (2S)-2-(4-([1,2,4]oxadiazol-3-yl)phenyl)piperazine dihydrochloride (1.3 g, 95%) as white crystals.

^{1}H-NMR(DMSO) δ : 3.43-3.72 (6H, m), 4.82 (1H, d = 10.2 Hz), 7.89 (2H, d, J = 7.0 Hz), 8.15 (2H, d, J = 7.0 Hz), 9.79 (1H, s), 10.21 (4H, br).

Reference Example 11:

Synthesis of (2S)-2-(4-(5-methyl-[1,2,4]oxadiazol-3-yl)phenyl)piperazine dihydrochloride

[0086] Hydroxylamine hydrochloride (1.3 g, 20.2 mmol) and sodium carbonate (3.4g, 32.1 mmol) were added to a solution of di-tert-butyl (2S)-2-(4-cyanophenyl)piperazine-1,4-dicarboxylate (2.5 g, 6.45 mmol) in ethanol (15 ml) and water (15 ml) at room temperature and the solution was stirred at 80 ˚C for 2 hours. The mixture was partitioned between water and chloroform. The organic layer was washed with brine, dried over magnesium sulfate and concentrated in vacuo. Triethyl orthoacetate (10.5 g, 64.7 mmol) and p-toluenesulfonic acid monohydrate (0.12g, 0.63 mmol) were added to the solution of the residue in toluene (25 ml) and the solution was stirred at 90 ˚C for 2 hours. The mixture was partitioned between water and ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography eluting 10-20% ethyl acetate in hexane to furnish (2S)-2-(4-(5-methyl-[1,2,4]oxadiazol-3-yl)phenyl)piperazine-1,4-dicarboxylate (1.0 g, 35 %) as a colorless oil. Hydrogen chloride in ethyl acetate(4N) was added to a solution of (2S)-2-(4-(5-methyl-[1,2,4]oxadiazol-3- yl)phenyl)piperazine-1,4-dicarboxylate (1.0 g, 2.26 mmol) in methanol and the mixture stirred at room temperature for one hour. The solvent was

evaporated under reduced pressure to give a white solid, which was washed with ethyl acetate to afford (2S)-2-(4-(5-Methyl-[1,2,4]oxadiazol-3-yl)phenyl)piperazine dihydrochloride (0.64 g, 100 %) as white crystals.
^{1}H-NMR(DMSO) δ : 2.69 (3H, s), 3.45-3.73 (6H, m), 4.80 (1H, d, J = 10.2 Hz), 7.86 (2H, d, J = 7.2 Hz), 8.10 (2H, d, J = 7.2 Hz), 10.12(4H, br).

Reference Example 12:

Synthesis of morpholin-4-yl-((2S)-4-morpholin-2-yl-phenyl)-methanone

4-[(2S)-4-((1R)-1-phenylethyl)-morpholin-2-yl]-benzoic acid

[0087] To a suspension of (2S)-2-(4-bromophenyl)-4-((1R)-1-phenylethyl)morpholine (3.46 g, 10.0 mmol) in tetrahydrofuran (80 ml) was added n-butyllithium (7.7 ml, 12.0 mmol, 1.56 M in hexane) at -78˚C. After stirring for 10 minutes, excess of dry ice was added to the mixture and the reaction mixture was maintained at -78˚C for 1.5 hours and then partitioned between diethyl ether and 0.2 N aqueous sodium hydroxide. The aqueous layer was washed with diethyl ether and neutralized with 1N hydrochloric acid. The resulting aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate and concentrated in vacuo. Filtration of the precipitate gave 4-[(2S)-4-((1R)-1-phenyl-ethy)-mlorpholin-2-yl]-benzoic acid (3.05 g, 98%) as white crystals.
^{1}H-NMR($CDCl_3$) δ : 1.39(3H, d, J=6.9 Hz), 2.10-2.18(2H,m), 2.63(1H,m), 3.15(1H,m), 3.41(1H, q, J=6.9 Hz), 3.78(1H, m), 3.93(1H, m), 4.55(1H, dd, J=10.2, 2.1 Hz), 7.25-7.39(5H,m), 7.47(2H, d, J=8.4 Hz), 8.07(2H, d, J=8.4 Hz).

Morpolin-4-yl-{4-[(2S)-4-((1R)-1-phenyl-ethyl)-morpholin-2-yl]-phenyl}-methanone

[0088] 1,1'-Carbonyldiimidazole (357 mg, 2.20 mmol) was added to a solution of 4-[(2S)-4-((1R)-1-phenylethyl)-morpholin-2-yl]-benzoic acid (623 mg, 2.00 mmol) in dichloromethane at 0 ˚C. After stirring for 2 hours, morpholine (0.35 ml, 4.0 mmol) was added to the reaction mixture. After stirring over night, the resulting suspension was concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/ethyl acetate) to afford morpholin-4-yl-{4-[(2S)-4-((1R)-1-phenylethyl)-morpholin-2-yl]-phenyl}-methanone (465 mg, 60%.) as a colorless oil. ^{1}H-NMR($CDCl_3$) δ : 1.36(3H, d, J = 6.9 Hz), 2.01-2.14(2H,m), 2.59-2.63(1H, m), 3.07-3.12(1H,m), 3.36(1H, q, J = 6.9 Hz), 3.37-3.78(9H, m), 3.90-3.91(1H, m), 4.62(1H, dd, J = 10.2, 2.4 Hz), 7.24-7.44(9H, m).

Morpholin-4-yl-((2S)-4-morpholin-2-yl-phenyl)-methanone

[0089] A solution of morpholin-4-yl-{4-[(2S)-4-((1R)-1-phenylethyl)-morpholin-2-yl]-phenyl}-methanone (465 mg, 1.20 mmol) and 20% palladium hydroxide on carbon (0.50 g) in ethanol (6.0 ml) was stirred under hydrogen atmosphere at room temperature for 10 hours. The mixture was passed through Celite column and the organic layer was concentrated under reduced pressure to yield morpholin-4-yl-((2S)-4-morpholin-2-yl-phenyl)-methanone (331mg, 100%) as a clear oil. MS(M+1) : 277

Reference Example 13:

Synthesis of N^2,N^2-Dimethyl-N^1-(4-((2S)-morpholin-2-yl)phenyl)glycinamide

2-Chloro-N-[(2S)-4-{((1R)-1-phenylethyl)morpholin-2-yl}phenyl]acetamide

[0090] To a solution of (2S)-2-(4-aminophenyl)-4-((1R)-1-phenylethyl)morpholine (2.93 g, 10 mmol) and triethylamine (3.0 g, 30 mmol) in tetrahydrofuran (50 ml) was added chloroacetyl chloride (2.26 g, 20 mmol). The mixture was stirred at room temperature for 2 hours and partitioned between water and dichloromethane. The organic extract was washed with brine and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the precipitated crystals were collected by filtration, washed with isopropyl ether to give 2-chloro-N-((2S)-4-(((1R)-1-phenylethyl) morpholin-2-yl)phenyl)acetamide (3.5 g, 97%) as yellow crystals. ^{1}H-NMR($CDCl_3$) δ : 1.35 (3H, d, J = 6.6 Hz), 2.02-2.17 (2H, m), 2.60 (1H, d, J = 11.1 Hz), 3.08 (1H, d, J = 11.1 Hz), 3.36 (1H, q, J = 6.9 Hz), 3.75 (1H, td, J = 11.4 Hz and 2.4 Hz), 3.91 (1H, dd, J = 9.9 Hz and 1.5 Hz), 4.19 (2H, s), 4.57 (1H, dd, J = 10.2 Hz and 2.1 Hz), 7.23-7.32 (5H, m), 7.36 (2H, d, J = 8.4 Hz), 7.51 (2H, d, J = 8.1 Hz), 8.21 (1H, br.s).

N^2,N^2-Dimethyl-N^1-(4-((2S)-4((1R)-1-phenylethyl)morpholin-2-yl)phenyl)glycinamide

[0091] A solution of 2-chloro-N-((2S)-4-(((1R)-1-phenylethyl)morpholin-2-yl)phenyl)acetamide (0.9 g, 2.5 mmol), po-

tassium carbonate (1.72 g, 12.5 mmol), and dimethylamine hydrochloride (1.00 g, 12.5 mmol) in tetrahydrofuran (40 ml) and acetonitrile (80 ml) was stirred at 95 ˚C for 10 hours. After filtration, the solvent was removed *in vacuo* and the residue was partitioned between water and dichloromethane. The organic layer was dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure give N^2,N^2-dimethyl-N^1-(4-((2S)-4-((1R)-1-phenylethyl)morpholin-2-yl) phenyl)glycinamide (1.15 g, quant.) as an yellow oil. ^{1}H-NMR($CDCl_3$) δ : 1.35 (3H, d, J = 6.6 Hz), 2.05-2.13 (2H, m), 2.38 (6H, s), 2.57 (1H, m), 3.07 (2H, s), 3.10 (1H, m), 3.35 (1H, q, J = 6.6 Hz), 3.72 (1H, m), 3.90 (1H, m), 4.56 (1H, dd, J = 10.2 Hz and 2.1 Hz), 7.20-7.39 (7H, m), 7.56 (2H, d, J = 8.4 Hz), 9.90 (1H, br.s).

N^2,N^2-Dimethyl-N^1-(4-((2*S*)-morpholin-2-yl)pbenyl)glycinamide

[0092] To a solution of N^2,N^2-dimethyl-N^1-(4-((2S)-4-((1R)-1-phenylethyl)morpholin-2-yl) phenyl)glycinamide (0.91 g, 2.5 mmol) and ammonium formate (0.79 g, 12.5 mmol) in mixture of tetrahydrofuran (20 ml), methanol (40 ml) and water (7 ml) was added 10% palladium on carbon (wet, 300 mg) and stirred at 95 ˚C for 3 hours. After filtration, the solvent was removed *in vacuo* and the residue was partitioned between water and dichloromethane. The organic layer was dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure to give N^2,N^2-dimethyl-N^1-(4-((2S)-morpholin-2-yl)pheny)glycinamide (0.63 g, 96%) as a colorless oil.
^{1}H-NMR($CDCl_3$) δ : 2.05-2.13 (2H, m), 2.38 (6H, s), 2.57 (1H, m), 3.07 (2H, s), 3.10 (1H, m), 3.72 (1H, m), 3.90 (1H, m), 4.56 (1H, dd, J = 10.2 Hz and 2.1 Hz), 7.35 (2H, d, J = 8.4 Hz), 7.56 (2H, d, J = 8.4 Hz), 9.90 (1H, br.s).

Reference Example 14:

Synthesis of 2-Trimethyl-N-(4-((2S)-morpholin-2-yl)phenyl)acetamide

2-Trimethyl-N-(4-((2S)-4-((1R)-1-phenylethyl)morpholin-2-yl)phenyl)acetamide

[0093] To a solution of (2S)-2-(4-aminophenyl)-4-((1R)-1-phenylethyl)morpholine (0.68 g, 2.4 mmol) and triethylamine (0.73 g, 7.2 mmol) in tetrahydrofuran (50 ml) was added trimethylacetyl chloride (0.44 g, 3.6 mmol). The mixture was stirred at room temperature for 2 hours and partitioned between water and ethyl acetate. The organic extract was washed with brine and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the precipitated crystals were collected by filtration, washed with isopropyl ether to give 2-trimethyl-N-(4-((2S)-4-((1R)-1-phenylethyl)morpholin-2-yl)phenyl)acetamide (0.88 g, quant.) as yellow crystals.
^{1}H-NMR($CDCl_3$) δ :1.30 (9H, s), 1.34 (3H, d, J = 6.3 Hz), 2.01-2,12 (2H, m), 2.58 (1H, dd, J = 11.4 Hz, 1.2 Hz), 3.06 (1H, d, J = 11.4 Hz), 3.34 (1H, q, J = 6.9 Hz), 3.72 (1H, m), 3.88 (1H, m), 4.57 (1H, dd, J = 10.2 Hz and 2.1 Hz), 6.98-7.56 (10H, m).

2-Trimethyl-N-(4-((2S)-mornholin-2-yl)phenyl)acetamide

[0094] To a solution of N^2,N^2-dimethyl-N^1-(4-((2S)-4-((1R)-1-phenylethyl)morpholin-2-yl) phenyl)glycinamide (0.88 g, 3.2 mmol) and ammonium formate (1.00 g, 16 mmol) in mixture of tetrahydrofuran (500 ml), methanol (100 ml) and water (50 ml) was added 10% palladium on carbon (wet, 300 mg) and the solution was stirred at 95˚C for 3 hours. After filtration, the solvent was removed *in vacuo* and the residue was partitioned between water and dichloromethane. The organic layer was dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure to give 2-trimethyl-N-(4-((2S)- morpholin-2-yl)phenyl)acetamide (0.63 g, 96%) as a colorless oil.

Reference Example 15:

Synthesis of (3R)-3-(4-Bromophenyl)piperidine

N-Acetyl-(3R)-3-(4-bromophenyl)piperidine

[0095] Chiral resolution of the racemate of N-acetyl-3-(4-bromophenyl)piperidine by HPLC (column: CHIRALPAK AS-H, eluent: n-hexane/ethanol = 80/20 (v/v)) afforded N-acetyl-(3R)-3-(4-bromophenyl)piperidine as colorless crystals.
^{1}H-NMR($CDCl_3$) δ : 1.58-1.71 (3H, m), 1.34 (1H, d, J = 11.4 Hz), 2.11 (3H, s), 2.49 (2H, m), 3.06 (1H, td, J = 11.7 Hz, 4.8 Hz), 3.86 (1H, m), 4.69 (1H, m), 7.11 (2H, d, J = 8.4 Hz), 7.45 (2H, d, J = 8.4 Hz, 10.5 Hz).

(3R)-3-(4-Bromophenyl)piperidine

[0096] To a solution of N-acetyl-(3R)-3-(4-bromophenyl)piperidine (2.88 g, 13.2 mmol) in mixture of tetrahydrofuran

(24 ml), methanol (24 ml) and water (12 ml) was added lithium hydroxide monohydrate (3.8 g, 92.4 mmol) and stirred at 95 ˚C for 2 hours. After filtration, the solvent was removed *in vacuo* and the residue was partitioned between water and dichloromethane. The organic layer was dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure to give (3R)-3-(4-bromophenyl)piperidine (2.3 g, 87%) as colorless crystals that was used in the next step without further purification.

Example 1: 6-(3-Fluoro-pyridin-4-yl)-3-methyl-2-((3S)-3-(4-morpholin-4-yl-phenyl)-piperazin-1-yl)-3H-pyrimidin-4-one (Compound No. 7)

[0097] (3R)-3-(4-(morpholin-4-yl)phenyl)piperazine trihydrochloride was prepared from di-tert-butyl (2R)-2-(4-bromophenyl)-piperazine-1,4-dicarboxylate by the same route as that in Reference Example 10.

[0098] To a solution of the above prepared (3R)-3-(4-(morpholin-4-yl)phenyl)piperazine trihydrochloride (0.5 g, 1.40 mmol) and triethylamine (0.8 g, 7.91 mmol) in tetrahydrofuran (10 ml) was added 2-chloro-6-(3-fluoropyridin-4-yl)-3-methyl-(3H)-pyrimidin-4-one (0.3 g, 1.25 mmol) which was prepared by Reference Example 1 portionwise. After stirring for 12 hours, the resulting suspension was partitioned between chloroform and 1N sodium hydroxide and the aqueous layer was extracted with chloroform. The combined organic layer was washed with brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluting 5-10% methanol in chloroform to furnish 6-(3-ffuoro-pyridin-4-yl)-3-methyl-2-((3S)-3-(4-morpholin-4-yl-phenyl)-piperazin-1-yl)-3H-pyrimidin-4-one (0.41 g, 0.91 mmol, 73%) as white crystals.

Example 2: 6-(3-Fluoro-pyridin-4-yl)-3-methyl-2-((3S)-3-(4-piperidin-1-yl-phenyl)-piperazin- 1-yl)-3H-pyrimidin-4-one (Compound No. 14)

[0099] A solution of (2S)-2-(4-piperidin-1-yl-phenyl)-piperazine trihydrochloride obtained in Reference Example 3 (199 mg, 0.561 mmol) and triethylamine (427 μl, 306 mmol) in tetrahydrofuran was refluxed for 15 minutes- After cooling to room temperature, 2-chloro-6-(3-fluoropyridin-4-yl)-3-methyl-3H-pyrimidin-4-one (122 mg, 0.510 mmol) was added portionwise and the mixture was stirred overnight. The reaction mixture was concentrated in vacuo and the residue was dissolved in dichloromethane and aqueous sodium bicarbonate, and the solution was passed through CHEM ELUT CE1010 (manufactured by VARIAN). The filtrate was concentrated, and the resulting residue was washed with diethyl ether. Hydrogen chloride in ethyl acetate (4N) was added to a solution of the resulting solids in ethyl acetate, and the precipitate was collected by the filtration and dried to furnish 6-(3-fluoro-pyridin-4-yl)-3-methyl- 2-((3S)-3-(4-piperidin-1-yl-phenyl)-piperazin-1-yl)-3H-pyrimidin-4-one trihydrochloride (267 mg, 0.479 mmol, 94%) as pale yellow powder.

Example 3: 2-((2S)-2-(4-(Dimethylamino)phenyl)morpholin-4-yl)-6-(3-fluoropyridin-4-yl)-3-methyl-3H-pyrimidin-4-one (Compound No. 36)

[0100] A solution of (2S)-2-(4-(dimethylamino)phenyl)morpholine hydrochloride (0.20 g, 0.64 mmol), 2-chloro-1-methyl-6-oxo-4-(3-fluoropyridin-4-yl)-1,6-dihydropyrimidine (0.12 g, 0.53 mmol), and triethylamine (0.19 g, 1.92 mmol) in tetrahydrofuran (10 ml) was stirred at 95˚C for 3 hours. The solvent was evaporated off *in vacuo* and the residue treated with water and dichloromethane. The organic layer was dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The obtained residue was purified by column chromatography on silica gel (chloroform-methanol, 10:1) to afford
2-((2S)-2-(4-(dimethylamino)phenyl)morpholin-4-yl)- 6-(3-fluoropyridin-4-yl)-3-methyl-3H-pyrimidin-4-one (0.10 g, 50%) as yellow crystals

Example 4: N-(4-((2S)-4-((4-(3-Fluoro-pyridin-4-yl)-1-methyl-6-oxo-1,6-dihydro-pyrunidin-2-yl)-morpholin-2-yl)-phenyl)-acetamide (Compound No. 143)

[0101] A solution of N-(4-((2S)-morpholin-2-yl)phenyl)acetamide obtained in Reference Example 4 (0.20 g, 0.91 mmol), 2-chloro-1-methyl-6-oxo-4-(3-fluoropyridin-4-yl)-1,6-dihydropyrimidine (0.19 g, 0.82 mmol), and triethylamine (0.41 g, 4.05 mmol) in tetrahydrofuran (10 ml) was stirred at 95˚C for 3 hours. The solvent was evaporated off *in vacuo* and the residue was treated with water and dichloromethane. The organic layer was dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The obtained residue was purified by column chromatography on silica gel (chloroform-methanol, 10:1) to afford N-(4-((2S)-4-((4-(3-fluoro-pyridin-4-yl)-1-methyl-6-oxo-1,6-dihydro-pyrimidin-2-yl)-morpholin-2-yl)-phenyl)-acetamide (0.05 g, 14%) as a yellow oil.

Example 5: (removed)

Example 6-1: (removed)

Example 10-1: and 10 - 2 removed

Example 11 : 6-(3-Fluoropyridin-4-yl)-2-((2S)-2-(4-(N-methyl-N-((3R)-tetrahydrofuran-3yl)amino)phenyl)morpholin-4-yl)-3-methyl-3H-pyrimidin-4-one (Compound No. 221)

[0102] 2-Chloro-3-methyl-6-(3-fluoropyridin-4-yl)-3H-pyrimidin-4-one (0.26 g, 1.09 mmol) was added to a solution of (2S)-2-(4-(N-methyl-N-((3R)-tetrahydrofuran-3yl)amino)phenyl)morpholine hydrochloride obtained in Reference Example 6 (0.4 g, 1.19 mmol) and triethylamine (0.6 g, 5.93 mmol) in tetrahydrofuran (20 ml) at room temperature for 15 hours. The mixture was partitioned between water and chloroform. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluting 5-10% methanol in chloroform to furnish 6-(3-fluoropyridin-4-yl)-2-((2S)-2-(4-(N-methyl-N-((3R)-tetrahydrofuran-3-yl) amino)-phenyl)morpholin-4-yl)-3-methyl-3H-pyrimidin-4-one (0.20 g, 39%) as white crystals.

Example 12: 2-((2S)-2-(4-(1-Acetylpiperidin-4-yloxy)phenyl)morpholin-4-yl)-6-(3-fluoropyridin-4-yl)-3-methyl-pyrimidin-4-one (Compound No. 238)

[0103] 2-Chloro-3-methyl-6-(3-fluoropyridin-4-yl)-3H-pyrimidin-4-one (0.21 g, 0.88 mmol) was added to a solution of (2S)-2-(4-(1-acetylpiperidin-4-yloxy)phenyl)-morpholine hydrochloride obtained in Reference Example 8 (0.30 g, 0.88 mmol) and triethylamine (0.45 g, 4.15 mmol) in tetrahydrofuran (20 ml) and the solution was stirred at room temperature for 15 hours. The mixture was partitioned between water and chloroform. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluting 5-10% methanol in chloroform to furnish 2-((2S)-2-(4-(1-acetylpiperidin-4-yloxy)phenyl)morpholin-4-yl)-6-(3-fluoropyridin-4-yl)-3-methyl-pyrimidin-4-one (0.26 g, 58 %) as white crystals.

Example 13: 2-((2S)-2-(4-Aminophenyl)morpholin-4-yl)-6-(3-fluoropyridin-4-yl)-3-methyl-3H-pyrimidin-4-one (Compound No. 158)

[0104] 2-Chloro-3-methyl-6-(3-fluoropyridin-4-yl)-3H-pyrimidin-4-one (1.1 g, 4.59 mmol) was added to a solution of (2S)-2-(4-aminophenyl)morpholine hydrochloride (1.0 g, 4.66 mmol) and triethylamine (1.4 g, 13.8 mmol) in tetrahydrofuran (20 ml) at room temperature and the solution was stirred for 15 hours. The solvent was removed in vacuo and the residue was partitioned between water and chloroform. The organic layer was dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The resulting residue was purified by silica gel column chromatography eluting 5-10% methanol in chloroform to furnish 2-((2S)-2-(4-aminophenyl)morpholin-4-yl)-6-(3-fluoropyridin-4-yl)-3-methyl-3H-pyrimidin-4-one (0.80 g, 46 %) as white crystals.

Example 14: Methyl (4-((2S)-4-(6-(3-fluoropyridin-4-yl)-3-methyl-4-oxo- 3H-pyrimidin-2-yl)morpholin-2-yl)phenyl)carbamate (Compound No. 295)

[0105] Methyl chloroformate (0.13 g, 1.38 mmol) was added to a solution of 2-((2S)-2-(4-aminophenyl)morpholine-4-yl)-6-(3-fluoropyridin-4-yl)-3-methyl-3H-pyrimidin-4-one obtained in Example 13 (0.35 g, 0.92 mmol) and triethylamine (0.25 g, 2.47 mmol) in tetrahydrofuran (20 ml) and the solution was stirred at room temperature for one hour. The mixture was partitioned between water and chloroform. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluting 5-10% methanol in chloroform to furnish methyl (4-((2S)-4-(6-(3-fluoropyridin-4-yl)-3-methyl-4-oxo-3H-pyrimidin-2-yl)morpholin-2-yl)phenyl)carbamate (0.17 g, 42%) as white crystals.

Example 15: N'-(4-((2S)-4-(6-(3-Fluoropyridin-4-yl)-3-methyl-4-oxo-3H-pyrimidin-2-yl)morpholin-2-yl)phenyl)-N,N-dimethylurea (Compound No. 298)

[0106] N,N-Dimethylcarbamoyl chloride (0.26 g, 2.41 mmol) was added to a solution of 2-((2S)-2-(4-aminophenyl)morpholine-4-yl)-3-methyl-6-(3-fluoropyridin-4-yl)-3H-pyrimidin-4-one (0.45 g, 1.18 mmol) and triethylamine (1.2 g, 11.9 mmol) in tetrahydrofuran (20 ml) and the solution was stirred at 50 ˚C for 48 hours. The mixture was partitioned between water and chloroform. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluting 5-10% methanol in chloroform to furnish

N'-(4-((2S)-4-(6-(3-fluoropyridin-4-yl)-3-methyl-4-oxo-3H-pyrimidin-2- yl)morpholin-2-yl)phenyl)-N,N-dimethylurea (0.35 g, 67%) as white crystals.

Example 16: 6-(3-Fluoropyridin-4-yl)-3-methyl-2-((3S)-3-(4-([1,2,4]oxadiazol-3-yl)phenyl)piperazin-1-yl)-3H-pyrimidin-4-one (Compound No. 322)

[0107] 2-Chloro-3-methyl-6-(3-fluoropyridin-4-yl)-3H-pyrimidin-4-one (0.31 g, 1.29 mmol) was added to a solution of (2S)-2-(4-([1,2,4]oxadiazol-3-yl)phenyl)-piperazine dihydrochloride obtained in Reference Example 10 (0.40 g, 1.32 mmol) and triethylamine (0.70 g, 6.92 mmol) in tetrahydrofuran (20 ml) at room temperature and the solution was stirred for 15 hours. The mixture was partitioned between water and chloroform. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluting 5-10% methanol in chloroform to furnish 6-(3-fluoropyridin-4-yl)-3-methyl-2-((3S)-3-(4-([1,2,4]oxadiazol-3-yl)phenyl)piperazin-1-yl)-3H-pyrimidin-4-one (0.46 g, 82%) as white crystals.

Example 17: 6-(3-Fluoropyridin-4-yl)-3-methyl-2-((3S)-3-(4-(5-methyl- [1,2,4]oxadiazol-3-yl)phenyl)piperazin-1-yl)-3H-pyrimidin-4-one (Compound No. 334)

[0108] 2-Chloro-3-methyl-6-(3-fluoropyridin-4-yl)-3H-pyrimidin-4-one (0.17 g, 0.71 mmol) was added to a solution of (2S)-2-(4-(5-methyl-[1,2,4]oxadiazol-3-yl)phenyl)piperazine dihydrochloride obtained in Reference Example 11 (0.20 g, 0.71 mmol) and triethylamine (0.35 g, 3.46 mmol) in tetrahydrofuran (10 ml) at room temperature and the solution was stirred for 15 hours. The mixture was partitioned between water and chloroform. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatographyeluting5-10%methanolinchloroformtofurnish6-(3-ffuoropyridin-4-yl)-3-methyl-2-((3S)-3-(4-(5-methyl-[1,2,4)oxadiazol-3-yl)phenyl)piperazin-1-yl)-3H-pyrimidin-4-one (0.16 g, 51%) as white crystals.

Example 18: 6-(3-Fluoro-pyridin-4-yl)-3-methyl-2-{(2S)-2-[4-morpholine-4-carbonyl]-phenyl}-morpholin-4-yl}-3H-pyrimidin-4-one (Compound No. 310)

[0109] A solution of morpholin-4-yl-((2S)-4-morpholin-2-yl-phenyl)-methanone obtained in Reference Example 12 (110 mg, 0.40 mmol), 2-chloro-3-methyl-6-(3-fluoro-4-pyridyl)-pyrimidine-4-one (71 mg, 0.30 mmol) and triethylamine (0.20 ml) in tetrahydrofuran (4.0 ml) was stirred at room temperature for 6 hours. The reaction mixture was evaporated *in vacuo* and the residue was washed with water and diethyl ether. Filtrating the precipitate gave 6-(3-fluoro-pyridin-4-yl)-3-methyl-2-{(2S)-2-[4-morpholine-4-carbonyl]-phenyl}-morpholin-4-yl}-3H-pyrimidin-4-one (99.6 mg, 69%) as white crystals.

Example 19: 2-((2S)-2-(4-(N-((3R)-Tetrahydrofuran-3-yl)amino)phenyl)morpholin-4-yl)-3-methyl-6-(3-fluoropyridin-4-yl)-3*H*-pyrimidin-4-one (Compound No. 220)

[0110] A solution of 2-chloro-6-(3-fluoropyridin-4-yl)-3-methyl-3H-pyrimidin-4-one (0.08 g, 0.35 mmol), (2S)-2-(4-(N-((3R)-tetrahydrofuran-3-yl)amino)phenyl)morpholine obtained in Reference Example 7 (0.11g, 0.44 mmol) and triethylamine (0.22 g, 2.2 mmol) in tetrahydrofuran (10 ml) was stirred at 95˚C for 3 hours. The mixture was partitioned between water and dichloromethane, and the organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated in *vacuo.* The residue was purified by silica gel column chromatography eluting 5-10% methanol in chloroformtofurnish2-((2S)-2-(4-(N-((3R)-tetrahydrofuran-3-yl)amino)phenyl)-morpholin-4-yl)-3-methyl-6-(3-fluoropyridin-4-yl)-3H-pyrimidin-4-one (0.07 g, 47%) as pale yellow crystals.

Example 20: N^2,N^2-Dimethyl-N^1-(4-((2S)-4-(3-methyl-4-oxo-3,4-dihydro-6-(3-fluoropyridin-4-yl)pyrimidin-2-yl) morpholin- 2-yl)phenyl)glycinamide (Compound No. 288)

[0111] A solution of N^2,N^2-dimethyl-N^1-(4-((2S)-morpholin-2-yl)pheny)glycinamide obtained in Reference Example 13 (0.21 g, 0.8 mmol), 2-chloro-6-(3-fluoropyridin-4-yl)-3-methyl-3H-pyrimidin-4-one (0.15 g, 0.64 mmol), and triethylamine (0.40 g, 4 mmol) in tetrahydrofuran (10 ml) was stirred at 95˚C for one hour. The solvent was removed *in vacuo* and the residue was partitioned between water and dichloromethane. The organic layer was dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The resulting residue was purified by silica gel column chromatography (chloroform/methanol = 10/1) to afford N^2,N^2-dimethyl-N^1-(4-((2S)-4-(3-methyl- 4-oxo-3,4-dihydro-6-(3-fluoropyridin-4-yl)pyrimidin-2-yl)-morpholin-2- yl)phenyl)glycinamide (0.15 g, 50%) as colorless crystals.

Example 21: 2-Trimethyl-N-(4-((2S)-4-(3-methyl-4-oxo-3,4-dihydro-6-(3-fluoropyridin-4-yl))pyrimidin-2-yl)morpholin-2-yl)phenyl)acetamide (Compound No. 215)

[0112] A solution of 2-trimethyl-N-(4-((2S)-morpholin-2-yl)phenyl)acetamide obtained in Reference Example 14 (0.13 g, 0.5 mmol), 2-chloro-6-(3-fluoropyridin-4-yl)-3-methyl-3H-pyrimidine-4-one (0.08 g, 0.4 mmol), and triethylamine (0.25 g, 2.5 mmol) in tetrahydrofuran (10 ml) was stirred at 95˚C for one hour. The solvent was removed *in vacuo* and the residue was partitioned between water and dichloromethane. The organic layer was dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The resulting residue was purified by silica gel column chromatography (chloroform/methanol = 10/1) to afford 2-trimethyl-N-(4-((2S)-4-(3-methyl-4-oxo-3,4-dihydro-6-(3-fluoropyridin-4-yl))pyrimidin-2-yl)morphol in-2-yl)phenyl)acetamide (0.17 g, 47%) as colorless crystals.

Example 22: (removed)

[0113] The compounds in the following table were prepared in the same manner as the methods described above. The compound numbers in the following table correspond to those shown in the above-described table of preferred compounds.

Table 2

Compound No.	1H-NMR δ:	[M+1]
1	2.97-3.00(1H, m), 3.14-3.17(1H. m), 3.47(3H, s), 3.66-3.74(2H, m), 3.85-3.89(1H, m), 4.03-4.07(1H, m), 4.74(1H. dd, J=1.2, 10.2Hz), 6.60(1H, s), 7.20(2H, dd, J=6.8, 7.3Hz), 7.48(2H, dd, J=6.8. 7.3Hz), 7.98(1H, dd, J=1.2, 4.2Hz), 8.56(1H, d, J=4.2Hz). 8.68(1H. d, J=1.2Hz)(DMSO-d6)	385
3	2.71-2.78(1H, m), 3.14-3.18(1H, m), 3.47(3H, s), 3.62-3.66(1H. m), 3.78-3.91(5H, m), 4.06-4.10(1H, m), 4.95(1H, dd, J=1.2, 10.2Hz), 6.60(1H, s), 7.05(1H, d, =7.3Hz), 7.12(1H, s), 7.42(1H, d, J=7.3Hz), 8.00(1H, dd, J=1.2, 4.2Hz), 8.56(1H, d, J=4.2Hz), 8.69(1H, d, J=1.2Hz)(DMSO-d6)	431
4	3.23-3.27(1H, m), 3.32-3.35(1H, m), 3.47(3H, s), 3.62-3.66(1H, m), 3.88-4.05(3H, m), 5.00(1 H, dd, J=1.2, 10.2Hz), 6.62(1 H, s), 6.98(1 H, s), 7.23-7.35(2H, m), 7.58-7.66(2H, m), 8.01(1H, dd, J=1.2, 4.2Hz), 8.57(1H, d, J=4.2Hz), 8.71(1H, d, J=1.2Hz)(DMSO-d6)	407
5	3.22-3.27(1H, m), 3.48(3H, s), 3.49-3.51(1H, m), 3.64-3.88(3H, m), 4.00-4.04(1H, m), 5.27(1H, dd, J=1.2, 10.2Hz), 6.61(1H, s), 7.25-7.50(3H, m), 8.55(1H, d, J=4.2Hz), 8.70(1H. d, J=1.2Hz)(DMSO-d6)	419
6	2.76-2.84(1H, m), 3.18-3.23(1H, m), 3.48(3H, s), 3.63-3.67(1H, m), 3.83-3.93(5H, m), 4.09-4.14(1H, m), 5.00(1H, dd, J=1.2, 10.2Hz), 6.61 (1H, s), 7.24(1H, d, J=7.3Hz), 7.76(1H, s), 7.85(1H, d, J=7.3Hz), 7.99-8.03(1H, m), 8.57(1H, d, J=4.2Hz), 8.70(1H, d, J=1.2Hz)(DMSO-d6)	422
7	2.81-2.86(1H, m), 2.98-3.10(7H, m), 3.43(3H, s), 3.55-3.75(6H, m), 3.87-3.90(1H, m), 6.56(1H, s), 6.93(2H, d, J=7.3Hz), 7.32(2H, d, J=7.3Hz), 7.94-7.98(1H, m), 8.32(1H, s), 8.56(1H, d, J=4.2Hz), 8.69(1H, d, J=1.2Hz)(DMSO-d6)	451
8	3.07-3.19(5H, m), 3.28(1H, m), 3.50-3.63(2H, m), 3.56(3H, s), 3.86(4H, m), 3.97(1H, m), 4.13(1H, m), 4.65(1H, dd, J=1.9,10.4Hz), 6.88(1H, s), 6.93(2H, d, J=8.7Hz), 7.31(2H, d, J=8.7Hz), 7.95(1H, dd, J=5.4, 6.9Hz), 8.51(1H, d, J=5.4Hz), 8.55(1H, d, J=3.3Hz)($CDCl_3$)	452
9	2.05(6H, m), 2.22(1H, m), 2.84(1H, m), 3.98(1H, m), 3.00-3.60(8H, m), 3.56(3H, s), 3.97(1H, m), 4.12(1H, m), 4.60(1H, d, J=10.4Hz), 6.56(2H, d, J=8.7Hz), 6.88(1H, s), 7.29(2H, d, J=8.7Hz), 7.96(1H, dd, J=5.4, 6.9Hz), 8.50(1H, d, J=5.4Hz), 8.55(1H, d, J=3.3Hz)($CDCl_3$)	480
10	3.05(1H, dd, J=10.5, 12.9Hz), 3.27(1H, m), 3.50-3.63(2H, m), 3.58(3H, s), 4.00(1H, m), 4.15(1H, m), 4.70(1H, dd, J=1.9, 10.4Hz), 6.89(1H, s), 7.29(2H, d, J=9.0Hz), 7.54(2H, d, J=9.0Hz), 7.92(1H, dd, J=5.4, 6.9Hz), 8.51 (1H, d, J=5.4Hz), 8.56(1H, d, J=3.3Hz)($CDCl_3$)	446

(continued)

Compound No.	1H-NMR δ:	[M+1]
11	2.29(3H, s), 3.02-3.04(5H, m), 3.21-3.23(5H, m), 3.58(3H, s), 3.52-3.61(2H, m), 3.98(1H, m), 4.14(1H, m), 4.63(1H, dd, J=1.2, 9.6Hz), 5.73(1H, s), 6.88(1H, s), 6.93(2H, d, J=8.7Hz), 7.23(3H, m), 7.41 (2H, dd, J=7.5, 8.1Hz), 7.79(2H, d, J=9.3Hz), 7.94(1H, dd, J=5.4, 6.9Hz), 8.51 (1H, d, J=5.4Hz), 8.56(1 H, d, J=3.3Hz)($CDCl_3$)	607
12	2.86-2.89(1H, m), 3.08-3.12(1H, m), 3.52-3.62(5H, m), 3.86-4.06(2H, m), 4.73(1H, dd, J=1.2, 10.2Hz), 7.22(2H, dd, J=6.8Hz. 7.3Hz), 7.46(2H, dd, J=6.8Hz, 7.3Hz), 7.71-7.75(1H, m), 8.60(1H, d, J=4.2Hz), 8.75(1H, s)(DMSO-d6)	403
13	1.96 (4H, m), 3.24 (4H, m), 3.38 (2H, m), 3.43 (3H, s), 3.50 (2H, m), 3.77 (1H, d. J = 14.0 Hz), 3.88 (1H. d, J = 13.6 Hz), 4.48 (1H, t, J = 10.4 Hz), 6.61 (2H, d, J = 8.8 Hz), 6.65 (1H, s), 7.44 (2H, d, J = 8.8 Hz), 7.98 (1H, dd, J = 4.8, 2.8 Hz), 8.60 (1H, d, J = 4.8 Hz), 8.73 (1H, d, J = 2.8 Hz), 9.55 (1H, d, J = 7.6 Hz), 9.78 (1H, br s) (DMSO-d6)	435
14	1.63 (2H, m), 1.86 (4H, m), 3.42 (5H, m), 3.44 (3H, s), 3.56 (3H, m), 3.88 (2H, m), 4.64 (1H, br s), 6.66 (1H, s), 7.72 (4H, br s), 8.00 (1H, dd, J = 5.2, 3.2 Hz), 8.60 (1H, d, J = 5.2 Hz), 8.73 (1H, d, J = 3.2 Hz), 9.83 (1H, br s), 10.10 (1H, br s) (DMSO-d6)	449
15	2.30 (1H, m), 2.41 (1H, m), 2.80 (3H, d, J = 5.2 Hz), 2.81 (3H, d, J = 5.2 Hz), 3.27 (1H, m), 3.42 (2H, m), 3.43 (3H, s), 3.52 (4H, m), 3.65 (1H, m), 3.76 (1H, d, J = 13.3 Hz), 3.89 (1H, d, J = 13.6 Hz), 4.00 (1H. m), 4.51 (1H, t, J = 11.6 Hz), 6.65 (1H, s), 6.68 (2H, d, J = 8.4 Hz), 7.50 (2H, d, J = 8.4 Hz), 7.99 (1H, dd, J = 4.8, 2.8 Hz), 8.59 (1H, d, J = 4.8 Hz), 8.73 (1H, d, J = 2.8 Hz), 9.64 (1H, d, J = 8.4 Hz), 9.94 (1H, s), 11.24 (1H, s) (DMSO-d6)	478
16	2.28 (1H, m), 2.41 (1H, m), 2.81 (3H, d, J = 5.0 Hz), 2.82 (d, J = 5.0 Hz), 3.27 (1H, m), 3.39 (2H, m), 3.43 (3H, s), 3.63 (4H, m), 3.80 (4H, m), 4.51 (1H, t, J = 11.2 Hz), 6.65 (1H, s), 6.69 (2H, d, J = 6.4 Hz), 7.49 (2H, d, J = 6.4 Hz), 7.98 (1H, dd, J = 4.8, 2.8 Hz), 8.59 (1H, d, J = 4.8 Hz), 8.73 (1H, d, J = 2.8 Hz), 9.60 (1H ,br s), 9.82 (1H, br s), 11.09 (1H, br s) (DMSO-d6)	478
17	1.67-2.14(9H, m), 2.60-2.83(6H, m), 3.06-3.14(1H, m), 3.26-3.33(1H, m), 3.50-3.73(7H, m), 3.93-4.00(1H, m), 4.13-4.17(1H, m), 4.62(1H, dd, J=1.2, 10.ZHz), 6.87(1H, s), 6.93(2H, d, J=7.3Hz), 7.26(2H, d, J=7.3Hz), 7.94(1H, dd, J=1.2, 4.2Hz), 8.50-8.55(2H, m)($CDCl_3$)	519
18	1.44-1.92(10H, m), 2.32-2.55(5H, m), 2.72-2.76(2H, m), 3.07-3.14(1H, m), 3.26-3.32(1H, m), 3.50-3.60(5H, m), 3.75-3.79(2H, m), 3.92-4.00(1 H, m), 4.12-4.16(1H, m), 4.63(1H, dd, J=1.2, 10.2Hz), 6.87(1H, s), 6.93(2H, d, J=7.3Hz), 7.28(2H, d, J=7.3Hz), 7.95(1H, dd, J=1.2, 4.2Hz), 8.49-8.55(2H, m)($CDCl_3$)	533
19	1.62-1.69(3H, m), 1.98-2.06(2H, m), 2.92-2.98(2H, m), 3.07-3.15(1H, m), 3.25-3.32(1H, m), 3.51-3.60(7H, m), 3.87-3.92(2H, m), 4.12-4.16(1H, m), 4.63(1H, dd, J=1.2, 10.2Hz), 6.87(1H, s), 6.95(2H, d, J=7.3Hz), 7.28(2H, d, J=7.3Hz), 7.94(1H, dd, J=1.2, 4.2Hz), 8.50-8.55(2H, m)($CDCl_3$)	466
20	1.61-1.66(2H, m), 1.91-1.96(2H, m), 2.30-2.31(1H, m), 2.32(6H, s), 2.69-2.74(2H, m), 3.08-3.15(1H, m), 3.20-3.28(1H, m), 3.50-3.61(5H, m), 3.74-3.77(2H, m), 3.94-4.00(1H, m), 4.12-4.16(1H, m), 4.62(1H, dd, J=1.2, 10.2Hz), 6.88(1H, s), 6.96(2H, d, J=7.3Hz), 7.28(2H, d, J=7.3Hz), 7.94(1H, dd, J=1.2, 4.2Hz), 8.50-8.56(2H, m)($CDCl_3$)	493
21	2.81 (3H, d, J = 4.4 Hz), 3.11 (4H, m), 3.39 (3H, s), 3.95-3.35 (10H, m), 4.55 (1H, t, J = 10.8 Hz), 6.65 (1H, s), 7.10 (2H, d, J = 8.8 Hz), 7.56 (2H, d, J = 8.8 Hz), 7.98 (1H, dd, J = 4.8, 2.8 Hz), 8.59 (1H, d, J = 4.8 Hz), 8.73 (1H, d, J = 2.8 Hz), 9.70 (1H, br s), 10.03 (1H, br s), 10.81 (1H, br s) (DMSO-d6)	464
22	3.44 (3H, s), 3.57 (12H, m), 3.82 (1H, d, J = 13.2 Hz), 3.90 (1H, d, J = 13.2 Hz), 4.56 (1H, t, J = 10.8 Hz), 6.66 (1H, s), 7.07 (1H, br s), 7.18 (2H, d, J = 8.4 Hz), 7.36 (4H, br s), 7.60 (2H, d, J = 8.4 Hz), 8.01 (1H, dd, J = 5.2, 2.8 Hz), 8.60 (1H, d, J = 5.2 Hz), 8.74 (1H, d, J = 2.8 Hz), 9.74 (1H, br s), 10.12 (1H, br s) (DMSO-d6)	526

(continued)

Compound No.	1H-NMR δ:	[M+1]
23	1.86 (4H, m), 1.99 (2H, m), 2.14 (2H, m), 2.79 (2H, t, J = 11.6 Hz), 3.02 (2H, m), 3.28 (1H, m), 3.39 (2H, m), 3.43 (3H, s), 3.52 (3H, m), 3.61 (1H, m), 3.81 (1H, d, J = 12.6 Hz), 3.91 (3H, m), 4.54 (1H, t, J = 9.6 Hz), 6.56 (1H, s), 7.15 (2H, d, J = 8.0 Hz), 7.57 (2H, d, J = 8.0 Hz), 8.00 (qH, dd, J = 5.2, 2.8 Hz), 8.60 (1H, d, J = 5.2 Hz), 8.74 (1H, d, J = 2.8 Hz), 9.76 (1H, d, J = 8.8 Hz), 10.15 (1H, br s), 11.10 (1H, br s) (DMSO-d6)	518
24	1.40 (1H, m), 1.86 (8H, m), 2.20 (2H, d, J = 12.0 Hz), 2.80 (2H, m), 2.90 (2H, m), 3.43 (3H, s), 3.70-3.30 (6H, m), 3.80 (1H, d, J = 10.0 Hz), 3.90 (3H, m), 4.65 (1H, t, J = 8.8 Hz), 6.65 (1H, s), 7.15 (2H, d, J = 8.4 Hz), 7.57 (2H, d, J = 8.4 Hz), 8.00 (1H, dd, J = 5.2, 2.8 Hz), 8.60 (1H, d, J = 5.2 Hz), 8.74 (1H, d, J = 2.8 Hz), 9.78 (1H, d, J = 8.8 Hz), 10.19 (1H, br s), 10.54 (1H, br s) (DMSO-d6)	532
25	1.71(2H, m), 2.12(2H, m), 2.73(6H, d, J=5.1 Hz), 2.74-2.81(3H, m), 3.30-3.95(8H, m), 3.39(3H, s), 4.54(1H, m), 6.65(1H, s), 7.10(2H, d, J=8.7 Hz), 7.53(2H, d, J=8.7 Hz), 7.99(1H, dd, J=6.6, 5.1 Hz), 8.59(1H, d, J=4.5 Hz), 8.74(1H, d, J=3.3 Hz), 9.71(1H, m), 10.02(1H, m), 10.66(1H, m), (DMSO-d6)	492
26	1.64(2H, m), 1.91(2H, m), 3.13-3.90(11H, m), 3.48(3H, s), 4.59(1H, m), 6.65(1H, s), 7.36(2H, d, J=8.4 Hz), 7.61(2H, d, J=8.4 Hz), 7.99(1H, dd, J=6.9, 5.1 Hz), 8.59(1H, d, J= 5.1 Hz), 8.72(1H, d, J= 3.0 Hz), 9.67(1H, m), 9.91 (1H, m) (DMSO-d6)	465
27	1.91-2.05(2H, m), 3.09(1H, m), 3.28-3.57(7H, m), 3.41 (3H, s), 3.74-3.86(2H, m), 4.41-4.73(2H, m), 6.58(2H, d, J=8.4 Hz), 6.65(1H, s), 7.44(2H, d, J=8.4 Hz), 7.99(1H, dd, J= 6.6, 5.1 Hz), 8.60(1H, d, J= 5.1 Hz), 8.74(1H, d, J= 3.0 Hz), 9.59(1H, m), 9.86(1H, m)	451
28	1.89-2.01(2H, m), 2.93-3.29(6H, m), 3.44(3H, s), 3.58-3.66(2H, m), 3.80-3.86(1H, m), 3.90-4.00(1H, m), 4.37-4.40(1H, m), 4.55-4.58(1H, m), 4.94(1H, d, =10.2Hz), 6.48(2H, d, J=7.2Hz), 6.59(1H, s), 7.20(2H, d, J=7.2Hz), 7.96(1H, dd, J=1.2, 4.2Hz), 8.56(1H, d, J=4.2Hz), 8.70(1H, d, J=1.2Hz)($CDCl_3$)	452
29	1.76-2.02(2H, m), 2.97-3.29(6H, m), 3.46(3H, s), 3.60-3.69(2H, m), 3.82-3.89(1H, m), 4.01-4.05(1H, m), 4.37-4.40(1H, m), 4.55-4.58(1H, m), 4.95(1H, d, =10.2Hz), 6.50(2H, d, J=7.2Hz), 6.99(1H, s), 7.23(2H, d, J=7.2Hz), 8.18(1H, dd, J=1.2, 4.2Hz), 8.99(1H, d, J=4.2Hz), 9.29(1H, d, J=1.2Hz)($CDCl_3$)	452
30	1.17(1H, m), 1.33-1.43(4H, m), 1.61-1.64(3H, m), 1.75(2H, d, J=12.0Hz). 2.70(3H, s), 2.98(2H, dd, J=10.6, 12.8Hz), 3.44(3H, s), 3.58(3H, m), 3.84(1H, m), 4.00(1H, m), 4.56(1H, dd, J=1.4, 10.4Hz), 7.20(2H, d, J=8.6Hz), 7.97(1H, dd, J=5.2, 6.7Hz), 8.56(1H, d, J=5.2Hz), 8.69(1H, d, J=3.1 Hz)(DMSO-d6) 162	477
31	1.31(6H, d, J=6.5Hz), 2.74(2H, dd, J=11.7, 12.4Hz), 2.94(1H, dd, J=10.7, 12.5Hz), 3.15(1H, m), 3.30-3.39(2H, m), 3.46(3H, s), 3.65(2H, d, J=12.8Hz), 3.81-3.89(3H, m), 4.03(1H, d, J=7.9Hz), 4.63(1H, d, J=9.4Hz), 6.60(1H, s), 7.02(2H, d, J=8.6Hz), 7.30(1H, d, J=8.6Hz), 7.97(1H, dd, J=5.2, 6.7Hz), 8.58(1H, d, J=5.2Hz), 8.74(1H, d, J=3.1 Hz), 9.11(1H, br), 9.71 (1H, br.d, J=8.3Hz)(DMSO-d6)	478
32	1.58-1.70(6H, m), 3.08-3.20(6H, m), 3.50-3.61(2H, m), 3.57(3H, s), 4.10(1H, m), 4.13(1H, m), 4.64(1H, dd, J=2.4, 10.8Hz), 6.88(1H, s), 6.95(2H, d, J=8.7Hz), 7.30(2H, d, J=8.7Hz), 7.98(1H, dd, J=5.1, 5.1 Hz), 8.51(1H, d, J=5.4Hz), 8.57(1H, d, J=3.3Hz)($CDCl_3$)	450
33		
34	1.58-1.70(4H, m), 3.08-3.20(6H, m), 3.50-3.61(2H, m), 3.57(3H, s), 4.10(1H, m), 4.13(1H, m), 4.64(1H, dd, J=2.4, 10.8Hz), 6.88(1H, s), 6.95(2H, d, J=8.7Hz), 7.30(2H, d, J=8.7Hz), 7.98(1H, dd, J=5.1, 5.1Hz), 8.51(1H, d, J=5.4Hz), 8.57(1H, d, J=3.3Hz)($CDCl_3$)	436
35	2.05(6H, m), 2.22(1H, m), 2.84(1H, m), 3.98(1H, m), 3.00-3.60(8H, m), 3.56(3H, s), 3.97(1H, m), 4.12(1H, m), 4.60(1 H, d, J=10.4Hz), 6.56(2H, d, J=8.7Hz), 6.88(1H, s), 7.29(2H, d, J=8.7Hz), 7.96(1H, dd, J=5.4, 6.9Hz), 8.50(1H, d, J=5.4Hz), 8.55(1 H, d, J=3.3Hz)($CDCl_3$)	479

(continued)

Compound No.	1H-NMR δ:	[M+1]
36	2.97(6H, s), 3.13(1H, dd, J=10.5, 12.9Hz), 3.29(1H, m), 3.50-3.60(2H, m), 3.56(3H, s), 3.98(1H, m), 4.15(1H, dd, J=2.1, 9.9Hz), 4.61 (1H, dd, J=2.1, 10.5Hz), 6.74(2H, d, J=8.7Hz), 6.88(1H, s), 7.29(2H, d, J=8.7Hz), 7.96(1H, dd, J=5.1, 5.1Hz), 8.51 (1H, d, J=5.4Hz), 8.55(1H, d, J=3.3Hz)($CDCl_3$)	410
37	1.10(6H, d, J=6.3Hz), 2.69(5H, m), 3.11(1H, dd, J=10.5, 12.9Hz), 3.24-3.31(5H, m), 3.50-3.57(2H, m), 3.56(3H, m), 3.96(1H, m), 4.14(1H, dd, J=2.1, 9.9Hz), 4.63(1H, dd, J=2.1, 10.5Hz), 6.87-6.95(4H, m), 7.30(2H, m), 8.50(1H, d, J=5.1Hz), 8.55(1H, d, J=3.0Hz)($CDCl_3$)	493
38	1.66(1H, br.s), 2.62(2H, t, J=5.4Hz), 2.68(4H, t, J=4.9Hz), 3.10(1H, dd, J=10.8, 12.9Hz), 3.23(4H, t, J=4.8Hz), 3.30(1H, m), 3.61-3.68(2H, m), 3.67(3H, s), 3.67(2H, dd, J=5.1, 5.4Hz), 3.97(1H, m), 4.13(1H, m), 4.63(1H, dd, J=2.4, 10.8Hz), 6.88(1H, s), 6.93(2H, d, J=8.7Hz), 7.30(2H, d, J=8.7Hz), 7.95(1H, dd, J=5.1, 5.1Hz), 8.50(1H, d, J=5.4Hz), 8.55(1H, d, J=3.3Hz)($CDCl_3$)	495
40	1.09 (1H, m), 1.33 (2H, m), 1.45 (2H, m), 1.61 (2H, m), 1.79 (3H, m), 2.80 (3H, m), 3.44 (3H, s), 3.50 (2H, m), 3.52 (3H, s), 3.85 (2H, m), 4.57 (1H, m), 6.65 (1H, s), 7.50 (2H, m), 7.99 (1H, dd, J = 4.8, 2.8 Hz), 8.60 (1H, d, J = 4.8 Hz), 8.73 (1H, d, J = 2.8 Hz), 9.53 (1H, br s) (DMSO-d6)	477
41	3.46 (3H, s), 3.52 (4H, m), 3.81 (3H, s), 3.92 (2H, d, J = 13.3 Hz), 4.69 (1H, t, J = 11.0 Hz), 6.66 (1H, s), 7.05 (2H, d, J = 8.7 Hz), 7.71 (6H, m), 8.01 (1H, dd, J = 4.9, 2.7 Hz), 8.60 (1H, d, J = 4.9 Hz), 8.73 (1H, d, J = 2.7 Hz), 9.71 (1H, br s), 9.89 (1H, br s) (DMSO-d6)	472
42	2.98 (6H, s), 3.43 (1H, m), 3.44 (3H, s), 3.55 (2H, m), 4.40-3.80 (3H, m), 4.55 (1H, t, J = 10.0 Hz), 6.65 (1H, s), 7.04 (2H, br s), 7.57 (2H, br s), 8.00 (1H, dd, J = 5.2, 2.8 Hz), 8.60 (1H, d, J = 5.2 Hz), 8.73 (1H, d, J = 2.8 Hz), 9.69 (1H, br s), 10.00 (1H, br s) (DMZO-d6)	409
43	3.18-3.22(4H, m), 3.44-3.92(15H, m), 4.52-4.55(1H, m), 5.11(2H, s), 6.64(1H, s), 7.04(2H, d, J=7.2Hz), 7.36-7.39(5H, m), 7.48(2H, d, J=7.2Hz), 7.96-8.00(1H, m), 8.58(1H, d, J=4.2Hz), 8.72(1H, d, J=4.2Hz), 9.42-9.65(2H, br)(DMSO-d6)	584
44	3.16-3.20(4H, m), 3.39-3.91(13H, m), 4.51-4.58(1H, m), 6.65(1H, s), 7.06-7.10(2H, m), 7.43-7.66(4H, m), 7.97-8.01(1H, m), 8.60(1H, d, J=4.2Hz), 8.73(1H, s), 9.20(1H, brs), 9.70-9.72(1H, br), 10.02-10.05(1H, br)(DMSO-d6)	450
45	1.32(6H, d, J=6.8Hz), 3.26-3.88(18H, m), 4.60-4.65(2H, m), 6.65(1H, s), 7.10(2H, d, J=7.2Hz), 7.60(2H, d, J=7.2Hz), 7.99-8.03(1H. m), 8.61(1H, d, J=4.2Hz), 8.75(1H, d, J=1.2Hz), 9.75-9.85(1H, br), 10.30-10.33(1H, br), 11.05-11.10(1H, br)(DMSO-d6)	492
46	3.18-3.24(8H, m), 3.43-3.60(13H, m), 4.51-4.55(1H, m), 6.65(1H, s), 7.09(2H, d, J=7.2Hz), 7.60(2H, d, J=7.2Hz), 7.99(1H, dd, J=1.2Hz, 4.2Hz), 8.59(1 , d, J=4.2Hz), 8.72(1H, d, J=1.2Hz), 9.81-9.84(1H, br), 10.18-10.32(3H, br), 10.62-10.66(1H, br)(DMSO-d6)	494
47	2.09(3H, s), 3.18-3.24(5H, m), 3.40-3.91(15H, m), 4.42-4.50(3H, m), 6.65(1H, s), 7.10(2H, d, J=7.2Hz), 7.56(2H, d, J=7.2Hz), 7.98(1H, dd, J=1.2Hz, 4.2Hz), 8.60(1H, d, J=4.2Hz), 8.72(1H, d, J=1.2Hz), 9.70-9.74(1H, br), 9.89-9.97(1H, br), 11.13-11.16(1H, br)(DMSO-d6)	536
48	2.69-2.76(1H, m), 3.10-3.14(1H, m), 3.51-3.52(1H, m), 3.53(3H, s), 3.68-3.73(1H, m), 3.80-3.93(4H, m), 4.06-4.10(1H, m), 4.99(1H, dd, J=1.2Hz, 10.2Hz), 7.21(1H, d, J=7.3Hz), 7.70-7.74(2H, m), 7.82(1H, dd, J=1.2Hz, 4.2Hz), 8.60(1H, d, J=4.2Hz), 8.75(1H, d, J=1.2Hz)(DMSO-d6)	440
49	3.28-3.61 (7H, m), 3.81-3.88(1H, m), 3.98-4.02(1H, m), 5.27(1H, dd, J=1.2Hz, 10.2Hz), 7.23-7.47(3H, m), 7.72-7.76(1H, m), 8.58(1H, d, J=4.2Hz), 8.75(1H, s)(DMSO-d6)	437
50	1.91-2.03(2H, m), 3.09(1H, m), 3.30-3.52(6H, m), 3.41 (3H, s), 3.75-3.87(2H, m), 4.40-4.52(3H, m), 6.58(2H, d, J=8.7 Hz), 6.65(1H, s), 7.40(2H, d, J=8.7 Hz), 7.97(1H, dd, J= 6.6, 5.1 Hz), 8.59(1H, d, J= 5.1 Hz), 8.72(1H, d, J= 3.0 Hz), 9.48-9.58(2H, m) (DMSO-d6)	451

(continued)

Compound No.	1H-NMR δ:	[M+1]
51	1.15(6H, d, J= 6.0 Hz), 2.31(2H, dd, J= 11.1 Hz), 2.97-3.21(6H, m), 3.52-3.62(4H, m), 3.55(3H, s), 3.95(1H, dd, J= 10.5, 2.4 Hz), 6.85(1H, s), 6.93(2H, d, J= 9.0 Hz), 7.32(2H, d, J= 9.0 Hz), 7.97(1H, dd, J= 6.9, 5.4 Hz), 8.50(1H, d, J= 4.5 Hz), 8.54(1H, d, J= 3.3 Hz) ($CDCl_3$)	478
52	1.27(6H, d, J= 6.3 Hz), 2.42(2H, dd, J= 11.1, 11.1 Hz), 3.00(1H, dd, J= 12.3,10.8 Hz), 3.16-3.22(3H, m), 3.45-3.60(4H, m), 3.55(3H, s), 3.81 (1H, m), 3.95(1H, m), 6.85(1H, s), 6.92(2H, d, J= 8.4 Hz), 7.33(2H, d, J= 8.4 Hz), 7.97(1H, m), 8.50(1H, d, J= 5.1 Hz), 8.54(1H, d, J= 3.0 Hz) ($CDCl_3$)	479
55	2.98(1H, m), 3.15(1H, m), 3.23-3.30(6H, m), 3.45(3H, s), 3.63-3.68(2H, m), 3.86(1H, m), 4.03(1H, m), 4.64(1H, m), 6.59(1H, s), 6.81(1H, dd, J=7.2, 7.2 Hz), 6.98-7.01 (4H, m), 7.21-7.32(4H, m), 7.98(1H, dd, J=6.9, 5.1 Hz), 8.57(1H, d, J=4.8Hz), 8.69(1H, d, J=3.0Hz) (DMSO-d6)	527
57	2.83-3.09(5H, m), 3.26(3H, s), 3.46(3H, s), 3.67-3.76(2H, m), 4.01-4.04(1H, m), 6.57(1H, s), 7.62(2H, d, J=7.2Hz), 7.76(2H, d, J=7.2Hz), 7.95-8.05(5H, m), 8.56(1H, d, J=4.2Hz), 8.69(1H, d. J=1.2Hz)(DMSO-d6)	520
58	2.82-3.10(5H, m), 3.46(3H, s), 3.66-3.69(2H, m), 4.00-4.03(1H, m), 6.56(1H, s), 7.60(2H, d, J=7.2Hz), 7.75(2H, d, J=7.2Hz), 7.90-7.98(5H, m), 8.56(1H, d, J=4.2Hz), 8.69(1H, d, J=1.2Hz)(DMSO-d6)	467
64	1.48-1.49(2H, m), 1.61-1.67(4H, m), 1.92-2.00(1H, m). 2.20-2.30(1H, m), 2.48-2.95(4H, m), 3.12-3.32(9H, m), 3.66(3H, s), 3.96(1H, m), 4.11(1H, m), 4.60(1H, dd, J=2.4, 10.8Hz), 6.48-6.56(2H, m), 6.87(1H, s), 7.18-7.23(2H, m), 7.96(1H, dd, J=5.1, 5.1 Hz), 8.50(1H, d, J=5.4Hz), 8.54(1H, d, J=3.3Hz)($CDCl_3$)	519
66	3.06 (1H, dd, J = 12.0, 10.4 Hz), 3.25 (3H, m), 3.58 (3H, s), 3.65 (2H, m), 4.09 (1H, dd, J = 10.4, 2.4 Hz), 6.86 (1H, s), 7.29 (2H, d, J = 8.4 Hz), 7.53 (2H, d, J = 8.4 Hz), 7.56 (2H, d, J = 8.4 Hz), 7.60 (2H, d, J = 8.4 Hz), 7.97 (1H, dd, J =4.8, 2.8 Hz), 8.50 (1H, d, J =4.8 Hz), 8.55 (1H, d, J = 2.8 Hz) ($CDCl_3$)	526
67	3.06 (1H, dd, J = 12.4, 10.4 Hz), 3.25 (3H, m), 3.58 (3H, s), 3.66 (2H, m), 4.10 (1H, dd, J = 10.4, 2.2 Hz), 6.86 (1H, s), 7.56 (2H, d, J = 8.4 Hz), 7.62 (2H, d, J = 8.4 Hz), 7.70 (4H, s), 7.97 (1H, dd, J = 4.8. 3.1 Hz), 8.51 (1H, d, J = 4.8 Hz), 8.55 (1H, d, J = 3.1 Hz) ($CDCl_3$)	510
68	1.44 (3H, t, J = 6.8 Hz), 3.06 (1H, dd, J = 12.4, 10.8 Hz), 3.21 (3H, m), 3.57 (3H, s), 3.62 (2H, m), 4.05 (1H, m), 4.08 (2H, q, J = 6.8 Hz), 6.86 (1H, s), 6.97 (2H, d, J = 8.8 Hz), 7.53 (6H, m), 7.98 (1H, dd, J = 4.8, 3.2 Hz), 8.51 (1H, d, J = 4.8 Hz), 8.55 (1H, d, J = 3.2 Hz) ($CDCl_3$)	486
69	1.90 (3H, m), 2.01 (1H, m), 2.50 (3H, s), 2.84 (1H, m), 3.16 (1H, m), 3.38 (3H, m), 3.44 (3H, s), 3.70 (9H, m), 4.59 (1H, br s), 6.65 (1H, s), 7.39 (2H, br s), 7.66 (2H, br s), 8.00 (1H, dd, J = 5.2, 2.4 Hz), 8.59 (1H, d, J = 5.2 Hz), 8.73 (1H, d, J = 2.4 Hz), 9.79 (1H, br s), 10.24 (1H, br s), 11.15 (1H, br s) (DMSO-d6)	518
70	1.83 (4H, m), 1.99 (1H, m), 2.21 (1H, m), 2.61 (4H, m), 2.86 (1H, m), 3.01 (1H, dd, J = 12.4, 10.4 Hz), 3.20 (4H, m), 3.33 (1H, q, J = 6.8 Hz), 3.47 (2H, m), 3,54 (3H, s), 3.59 (2H, m), 3.88 (1H, dd, J = 10.4, 2.4 Hz), 6.55 (2H, d, J = 8.4 Hz), 6.85 (1H, s), 7.29 (2H, d, J = 8.4 Hz), 7.98 (1H, dd, J = 5.2, 3.2 Hz), 8.49 (1H, d, J = 5.2 Hz), 8.54 (1H, d, J = 3.2 Hz) ($CDCl_3$)	504
71	1.60 (6H, s), 2.82 (1H, dd, J = 12.8, 10.0 Hz), 3.34 (1H, td, J = 11.9, 2.8 Hz), 3.55 (1H, d, J = 11.9 Hz), 3.62 (3H, s), 3.81 (1H, d, J = 12.8 Hz), 3.85 (3H, s), 4.00 (1H, td, J = 11.9, 2.8 Hz), 4.23 (1H, dd, J = 11.9, 2.2 Hz), 5.06 (1H,dd, J = 10.0, 2.2 Hz), 6.87 (1H,d,J= 9.2 Hz), 6.88 (1H, s), 7.43 (H ,dd, J = 9.2. 2.4 Hz), 7.66 (1H, d, J = 2.4 Hz), 8.01 (1H, dd, J = 5.2, 3.2 Hz), 8.51 (1H, d, J = 5.2 Hz), 8.55 (1H,d, J = 3.2 Hz) ($CDCl_3$)	455

(continued)

Compound No.	1H-NMR δ:	[M+1]
73	1.94(1H, m), 2.20(1H, m), 2.54(4H,m), 3.00(1H, m), 3.16-3.62(8H, m), 3.56(3H, s), 3.75(4H, t, J=4.6Hz), 3.96(1H, m), 4.12(1H, m), 4.60(1H, dd, J=1.9, 10.4Hz), 6.55(2H, d, J=8.7Hz), 6.87(1H, s), 7.25(2H, d, J=8.6Hz), 7.96(1H, dd, J=5.1, 5.1Hz), 8.50(1H, d, J=5.4Hz), 8.55(1H, d, J=3.3Hz)($CDCl_3$)	521
75	1.83-2.05(5H,m),2.20(1H,m),3.00(1H,m),3.15-3.63(8H,m),3.56(3H,s),3.97(1H,m),4.16(1H,m),4.61(1H dd,J,=1.9,10.4Hz),6.56(2H,d,J=8.7Hz),6.69(1H,s),8.71(2H,d,J=0.6Hz),7.30(2H,d,J=3.3Hz)($CDCl_3$)	MS
77	2.31 (2H ,q, d = 5.1 Hz), 3.01 (1H, t, J =10.0 Hz), 3.10 (1H, m), 3.20 (3H, m), 3.35 (1H, q, J = 6.9 Hz), 3.53 (3H, s), 3.54 (5H, m), 3.91 (1H, dd, J = 10.8, 2.8 Hz), 5.34 (1H, br s), 5.65 (1H, br s), 6.60 (2H, d, J = 8.8 Hz), 6.85 (1H, s), 7.28 (2H, d, J = 8.8 Hz), 7.98 (1H, dd, J = 5.2, 3.2 Hz), 8.50 (1H, d, J = 5.2 Hz), 8.54 (1H, d, J = 3.2 Hz) ($CDCl_3$)	478
78	2.41 (2H, m), 3.00 (1H, t, J = 10.0 Hz), 3.18 (3H, m), 3,24 (1H, m), 3.43 (1H, m), 3.55 (3H, s), 3.59 (6H, m), 3.90 (1H, dd, J = 10.8, 2.8 Hz), 6.58 (2H, d, J = 8.4 Hz), 6.85 (1H, s), 7.32 (2H, d, J = 8.4 Hz), 7.97 (1H, dd, J = 5.2, 3.2 Hz), 8.50 (1H, d, J = 5.2 Hz), 8.54 (1H, d. J = 3.2 Hz) ($CDCl_3$)	460
79	1.48-2.05(7H, m), 2.20(1H, m), 2.55(4H,m), 3.00(1H, m), 3.09-3.60(8H, m), 3.56(3H, s), 3.97(1H, m), 4.16(1H, m), 4.60(1H, dd, J=1.9, 10.4Hz), 6.57(2H, d, J=8.7Hz), 6.88(1H, s), 7.24(2H, d, J=8.7Hz), 7.96(1H, dd, J=5.1, 5.1 Hz), 8.50(1H, d, J=5.4Hz), 8.55(1H, d, J=3.3Hz)($CDCl_3$)	MS
80	1.94(1H, m), 2.20(1H, m), 2.54(4H,m), 3.00(1H, m), 3.16-3.62(8H, m), 3.56(3H, s), 3.75(4H, t, J=4.6Hz), 3.96(1H, m), 4.16(1H, m), 4.60(1H, dd, J=1.9, 10.4Hz), 6.55(2H, d, J=8.7Hz), 6.87(1H, s), 7.25(2H, d, J=8.6Hz), 7.96(1H, dd, J=5.1, 5.1Hz), 8.50(1H, d, J=5.4Hz), 8.55(1H, d, J=3.3Hz)($CDCl_3$)	MS
81	1.11 (1H, m), 1.41 (4H, m), 1.63 (3H, m), 1.75 (2H, m), 2.70 (3H, s), 2.85-3.98 (11H, m), 6.56 (1H, s), 6.59 (2H, s), 6.74 (2H, d, J = 8.6 Hz), 7.26 (2H, d, J = 8.6 Hz), 7.96 (1H, dd, J = 5.3, 3.1 Hz), 8.57 (1H, d, J = 5.3 Hz), 8.69 (1H, d, J = 3.1 Hz) (DMSO-d6)	477
82	1.68-1.70(4H, m), 1.87-1.90(1H, m), 2.06-2.10(1H, m), 3.01-3.16(10H, m), 3.40(3H, s), 3.53-3.58(3H, m), 3.83-3.98(2H, m), 4.56(1H, dd, J=1.2Hz, 10.2Hz), 6.51 (2H, d, J=7.2Hz), 6.59(1H, s), 7.20(2H, d, J=7.2Hz), 7.96(1H, dd, J=1.2Hz, 4.2Hz), 8.56(1H, d, J=4.2Hz), 8.69(1 H, d, J=1.2Hz)(DMSO-d6)	505
84	1.26(6H, d, J=6.0Hz), 2.42(2H, t, J=10.8Hz), 3.11(1H, dd, J=11.7, 13.8Hz), 3.16-3.61 (5H, m), 3.57(3H, s), 3.79(2H, m), 3.97(1H, m), 4.12(1H, m), 4.64(1H, dd, J=1.9,10.4Hz), 6.87(1H, s), 6.91(2H, d, J=8.6Hz), 7.25(2H, d, J=8.6Hz), 7.94(1H, dd, J=5.1, 5.1Hz), 8.50(1H, d, J=5.4Hz), 8.55(1H, d, J=3.3Hz)($CDCl_3$)	MS
85	3.07 (1H, dd, J = 12.4, 11.2 Hz), 3.22 (3H, m), 3.57 (3H, s), 3.65 (2H, m), 3.82 (3H, s), 3.86 (3H, s), 4.05 (1H, dd, J =10.4, 2.4 Hz), 6.58 (2H, m), 6.87 (1 H, s), 7.24 (2H, m), 7.46 (2H, d, J = 8.0 Hz), 7.53 (2H, d, J = 8.0 Hz), 8.00 (1H, dd, J = 4.8,2.8 Hz), 8.52 (1H, d, J = 4.8 Hz), 8.55 (1 H, d, J = 2.8 Hz) ($CDCl_3$)	502
86	3.06 (1H, dd, J = 12.4, 10.4 Hz), 3.23 (3H, m), 3.57 (3H, s), 3,65 (2H, m), 3.93 (3H, s), 3.96 (3H, s), 4.07 (1H, dd, J = 10.0, 2.0 Hz), 6.86 (1H, s), 6.95 (1H, d, J = 8.0 Hz), 7.11 (1H, d, J = 2.0 Hz), 7.15 (1H, dd, J = 8.0, 2.0 Hz), 7.50 (1H, d, J = 8.4 Hz), 7.57 (1H, d, J = 8.4 Hz), 7.98 (1H, dd, J = 4.8, 3.2 Hz), 8.50 (1H, d, J = 4.8 Hz), 8.55 (1H, d, J = 3.2 Hz) ($CDCl_3$)	502

(continued)

Compound No.	1H-NMR δ:	[M+1]
87	3.05 (1H, dd, J = 12.4, 10.4 Hz), 3.25 (3H, m), 3.57 (3H, s), 3.64 (2H, m), 4.08 (1H, dd, J= 10.4, 2.4 Hz), 6.86 (1H, s), 7.41 (2H, d, J = 8.4 Hz), 7.52 (4H, d, J = 8.4 Hz), 7.57 (2H, d, J = 8.4 Hz), 7.97 (1H, dd, J = 5.2, 2.8 Hz), 8.50 (1H, d, J = 5.2 Hz), 8.55 (1H, d, J = 2.8 Hz) ($CDCl_3$)	476
88	3.43 (2H, m), 3.46 (3H, s), 3,62 (2H, m), 3.93 (2H, d, J = 13.6 Hz), 4.74 (1H, t, J = 10.6 Hz), 6.66 (1H, s), 7.46 (2H, d, J = 8.4 Hz), 7.54 (3H, m), 7.77 (1H, d, J = 2.0 Hz), 7.83 (2H, d, J = 8.4 Hz), 8.03 (1H, dd, J = 4.8, 2.8 Hz), 8.61 (1H, d, J = 4.8 Hz), 8.74 (1H, d, J = 2.8 Hz), 9.90 (1H, d, J = 8.8 Hz), 10.40 (1H, br s) (DMSO-d6)	510
89	3.05 (1H, dd, J = 12.4, 10.8 Hz), 3.25 (3H, m), 3.57 (3H, s), 3.63 (2H, m), 4.09 (1H, dd, J = 10.4, 2.4 Hz), 6.86 (1H, s), 7.42 (1H, dd, J = 8.0, 2.0 Hz), 7.54 (5H, m), 7.67 (1H, d, J = 2.0 Hz), 7.96 (1H, dd, J = 5.2, 3.2 Hz), 8.50 (1H, d, J = 5.2 HZ), 8.55 (1H, d, J = 3.2 Hz) ($CDCl_3$)	510
90	3.04 (1H, dd, J = 12.4, 10.8 Hz), 3.24 (3H, m), 3.58 (3H,s), 3,64 (2H, m), 4.13 (1H, dd, J = 10.0, 2.0 Hz), 6.87 (1H, s), 7.61 (2H, d, J = 8.0 Hz), 7.95 (1H, dd, J = 4.8, 2.8 Hz), 8.14 (1H, d, J = 8.0 Hz), 8.50 (1H, d, J = 4.8 Hz), 8.55 (1H, d, J = 2.8 Hz), 8.77 (1H, s) ($CDCl_3$)	434
91	0.37(2H, m), 0.66(2H, m), 1.30(1H, m), 3.05(1H, dd, J=12.6, 10.8 Hz), 3.19-3.25(3H, m), 3.57(3H, s), 3.62-3.70(2H, m), 3.85(2H, d, J= 6.9 Hz), 4.06(1H, m), 6.86(1H, s), 6.98(2H, d, J= 8.7 Hz), 7.46-7.58(6H, m), 7.92(1H, m), 8.50(1H, d, J= 5.1 Hz), 8.54(1H, d, J= 3.0 Hz) ($CDCl_3$)	512
92	1.37(6H, d, J= 6.0 Hz), 3.05(1H, dd, J=12.3, 10.8 Hz), 3.19-3.25(3H, m), 3.57(3H, s), 3.62-3.67(2H, m), 4.06(1H, dd, J=10.2, 2.7 Hz), 4.59(1H, m), 6.86(1H, s), 6.96(2H, d, J= 9.0 Hz), 7.49-7.58(6H, m), 7.98(1H, m), 8.51 (1H, d, J= 5.1Hz), 8.55(1H, d, J= 3.3 Hz) ($CDCl_3$)	500
93	0.99(3H, t, J= 7.5 Hz), 1.47-1.82(4H, m), 3.06(1H, dd, J=12.6,10.8 Hz), 3.19-3.26(3H, m), 3.57(3H, s), 3.62-3.67(2H, m), 4.01(2H, t, J= 6.3 Hz), 4.04(1H, m), 6.86(1H, s), 6.97(2H, d, J= 8.4 Hz), 7.50-7.58(6H, m), 7.98(1H, m), 8.51(1H, d, J= 5.1 Hz), 8.55(1H, d, J= 3.0 Hz) ($CDCl_3$)	514
98	3.02(4H, t, J=4.7Hz), 3.22(4H, t, J=4.2Hz), 3.48(3H, s), 6.83(1H, s), 6.91-6.83(2H, m), 7.33-7.26(4H, m), 7.41(1H, dd, J=6.9, 7.8Hz), 7.65(2H, d, J=8.3Hz), 7.94(1H, dd, J=5.4, 6.9Hz), 8.51(1H, d, J=5.4Hz), 8.54(1H, d, J=3.3Hz)($CDCl_3$)	424
99	3.02(4H, t, J=4.7Hz), 3.22(4H, t, J=4.2Hz), 3.48(3H, s), 6.83(1H, s), 6.91-6.83(2H, m), 7.33-7.26(4H, m), 7.41(1H, dd, J=6.9, 7.8Hz), 7.65(2H, d, J=8.3Hz), 7.94(1H, dd, J=5.4, 6.9Hz), 8.51(1H, d, J=5.4Hz), 8.54(1H, d, J=3.3Hz)($CDCl_3$)	488
100	3.02(4H, t, J=4.7Hz), 3.22(4H, t, J=4.2Hz), 3.48(3H, s), 6.83(1H, s), 6.91-6.83(2H, m), 7.33-7.26(4H, m), 7.41 (1H, dd, J=6.9, 7.8Hz), 7.65(2H, d, J=8.3Hz), 7.94(1H, dd, J=5.4, 6.9Hz), 8.51(1H, d, J=5.4Hz), 8.54(1H, d, J=3.3Hz)($CDCl_3$)	438
101	3.02(4H, t, J=4.7Hz), 3.22(4H, t, J=4.2Hz), 3.48(3H, s), 6.83(1H, s), 6.91-8.83(2H, m), 7.33-7.26(4H, m), 7.41(1H, dd, J=6.9, 7.8Hz), 7.65(2H, d, J=8.3Hz), 7.94(1H, dd, J=5.4, 6.9Hz), 8.51(1H, d, J=5.4Hz), 8.54(1H, d, J=3.3Hz)($CDCl_3$)	456
102	3.02(4H, t, J=4.7Hz), 3.22(4H, t, J=4.2Hz), 3.48(3H, s), 6.83(1H, s), 6.91-6.83(2H, m), 7.33-7.26(4H, m), 7.41 (1H, dd, J=6.9, 7.8Hz), 7.65(2H, d, J=8.3Hz), 7.94(1H, dd, J=5.4, 6.9Hz), 8.51(1H, d,J=5.4Hz), 8.54(1H, d, J=3.3Hz)($CDCl_3$)	498
103	3.02(4H, t, J=4.7Hz), 3.22(4H, t, J=4.2Hz), 3.48(3H, s), 6.83(1H, s), 6.91-6.83(2H, m), 7.33-7.26(4H, m), 7.41(1H, dd, J=6.9, 7.8Hz), 7.65(2H, d, J=8.3Hz), 7.94(1H, dd, J=5.4, 6.9Hz), 8.51(1H, d, J=5.4Hz), 8.54(1H, d, J=3.3Hz)($CDCl_3$)	484

(continued)

Compound No.	1H-NMR δ:	[M+1]
110	1.59 (6H, s), 3.12 (1H, dd, J = 12.8, 10.4 Hz), 3.31 (1H, td, J = 11.8, 2.0 Hz), 3.54 (1H, d, J = 11.8 Hz), 3.58 (3H, s), 3.64 (1H, d, J = 12.8 Hz), 3.99 (1H, td, J = 11.6, 2.0 Hz), 4.18 (1H, dd, J = 11.8, 2.0 Hz), 4.73 (1H, dd, J = 10.4, 2.0 Hz), 6.89 (1H, s), 7.39 (2H, d, J = 8.4 Hz), 7.53 (2H, d, J = 8.4 Hz), 7.95 (1H, dd, J = 4.8, 3.2 Hz), 8.51 (1H, d, J = 4,8 Hz), 8.55 (1H, d, J = 3.2 Hz) ($CDCl_3$)	424
111	1.77 (2H, m), 2.20 (2H, m), 2.37 (3H, s), 2.45 (2H, t, J =11.2 Hz), 2.78 (3H, m), 3.30 (1H, td, J = 11.4,2.0 Hz), 3.55 (1H, d, J = 13.2 Hz), 3.62 (3H, s), 3.80 (1H,d, J = 12.8 Hz), 3.85 (3H, s), 3.99 (1H, td, J = 11.4,2.0 Hz), 4.20 (1H, dd, J = 11.4.2.0 Hz), 5.05 (1H, dd, J = 10.0, 2.0 Hz), 6.87 (1H, d, J = 8.8 Hz), 6.89 (1H, s), 7.44 (1H, dd, J = 8.8, 2.4 Hz), 7.71 (1H, d, J = 2.4 Hz), 8.00 (1H, dd, J = 4.8, 3.2 Hz), 8.51 (1H, d, J = 4.8 Hz), 8.55 (1H, d, J = 3.2 Hz) ($CDCl_3$)	510
112	3.11 (1H, dd, J=10.8, 12.9Hz), 3.32(1H, td, J=3.2, 12.0Hz), 3.52-3.66(2H, m), 3.58(3H, s), 3.99(1H, m), 4.16(1H, m), 4.74(1H, dd, J=3.3, 11.1 Hz), 6.89(1H, m), 7.33-7.42(SH, m), 7.94(1H, dd, J=5.4, 6.9Hz), 8.51(1H, d, J=5.4Hz), 8.55(1H, d, J=3.3Hz)($CDCl_3$)	367
113	2.84(3H, s), 3.12(1H, dd, J=10.5, 12.6Hz), 3.33(1H, td, J=3.2, 12.0Hz), 3.50-3.60(2H, m), 3.56(3H, s), 3.96(1H, m), 4.15(1H, m), 4.59(1H, d, J=9.0Hz). 6.61(2H, d, J=8.4Hz), 6.88(1H, s), 7.22(2H, d, J=8.4Hz), 7.32(1H, m), 7.96(1H, dd, J=5.0, 6.7Hz), 8.50(1H, d, J=5.0Hz), 8.55(1H, d, J=3.0Hz)($CDCl_3$)	395
115	2.98(1H, dd, J=10.5, 12.6Hz), 3.17(1H, td, J=3.2, 12.0Hz), 3.41(3H, s), 3.69(2H, m), 3.88(1H, m), 4.04(1H, dd, J=3.3, 11.1Hz), 4.71(1H, d, J=9.0Hz), 5.40(1H, s), 6.21 (2H. br.s), 6.57(1H, s). 6.63(2H, d, J=8.4Hz), 7.33-7.55(6H, m), 7.97(1H, dd, J=5.0, 6.7Hz), 8.56(1H, d, J=5.0Hz), 8.69(1H, d, J=3.0Hz)(DMSO-d6)	456
116	2.67 (3H, s), 3.03 (1H, dd, J = 12.4,10.4 Hz), 3.23 (3H, m), 3.57 (3H, s), 3.63 (2H, m), 4.11 (1H, dd, J = 10.0, 2.0 Hz), 6.87 (1H, s), 8.58 (2H, d, J = 8.4 Hz), 7.96 (1H, dd, J = 5.2, 3.2 Hz), 8.08 (2H, d, J = 8.4 Hz), 8.50 (1H, d, J = 5.2 Hz), 8.55 (1H, d, J = 3.2 Hz) ($CDCl_3$)	448
118		
119	3.13(1H, dd, J=10.5,12.9Hz), 3.29(1H, m), 3.50-3.60(2H, m), 3.57(3H, s), 3.82(3H, s), 3.98(1H, m), 4.14(1H, dd, J=2.1, 9.9Hz), 4.67(1H, dd, J=2.1, 10.5Hz), 6.88(1H, s), 6.94(2H, d, J=8.7Hz), 7.33(2H, d, J=8.7Hz), 7.94(1H, dd, J=5.1, 5.1 Hz), 8.51(1H, d, J=5.4Hz), 8.55(1H, d, J=3.3Hz)($CDCl_3$)	396
120	3.05(1H, dd, J=10.5, 12.9Hz), 3.23(1H, m), 3.50(2H, t J=11.1, 12.6Hz), 3.62(3H, s), 3.80(3H, s), 3.98(1H, m), 4.14(1H, dd, J=2.1, 9.9Hz), 4.67(1H, dd, J=2.1, 10.5Hz), 6.89(2H, d, J=8.7Hz), 7.21(2H, d, J=8.7Hz), 7.37(1H, dd, J=5.1, 5.1 Hz), 8.51(1H, d, J=5.4Hz), 8.55(1H, d, J=3.3Hz)($CDCl_3$)	474
121	1.97(1H, m), 1.98(3H, s), 2.30(1H, m), 3.11-3.61(9H, m), 3.56(3H, s), 3.97(1H, m), 4.59-4.63(2H, m), 5.62(1H, m), 6.58(2H, d, J= 8.7 Hz), 6.87(1H. s), 7.28(2H, d, J= 9.0 Hz), 7.94(1H, m), 8.49(1H, d, J= 4.5 Hz), 8.55(1H, d, J= 3.0 Hz) ($CDCl_3$)	493
133	1.60 (4H, m), 1.73 (2H, m), 1.88 (2H, m), 2.80 (3H, s), 3.14 (1H, dd, J = 12.8, 10.4 Hz), 3.28 (1H, td, J = 11.4, 2.0 Hz), 3.55 (2H, m), 3.56 (3H, s), 3.96 (1H, td, J = 11.4, 2.4 Hz), 4.16 (2H, m), 4.60 (1H, dd, J = 10.4, 2.4 Hz), 6.81 (1H, d, J = 8.8 Hz), 6.87 (1H, s), 7.24 (1H, d, J = 8.8 Hz), 7.96 (1H, dd, J = 5.2, 3.2 Hz), 8.51 (1H, d, J = 5.2 Hz), 8.55 (1H, d, J = 3.2 Hz) ($CDCl_3$)	464
134	1.50 (4H, m), 1.64 (4H, m), 1.72 (2H, m), 1.83 (2H, m), 2.76 (3H, s), 3..14 (1H, dd, J = 12.8, 10.4 Hz), 3.28 (1H, td, J = 11.4, 2.0 Hz), 3.56 (2H, m), 3.57 (3H, s), 3.77 (1H, m), 3.96 (1H, td, J =11.4, 1.6 Hz), 4.14 (1H, dd, J = 11.4, 1.6 Hz), 4.59 (1H, dd, J = 10.4, 2.0 Hz), 6.74 (2H, d, J = 8.8 Hz), 7.24 (2H, d, J = 8.8 Hz), 7.96 (1H, dd, J = 4.8, 3.2 Hz), 8.51 (1H, d, J = 4.8 Hz), 8.55 (1H, d, J = 3.2 Hz) ($CDCl_3$)	492

(continued)

Compound No.	1H-NMR δ:	[M+1]
135	1.18 (3H, m), 1.37 (2H, m), 1.62 (1H, m), 1.77 (2H, m), 2.05 (2H, m), 3.12 (1H, dd, J = 12.9, 11.4 Hz), 3.27 (2H, m), 3.55 (3H, m), 3.56 (3H, s), 3.95 (1H, td, J = 11.4, 1.8 Hz), 4.13 (1H, dd, J = 11.4, 1.8 Hz), 4.57 (1H, dd, J = 10.5, 2.1 Hz), 6.58 (2H, d, J = 8.4 Hz), 6.88 (1H, s), 7.18 (2H, d, J = 8.4 Hz), 7.96 (1H, dd, J = 4.5, 3.3 Hz), 8.51 (1H, d, J = 4.5 Hz), 8.55 (1H, d, J = 3.3 Hz) ($CDCl_3$)	464
136	1.44 (2H, m), 1.62 (2H, m), 1.71 (2H, m), 2.02 (2H, m), 3.12 (1H, dd, J = 12.8, 10.8 Hz), 3.28 (1H, td, J = 11.4, 2.0 Hz), 3.54 (2H, m), 3.56 (3H, s), 3.69 (1H, br s), 3.77 (1H, m), 3.96 (1H, td, J = 11.4, 2.0 Hz), 4.13 (1H, dd, J = 11.4, 2.0 Hz), 4.58 (1H, dd, J = 10.8, 2.4 Hz), 6.60 (2H, d, J = 8.4 Hz), 6.87 (1H, s), 7.19 (2H, d, J = 8.4 Hz), 7.96 (1H, dd, J = 4.8, 2.1 Hz), 8.51 (1H, d, J = 4.8 Hz), 8.55 (1H, d, J = 2.1 Hz) ($CDCl_3$)	450
137	1.26(6H, d, J=7.2Hz), 2.92(1H, m), 3.12(1H, dd, J=10.8, 12.9Hz), 3.31(1H, td, J=3.2, 12.0Hz), 3.51-3.66(2H, m), 3.57(3H, s), 3.97(1H, m), 4.14(1H, m), 4.71 (1H, dd, J=2.5, 10.1Hz), 6.88(1H, s), 7.26(2H, d, J=8.4Hz), 7.33(2H, d, J=8.4Hz), 7.95(1H, dd, J=5.1, 6.6Hz), 8.51 (1H, d, J=4.5Hz), 8.55(1H, d, J=3.0Hz)($CDCl_3$)	409
138	2.28(1H, br.s), 3.13(1H, dd, J=10.8, 12.9Hz), 3.30(1H, m), 3.56(3H, s), 3.50-3.72(4H, m), 3.97-4.22(4H, m), 4.59(1H, dd, J=1.9, 10.4Hz), 4.76(1H, m), 6.49(2H, d, J=8.6Hz), 6.88(1H, s), 7.24(2H, d, J=8.6Hz), 7.96(1H, dd, J=5.1, 6.6Hz), 8.50(1H, d, J=4.5Hz), 8.55(1H, d, J=3.0Hz)($CDCl_3$)	438
139	3.10(1H, dd, J=10.8, 12.9Hz), 3.31(1H, td, J=3.2, 12.0Hz), 3.51-3.62(2H, m), 3.57(3H, s), 3.96-4.17(6H, m), 4.65(1H, dd, J=2.5, 10.1Hz), 6.88(1H, s), 6.93(2H, d, J=8.4Hz), 7.33(2H, d, J=8.4Hz), 7.95(1H, dd, J=5.1, 6.6Hz), 8.51(1H, d, J=4.8Hz), 8.55(1H, d, J=3.0Hz)($CDCl_3$)	546
143	2.19(3H, s), 3.07(1H, dd, J=10.8, 12.9Hz), 3.29(1H, m), 3.52-3.65(2H, m), 3.57(3H, s), 3.98(1H, m), 4.16(1H, m), 4.70(1H, dd, J=1.9, 10.4Hz), 6.89(1H, s), 6.91 (1H, s), 7.36(2H, d, J=8.5Hz), 7.54(2H, d, J=8.5Hz), 7.94(1H, dd, J=5.1, 6.6Hz), 8.51 (1H, d, J=4.8Hz), 8.55(1H, d, J=3.0Hz)($CDCl_3$)	424
144	1.58-1.65(2H. m), 1.81-1.92(6H, m), 3.11 (1H, dd, J= 13.2, 10.8 Hz), 3.30(1H, m), 3.51-3.63(2H, m), 3.58(3H, s), 3.98(1H, m), 4.15(1H, m), 4.66(1H, dd, J= 10.5, 2.1 Hz), 4.77(1H, m), 6.90(2H, d, J= 8.1 Hz), 6.91 (1H, s), 7.31(2H, d, J= 8.1 Hz), 7.96(1H, dd, J= 6.6, 5.1 Hz), 8.52(1H, d, J= 4.8 Hz), 8.57(1H, d, J= 3.0 Hz) ($CDCl_3$)	451
145	1.33(6H, d, J= 6.0 Hz), 1.81-1.92(6H, m), 3.11(1H, m), 3.29(1H, m), 3.50-3.62(2H, m), 3.57(3H, s), 3.98(1H, m), 4.15(1H, m), 4.63(1H, m), 4.65(1H, m), 6.87(1H, s), 6.91 (2H, d, J= 8.4 Hz), 7.31(2H, d, J= 8.4 Hz), 7.95(1H, dd, J= 6.3, 5.1 Hz), 8.51 (1H, d, J= 5.1Hz), 8.55(1H, d, J= 3.0 Hz) ($CDCl_3$)	425
146	0.36(2H, m), 0.66(2H, m), 1.27(1H, m), 3.11(1H, dd, J= 13.2, 10.5 Hz), 3.29(1H, m), 3.57-3.61(2H, m), 3.58(3H, s), 3.82(2H, d, J= 6.9 Hz), 3.98(1H, m), 4.15(1H, m), 4.67(1H, dd, J= 10.5, 2.1 Hz), 6.89(1H, s), 6.93(2H, d, J= 8.7 Hz), 7.32(2H, d, J= 8.7 Hz), 7.95(1H, dd, J= 6.6, 5.1Hz), 8.52(1H, d, J= 5.1 Hz), 8.56(1H, d, J= 3.0 Hz) ($CDCl_3$)	437
147	3.11(1H, m), 3.29(1 H, m), 3.57-3.66(2H. m), 3.58(3H, s), 3.99(1H, m), 4.16(1H, m), 4.75(1H, dd, J= 10.5, 2.1 Hz), 6.89(1H, s), 7.25(2H, d, J= 8.7 Hz), 7.45(2H, d, J= 8.7 Hz), 7.92(1H, dd, J= 6.6, 5.1 Hz), 8.52(1H, d, J= 5.1 Hz), 8.56(1 H, d, J= 3.0 Hz) ($CDCl_3$)	451
148	1.25-1.65(4H, m), 1.80-1.97(6H, m), 3.11 (1H, dd, J= 13.2, 10.5 Hz), 3.29(1H, m), 3.51-3.63(2H, m), 3.57(3H, s), 3.98(1H, m), 4.14(1H, m), 4.25(1H, m), 4.65(1H, dd, J= 10.6, 2.1 Hz), 6.88(1H, s), 6.92(2H, d, J= 9.0 Hz), 7.31(2H, d, J= 9.0 Hz), 7.95(1H, dd, J= 6.6, 5.1Hz), 8.51 (1H, d, J= 5.1 Hz), 8.56(1 H, d, J= 3.0 Hz) ($CDCl_3$)	465

(continued)

Compound No.	1H-NMR δ:	[M+1]
149	1.69 (2H, dd, J = 11.2, 4.4 Hz), 1.88 (2H, qd, J = 11.4, 4.4 Hz), 2.81 (3H, s), 3.13 (1H, dd, J = 12.8, 10.8 Hz), 3.28 (1H, td, J =11.4, 2.8 Hz), 3.49 (3H, m), 3.56 (3H, s), 3.57 (2H, m), 3.82 (1H, m), 3.96 (1H, td, J = 11.4, 2.4 Hz), 4.07 (2H, dd, J = 11.2, 4.0 Hz), 4.15 (1H, dd, J = 11.4, 2.4 Hz), 4.61 (1H, dd, J = 10.4, 2.0 Hz), 6.82 (2H, d, J = 8.4 Hz), 6.87 (1H, s), 7.27 (2H, d, J = 8.4 Hz), 7.95 (1H, dd, J = 5.2, 3.2 Hz), 8.50 (1H, d, J = 5.2 Hz), 8.55 (1H, d, J = 3.2 Hz) ($CDCl_3$)	480
150	2.38(2H, t, J=7.3Hz), 3.13(1H, dd, J=10.8, 12.9Hz), 3.28(1H, m), 3.56(3H, s), 3.50-3.59(2H, m), 3.88(4H, t, J=7.3Hz), 3.96(1H, td, J=2.2, 11.6Hz), 4.14(1H, d, J=11.8Hz), 4.60(1H, dd, J=2.1, 10.4Hz), 6.45(2H, d, J=8.6Hz), 6.88(1H, s), 7.24(2H, d, J=8.6Hz), 7.96(1H, dd, J=5.1, 6.6Hz), 8.51 (1H, d, J=4.5Hz), 8.55(1H, d, J=3.0Hz)($CDCl_3$)	422
151	1.18(6H, t, J=6.9Hz), 2.89(1H, dd, J=10.8, 12.9Hz), 3.28(1H, m), 3.36(4H, q, J=6.9Hz), 3.57(3H, s), 3.50-3.60(2H, m), 3.73(3H, s), 3.98(1H, td, J=2.2, 11.6Hz), 4.14(1H, d, J=11.8Hz), 4.96(1H, dd, J=2.1, 10.4Hz), 6.19(1H, d, J=2.1Hz), 6.31 (1H, dd, J=2.4, 8.4Hz), 6.88(1H, s), 7.26(1H, d, J=1.8Hz), 8.02(1H, dd, J=5.1, 6.6Hz), 8.51(1H, d, J=4.5Hz), 8.55(1H, d, J=3.0Hz)($CDCl_3$)	468
155	0.88 (1H, m), 1.02 (4H, m), 1.40 (2H, m), 1.59 (1H, m), 1.71 (2H, m), 1.73 (3H, s), 1.81 (2H, m), 3.12 (1H, dd, J = 12.8,10.6 Hz), 3.33 (1H, td, J = 12.4, 4.4 Hz), 3.55 (1H, d, J = 12.4 Hz), 3.60 (3H, s), 3.68 (1H, d, J = 12.8, 1H), 4.01 (1H, td, J = 12.4, 2.4 Hz), 4.20 (1H, d, J = 12.4, 2.0 Hz), 4.60 (1H, m), 4.78 (1H, dd, J = 10.6, 2.0 Hz), 6.87 (1H, s), 7.13 (2H, d, J = 8.4 Hz), 7.45 (2H, d, J = 8.4 Hz), 7.93 (1H, dd, J = 4.8, 3.2 Hz), 8.52 (1H, d, J = 4.8 Hz), 8.56 (1H, d, J = 3.2 Hz) ($CDCl_3$)	506
156	1.13 (m, 1H), 1.16 (3H, t, J = 6.9 Hz), 1.37 (m, 4H), 1.70 (m, 1H), 1.84 (m, 4H), 3.16 (1H, dd, J = 12.9, 10.5 Hz), 3.28 (3H, m), 3.55 (3H, m), 3.56 (s, 3H), 3.96 (1H, t, J=11.4 Hz), 4.13 (1H, d, J = 11.4 Hz), 4.58 (1H, d, J = 8.1 Hz), 6.72 (2H, d, J = 9.0 Hz), 6.88 (1H, s), 7.23 (2H, d, J = 9.0 Hz), 7,97 (1H, dd, J = 5.1, 3.3 Hz), 8.51 (1H, d, J = 5.1 Hz), 8.55 (1H, d, J = 3.3 Hz) ($CDCl_3$)	492
157	2.34(6H, s), 2.72-2.76(2H, m), 3.11 (1H, dd, J= 12.6, 10.8 Hz), 3.29(1H, m), 3.51-3.61(2H, m), 3.57(3H, s), 3.94-4.18(4H, m), 4.66(1H, dd, J= 11.4, 2.1 Hz), 6.84(1H, s), 6.95(2H, d, J= 8.7 Hz), 7.32(2H, d, J= 8.7 Hz), 7.95(1H, m), 8.51(1H, d, J= 5.1 Hz), 8.55(1H, d, J= 3.0 Hz) ($CDCl_3$)	454
158	3.15(1H, dd, J=10.8, 12.9Hz), 3.29(1H, m), 3.52-3.65(2H, m), 3.61(3H, s), 3.76(2H, br.s), 3.98(1H, m), 4.16(1H, m), 4.62(1H, dd, J=1.9, 10.4Hz), 6.68(2H, d, J=8.7Hz), 6.88(1 H, s), 7.24(2H, d, J=8.7Hz), 7.96(1H, dd, J=5.4, 6.9Hz), 8.51 (1H, d, J=5.4Hz), 8.55(1H, d, J=3.3Hz)($CDCl_3$)	382
159	3.15(1H, dd, J=10.8, 12.9Hz), 3.29(1H, m), 3.52-3.65(2H, m), 3.61(3H, s), 3.99(1H, m), 4.16(1H, m), 4.71(1H, d, J=10.1Hz), 6.90-7.01(5H, m), 7.17-7.59(8H, m), 7.94(1H, dd, J=5.4, 6.9Hz), 8.33(2H, d, J=4.6Hz), 8.56(2H, m)($CDCl_3$)	536
160	3.15(1H, dd, J=10.8, 12.9Hz), 2.97(6H, s), 3.30(1H, m), 3.54(1H, m), 3.60(3H, s), 3.72(1H, m), 3.85(3H, s), 3.98(1H, m), 4.16(1H, m), 4.98(1H, dd, J=1.9, 10.4Hz), 6.24(1H, d, J=2.4Hz), 6.36(1H, dd, J=2.4, 8.3Hz), 6.68(1H, s), 7.34(1H, d, J=4.2Hz), 7.81 (2H, d, J=6.0Hz), 8.70(2H, d, J=6-0Hz)($CDCl_3$)	440
161	3.15(1H, dd, J=10.8, 12.9Hz), 3.29(1H, m), 3.52-3.65(2H, m), 3.61(3H, s), 3.99(1H, m), 4.16(1H, m), 4.69(1H, dd, J=1.9, 10.4Hz), 6.58(1H, br.s), 6.74-6.77(1H, m), 6.85(1H, d, J=8.4Hz), 6.89(1H, s), 7.38(4H, m), 7.49-7.51(1H, m), 7.96(1H, dd, J=5.4, 6.9Hz), 8.21(1H, d, J=6.0Hz), 8.52(1H, d, J=5.4Hz), 8.56(1H, d, J=3.3Hz)($CDCl_3$)	459

(continued)

Compound No.	1H-NMR δ:	[M+1]
162	3.14(1H, dd, J=10.8, 12.9Hz), 3.30(1H, m), 3.58-3.67(2H, m), 3.59(3H, s), 4.00(1H, m), 4.16(1H, m), 4.70(1H, dd, J=1.9, 10.44Hz), , 6.78(1H, s), 6.88(1H, s), 7.23(1H, s), 7.38(2H, d, J=8.3Hz), 7.55(2H, d, J=8.3Hz), 8.72(2H, m), 8.40(1H, d, J=2.7Hz), 8.52(2H, m), 8.56(1H, d, J=3.3Hz)($CDCl_3$)	459
163	3.12(1H, dd, J=10.8, 12.9Hz), 3.29(1H, m), 3.52-3.64(2H, m), 3.59(3H, s), 3.99(1H, m), 4.16(1H, m), 4.68(1H, dd, J=1.9, 10.4Hz), 5.81(1H, br.s), 6.88(1H, s), 7.10(2H, d, J=8.4Hz), 7.19(1H, dd, J=4.8, 8.4Hz), 7.33(2H, d, J=8.4Hz), 7.40(1H, m), 7.96(1H, dd, J=5.4, 6.9Hz), 8.21 (1H, d, J=6.0Hz), 8.40(1H, d, J=2.7Hz), 8.52(1H, d, J=5.4Hz), 8.56(1H, d, J=3.3Hz)($CDCl_3$)	459
197	1.16 (3H, t, J = 6.9 Hz), 1.13 (1H, m), 1.37 (4H, m), 1.70 (1H, m), 1.84 (4H, m), 3.16 (1H, dd, J = 12.9, 10.5 Hz), 3.28 (3H, m), 3.55 (m, 3H), 3.56 (3H, s), 3.96 (1H, t, J = 11.4 Hz), 4.13 (1H, d, J = 11.4 Hz), 4.58 (1H, d, J = 8.1 Hz), 6.72 (2H, d, J = 9.0 Hz), 6.88 (1H, s), 7.23 (2H, d, J = 9.0 Hz), 7.97 (1H, dd, J = 5.1, 3.3 Hz), 8.51 (1H, d, J = 5.1 Hz), 8.55 (1H, d, J = 3.3 Hz) ($CDCl_3$)	492
198	0.88 (1H, m), 1.14 (2H, m), 1.38 (2H, m), 1.57 (1H, m), 1.76 (2H, m), 1.93 (2H, m), 2.97 (3H, s), 3.11 (1H, dd, J = 12.8, 10.8 Hz), 3.28 (1H, td, J = 11.2, 2.2 Hz), 3.53 (1H, d, J = 11.2 Hz), 3.58 (3H, s), 3.68 (1H, d, J = 12.8 Hz), 3.99 (1H, td, J = 11.2, 2.2 Hz), 4.06 (1H, m), 4.19 (1H, dd, J = 11.2, 2.2 Hz), 4.77 (1H, dd, J = 10.8, 2.0 Hz), 6.88 (1H, s), 7.29 (2H, d, J = 8.4 Hz), 7.45 (2H, d, J = 8.4 Hz), 7.95 (1H, dd. J = 5.2, 3.2 Hz), 8.53 (1H, d, J = 5.2 Hz), 8.56 (1H, d, J = 3.2 Hz) ($CDCl_3$)	542
199	0.97 (1H, m), 1.21 (2H, m), 1.41 (2H, m), 1.61 (1H, m), 1.89 (2H, m), 1.97(2H,m), 2.99 (1H,dd, J=12.4, 10.4Hz), 3.26(1H,td, J=11.2,2.4 Hz), 3.50 (1H, d, J = 11.2 Hz), 3.56 (1H, d, J = 11.2 Hz), 3.97 (1H, td, J = 11.2, 2.4 Hz), 4.15 (1H, d, J = 11.2 Hz), 4.65 (1H, m), 4.66 (1H, dd, J = 10.4, 2.0 Hz), 6.86 (1H, s), 7.05 (2H, d, J = 8.4 Hz), 7.14 (1H, t, J = 8.4 Hz), 7.24 (2H, t, J = 8.4 Hz), 7.90 (1H, dd, J = 5.2, 3.2 Hz), 8.52 (1H, d, J = 5.2 Hz), 8.56 (1H, d, J = 3.2 Hz) ($CDCl_3$)	568
200	0.50 (2H, m), 0.90 (1H, m), 0.98 (2H, m), 1.04 (2H, m), 1.39 (2H, m), 1.58 (1H, m), 1.73 (2H, m), 1.82 (2H, m), 3.13 (1H, dd, J =12.8, 10.4 Hz), 3.33 (1H, td, J = 13.2 Hz), 3.55 (1H, d, J = 13.2 Hz), 3.60 (3H, s), 3.68 (1H, d, J =12.8 Hz), 4.00 (1H, td, J = 13.2, 2.4 Hz), 4.20 (1H, dd, J =13.2, 2.4 Hz), 4.60 (1H, m), 4.78 (1H, dd, J = 10.4, 2.0 Hz), 6.87 (1H, s), 7.22 (2H ,d, J = 8.0 Hz), 7.46 (2H, d, J = 8.0 Hz), 7.94 (1H, dd, J = 4.8. 2.8 Hz), 8.53 (1H, d, J = 4.8 Hz), 8.57 (1H, d, J = 2.8 Hz) ($CDCl_3$)	532
201	0.80 (1H, m), 1.02 (2H, m), 1.32 (2H, m), 1.49 (1H, m), 1.70 (2H, m), 1.80 (2H, m), 3.11 (1H, dd, J = 12.5, 11.0 Hz), 3.30 (1H, t, J =12.6 Hz), 3.53 (1H, d, J =12.6 Hz), 3.59 (3H, s), 3.67 (1H, d, J = 12.5 Hz), 3.99 (1H, t, J = 12.6 Hz), 4.16 (2H, m), 4.74 (1H, d, J = 11.0 Hz), 6.88 (1H, s), 7.06 (2H, d, J = 8.2 Hz), 7.37 (2H, d, J = 8.2 Hz), 7.47 (2H, t, J = 7.6 Hz), 7.56 (1H, t, J = 7.6 Hz), 7.76 (2H, d, J = 7.6 Hz), 7.96 (1H, dd, J = 4.9, 2.8 Hz), 8.54 (1H, d, J =4.9 Hz), 8.56 (1H, d, J = 2.8 Hz) ($CDCl_3$)	604
202	1.13 (1H, m), 1.39 (4H, m), 1.70 (1H, m), 1.82 (4H, m), 3.13 (1H, dd, J = 12.8, 10.4 Hz), 3.28 (1H, m), 3.89 (1H, t, J = 4.8 Hz), 3.52 (2H, m), 3.56 (3H, s), 3.59 (1H, m), 3.69 (1H, q, J = 4.8 Hz), 3.96 (1H, td, J = 11.4, 2.0 Hz), 4.15 (1H, d, J = 11.4 Hz), 4.61 (1H, dd, J = 10.4, 2.0 Hz), 6.86 (2H, d, J = 8.8 Hz), 6.87 (1H, s), 7.24 (2H, d, J = 8.8 Hz), 7.95 (1H, dd, J = 4.8, 2.4 Hz), 8.51 (1H, d, J = 4.8 Hz), 8.55 (1H, d, J = 2.4 Hz) ($CDCl_3$)	508
204	3.03-3.33(4H, m), 3.59(3H, s), 3.67-3.73(2H, m), 3.88-3.95(3H, m), 4.03-4.08(1H, m), 4.44(2H, br), 4.70(1H, dd, J=1.2Hz, 10.2Hz), 6.61-6.70(2H, m), 7.16-7.25(2H, m), 7.41 (2H, d, J=7.2Hz), 7.89-8.00(2H, m), 8.58-8.61(2H, m), 8.72-8.77(2H, m)(DMSO-d6).	484 (M+1)

(continued)

Compound No.	1H-NMR δ:	[M+1]
205	0.86-1.24(6H, m), 1.52-1.63(7H, m), 2.32-2.36(1H, m), 2.64-2.70(1H, m), 2.95-3.16(3H, m), 3.46(3H, s), 3.64-3.73(2H, m), 3.84-3.88(1H, m), 4.00-4.03(1H, m), 4.68(1H, dd, J=1.2Hz, 10.2Hz), 6.59(1H, s), 7.10(2H, d, J=7.2Hz), 7.34(2H, d, J=7.2Hz), 7.98(1H, dd, J=1.2Hz, 4.2Hz), 8.57(1H, d, J=4.2Hz), 8.70(1H, d, J=1.2Hz)(DMSO-d6).	504 (M+1)
206		
209	1.25-2.04 (10H, m), 2.23 (1H, m), 3.07 (1H, dd, J = 10.8, 13.2 Hz), 3.27 (1H, td, J = 3.0, 12.0 Hz), 3.50-3.61 (2H, m), 3.57 (3H, s), 3.98 (1H, td, J = 2.1, 11.4 Hz), 4.14 (1H, dd, J = 1.2, 11.1 Hz), 4.70 (1H, dd, J = 2.1, 10.5 Hz), 6.88 (1H, s), 7.20 (1H, br.s), 7.37 (2H, d, J = 8.4 Hz), 7.56 (2H, d, J = 8.4 Hz), 7.93 (1H, dd, J= 5.1, 6.6 Hz), 8.51 (1H, d, J = 5.4 Hz). 8.55 (1H, d, J = 3.3 Hz) ($CDCl_3$)	492
210	2.42 (3H, s), 3.05 (1H, dd, J = 10.5, 12.9 Hz), 3.29 (1H, td, J = 3.3, 12.3 Hz), 3.51-3.63 (2H, m), 3.62 (3H, s), 3.98 (1H, td, J = 2.3, 11.6 Hz), 4.15 (1H, dd, J = 2.1, 13.2 Hz), 4.66 (1H, dd, J = 2.1, 10.5 Hz), 6.88 (1H, s), 7.07 (1H, dd, J = 2.1, 8.4 Hz), 7.29 (1H, d, J = 1.5 Hz), 7.55 (1H, d, J = 8.1 Hz), 7.93 (1H, dd, J = 5.1, 6.6 Hz), 8.51 (1H, d, J = 5.1 Hz), 8.56 (1H, d, J = 3.3 Hz) ($CDCl_3$)	460
211	3.10 (1H, dd, J = 10.8, 13.2 Hz), 3.29 (1H, td, J = 3.0, 12.0 Hz), 3.52-3.65 (2H, m), 3.58 (3H, s), 4.00 (1H, td, J =2.1, 11.4 Hz), 4.16 (1H, dd, J = 1.2, 11.1 Hz), 4.73 (1H, dd, J = 2.1, 10.5 Hz), 6.89 (1H, s), 7.43 (2H, d, J = 8.4 Hz), 7.50-7.57 (2H, m), 7.69 (2H, d, J = 8.4 Hz), 7.85-7.96 (5H, m), 8.52 (1H, d, J = 5.4 Hz), 8.56 (1H, d, J = 3.3 Hz) ($CDCl_3$)	486
212	3.14 (1H, dd, J = 10.8, 13.2 Hz), 3.35 (1H, td, J = 3.0, 12.0 Hz), 3.48 (3H, s), 3.52-3.69 (2H, m), 3.59 (3H, s), 4.00 (1H, td, J = 2.1, 11.4 Hz), 4.17 (1H, dd, J = 1.2, 11.1 Hz), 4.72 (1H, dd, J = 2.1, 10.5 Hz), 6.58 (2H, m), 6.87 (1H, s), 7.26-7.29 (1H, m), 7.31 (2H, d, J = 8.3 Hz), 7.43 (2H, d, J =8.3 Hz), 7.06 (1 H, m), 8.24 (1H, d, J = 3.6 Hz), 8.52 (1H, d, J = 5.0 Hz), 8.55 (1H, d, J = 3.0 Hz) ($CDCl_3$)	473
213	0.77-0.88 (2H, m), 1.03-1.11 (2H, m), 1.49 (1H, m), 3.07 (1H, dd, J = 10.6, 13.0 Hz), 3.27 (1H, d, J = 13.0 Hz), 3.50-3.62 (2H, m), 3.57 (3H, s), 3.97 (1H, t, J = 11.7 Hz), 4.16 (1H, d, J = 11.1 Hz), 4.69 (1H, d, J = 10.2 Hz), 6.88 (1H, s), 7.35 (2H, d, J = 8.4 Hz), 7.46 (1H, br.s), 7.55 (2H, d, J = 8.1 Hz), 7.93 (1H, m), 8.50 (1H, d, J = 5.1 Hz), 8.54 (1H, d, J = 2.7 Hz) ($CDCl_3$)	450
214	1.05 (6H, d, J = 6.9 Hz), 1.74 (3H, s), 3.12 (1H, dd, J = 10.5, 12.9 Hz), 3.34 (1H, td, J = 2.9, 13.0 Hz), 3.53-3.70 (2H, m), 3.60 (3H, s), 4.02 (1H, dd, J = 9.3, 11.7 Hz), 4.20 (1H, d, J = 11.9 Hz), 4.79 (1H, d, J = 8.1 Hz), 5.07 (1H, q, J = 6.9 Hz), 6.72 (1H, s), 7.15 (2H, d, J = 8.4 Hz), 7.48 (2H, d, J = 8.4 Hz), 7.94 (1H, dd, J = 5.1, 6.6 Hz), 8.53 (1H, d, J = 4.8 Hz), 8.57 (1H, d, J = 3.0 Hz) ($CDCl_3$)	466
215	1.32 (9H, s), 3.07 (1H, dd, J = 9.3, 11.7 Hz), 3.27 (1H, td, J = 2.9, 13.0 Hz), 3.50-3.62 (2H, m), 3.57 (3H, s), 4.00 (1H, td, J = 2.4, 12.4 Hz), 4.17 (1H, dd, J = 2.4, 12.0 Hz), 4.69 (1H, dd, J = 2.4, 10.8 Hz), 6.88 (1H, s), 7.33 (2H, d, J = 8.4 Hz), 7.55 (2H, d, J = 8.4 Hz), 7.93 (2H, d, J = 6.0 Hz), 8.50 (1H, d, J = 5.4 Hz), 8.55 (1H, d, J = 3.3 Hz) ($CDCl_3$)	466
216	1.62-1.68 (5H, m), 1.89 (6H, m), 2.04-2.11 (3H, m), 3.12 (1H, dd, J = 10.8, 12.9 Hz), 3.28 (1H, m), 3.30 (1H, m), 3.54 (3H, s), 3.50-3.73 (2H, m), 3.96 (1H, m), 4.12 (1H, dd, J = 9.9, 11.7 Hz), 4.59 (1H, dd, J = 8.7, 10.5 Hz), 6.78 (2H, d, J = 8.4 Hz), 6.87 (1H, s), 7.17 (2H, d, J = 8.4 Hz), 7.96 (1H, dd, J = 5.1, 6.3 Hz), 8.51 (1H, d, J = 5.1 Hz), 8.55 (1H, d, J = 3.3 Hz) ($CDCl_3$)	516
217	1.35-1.67 (11H, m), 2.07 (3H, m), 2.79 (3H, s), 3.14 (1H, dd, J = 10.5, 12.9 Hz), 3.29 (1H, td, J = 3.0, 12.0 Hz), 3.54-3.69 (1H, td, J = 3.0, 12.0 Hz), 3.54-3.69 (2H, m), 3.58 (3H, s), 3.99 (1H, td, J = 2.4, 11.8 Hz), 4.17 (1H, dd, J = 2.4, 11.7 Hz), 4.70 (1H, dd, J = 2.1, 10.5 Hz), 6.87 (1H, s), 7.15 (2H, d, J = 8.4 Hz), 7.30 (2H, d, J = 8.4 Hz), 7.96 (1H, dd, J = 5.1, 6.3 Hz), 8.52 (1H, d, J = 4.8 Hz), 8.56 (1H, d, J = 3.0 Hz) ($CDCl_3$)	530

(continued)

Compound No.	1H-NMR δ:	[M+1]
218	1.57-2.01 (13H, m), 3.12 (1H, dd, J = 10.6, 12.7 Hz), 3.30 (1H, td, J = 3.3, 12.0 Hz), 3.51-3.64 (4H, m), 3.57 (3H, s), 3.96 (1H, td, J = 2.1, 11.8 Hz), 4.12 (1H, dd, J = 2.1, 4.4 Hz), 4.58 (1H, dd, J = 8.4, 10.8 Hz), 6.60 (2H, d, J = 8.4 Hz), 6.87 (1H, s), 7.17 (2H, d, J = 8.4 Hz), 7.96 (1H, dd, J = 4.8, 6.6 Hz), 8.51 (1H, d, J = 4.8 Hz), 8.55 (1H, d, J = 3.0 Hz) ($CDCl_3$)	516
219	1.43 (2H, d, J = 11.4 Hz), 1.71-1.65 (8H, m), 2.04-2.10 (4H, m), 2.77 (3H, s), 3.14-3.20 (2H, m), 3.30 (1H, td, J = 3.3, 12.0 Hz), 3.51-3.64 (2H, m), 3.57 (3H, s), 3.96 (1H, td, J = 2.1, 11.8 Hz), 4.12 (1H, dd, J = 2.1, 4.4 Hz), 4.65 (1H, dd, J = 8.4, 10.8 Hz), 6.87 (1H, s), 7.06 (2H, d, J = 8.4 Hz), 7.29 (2H, d, J = 8.4 Hz), 7.96 (1H, dd, J = 4.8, 6.6 Hz), 8.52 (1H, d, J = 4.8 Hz), 8.55 (1H, d, J = 3.0 Hz) ($CDCl_3$)	530
220	1.90 (1H, m), 2.27 (1H, m), 3.14 (1H, dd, J = 10.5, 12.9 Hz), 3.30 (1H, td, J = 3.0, 12.0 Hz), 3.55-3.58 (2H, m), 3.55 (3H, s), 3.70-4.12 (7H, m), 4.59 (1H, dd, J = 2.1, 10.5 Hz), 6.21 (2H, J = 8.7 Hz), 6.87 (1H, s), 7.21 (2H, d, J = 8.7 Hz), 7.95 (1H, dd, J = 5.1, 6.6 Hz), 8.56 (1H, d, J = 5.1 Hz), 8.54 (1H, d, J = 3.3 Hz) ($CDCl_3$)	452
221	1.92-1.97 (1H, m), 2.22-2.24 (1H, m), 2.87 (3H, s), 3.13 (1H, dd, J = 10.8, 12.9 Hz), 3.29 (1H, td, J = 3.0, 12.0 Hz), 3.50-3.61 (2H, m), 3.59 (3H, s), 3.75-4.49 (6H, m), 4.50 (1H, m), 4.62 (1H, dd, J = 10.5 Hz), 6.83 (2H, J = 8.7 Hz), 6.87 (1H, s), 7.28 (2H, d, J = 8.7 Hz), 7.75 (1H, d, J = 6.3 Hz), 8.50 (1H, d, J = 5.1 Hz), 8.55 (1H, d, J = 3.3 Hz) ($CDCl_3$)	466
222	1.79-1.83(4H, m), 2.60-2.63(4H, m), 2.90(2H, dd, J=6.0, 6.0 Hz), 3.10(1H, dd, J=12.9, 10.8 Hz), 3.29(1H, m), 3.50-3.62(2H, m), 3.57(3H, s), 3.98(1H, m), 4.10-4.14(3H, m), 4.66(1H, dd, J=10.5, 2.1 Hz), 6.88(1H, s), 6.94(1H, d, J=8.7 Hz), 7.32(1H, d, J=8.7 Hz), 7.94(1H, dd, J=6.6, 5.4 Hz), 8.51 (1H, d, J=5.1 Hz), 8.55(1H, d, J=3.0 Hz) ($CDCl_3$)	480 (M+1)
223	1.88 (3H, s), 3.11 (1H, dd, J = 10.6, 12.9 Hz), 3.26 (3H, s), 3.32 (1H, td, J = 10.5, 12.9 Hz), 3.48-3.60 (2H, m), 3.59 (3H, s), 4.01 (1H, td, J = 2.7, 11.4 Hz), 4.20 (1H, dd, J = 9.6, 11.5 Hz), 4.77 (1H, dd, J = 8.7, 10.1 Hz), 6.87 (1H, s), 7.20 (2H, d, J = 8.4 Hz), 7.47 (2H, d, J = 8.2 Hz), 7.93 (1H, dd, J = 5.1, 6.4 Hz), 8.51 (1H, d, J = 5.1 Hz), 8.55 (1H, d, J = 3.0 Hz) ($CDCl_3$)	438
224	2.86-3.20(4H, m), 3.20-4.06(16H, m), 4.42-4.46(2H, m), 4.70(1H, dd, J=1.2Hz, 10.2Hz), 6.60(1H, s), 7.02(2H, d, J=7.2Hz), 7.39(2H, d, J=7.2Hz), 7.98(1H, dd, J=1.2Hz, 4.2Hz), 8.57(1H, d, J=4.2Hz), 8.71 (1H, d, J=1.2Hz), 11.31 (1H, br)(DMSO-d6).	496 (M+1)
225	2.92-3.00(1H, m), 3.06-3.13(1H, m), 3.45(3H, s), 3.62-3.67(2H, m), 5.84-5.88(1H, m), 3.99-4.03(1H, m), 4.60(1H, dd, J=1.2Hz, 10.2Hz), 6.59(1H, s), 6.72(2H, d, J=7.2Hz), 7.22(2H, d, J=7.2Hz), 7.97(1H, dd, J=1.2Hz. 4.2Hz), 8.56(1H, d, J=4.2Hz), 8.69(1H, d, J=1.2Hz), 9.40(1H, brs)(DMSO-d6).	383 (M+1)
226	1.27(6H, t, J=7.2Hz), 2.88-3.22(6H, m), 3.46-3.49(5H, m), 3.66-3.70(2H, m), 3.88-3.96(1H, m), 4.02-4.07(1 H, m), 4.40-4.71 (4H, m), 6.61 (1H, s), 6.70(2H, d, J=7.2Hz), 7.40(2H, d, J=7.2Hz), 8.03(1H, dd, J=1.2Hz, 4.2Hz), 8.60(1H, d, J=4.2Hz), 8.78(1H, d, J=1.2Hz), 10.91(1H, br)(DMSO-d6).	482 (M+1)
227	1.36-1.41 (1H, m), 1.68-1.91 (5H, m), 2.95-3.18(4H, m), 3.47-3.50(7H, m), 3.67-3.71 (2H, m), 3.88-4.07(2H, m), 4.46-4.50(2H, m), 4.70(1H, dd, J=1.2Hz, 10.2Hz), 6.63(1H, s), 6.88(1H, br), 7.01(2H, d, J=7.2Hz), 7.43(2H, d, J=7.2Hz), 8.12(1H, dd, J=1.2Hz, 4.2Hz), 8.65(1H, d, J=4.2Hz), 8.86(1H, d, J=1.2Hz), 11.25(1H, br)(DMSO-d6).	494 (M+1)
228	2.94-3.20(2H, m), 3.41-4.06(17H, m), 4.44-4.47(2H, m), 4.70(1H, dd, J=1.2Hz, 10.2Hz), 6.01(2H, br), 8.61 (1H, s), 7.03(2H, d, J=7.2Hz), 7.41 (2H, d, J=7.2Hz), 8.06(1H, dd, J=1.2Hz, 4.2Hz), 8.62(1H, d, J=4.2Hz), 8.80(1H, d, J=4.2Hz), 10.14(1H, br)(DMSO-d6).	495 (M+1)

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Compound No.	1H-NMR δ:	[M+1]
229	2.85-3.17(5H, m), 3.48(3H, s), 3.60-4.03(14H, m), 4.46-4.48(2H, m), 4.70(1H, dd, J=1.2Hz, 10.2Hz), 5.54(2H, br), 6.63(1H, s), 7.00(2H, d, J=7.2Hz), 7.40(2H, d, J=7.2Hz), 8.10(1H, dd, J=1.2Hz, 4.2Hz), 8.64(1H, d, J=4.2Hz), 8.85(1H, d, J=1.2Hz), 12.28(1H, br)(DMSO-d6).	509
230	2.06(3H, s), 2.98-3.20(4H, m), 3.45(3H, s), 3.50-4.03(12H, m), 4.46-4.50(2H, m), 4.70(1H, dd, J=1.2Hz, 10.2Hz), 5.43(1H, br), 6.30(1H, s), 7.01(2H, d, J=7.2Hz), 7.40(2H, d, J=7.2Hz), 8.10(1H, dd, J=1.2Hz, 4.2Hz), 8.64(1H, d, J=4.2Hz), 8.84(1H, d, J=1.2Hz), 11.92(1H, br)(DMSO-d6).	537 (M+1)
231	2.94-2.98(1H, m), 3.16-4.07(18H, m), 4.41-4.50(2H, m), 4.70(1H, dd, J=1.2Hz, 10.2Hz), 6.21(1H, br), 6.63(1H, s), 7.02(2H, d, J=7.2Hz), 7.38(2H, d, J=7.2Hz), 7.46-7.50(5H, m), 8.10(1H, dd, J=1.2Hz, 4.2Hz), 8.64(1H, d, J=4.2Hz), 8.85(1H, d, J=1.2Hz), 12.07(1H, br)(DMSO-d6).	599 (M+1)
232	2.16-2.21 (2H, m), 2.78(6H, m), 2.96-3.02(1H, m), 3.18-3.23(3H, m), 3.47(3H, s), 3.66-3.70(2H, m), 3.81-3.85(1H, m), 4.03-4.11(3H, m), 4.69(1H, dd, J=1.2Hz, 10.2Hz), 6.63(1H, s), 6.97(2H, d, J=7.2Hz), 7.36-7.45(3H, m), 8.14(1H, dd, J=1.2Hz, 4.2Hz), 8.66(1H, d, J=4.2Hz), 8.89(1H, d, J=1.2Hz)(DMSO-d_6).	468 (M+1)
233	1.25(6H, t, J=7.3Hz), 2.16-2.18(2H, m), 2.86-3.20(8H, m), 3.47(3H, s), 3.66-3.70(2H, m), 3.80-4.11(4H, m), 4.68(1H, dd, J=1.2Hz, 10.2Hz), 6.40(1H, br), 6.23(1H, s), 6.96(2H, d, J=7.2Hz), 7.38(2H, d, J=7.2Hz), 8.08(1H, dd, J=1.2Hz, 4.2Hz), 8.63(1H, d, J=4.2Hz), 8.82(1H, d, J=1.2Hz), 10.98(1H, br)(DMSO-d6).	496 (M+1)
234	2.24-2.30(2H, m), 3.12-3.27(6H, m), 3.43-3.47(5H, m), 3.66-3.70(2H, m), 3.87-4.10(8H, m), 4.69(1H, dd, J=1.2Hz, 10.2Hz), 6.21(1H, br), 6.63(1H, s), 6.96(2H, d, J=7.2Hz), 7.37(2H, d, J=7.2Hz), 8.13(1H, dd, J=1.2Hz, 4.2Hz), 8.65(1H, d, J=4.2Hz), 8.87(1H, d, J=1.2Hz), 11.77(1H, br)(DMSO-d6).	510 (M+1)
235	1.90 (1H, m), 2.60 (1H, m), 2.90-3.01 (2H, m), 3.14 (1H, dd, J = 10.8, 12.9 Hz), 3.29 (1H, td, J = 3.2, 12.3 Hz), 3.51-3.62 (2H, m), 3.57 (3H, s), 4.00 (2H, td, J = 2.1, 11.8 Hz), 4.14 (1H, dd, J = 2.1, 10.5 Hz), 4.62 (1H, dd, J = 2.1, 10.5 Hz), 5.00 (1H. m), 6.70 (2H, d, J = 8.4 Hz), 6.88 (1H, s), 7.18-7.37 (6H, m), 7.96 (1H, dd, J = 5.1, 6.4 Hz), 8.51 (1H. d, J = 5.1 Hz), 8.55 (1H, d, J = 3.0 Hz) ($CDCl_3$)	498
236	1.66-1.70(2H, m), 1.93-1.97(2H, m), 2.28-2.38(5H, m), 2.72-2.76(2H, m), 2.93-3.00(1H, m), 3.15-3.20(1H, m), 3.46(3H, s), 3.64-3.68(2H, m), 3.86-4.05(2H, m), 4.38-4.42(1H, m), 4.66(1H, dd, J=1.2Hz, 10.2Hz), 6.58(1H, s), 6.95(2H, d, J=7.2Hz), 7.33(2H, d, J=7.2Hz), 7.97(1H, dd, J=1.2Hz, 4.2Hz), 8.56(1H, d, J=4.2Hz), 8.69(1H, d, J=1.2Hz)(DMSO-d6).	480 (M+1)
237	1.60-1.64(2H, m), 1.97-2.00(2H, m), 2.94-3.00(1H, m), 3.14-3.17(1H, m), 3.25-3.50(6H, m), 3.64-3.68(2H, m), 3.85-4.10(3H, m). 4.65-4.68(2H, m), 6.59(1H, s), 6.98(2H, d, J=7.2Hz), 7.33-7.46(7H, m), 7.98(1H, dd, J=1.2Hz, 4.2Hz), 8.56(1H, d, J=4.2Hz), 8.70(1H, d, J=1.2Hz)(DMSO-d6).	570 (M+1)
238	1.46-1.62(2H, m), 1.92-2.02(2H, m), 2.02(3H, s), 2.94-3.00(1H, m), 3.15-3.23(3H, m), 3.46(3H, s), 3.65-3.69(3H, m), 3.83-3.87(2H, m), 4.02-4.06(1H, m)4.60-4.68(2H, m), 6.59(1H, s), 6.99(2H, d, J=7.2Hz), 7.35(2H, d, J=7.2Hz), 7.97(1H, dd, J=1.2Hz, 4.2Hz), 8.56(1H, d, J=4.2Hz), 8.69(1H, d, J=1.2Hz)(DMSO-d6).	508 (M+1)
239	2.04-2.26(2H, m), 2.13(3H, s), 2.94(3H, s), 3.13-3.60(7H, m), 3.56(3H, s), 3.97-4.16(2H, m), 4.61-4.64(1H, m), 5.43(1H, m), 6.59(2H, m), 6.87(1H, s), 7.28(2H, m), 7.95(1H, m), 8.51 (1H. d, J=4.5 Hz), 8.55(1H, d, J=3.3 Hz) ($CDCl_3$)	507 (M+1)

(continued)

Compound No.	1H-NMR δ:	[M+1]
240	2.66 (4H, t, J = 4.5 Hz), 3.08 (1H, dd, J = 10.6, 13.0 Hz), 3.12 (2H, s), 3.30 (1H, t, J = 12.3 Hz), 3.51-3.66 (2H, m), 3.57 (3H, s), 3.78 (4H, t, J = 4.8 Hz), 3.99 (1H, td, J =2.1, 11.7 Hz), 4.15 (1H, dd, J = 9.0 Hz), 4.71 (1H, d, J = 10.2Hz), 6.89 (1H, s), 7.39 (2H, d, J = 8.4 Hz), 7.61 (2H, d, J = 8.4 Hz), 7.94 (1H, dd, J = 5.1, 6.6 Hz), 8.51 (1H, d, J = 4.8 Hz), 8.55 (1H. d, J = 5.1 Hz), 9.11 (1H, s) ($CDCl_3$)	509
241	3.06 (1H. dd, J = 10.8, 13.2 Hz), 3.29 (1H, td, J = 3.0, 12.0 Hz), 3.53 (1H, d, J = 12.6 Hz), 3.57 (3H, s), 3.64 (1H, d, J = 13.2 Hz), 3.99 (1H, m), 4.17 (1H, dd, J = 2.1,12.1 Hz), 4.66 (2H, d, J = 5.7 Hz), 4.79 (1H, dd, J = 2.1,10.5 Hz), 6.41 (1H, br.t), 7.69 (1H, s), 7.31-7.38 (5H, m), 7.48 (2H, d, J = 8.1 Hz), 7.84 (2H, d, J = 8.1 Hz), 7.91 (1H, dd, J = 5.1, 6.6 Hz), 8.50 (1H, d, J = 5.1 Hz), 8.55 (1H, d, J = 3.3 Hz) ($CDCl_3$)	500
242	2.33 (3H, s), 2.51-2.67 (8H, s), 3.08 (1H, dd, J = 10.2, 12.9 Hz), 3.15 (2H, s), 3.28 (1H, m), 3.47-3.63 (2H, m), 3.57 (3H, s), 3.98 (1H, td, J = 2.1,11.8 Hz), 4.15 (1H,dd,J= 2.1, 10.5 Hz), 4.71 (1H,dd,J=8.4, 10.5 Hz), 6.88 (1H, s), 7.38 (2H, d, J = 8.4 Hz), 7.61 (2H, d, J = 8.4 Hz), 7.93 (1H, dd, J = 4.8, 6.3 Hz), 8.50 (1H, d, J = 4.8 Hz), 8.55 (1H, d, J = 3.0 Hz), 9.17 (1H, s) ($CDCl_3$)	522
243	2.80 (4H, t, J = 4.5 Hz), 3.08 (1H, dd, J = 10.2, 12.9 Hz), 3.22 (2H, s), 3.27 (4H, t, J = 4.5 Hz), 3.30 (1H, m), 3.50-3.63 (2H, m), 3.57 (3H, s), 3.62 (1H, td, J = 2.1, 11.8 Hz), 4.15 (1H, dd, J = 8.4, 10.5 Hz), 4.71 (1H, dd, J = 8.4, 10.5 Hz), 6.88 (1H, s), 6.89-6.97 (3H, m), 7.26-7.29 (2H, m), 7.39 (2H, d, J = 8.4 Hz), 7.60 (2H, d, J = 8.4 Hz), 7.93 (1H, dd, J = 4.8, 6.3 Hz), 8.50 (1H, d, J = 5.4 Hz), 8.55 (1H, d, J = 3.0 Hz), 9.19 (1H, br.s) ($CDCl_3$)	584
244	1.86-2.04(6H, m), 2.93-3.19(8H, m), 346(3H, s), 3.64-3.68(2H, m), 3.87-3.90(1H, m), 4.03-4.07(3H, m), 4.67(1H, dd, J=1.2Hz, 10.2Hz), 6.60(1H, s), 6.94(2H, d, J=7.2Hz), 7.36(2H, d, J=7.2Hz), 7.97(1H, dd, J=1.2Hz, 4.2Hz), 8.56(1H, d, J=4.2Hz), 8.70(1H, d, J=1.2Hz)(DMSO-d6).	494 (M+1)
245	1.72-1.86(6H, m), 2.14-220(2H, m), 2.88-3.00(3H, m), 3.10-3.17(3H, m), 3.30-3.34(2H, m), 3.46(3H, s), 3.64-3.69(2H, m), 3.83-3.90(1H. m), 4.03-4.08(3H, m), 4.68(1H, dd, J=1.2Hz, 10.2Hz), 6.60(1H, s), 6.95(2H, d, J=7.2Hz), 7.36(2H, d, J=7.2Hz), 7.97(1H, dd, J=1.2Hz, 4.2Hz), 8.56(1H, d, J=4.2Hz), 8.70(1H, d, J=1.2Hz)(DMSO-d6).	508 (M+1)
246	1.83-1.89(2H, m), 2.16(3H, s), 2.35-2.43(9Hm), 2.93-3.00(1H, m), 3.11-3.17(1H, m), 3.31-3.33(1H, m), 3.46(3H, s), 3.64-3.68(2H, m), 3.83-4.05(4H, m), 4.66(1H, dd, J=1.2Hz, 10.2Hz), 6.59(1H, s), 6.92(2H, d, J=7.2Hz), 7.33(2H, d, J=7.2Hz), 7.98(l H, dd, J=1.2Hz, 4.2Hz), 8.56(1H, d, J=4.2Hz), 8.69(1H, d, J=1.2Hz)(DMSO-d6).	523 (M+1)
280	1.19-1.47 (5H, m), 1.56-1.79 (3H, m), 2.03-2.06 (2H, m), 3.06 (1H, dd, J=12.9Hz, 10.5Hz), 3.29 (1H, m), 3.51-3.56 (1H, m), 3.58 (3H, s), 3.62-3.67 (1H, m), 3.96-4.01 (2H, m), 4.18-4.21 (1H, m), 4.79 (1H, d, J=8.7Hz), 5.94 (1H, d, J=7.8Hz), 6.78 (1H, s), 7.47 (2H, d, J=8.1Hz), 7.79 (2H, d, J=8.4Hz), 7.92 (1H, dd, J=6.6Hz, 6.6Hz), 8.51 (1H, d, J=4.8Hz), 8.57 (1H, d, J=3.0Hz). ($CDCl_3$)	492
283	3.06 (1H, dd, J=12.9Hz, 10.5Hz), 3.29 (1H, m), 3.51-3.56 (1H, m), 3.58 (3H, s), 3.63-3.68 (3H, m), 3.83-3.88 (2H, m), 4.01 (1H, m), 4.17-4.22 (1H, m), 4.80 (1H, dd, J=10.8Hz, 2.4Hz), 6.59 (1H, m), 6.89 (1H, s), 7.48 (2H, d, J=8.4Hz), 7.83(2H, d, J=8.4Hz), 7.92 (1H, dd, J=6.6Hz, 5.4Hz), 8.51 (1H, d, J=5.1Hz), 8.56 (1H, d, J=3.0Hz) ($CDCl_3$)	454
284	2.99-3.11 (7H, m), 3.28 (1H, m), 3.51-3.56 (1H, m), 3.58 (3H, s), 3.60-3.66 (1H, m), 4.00 (1H, m), 4.17-4.10 (1H, m), 4.77 (1H, d, J=10.5Hz, 2.4Hz), 6.89 (1H, s), 7.45 (4H, s), 7.93 (1H, dd, J=6.6Hz, 5.1 Hz), 8.52 (1H, d, J=5.1Hz), 8.56 (1H, d, J=3.0Hz). ($CDCl_3$)	438

(continued)

Compound No.	1H-NMR δ:	[M+1]
285	2.03 (3H, s), 3.08 (1H, t, J=11.9Hz), 3.28 (1H, m), 3.58 (3H, s), 3.51-3.64 (2H, m), 3.99 (1H, t, J=11.7Hz), 4.16 (1H, d, J=11.7Hz), 4.74 (1H, dd, J=10.8Hz, 2.1Hz), 6.68 (1H, br.s), 6.88 (1H, s), 7.26 (2H, d, J=8.4Hz), 7.41 (2H, d, J=8.4Hz), 7.93 (1H, dd, J=4.8Hz, 6.6Hz), 8.51 (1H, d, J=5.1Hz), 8.56 (1H, d, J=3.0Hz) ($CDCl_3$)	460
286	1.51 (2H, m), 1.60 (4H, m), 2.55 (4H, m), 3.08 (2H, s), 3.11 (1H, dd, J=2.4Hz, 13.2Hz), 3.29 (1H, td, J=3.OHz, 11.9Hz), 3.51-3.63 (2H, m), 358 (3H, s), 3.99 (1H, td, J=2.4Hz, 11.6Hz), 4.17 (1H, dd, J=1.5Hz, 11.7Hz), 4.71 (1H, dd, J=1.8Hz, 10.2Hz), 6.89 (1H, s), 7.38 (2H, d, J=8.7Hz), 7.61 (2H, d, J=8.7Hz), 7.95 (1H, d, J=5.1Hz), 8.51 (1H, d, J=4.8Hz), 8.55 (1H, d, J=3.0Hz), 9.34 (1H, br.s) ($CDCl_3$)	507
287	1.85 (4H, m), 2.70 (4H, m), 3.10 (1H, dd, J=10.8Hz, 12.9Hz), 3.29 (2H, s), 3.31-3.32 (1H, m), 3.51-3.64 (2H, m), 3.58 (3H, s), 3.99 (1H, td, J=2.1Hz. 11.7Hz), 4.18 (1H, dd, J=2.4Hz, 12.0Hz), 4.68 (1H, dd, J=2.1 Hz, 10.5Hz), 6.89 (1H, s), 7.37 (2H, d, J=8.7Hz), 7.61 (2H, d, J=8.7Hz), 7.94 (1H, d, J=5.1 Hz), 8.51 (1H, d, J=4.8Hz), 8.55 (1H, d, J=3.0Hz), 9.15 (1H, br.s) ($CDCl_3$)	493
288	2.39 (6H, s), 3.05-3.12 (1H, m), 3.08 (2H, s), 3.28 (1H, td, J=3.0Hz, 12.0Hz), 3.50-3.63 (2H, m), 3.58 (3H, s), 3.98 (1H, td, J=2.0Hz. 11.3Hz), 4.17 (1H, dd, J=12.0Hz, 2.4Hz), 4.71 (1H, dd, J=2.6Hz, 10.5Hz), 6.89 (1H, s), 7.38 (2H, d, J=8.7Hz), 7.63 (2H, d, J=8.7Hz), 7.94 (1H, d, J=5.1 Hz), 8.51 (1H, d, J=4.8Hz), 8.55 (1H, d, J=3.0Hz), 9.16 (1H, br.s) ($CnCl_3$)	467
289	1.25 (6H, t, J=7.3Hz), 3.07-3.14 (5H, m), 3.26-3.30 (3H, m), 3.50-3.56 (5H, m), 3.98-4..02 (1H, m), 4.12-4.15 (1H, m), 4.33-4.37 (2H, m), 4.65 (1H, dd, J=1.2Hz, 10.2Hz), 6.88 (1H, s), 6.98 (2H, d, J=7.2Hz), 7.32 (2H, d, J=7.2Hz), 7.93 (1H, dd, J=1.2Hz, 4.2Hz), 8.51 (1H, d, J=4.2Hz), 8.56 (1H, d, J=1.2Hz) (DMSO-d6)	482
290	1.60-1.69 (6H, m), 3.10 (1H, m), 3.28-3.38 (3H, m), 3.51-3.58 (1H, m), 3.58 (3H, s), 3.61-3.71 (3H, m), 4.00 (1H, m), 4.17-4.20 (1H, m), 4.76 (1H, d, J=9.9Hz), 6.89 (1H, s), 7.45 (4H, m), 7.93 (1H, dd, J=5.7Hz, 5.7Hz), 8.52 (1H, d, J=4.8Hz), 8.56 (1H, d, J=2.4Hz) ($CDCl_3$)	478
291	2.27 (3H, s), 3.07 (1H, dd, J=10.8Hz, 12.9Hz), 3.32 (1H, td, J=3.0Hz, 12.0Hz), 3.52-3.69 (2H, m), 3.58 (3H, s), 4.01 (1H, td, J=2.0Hz, 11.3Hz), 4.20 (1H, dd, J=12.0Hz, 2.4Hz), 4.82 (1H, dd, J=2.1Hz, 10.5Hz), 6.89 (1H, s), 7.40 (2H, d, J=8.7Hz), 7.91 (1H, dd, J=6.3Hz, 1.2Hz), 8.00 (2H, d, J=8.7Hz), 8.50 (1H, d, J=3.08Hz), 8.55 (1H, d, J=3.0Hz) ($CDCl_3$)	409
292	1.50 (3H, d, J=6.6Hz), 1.96 (1H, m), 3.10 (1H, dd, J=10.8Hz, 12.9Hz), 3.30 (1H, td, J=3.0Hz, 12.0Hz), 3.52-3.66 (2H, m), 3.58 (3H, s), 3.99 (1H, td, J=2.0Hz, 11.3Hz), 4.18 (1H, dd, J=12.0Hz, 2.4Hz), 4.73 (1H, dd, J=2.1Hz, 10.5Hz), 4.93 (1H, m), 6.88 (1H, s), 7.40 (2H, d, J=8.7Hz), 7.91 (1H, dd, J=6.3Hz, 1.2Hz), 8.00 (2H, d, J=8.7Hz), 8.50 (1H, d, J=3.1 Hz), 8.55 (1H, d, J=3.0Hz) ($CDCl_3$)	411
294	3.11 (1H, dd, J=12.9Hz, 10.5Hz), 3.14 (3H, d, J=4.5Hz), 3.30 (1H, td, J=12..0Hz, 3.0Hz), 3.48-3.67 (2H, m), 3.59 (3H, s), 4.01 (1H, td, J=2.4Hz, 12.0Hz), 4.18 (1H, dd, J=2.1Hz, 11.7Hz), 4.75 (1H, dd, J=2.1 Hz, 10.5Hz), 6.07 (1H, m), 6.88 (1H, s), 7.26 (2H, d, J=8.4Hz), 7.47 (2H, d, J=8.4Hz), 7.91 (1H, dd, J=6.6Hz, 1.7Hz), 8.51 (1H, d, J=5.0Hz). 8.56 (1H, d, J=3.1 Hz) ($CDCl_3$)	454
295	3.04-3.09 (1H, m), 3.26-3.31 (1H, m), 3.50-3.62 (5H, m), 3.79 (3H, s), 3.95-4.01 (1H, m), 4.14-4.17 (1H, m), 4.69 (1H, dd, J=1.2Hz, 10.2Hz), 6.71 (1H, br), 6.88 (1H, s), 7.30-7.43 (4H, m), 7.94 (1H, dd, J=1.2Hz, 4.2Hz), 8.51 (1H, d, J=4.2Hz), 8.56 (1H, d, J=1.2Hz) (DMSO-d6)	440
296	1.78-1.82 (4H, m), 2.49-2.55 (3H, m), 2.69-2.85 (3H, m), 3.09-3.13 (1H, m), 3.21-3.26 (1H, m), 3.55-3.61 (5H, m), 3.97-4.16 (5H, m), 4.66 (1H, dd, J=1.2Hz, 10.2Hz), 6.89 (1H, s), 6.95 (2H, d, J=7.2Hz), 7.32 (2H, d, J=7.2Hz), 7.94 (1H, dd, J=1.2Hz, 4.2Hz), 8.51 (1H, d, J=4.2Hz), 8.55 (1H, d, J=1.2Hz) ($CDCl_3$)	510

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Compound No.	1H-NMR δ:	[M+1]
297	3.04-3.11 (1H, m), 3.21-3.28 (1H, m), 3.48-3.61 (9H, m), 3.74-3.77 (4H, m), 3.91-4.00 (1H, m), 4.08-4.11 (1H, m), 4.68 (1H, dd, J=1.2Hz, 10.2Hz), 6.41 (1H, br.s), 7.35-7.42 (4H, m), 7.94 (1H, dd, J=1.2Hz, 4.2Hz), 8.51 (1H, d, J=1.2Hz), 8.54 (1H, d, J=4.2Hz) ($CDCl_3$)	495
298	3.04 (6H, s), 3.08-3.12 (1H, m), 3.26-3.30 (1H, m), 3.50-3.61 (5H, m), 3.94-4.01 (1H, m), 4.14-4.18 (1H, m), 4.66 (1H, dd, J=1.2Hz, 10.2Hz), 6.39 (1H, br.s), 6.88 (1H, s), 7.28 (2H, d, J=7.2Hz), 7.42 (2H, d, J=7.2Hz), 7.95 (1H, dd, J=1.2Hz, 4.2Hz), 8.50-8.55 (2H, m) ($CDCl_3$)	453
299	3.02 (1H, dd, J=10.6Hz, 12.8Hz), 3.26 (1H, td, J=12.1 Hz, 3.0Hz), 3.49-3.59 (2H, m), 3.56 (3H, s), 3.95 (1H, td, J=11.7Hz, 2.2Hz), 4.12 (1H, m), 4.66 (1H, dd, J=8.4Hz, 10.4Hz), 6.88 (1H, s), 7.00 (1H, br.s), 7.12 (2H, d, J=8.5Hz), 7.26-7.31 (2H, m), 7.42-7.47 (2H, m), 7.53 (1H, t, J=7.4Hz), 7.79 (2H, d, J=7.2Hz), 7.92 (1H, dd, J=5.0Hz. 6.5Hz), 8.51 (1H, d, J=5.0Hz), 8.56 (1H, d, J=3.0Hz) ($CDCl_3$)	522
300	3.10 (1H, dd, J=10.8Hz, 13.2Hz), 3.30 (1H, td, J=12.1Hz, 3.0Hz), 3.56 (3H, s), 3.58-3.66 (2H, m), 3.95 (1H, td, J=11.7Hz, 2.2Hz), 4.16 (1H, m), 4.33 (2H, s), 4.75 (1H, dd, J=2.1Hz, 10.5Hz), 6.87 (1H, s), 7.15 (1H, br.s), 7.19-7.411 (9H, m), 7.94 (1H, dd, J=5.1, 6.6Hz), 8.49 (1H, d, J=5.4Hz), 8.51 (1H, d, J=3.3Hz) ($CDCl_3$)	536
301	2.87 (6H, s), 2.97 (1H. dd, J=10.6Hz, 13.3Hz), 3.14 (1H, td, J=12.1Hz, 13.3Hz), 3.46-3.60 (2H, m), 3.53 (3H, s), 3.90 (1H, m), 4.08-4.16 (1H, m), 4.57 (1H, dd, J=10.4Hz, 1.9Hz,), 6.87 (1H, s), 7.00 (2H, d, J=8.5Hz), 7.19 (2H, d, J=8.5Hz), 7.40-7.60 (4H, m), 7.90 (1H, d, J=6.6Hz), 8.19 (1H, d, J=7.8Hz), 8.34 (1H, d, J=8.6Hz), 849 (1H, s), 8.51 (1H, d, J=2.4Hz), 8.56 (1H, d, J=3.0Hz) ($CDCl_3$)	615
302	3.09 (1H, dd, J=10.8Hz, 12.8Hz), 3.28 (1H, td, J=12.0Hz, 3.0Hz), 3.01-3.67 (2H, m), 3.58 (3H, s), 3.99 (1H, td, J=2.4Hz, 11 Hz), 4.10-4.19 (1H, m), 4.76 (1H, dd, J=2.4Hz, 10.8Hz), 6.88 (1H, s), 7.27 (1H, m), 7.43 (2H, d, J=8.7Hz), 7.50 (2H, d, J=8.7Hz), 7.93 (2H, td, J=6.6Hz, 1.5Hz), 8.04 (2H, m), 8.30 (1H, br,s), 8.46 (1H, dd, J=1.3Hz, 4.8Hz), 8.50 (1H, d, J=5.0Hz), 8.55 (1H, d, J=3.0Hz) ($CDCl_3$)	518
304	3.04-3.08 (1H, m), 3.26-3.31 (1H, m), 3.50-3.61 (5H, m), 3.95-4.91 (1H, m), 4.14-4.18 (1H, m), 4.68 (1H, dd, J=1.2Hz; 10.2Hz), 5.21 (2H, s), 6.78 (1H, br,s), 6.89 (1H, s), 7.33-7.45 (9H, m), 7.95 (1H, dd, J=1.2Hz, 4.2Hz), 8.50-8.56 (2H, m) ($CDCl_3$)	516
305	2.62-2.67 (2H, m), 2.97-3.10 (3H, m), 3.24-3.34 (1H, m), 3.52-3.62 (5H, m), 3.96-4.00 (1H, m), 4.12-4.16 (1H, m), 4.68 (1H, dd, J=1.2Hz, 10.2Hz). 6.78 (1H, d, J=7.2Hz), 6.88 (1H, dd, J=1.2Hz, 10.2Hz), 7.19-7.26 (2H, m), 7.93 (1H, dd, J=1.2Hz, 4.2Hz), 8.09 (1H, br.s), 8.51 (1H, d, J=4.2Hz), 8.57 (1H, d, J=1.2Hz) ($CDCl_3$)	436
306	1.36 (6H, s), 2.50 (2H, s), 3.07-3.14 (1H, m), 3.32-3.38 (1H, m), 3.53-3.64 (5H, m), 3.96-4.02 (1H, m), 4.15-4.20 (1H, m), 4.71 (1H, dd, J=1.2Hz, 10.2Hz), 6.81 (1H,d, J=7.2Hz), 6.88 (1H,s). 7.21 (1H.dd, J=1.2Hz, 7.2Hz), 7.33 (1H, d, J=1.2Hz), 7.93 (1H, dd, J=1.2Hz, 4.2Hz), 8.09 (1H, br), 8.51 (1H, d, J=4.2Hz), 8.56 (1H, d, J=1.2Hz) ($CDCl_3$)	464
307	1.30 (3H, t, J=7.2Hz), 3.04-3.12 (1H, m), 3.24-3.32 (1H, m), 3.50-3.62 (5H, m), 3.94-4.01 (1H, m), 4.15-4.24 (3H, m), 4.68 (1H, dd, J=1.2Hz, 10.2Hz). 6.66 (1H, br.s), 6.89 (1H, s), 7.35 (2H, d, J=7.2Hz), 7.42 (2H, d, J=7.2Hz), 7.94 (1H, dd, J=1.2Hz, 4.2Hz), 8.51 (1H, d, J=4.2Hz), 8.55 (1H, d, J=1.2Hz) ($CDCl_3$)	454
310	3.07 (1H, dd, J=12.9Hz, 10.8Hz), 3.28 (1H, m), 3.56-3.58 (1H, m), 3.58 (3H, s), 3.62-3.75 (9H, m), 4.00 (1H, m), 4.17 (1H, m), 4.78 (1H, dd, J=10.5Hz, 2.1 Hz), 6.89 (1H, s), 7.43-7.50 (4H, m), 7.93 (1H, dd, J=6-6Hz, 4.8Hz), 8.52 (1H, d, J=5.1Hz), 8.56 (1H, d, J=3.3Hz). ($CDCl_3$)	480

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Compound No.	1H-NMR δ:	[M+1]
311	3.09 (1H, dd, J=12.9Hz, 10.8Hz), 3.28 (1H, ddd, J=12.3Hz, 12.3Hz, 3.0Hz), 3.51-3.57 (1H, m), 3.57 (3H, s), 3.60-3.64 (1H, m), 3.94 (2H, m), 3.97 (1H, m), 4.14-4.17 (1H, m), 4.63 (1H, d, J=10.2Hz), 6.65-6.68 (1H, m), 6.75 (1H,s), 6.75-6.77(1H, m), 6.89 (1H, s), 7.17 (1H, dd, J=7.8Hz, 7.8Hz), 7.96 (1H, dd, J=6.0Hz. 5.4Hz), 8.51 (1H, d, J=5.4Hz), 8.55 (1H, d, J=3.3Hz). ($CDCl_3$)	382
312	2.77 (1H, dd, J=12.6Hz, 9.9Hz), 3.29 (1H, ddd, J=12.3Hz, 12.3Hz, 3.6Hz), 3.52-3.61 (3H, m), 3.62 (3H, s), 3.77 (3H, s), 3.77-3.82 (1H, m), 3.99 (1H, ddd, J=11.7Hz, 11.7Hz, 2.4Hz), 4.18-421 (1H, m), 5.00 (1H, dd, J=10.2Hz, 2.1 Hz), 6.63 (1H, dd, J=8.4Hz, 2.4Hz), 6.71 (1H, s), 6.88 (1H, s), 6.91 (1H, d, J=2.7Hz), 8.00 (1H, dd, J=6.6Hz, 5.1 Hz), 8.51 (1H, d, J=4.5Hz), 8.55 (1H, d, J=3.3Hz). ($CDCl_3$)	412
313	2.16 (3H, s), 2.78 (1H, dd, J=12.9Hz, 10.2Hz), 3.29 (1H, ddd, J=12.0Hz, 12.0Hz, 3.0Hz), 3.51-3.56 (1H, m), 3.62 (3H, s), 3.78-3.83 (1H, m), 3.84 (3H, s), 3.99 (1H, ddd, J=11.7Hz, 11.7Hz, 2.4Hz), 4.17-4.21 (1H, m), 5.02 (1H, dd, J=10.2Hz, 2.1 Hz), 6.86 (1H, d, J=8.7Hz), 6.89 (1H, s), 7.12 (1H, s), 7.46 (1H, d, J=2.4Hz), 7.59 (1H, dd, J=8.7Hz, 2.7Hz), 8.00 (1H, dd, J=6.6Hz, 5.1 Hz), 8.51 (1H, d, J=5.1 Hz), 8.55 (1H, d, J=3.3Hz). ($CDCl_3$)	454
314	2.19 (3H, s), 3.09 (1H, dd, J=12.9Hz, 10.6Hz), 3.29 (1H, ddd, J=12.7Hz, 12.7Hz, 3.0Hz), 3.50-3.54 (1H, m), 3.58 (3H, s), 3.64-3.68 (1H, m), 4.00 (1H, ddd, J=11.8Hz, 11.8Hz, 2.2Hz), 4.14-4.19 (1H, m), 4.74 (1H, dd, J=10.5Hz, 1.9Hz), 6.89 (1H, s), 7.14-7.20 (2H, m), 7.32-7.41 (2H, m), 7.70 (1H, s), 7.96 (1H, dd, J=5.4Hz, 5.4Hz), 8.53 (1H, d, J=5.1Hz), 8.55 (1H, d, J=3.3Hz) ($CDCl_3$)	424
315	1.88-1.97 (2H, m), 2.83-2.91 (3H, m), 3.26-3.38 (1H, m), 3.54-3.65 (1H, m), 3.61 (3H,s), 3.69-3.74 (1H, m), 4.00-4.25 (4H, m), 5.02 (1H, dd, J=1.8Hz, 9.9 Hz), 6.88 (1H, s), 6.90 (1H, d, J=8.4Hz), 6.99-7.04 (1H, m), 7.24-7.31 (1H, m), 7.51-7.54 (1H, m), 7.98 (1H, dd, J=5.1 Hz, 6.6 Hz), 8.53 (2H, m) ($CDCl_3$)	440
316	1.24 (6H, t, J=7.2Hz), 3.04-3.11 (1H, m), 3.27-3.42 (5H, m), 3.50-3.61 (5H, m), 3.94-4.00 (1H,m), 4.14-4.18 (1H, m), 4.67 (1H, dd, J=1.2Hz, 10.2Hz), 6.34 (1H, br), 6.90 (1H, s), 7.31 (2H, d, J=7.2Hz), 7.41 (2H, d, J=7.2Hz), 7.94 (1H, dd, J=1.2Hz, 4.2Hz), 8.51-8.55 (2H, m) ($CDCl_3$)	481
317	308-313 (1H, m), 3.24-3.32 (1H, m), 3.51-3.62 (7H, m), 3.96-4.02 (1H, m), 4.15-4.20 (1H, m), 4.68 (1H, dd, J=1.2Hz, 10.2Hz), 6.86-6.88 (2H, m), 7.24-7.32 (2H, m), 7.68 (1H, br.s), 7.92 (1H, dd, J=1.2Hz, 4.2Hz), 8.50 (1H, d, J=4.2Hz), 8.56 (1H, d, J=1.2Hz) ($CDCl_3$)	422
318	3.13 (1H, dd, J=10.5Hz, 12.9Hz), 3.37 (1H, m), 3.55-3.66 (2H, m), 3.59 (3H, s), 4.02 (1H. td, J=11.7Hz, 2.4Hz), 4.18 (1H, dd, J=11.7Hz, 2.1Hz), 4.50 (2H, s), 4.73 (1H, dd, J=10.5Hz, 1.8Hz), 6.87 (1H, s), 7.33 (2H, d, J=8.4Hz), 7.41 (2H, d, J=8.4Hz), 7.99 (1H, dd, J=6.6Hz, 1.2Hz)). 8.49 (1H, d, J=5.1Hz), 8.53 (1H, d, J=3.0Hz) ($CDCl_3$)	494
319	3.06 (1H, dd, J=12.9Hz, 10.5Hz), 3.26 (1H, ddd, J=12.0Hz, 12.0Hz. 3.0Hz), 3.50-3.56 (1H, m), 3.57 (3H, s), 3.58-3.60 (1H, m), 3.78 (2H, m), 3.97 (1H, m), 4.14-4.17 (1H, m), 4.61 (1H, dd, J=10.5Hz, 2.1Hz), 6.71 (1H, m), 6.85 (1H, dd, J=8.7Hz, 2.1Hz), 6.88 (1H, s), 6.99 (1H, dd, J=10.5Hz, 8.7Hz), 7.94(1H, dd, J=6.3Hz, 5.1Hz), 8.51 (1H, d, J=5.4Hz), 8.55 (1H, d, J=3.3Hz).($CDCl_3$)	400
320	3.03 (3H, s), 3.10 (1H, dd, J=12.9Hz, 10.8Hz), 3.31 (1H, ddd, J=12.0Hz, 12.0Hz, 3.0Hz), 3.52-3.56 (1H, m), 3.58 (3H, s), 3.65-3.69 (1H, m), 3.99 (1H, ddd, J=11.7Hz, 11.7Hz, 2.1 Hz), 4.18 (1H, m), 4.76 (1H, d, J=10.2Hz), 6.89 (1H, s), 6.80 (1H, s), 7.21-7.42 (4H, m), 7.94 (1H, dd, J=6.0Hz. 5.4Hz), 8.53 (1H, d, J=4.8Hz), 8.56 (1H, d, J=3.0Hz). ($CDCl_3$)	460
321	3.11-3.14 (1H, m), 3.32-3.37 (1H, m), 3.54-3.60 (4H, m), 3.69-3.73 (1H, m), 3.99-4.07 (1H, m), 4.20-4.24 (1H, m), 4.84 (1H, dd, J=1.2Hz, 10.2Hz), 6.89 (1H, s), 7.48-7.58 (3H, m), 7.68 (1H, s), 7.92 (1H, dd, J=1.2Hz. 4.2Hz), 8.50 (1H, d, J=4.2Hz), 8.55 (1H, d, J=1.2Hz), 8.98 (2H, s), 9.23 (1H, s) ($CDCl_3$)	445

(continued)

Compound No.	1H-NMR δ:	[M+1]
322	1.85 (1H, br.s), 3.00-3.08 (1H, m), 3.19-3.27 (3H, m), 3.56-3.67 (5H, m), 4.13 (1H, dd, J=1.2Hz, 10.2Hz), 6.87 (1H, s), 7.61 (2H, d, J=7.2Hz), 7.96 (1H, dd, J=1.2Hz, 4.2Hz), 8.14 (2H, d, J=7.2Hz), 8.50 (1H, d, J=4.2Hz), 8.55 (1H, d, J=1.2Hz), 8.78 (1H, s) ($CDCl_3$)	434
331	3.10 (1H, dd, J=10.6Hz, 12.8Hz), 3.33 (1H, td, J=12.1Hz, 3.0Hz), 3.52-3.73 (2H, m), 3.59 (3H, s), 4.01 (1H, t, J=10.7Hz), 4.21 (1H, d, J=11.3Hz), 4.83 (1H, d, J=9.8Hz), 6.90 (1H, s), 7.27 (3H, m), 7.88-7.99 (3H, m), 8.07 (1H, s), 8.51 (1H, d, J=6.5Hz), 8.56 (1H, d, J=3.0Hz) ($CDCl_3$).	450
332	2.73 (6H, s), 3.08 (1H, dd, J=10.6Hz, 12.9Hz), 3.31 (1H, td, J=12.6Hz, 3.3Hz), 3.52-3.71 (2H, m), 3.59 (3H, s), 4.03 (1H, td, J=11.7Hz, 2.1 Hz), 4.20 (1H, dd, J=11.4Hz, 2.1Hz), 4.86 (1H, dd, J=10.5Hz, 1.8Hz), 6.89 (1H, s), 7.60 (2H, d, J=8.4Hz), 7.81 (2H, d, J=8.4Hz), 7.94 (1H, s), 8.58 (2H, m) ($CDCl_3$)	474
334	2.00-2.04 (1H, m), 2.67 (3H, s), 3.00-3.11 (1H, m), 3.18-3.30 (3H, m), 3.57-3.66 (5H, m), 4.11 (1H, dd, J=1.2Hz, 10.2Hz), 6.86 (1H, s), 7.57 (2H, d, J=7.2Hz), 7.97 (1H, dd, J=1.2Hz, 4.2Hz), 8.08 (2H, d, J=7.2Hz), 8.50 (1H, d, J=4.2Hz), 8.55 (1H, d, J=1.2Hz) ($CDCl_3$)	448
335	1.46 (3H, t, J=7.3Hz), 2.95-3.02 (3H, m), 3.19-3.25 (3H, m), 3.57-3.66 (5H, m), 4.11 (1H, dd, J=1.2Hz, 10.2Hz), 6.86 (1H, s), 7.57 (2H, d, J=7.2Hz), 7.95 (1H, dd, J=1.2Hz, 4.2Hz), 8.10 (2H, d, J=7.2Hz), 8.50 (1H, d, J=4.2Hz), 8.54 (1H, d, J=1.2Hz) ($CDCl_3$)	462
336	3.07-3.11 (1H, m), 3.31-3.36 (1H, m), 3.53-3.71 (5H, m), 4.00-4.05 (1H, m), 4.19-4.23 (1H, m), 4.82 (1H, dd, J=1.2Hz, 10.2Hz), 6.89 (1H, s), 7.56 (2H, d, J=7.2Hz), 7.93 (1H, dd, J=1.2Hz, 4.2Hz), 8.16 (2H, d, J=7.2Hz), 8.51 (1H, d, J=4.2Hz), 8.55 (1H, d, J=1.2Hz), 8.78 (1H, s) ($CDCl_3$)	435
337	2.67 (3H, s), 3.07-3.14 (1H, m), 3.28-3.33 (1H, m), 3.53-3.70 (5H, m), 3.96-4.05 (1H, m), 4.18-4.22 (1H, m), 4.81 (1H, dd, J=1.2Hz, 10.2Hz), 6.89 (1H, s), 7.53 (2H, d, J=7.2Hz), 7.93 (1H, dd, J=1.2Hz, 4.2Hz), 8.10 (2H, d, J=7.2Hz), 8.51 (1H, d, J=4.2Hz), 8.56 (1H, d, J=1.2Hz) ($CDCl_3$)	449
338	2.67 (3H, s), 3.10-3.14 (1H, m), 3.31-3.36 (1H, m), 3.53-3.71 (5H, m), 3.98-4.04 (1H, m), 4.19-4.23 (1H, m), 4.83 (1H, dd, J=1.2Hz, 10.2Hz), 6.89 (1H, s), 7.60 (2H, d, J=7.2Hz), 7.93 (1H, dd, J=1.2Hz, 4.2Hz), 8.06 (2H, d, J=7.2Hz), 8.51 (1H. d, J=4.2Hz), 8.55 (1H, d, J=1.2Hz) ($CDCl_3$).	449
339	3.08 (1H, dd, J=10.6Hz, 12.9Hz), 3.31 (1H, td, J=12.6Hz, 3.3Hz), 3.52-3.71 (2H, m), 3.59 (3H, s), 4.01 (1H, td, J=11.7Hz, 2.1 Hz), 4.20 (1H, dd, J=11.4Hz, 2.1Hz), 4.87 (1H, dd, J=10.5Hz, 1.8Hz), 6.89 (1H, s), 7.60 (2H, d, J=8.8Hz), 7.90 (1H, dd, J=6.2Hz, 1.2Hz), 8.27 (2H, d, J=8.8Hz), 8.51 (1H, d, J=4.2Hz), 8.57 (1H, d, J=1.2Hz) ($CDCl_3$)	412
340	3.10-3.14 (1H, m), 3.31-3.36 (1H, m), 3.51-3.70 (5H, m), 3.96-4.02 (1H, m), 4.16-4.20 (1H, m), 4.87 (1H, dd, J=1.2Hz, 10.2Hz), 6.62 (1H. s), 7.44 (1H, dd, J=1.2Hz, 4.2Hz), 7.68 (2H, d, J=7.2Hz), 7.90-8.04 (3H, m), 8.57 (1H, d, J=4.2Hz), 8.71 (1H, d, J=1.2Hz) ($CDCl_3$).	435
341	1.25 (6H, t, J=7.3Hz), 3.00-3.18 (6H, m), 3.48 (3H, s), 3.66-3.73 (3H, m), 3.76-3.80 (1H, m), 4.02-4.06 (1H, m), 4.28 (2H, d, J=5.4Hz), 4.80 (1H, dd, J=1.2Hz, 10.2Hz), 6.61 (1H, s), 7.52 (2H, d, J=7.2Hz), 7.63 (2H, d, J=7.2Hz), 7.98 (1H, dd, J=1.2Hz, 4.2Hz), 8.57 (1H, d, J=4.2Hz), 8.72 (1H, d, J=1.2Hz), 10.46 (1H, br.s) (DMSO-d6).	452
342	1.82 (1H, br.s), 3.05-3.10 (1H, m), 3.30-3.38 (1H, m), 3.52-3.63 (5H, m), 3.96-4.02 (1H, m), 4.15-4.19 (1H, m), 4.72 (2H, s), 4.76 (1H, dd, J=1.2Hz, 10.2Hz), 6.88 (1H, s), 7.41-7.44 (4H, m), 7.93 (1H, dd, J=1.2Hz, 4.2Hz), 8.50 (1H, d, J=42Hz), 8.54 (1H, d, J=1.2Hz) ($CDCl_3$).	397

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Compound No.	1H-NMR δ:	[M+1]
343	2.43-2.46 (4H, m), 3.07-3.14 (1H, m), 3.30-3.34 (1H, m), 3.51 (2H, s), 3.58 (3H, s), 3.65-3.68 (2H, m), 3.68-3.72 (4H, m), 3.96-4.02 (1H, m), 4.15-4.18 (1H, m), 4.72 (1H, dd, J=1.2Hz, 10.2Hz), 6.88 (1H, s), 7.34-7.37 (4H, m), 7.95 (1H, dd, J=1.2Hz, 4.2Hz), 8.51 (1H, d, J=4.2Hz), 8.55 (1H, d, J=1.2Hz) ($CDCl_3$).	466
344	0.70 (1H, m), 1.14 (3H, d, J=6.0Hz). 1.21-1.28 (2H, m), 1.50 (1H, m), 3.07 (1H, dd, J=10.6Hz, 12.9Hz), 3.26 (1H, td, J=12.6Hz, 3.3Hz), 3.50-3.62 (2H, m), 3.57 (3H, s), 4.01 (1H, td, J=11.7Hz, 2.1Hz), 4.16 (1H, dd, J=11.4Hz, 2.1 Hz), 4.68 (1H, dd, J=10.5Hz, 1.8Hz), 6.87 (1H, s), 7.35 (2H, d, J=8.7Hz), 7.46 (1H, br.s), 7.53 (2H, d, J=8.8Hz), 7.94 (1H, dd, J=6.2Hz, 1.2Hz), 8.51 (1H, d, J=4.2Hz), 8.55 (1H, d, J=3.3Hz) ($CDCl_3$)	464
345	1.61-1.94 (8H, m), 2.69 (1H, t, J=8.1Hz), 3.09 (1H, dd, J=10.8Hz, 12.8Hz), 3.25 (1H, td, J=3.0Hz, 12.0Hz), 3.52-3.64 (2H, m), 3.57 (3H, s), 3.98 (1H, td, J=12.0Hz, 2.1 Hz), 4.15 (1H, dd, J=12.0Hz, 1.5Hz), 4.70 (1H, dd, J=10.8Hz, 2.1 Hz), 6.88 (1H, s), 7.21 (1H, br.s), 7.35 (2H, d, J=8.7Hz), 7.56 (2H, d, J=8.8Hz), 7.94 (1H, dd, J=6.2Hz, 1.2Hz), 8.51 (1H, d, J=4.2Hz), 8.55 (1H, d, J=3.3Hz) ($CDCl_3$)	478
346	0.69 (2H, m), 1.32 (2H, m), 1.47 (3H, s), 3.07 (1H, dd, J=10.8Hz, 13.4Hz), 3.27 (1H, td, J=7.0Hz, 12.0Hz), 3.52-3.64 (2H, m), 3.57 (3H, s), 4.01 (1H, td, J=11.4Hz, 2.1Hz), 4.17 (1H, d, J=12.0Hz), 4.69 (1H, d, J=9.4Hz), 6.88 (1H, s), 7.35 (2H, d, J=8.4Hz), 7.48 (1H, br.s), 7.54 (2H, d, J=8.4Hz), 7.94 (1H, dd, J=6.2Hz, 1.2Hz), 8.51 (1H, d, J=4.2Hz), 8.55 (1H, d, J=3.3Hz) ($CDCl_3$)	464
347	1.56 (6H, s), 2.50 (1H, br.s), 3.10 (1H, dd, J=10.7Hz, 13.0Hz). 3.30 (1H. td, J=2.9Hz, 12.2Hz), 3.52-3.64 (2H, m), 3.57 (3H, s), 4.00 (1H. td, J=11.4Hz, 1.9Hz), 4.16 (1H, dd, J=11.5Hz, 1.8Hz)). 4.70 (1H, dd, J=10.4Hz, 2.0Hz), 6.88 (1H, s), 7.37 (2H, d, J=8.4Hz), 7.61 (2H, d, J=8.4Hz), 7.94 (1H, dd, J=6.2Hz, 1.2Hz), 8.51 (1H, d, J=4.2Hz), 8.55 (1H. d, J=3.3Hz), 8.74 (1H. br.s) ($CDCl_3$)	468
348	2.93-2.98 (1H, m), 3.14-3.28 (2H, m), 3.48 (3H, s), 3.67-3.75 (2H, m), 3.89-3.94 (1H, m), 4.06-4.10 (1H. m), 4.84 (1H, dd, J=1.2Hz, 10.2Hz), 6.61 (1H, s), 7.57 (2H, d, J=7.2Hz), 7.95-8.00 (3H, m), 8.56 (1H, d, J=4.2Hz), 8.70 (1H, d, J=1.2Hz) ($CDCl_3$)	411
349	1.98 (1H, br), 2.93-2.97 (1H, m), 3.19-3.25 (3H, m), 3.56 (3H, s), 3.58-3.62 (2H, m), 4.13 (1H, dd, J=1.2Hz, 10.2Hz), 6.86 (1H, s), 7.60 (2H, d, J=7.2Hz), 7.69 (2H, d, J=7.2Hz), 7.92 (1H, dd, J=1.2Hz, 4.2Hz), 8.50 (1H, d, J=4.2Hz), 8.55 (1H, d, J=1.2Hz) ($CDCl_3$)	391
350	1.98 (1H, br), 2.93-2.97 (1H, m), 3.19-3.25 (3H, m), 3.56 (3H, s), 3.58-3.62 (2H, m), 4.13 (1H, dd, J=1.2Hz, 10.2Hz), 6.86 (1H, s), 7.60 (2H, d, J=7.2Hz), 7.69 (2H, d, J=7.2Hz), 7.92 (1H, dd, J=1.2Hz, 4.2Hz), 8.50 (1H, d, J=4.2Hz), 8.55 (1H, d, J=1.2Hz) ($CDCl_3$)	391
352	1.68-2.14 (4H, m), 2.48 (6H, s), 2.93-2.99 (3H, m), 3.55 (3H, s). 1.45 (3H, s), 1.47 (3H, s), 3.08-3.37 (2H, m), 3.19 (3H, s), 3.48 (3H, s), 3.58-3.67 (2H, m), 3.58 (3H, s), 4.00 (1H, td, J=11.5Hz, 1.8Hz), 4.16 (1H, dd, J=11.5Hz. 1.8Hz). 4.73 (1H, dd, J=10.5Hz, 2.1Hz), 6.89 (1H. s), 7.25 (2H, d, J=8.4Hz), 7.61 (2H, d, J=8.4Hz), 7.94 (1H, dd, J=6.2Hz, 1.2Hz), 8.51 (1H, d, J=4.2Hz), 8.55 (1H, d, J=3.3Hz), 8.74 (1H, br.s) ($CDCl_3$)	496
353	0.86-0.88 (2H, m), 1.10-1.11 (2H, m), 1.55 (1H, m), 3.09 (1H, m), 3.29 (1H, m), 3.49-3.57 (1H, m), 3.58 (3H, s), 3.65 (1H, m), 3.97 (1H, m), 4.16 (1H, m), 4.76 (1H, d, J=8.7Hz), 6.89 (1H, s), 7.13 (1H, m), 7.35-7.36 (4H, m), 7.79 (1H. s), 7.95 (1H. d, J=5.4Hz), 8.53 (1H, d, J=6.0Hz) ($CDCl_3$)	450
354	0.84-0.85 (2H, m), 1.07-1.10 (2H, m), 1.47 (1H, m), 2.79 (1H, dd, J=13.2Hz, 9.6Hz), 3.29 (1H, m), 3.51-3.56 (1H, m), 3.62 (3H, s), 3.83-3.95 (1H, m), 3.95 (3H, s), 4.02 (1H, m), 4.20 (1H, m), 5.03 (1H, d, J=9.3Hz), 6.86 (1H, m), 6.89 (1H, s), 7.32 (1H, m), 7.45-7.58 (2H, m), 8.00 (1H, d, J=6.0Hz), 8.51 (1H, d, J=4.8Hz), 8.55 (1H, d, J=3.0Hz) ($CDCl_3$)	480

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Compound No.	1H-NMR δ:	[M+1]
355	2.76 (1H, dd, J=12.9, 10.5Hz), 2.98 (3H, s), 3.32 (1H, ddd, J=12.3Hz, 12.3Hz, 3.0Hz), 3.53-3.57 (1H, m), 3.63 (3H, s), 3.81-3.86 (1H, m), 3.87 (3H, s), 4.00 (1H, ddd, J=11.7Hz, 11.7Hz, 2.4Hz), 4.22 (1H. dd, J=12.0Hz. 2.4Hz), 5.04 (1H. dd, J=10.2Hz, 1.8Hz), 6.55 (1H. s), 6.88-6.91 (2H, m), 7.26-7.30 (1H, m), 7.40 (1H, d, J=2.7Hz), 8.00 (1H, dd, J=6.6Hz, 5.1 Hz). 8.53 (1H, d, J=5.1 Hz). 8.56 (1H, d, J=3.3Hz) ($CDCl_3$)	490
356	2.88-2.96 (1H. m), 3.15-3.20 (1H, m), 3.45 (3H, s), 3.64-3.70 (2H, m), 3.84-3.91 (1H. m), 4.01-4.05 (1H, m), 4.57 (2H, s), 4.68 (1H, dd, J=1.2Hz, 10.2Hz), 6.60 (1H, s), 6.95-7.00 (3H, m), 7.96 (1H, dd, J=1.2Hz, 4.2Hz), 8.57 (1H, d, J=4.2Hz), 8.75 (1H, d, J=1.2Hz), 10.74 (1H, br.s) ($CDCl_3$)	438
357	3.06 (1H, dd, J=12.9Hz, 10.5Hz), 3.26 (1H, ddd, J=12.3Hz, 12.3Hz, 3.0Hz), 3.48-3.53 (1H, m), 3.56 (3H, s), 3.58-3.60 (1H, m), 3.77 (2H, m), 3.97 (1H, m), 4.14-4.17 (1H, m), 4.60 (1H, dd, J=10.5Hz, 2.1Hz), 6.78 (1H, m), 6.88 (1H, s), 6.95 (1H, m), 7.07 (1H, m), 7.94 (1H, dd, J=6.6Hz, 5.1Hz), 8.51 (1H, d, J=6.0Hz). 8.55 (1H, d, J=3.0Hz) ($CDCl_3$)	400
365	3.04-3.12 (1H. m) , 3.21-3.28 (1H, m), 3.51-3.64 (2H, m), 3.58 (3H, s), 3.99-4.16 (4H, m), 4.51 (2H, t, J=7.0Hz), 4.72 (1H, J=1.2Hz, 10.2Hz), 6.89 (1H, s), 7.43 (2H, d, J=7.2Hz), 7.58 (2H, d, J=7.2Hz), 7.94 (1H, dd, J=1.2Hz, 4.2Hz), 8.51 (1H, d, J=4.2Hz), 8.55 (1H, d, J=1.2Hz) ($CDCl_3$)	452
366	2.07-2.15 (2H, m), 3.06-3.14 (1H, m), 3.20-3.26 (1H, m), 3.38-3.72 (6H, m), 3.57 (3H, s), 3.95-4.00 (1 H, m), 4.12-0.16 (1 H, m), 4.70 (1 H, dd, J=1.2Hz, 10.2Hz), 5.05 (1H, br), 6.90 (1H, s), 7.32-7.49 (4H, m), 7.97 (1H, dd, J=1.2Hz, 4.2Hz), 8.52-8.56 (2H, m) ($CDCl_3$)	465
367	3.05-3.13 (1H, m), 3.25-3.29 (1H, m), 3.51-3.63 (4H, m), 3.57 (3H, s), 3.93-3.98 (3H, m), 4.15-4.19 (1H, m), 4.69 (1H, dd, J=1.2Hz, 10.2Hz), 5.01 (1 H, br), 6.89 (1H, s), 7.37 (2H, d, J=7.2Hz), 7.56 (2H, d, J=7.2Hz), 7.95 (1H, dd, J=1.2Hz, 10.2Hz), 8.51 (1H, d, J=4.2Hz), 8.55 (1 H, d, J=1.2Hz) ($CDCl_3$)	451
368	1.94-1.98 (4H, m), 2.56-2.60 (2H, m), 3.02-3.11 (1H. m), 3.20-3.30 (1 H, m), 3.50-3.67 (4H, m), 3.57 (3H, s), 3.95-4.01 (1H, m), 4.14-4.18 (1H, m), 4.72 (1 H, dd, J=1.2Hz, 10.2Hz), 6.90 (1H. s), 7.29 (2H, d, J=7.2Hz), 7.44 (2H, d, J=7.2Hz), 7.96 (1H, dd, J=1.2Hz, 4.2Hz), 8.52-8.57 (2H, m) ($CDCl_3$)	464
369	2.86 (1H, t, J=7.0Hz). 3.05-3.10 (1H, m), 3.23-3.29 (1 H, m), 3.45-3.65 (6H, m), 3.57 (3H, s), 3.82-3.97 (5H, m), 4.12-4.18 (1H, m), 4.67 (1 H, dd, J=1.2Hz, 10.2Hz), 6.88 (1H. s), 7.36 (2H, d, J=7.2Hz), 7.94 (2H, d, J=7.2Hz), 7.94 (1H, dd, J=1.2Hz, 4.2Hz), 8.49-8.56 (2H, m) ($CDCl_3$)	495
370	2.50 (3H, s), 3.10 (1H, dd, J=12.9Hz, 10.5Hz), 3.29 (1H, m), 3.53-3.66 (2H, m), 3.57 (3H, s), 3.98 (1H, td, J=11.7Hz, 2.4Hz), 4.17 (1H, d, J=10.8Hz), 4.70 (1H, dd, J=10.5Hz, 2.1Hz), 6.70 (1H, s), 7.27-7.34 (3H, m), 7.78-7.80 (2H, m), 8.71 (1H, d, J=4.8Hz), 8.72 (1H, d, J=4.5Hz). ($CDCl_3$)	413

Experiment 1: Inhibitory activity of the medicament of the present invention against P-GS1 phosphorylation by bovine cerebral TPK1

[0114] A mixture containing 100 mM MES-sodium hydroxide (pH 6.5), 1 mM magnesium acetate, 0.5 mM EGTA, 5 mM B-mercaptoethanol, 0.02% Tween 20, 10% glycerol, 12 μg/ml P-GS1, 41.7 μM [γ^{32}P] ATP (68 kBq/ml), bovine cerebral TPK1 and a compound shown in Table (a final mixture contained 1.7% DMSO deriving from a solution of a test compound prepared in the presence of 10% DMSO) was used as a reaction system. The phosphorylation was started by addingATP, and the reaction was conducted at 25˚C for 2 hours, and then stopped by adding 21% perchloric acid on ice cooling. The reaction mixture was centrifuged at 12,000 rpm for 5 minutes and adsorbed on P81 paper (Whatmann), and then the paper was washed four times with 75 mM phosphoric acid, three times with water and once with acetone. The paper was dried, and the residual radioactivity was measured using a liquid scintillation counter. The results are shown in the table below. The test compound markedly inhibited the P-GS1 phosphorylation by TPK1. The results

strongly suggest that the medicaments of the present invention inhibit the TPK1 activity, thereby suppress the Aβ neurotoxicity and the PHF formation, and that the medicaments of the present invention are effective for preventive and/or therapeutic treatment of Alzheimer disease and the above-mentioned diseases.

Table 3

Compound No.	IC_{50} (nM)
4	7.9
5	1.4
14	3.7
17	1.7
22	0.53
41	0.73
92	1.2
209	2.2
210	0.51
212	5.4
224	1.1
221	3.9
238	6.4
158	2.9
295	1.2
298	11
322	4.8
334	2.9
310	7.4
220	2.7
288	0.27
215	4.2
305	1.2
313	0.48
314	4.1

[0115] Compound N° 56, 105, 196, 247 and 303 was removed in table 3.

Experiment 2 : Inhibitory activity on tau phosphorylation in vivo

[0116] Test compound was administrated to male CD-1 mice of 5-6 weeks weighing 25-35 g (Charles River Japan, inc.) at 1, 3, 10, 30 mg/kg p.o. (0.5% Tween/H_2O suspension) and after 1hour, mice were decapitated and cortex was promptly removed, followed by being frozen in liquid N_2. Cortex was directly homogenized with 2.3% SDS homogenization buffer (62.5 mM Tris-HCl, 2.3% SDS, 1 mM each of EDTA, EGTA and DTT, protease inhibitor cocktail (sigma P2714) containing 0.2 μM M 4-(2-Aminoethyl)benzenesulfonyl fluoride (AEBSF), 13 μ M bestatin, 1.4 μM E-64, 0.1 mM leupeptin, 30 nM aprotinin, pH 6.8) and centrifuged at 15000 x g for 15 min at 4°C. Protein concentrations were determined using DC protein assay kit (BIO-RAD). Supernatants were diluted with sample buffer (62.5 mM Tris-HCl, 25% glycerol, 2% SDS, 0.01% Bromophenol Blue, pH6.8) to adjust the protein concentrations around 0.5 - 2 mg/mg and then boiled for 5 min. 10 μg of samples were applied on 10% SDS-PAGE mini slab gels and transferred onto PVDF membranes. Membranes were incubated with PBS containing 5% non-fat milk for 1h at room temperature and then probed with

pS396 anti-body (BIOSOURCE) over night at 4˚C- Anti-rabbit IgG HRP-conjugated anti-body (Promega) was used as secondary anti-body. Membranes were visualized by ECL kit (Amerasham Bioscience) and detected by LAS 1000 (Fuji Photo Film).

Formulation Example

(1) Tablets

[0117] The ingredients below were mixed by an ordinary method and compressed by using a conventional apparatus.

Compound of Example 1	30 mg
Crystalline cellulose	60 mg
Corn starch	100 mg
Lactose	200 mg
Magnesium stearate	4 mg

(2) Soft capsules

[0118] The ingredients below were mixed by an ordinary method and filled in soft capsules.

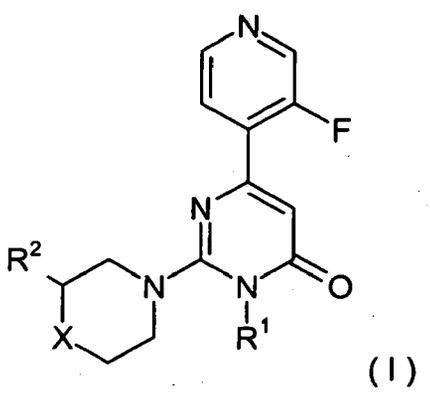
Compound of Example 1	30 mg
Olive oil	300 mg
Lecithin	20 mg

Industrial Applicability

[0119] The compounds of the present invention have TPK1 inhibitory activity and are useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of diseases caused by abnormal advance of TPK1 such as neurodegenerative diseases (e.g. Alzheimer disease) and the above-mentioned diseases.

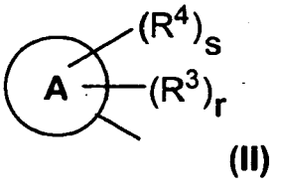
Claims

1. A compound represented by the formula (I), an optically active isomer thereof, or a pharmaceutically acceptable salt thereof:



(I)

wherein each symbol is as defined below. R^1 represents a C_1-C_{12} alkyl;
R^2 represents
a group represented by the following formula (II):

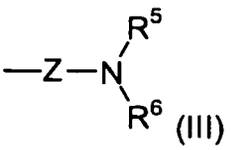


(II)

wherein A represents a C_6-C_{10} aryl or a heterocycle selected from the group consisting of benzofuran, dihydrobenzofuran, isobenzofuran, chromene, indole, indoline, isoindole, benzoxazolinone, tetrahydroisoquinoline, chroman, isochroman, benzothiophen, isoindoline, indazole, benzimidazole, benzotriazole,benzothiazolinone, quinoline, phthalazine, quinoxaline, quinazoline, cinnoline, benzothiazole, benzodioxole, benzodioxane, phthalimide;
R^3 may be the same or different and represents
hydrogen atom,
hydroxyl,
a halogen,
nitro,
cyano
a C_1-C_6 alkyl which may be substituted,
a C_2-C_6 alkenyl which may be substituted,
a C_2-C_6 alkynyl which may be substituted,
a C_3-C_7 cycloalkyl which may be substituted,
a C_3-C_7 cycloalkenyl which may be substituted,
a C_6-C_{10} aryl which may be substituted,
a heterocycle which may be substituted,
a C_1-C_6 alkyloxy which may be substituted,
a C_3-C_6 alkenyloxy which may be substituted,
a C_3-C_6 alkynyloxy which may be substituted,
a C_3-C_7 cycloalkyloxy which may be substituted,
a C_3-C_7 cycloalkenyloxy which may be substituted,
a C_6-C_{10} aryloxy which may be substituted,
a heterocycle-oxy group which may be substituted, mercapto,
a C_1-C_6 alkylthio which may be substituted,
a C_3-C_6 alkenylthio which may be substituted,
a C_3-C_6 alkynylthio which may be substituted,
a C_3-C_7 cycloalkylthio which may be substituted,
a C_3-C_7 cycloalkenylthio which may be substituted,
a C_6-C_{10} arylthio which may be substituted,
a heterocycle-thio group which may be substituted, amino,
a C_1-C_6 alkylamino which may be substituted,
a C_3-C_6 alkenylamino which may be substituted,
a C_3-C_6 alkynylamino which may be substituted,
a C_3-C_7 cycloalkylamino which may be substituted,
a C_3-C_7 cycloalkenylamino which may be substituted,
a C_6-C_{10} arylamino which may be substituted,
a heterocycle-amino which may be substituted,
a N,N-di-C_1-C_6 alkylamino which may be substituted,
a N-C_1-C_6 alkyl-N-C_3-C_6 alkenylamino which may be substituted,
a N-C_1-C_6 alkyl-N-C_3-C_6 alkynylamino which may be substituted,
a N-C_1-C_6 alkyl-N-C_3-C_7 cycloalkylamino which may be substituted,
a N-C_1-C_6 alkyl-N-C_3-C_7 cycloalkenylàmino which may be substituted,
a N-C_1-C_6 alkyl-N-C_6-C_{10} arylamino which may be substituted,
a N-C_1-C_6 alkyl-N-heterocycle-amino which may be substituted,
a N,N-di-C_3-C_6 alkenylamino which may be substituted,
a N-C_3-C_6 alkenyl-N-C_3-C_6 alkynylamino which may be substituted
a N-C_3-C_6 alkenyl-N-C_3-C_7 cycloalkylamino which may be substituted,
a N-C_3-C_6 alkenyl-N-C_3-C_7 cycloalkenylamino which may be substituted,

a N-C_3-C_6 alkenyl-N-C_6-C_{10} arylamino which may be substituted,
a N-C_3-C_6 alkenyl-N-heterocycle-amino which may be substituted,
a N,N-di-C_3-C_6 alkynylamino which may be substituted,
a N-C_3-C_6 alkynyl-N-C_3-C_7 cycloalkylamino which may be substituted,
a N-C_3-C_6 alkynyl-N-C_3-C_7 cycloalkenylamino which may be substituted,
a N-C_3-C_6 alkynyl-N-C_6-C_{10} arylamino which may be substituted,
a N-C_3-C_6 alkynyl-N-heterocycle-amino which may be substituted,
a N,N-di-C_3-C_7 cycloalkylamino which may be substituted,
a N-C_3-C_7 cycloalkyl-N-C_3-C_7 cycloalkenylamino which may be substituted,
a N-C_3-C_7 cycloalkyl-N-C_6-C_{10} arylamino which may be substituted,
a N-C_3-C_7 cycloalkyl-N-heterocycle-amino which may be substituted,
a N,N-di-C_3-C_7 cycloalkenylamino which may be substituted,
a N-C_3-C_7 cycloalkenyl-N-C_6-C_{10} arylamino which may be substituted,
a N-C_3-C_7 cycloalkenyl-N-heterocycle-amino which may be substituted,
a N,N-di-C_6-C_{10} arylamino which may be substituted,
a N-C_6-C_{10} aryl-N-heterocycle-amino which may be substituted,
a N,N-diheterocycle-amino which may be substituted,
a C_1-C_6 alkylcarbonyl which may be substituted,
a C_2-C_6 alkenylcarbonyl which may be substituted,
a C_2-C_6 alkynylcarbonyl which may be substituted,
a C_3-C_7 cycloalkylcarbonyl which may be substituted,
a C_3-C_7 cycloalkenylcarbonyl which may be substituted,
a C_6-C_{10} arylcarbonyl which may be substituted,
a heterocycle-carbonyl which may be substituted,
a C_1-C_6 alkylsulfonyl which may be substituted,
a C_3-C_6 alkenylsulfonyl which may be substituted,
a C_3-C_6 alkynylsulfonyl which may be substituted,
a C_3-C_7cycloalkylsulfonyl which may be substituted,
a C_3-C_7 cycloalkenylsulfonyl which may be substituted,
a C_6-C_{10} arylsulfonyl which may be substituted,
a heterocycle-sulfonyl which may be substituted, carboxyl,
a C_1-C_6 alkyloxycarbonyl which may be substituted,
a C_3-C_6 alkenyloxycarbonyl which may be substituted,
a C_3-C_6 alkynyloxycarbonyl which may be substituted,
a C_3-C_7 cycloalkyloxycarbonyl which may be substituted,
a C_3-C_7 cycloalkenyloxycarbonyl which may be substituted,
a C_6-C_{10} aryloxycarbonyl which may be substituted,
a heterocycle-oxycarbonyl which may be substituted, aminocarbonyl,
a C_1-C_6 alkylaminocarbonyl which may be substituted,
a C_3-C_6 alkenylaminocarbonyl which may be substituted,
a C_3-C_6 alkynylaminocarbonyl which may be substituted,
a C_3-C_7 cycloalkylaminocarbonyl which may be substituted,
a C_3-C_7 cycloalkenylaminocarbonyl which may be substituted,
a C_6-C_{10} arylaminocarbonyl which may be substituted,
a heterocycle-aminocarbonyl which may be substituted,
a N,N-di-C_1-C_6 alkylaminocarbonyl which may be substituted,
a N-C_1-C_6 alkyl-N-C_3-C_7 alkenylaminocarbonyl which may be substituted,
a N-C_1-C_6 alkyl-N-C_3-C_7 alkynylaminocarbonyl which may be substituted,
a N-C_1-C_6 alkyl-N-C_3-C_7 cycloalkylaminocarbonyl which may be substituted,
a N-C_1-C_6 alkyl-N-C_3-C_7 cycloalkenylaminocarbonyl which may be substituted,
a N-C_1-C_6 alkyl-N-C_6-C_{10} arylaminocarbonyl which may be substituted,
a N-C_1-C_6 alkyl-N-heterocycle-aminocarbonyl which may be substituted,
a N,N-di-C_3-C_6 alkenylaminocarbonyl which may be substituted,
a N-C_3-C_6 alkenyl-N-C_3-C_6 alkynylaminocarbonyl which may be substituted,
a N-C_3-C_6 alkenyl-N-C_3-C_7 cycloalkylaminocarbonyl which may be substituted,
a N-C_3-C_6 alkenyl-N-C_3-C_7 cycloalkenylaminocarbonyl which may be substituted,
a N-C_3-C_6 alkenyl-N-C_6-C_{10} arylaminocarbonyl which may be substituted,
a N-C_3-C_6 alkenyl- N-heterocycle-aminocarbonyl which may be substituted,

a N,N-di-C_3-C_6 alkynylaminocarbonyl which may be substituted,
a N-C_3-C_6 alkynyl-N-C_3-C_7 cycloalkylaminocarbonyl which may be substituted,
a N-C_3-C_6 alkynyl-N-C_3-C_7 cycloalkenylaminocarbonyl which may be substituted,
a N-C_3-C_6 alkynyl-N-C_6-C_{10} arylaminocarbonyl which may be substituted,
a N-C_3-C_6 alkynyl-N-heterocycle-aminocarbonyl which may be substituted,
a N,N-di-C_3-C_7 cycloalkylaminocarbonyl which may be substituted,
a N-C_3-C_7 cycloalkyl-N-C_3-C_7 cycloalkenylaminocarbonyl which may be substituted,
a N-C_3-C_7 cycloalkyl-N-C_6-C_{10} arylaminocarbonyl which may be substituted,
a N-C_3-C_7 cycloalkyl-N-heterocycle-aminocarbonyl which may be substituted,
a N,N-di-C_3-C_7 cycloalkenylaminocarbonyl which may be substituted,
a N-C_3-C_7 cycloalkenyl-N-C_6-C_{10} arylaminocarbonyl which may be substituted,
a N-C_3-C_7 cycloalkenyl-N-heterocycle-aminocarbonyl which may be substituted,
a N,N-di-C_6-C_{10} arylaminocarbonyl which may be substituted,
a N-C_6-C_{10} aryl-N-heterocycle-aminocarbonyl which may be substituted, or
a N,N-di-heterocycle-aminocarbonyl which may be substituted, aminothiocarbonyl,
a C_1-C_6 alkylaminothiocarbonyl which may be substituted,
a C_3-C_6 alkenylaminothiocarbonyl which may be substituted,
a C_3-C_6 alkynylaminothiocarbonyl which may be substituted,
a C_3-C_7 cycloalkylaminothiocarbonyl which may be substituted,
a C_3-C_7 cycloalkenylaminothiocarbonyl which may be substituted,
a C_6-C_{10} arylaminothiocarbonyl which may be substituted,
a heterocycle-aminothiocarbonyl which may be substituted,
a N,N-di-C_1-C_6 alkylaminothiocarbonyl which may be substituted,
a N-C_1-C_6 alkyl-N-C_3-C_7 alkenylaminothiocarbonyl which may be substituted,
a N-C_1-C_6 alkyl-N-C_3-C_7 alkynylaminothiocarbonyl which may be substituted,
a N-C_1-C_6 alkyl-N-C_3-C_7 cycloalkylaminothiocarbonyl which may be substituted,
a N-C_1-C_6 alkyl-N-C_3-C_7 cycloalkenylaminothiocarbonyl which may be substituted,
a N-C_1-C_6 alkyl-N-C_6-C_{10} arylaminothiocarbonyl which may be substituted,
a N-C_1-C_6 alkyl-N-heterocycle-aminothiocarbonyl which may be substituted,
a N,N-di-C_3-C_6 alkenylaminothiocarbonyl which may be substituted,
a N-C_3-C_6 alkenyl-N-C_3-C_6 alkynylaminothiocarbonyl which may be substituted,
a N-C_3-C_6 alkenyl-N-C_3-C_7 cycloalkylaminothiocarbonyl which may be substituted,
a N-C_3-C_6 alkenyl-N-C_3-C_7 cycloalkenylaminothiocarbonyl which may be substituted,
a N-C_3-C_6 alkenyl- N-C_6-C_{10} arylaminothiocarbonyl which may be substituted,
a N-C_3-C_6 alkenyl- N-heterocycle-aminothiocarbonyl which may be substituted,
a N,N-di-C_3-C_6 alkynylaminothiocarbonyl which may be substituted,
a N-C_3-C_6 alkynyl-N-C_3-C_7 cycloalkylaminothiocarbonyl which may be substituted,
a N-C_3-C_6 alkynyl-N-C_3-C_7 cycloalkenylaminothiocarbonyl which may be substituted,
a N-C_3-C_6 alkynyl-N-C_6-C_{10} arylaminothiocarbonyl which may be substituted,
a N-C_3-C_6 alkynyl-N-heterocycle-aminothiocarbonyl which may be substituted,
a N,N-di-C_3-C_7 cycloalkylaminothiocarbonyl which may be substituted,
a N-C_3-C_7 cycloalkyl-N-C_3-C_7 cycloalkenylaminothiocarbonyl which may be substituted,
a N-C_3-C_7 cycloalkyl-N-C_6-C_{10} arylaminothiocarbonyl which may be substituted,
a N-C_3-C_7 cycloalkyl-N-heterocycle-aminothiocarbonyl which may be substituted,
a N,N-di-C_3-C_7 cycloalkenylaminothiocarbonyl which may be substituted,
a N-C_3-C_7 cycloalkenyl-N-C_6-C_{10} arylaminothiocarbonyl which may be substituted,
a N-C_3-C_7 cycloalkenyl-N-heterocycle-aminothiocarbonyl which may be substituted,
a N,N-di-C_6-C_{10} arylaminothiocarbonyl which may be substituted,
a N-C_6-C_{10} aryl-N-heterocycle-aminothiocarbonyl which may be substituted, or
a N,N-di-heterocycle-aminothiocarbonyl which may be substituted,
R^4 represents hydrogen atom, or
a group represented by the following formula (III):

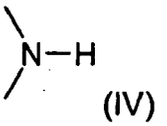


(III)

wherein Z represents a bond, carbonyl or sulfonyl,
R^5 and R^6 each independently represents hydrogen atom,
a C_1-C_6 alkyl which may be substituted,
a C_2-C_6 alkenyl which may be substituted,
a C_2-C_6 alkynyl which may be substituted,
a C_3-C_7 cycloalkyl which may be substituted,
a C_3-C_7 cycloalkenyl which may be substituted,
a C_6-C_{10} aryl which may be substituted,
a heterocycle which may be substituted,
a C_1-C_6 alkylcarbonyl which may be substituted,
a C_2-C_6 alkenylcarbonyl which may be substituted,
a C_2-C_6 alkynylcarbonyl which may be substituted,
a C_3-C_7 cycloalkylcarbonyl which may be substituted,
a C_3-C_7 cycloalkenylcarbonyl which may be substituted,
a C_6-C_{10} arylcarbonyl which may be substituted,
a heterocycle-carbonyl which may be substituted,
a C_1-C_6 alkylsulfonyl which may be substituted,
a C_3-C_6 alkenylsulfonyl which may be substituted,
a C_3-C_6 alkynylsulfonyl which may be substituted,
a C_3-C_7 cycloalkylsulfonyl which may be substituted,
a C_3-C_7 cycloalkenylsulfonyl which may be substituted,
a C_6-C_{10} arylsulfonyl which may be substituted,
a heterocycle-sulfonyl which may be substituted, carboxyl,
a C_1-C_6 alkyloxycarbonyl which may be substituted,
a C_3-C_6 alkenyloxycarbonyl which may be substituted,
a C_3-C_6 alkynyloxycarbonyl which may be substituted,
a C_3-C_7 cycloalkyloxycarbonyl which may be substituted,
a C_3-C_7 cycloalkenyloxycarbonyl which may be substituted,
a C_6-C_{10} aryloxycarbonyl which may be substituted,
a heterocycle-oxycarbonyl which may be substituted, aminocarbonyl,
a C_1-C_6 alkylaminocarbonyl which may be substituted,
a C_3-C_6 alkenylaminocarbonyl which may be substituted,
a C_3-C_6 alkynylaminocarbonyl which may be substituted,
a C_3-C_7 cycloalkylaminocarbonyl which may be substituted,
a C_3-C_7 cycloalkenylaminocarbonyl which may be substituted,
a C_6-C_{10} arylaminocarbonyl which may be substituted,
a heterocycle-aminocarbonyl which may be substituted,
a N,N-di-C_1-C_6 alkylaminocarbonyl which may be substituted,
a N-C_1-C_6 alkyl-N-C_3-C_7 alkenylaminocarbonyl which may be substituted,
a N-C_1-C_6 alkyl-N-C_3-C_7 alkynylaminocarbonyl which may be substituted,
a N-C_1-C_6 alkyl-N-C_3-C_7 cycloalkylaminocarbonyl which may be substituted,
a N-C_1-C_6 alkyl-N-C_3-C_7 cycloalkenylaminocarbonyl which may be substituted,
a N-C_1-C_6 alkyl-N-C_6-C_{10} arylaminocarbonyl which may be substituted,
a N-C_1-C_6 alkyl-N-heterocycle-aminocarbonyl which may be substituted,
a N,N-di-C_3-C_6 alkenylaminocarbonyl which may be substituted,
a N-C_3-C_6 alkenyl-N-C_3-C_6 alkynylaminocarbonyl which may be substituted,
a N-C_3-C_6 alkenyl-N-C_3-C_7 cycloalkylaminocarbonyl which may be substituted,
a N-C_3-C_6 alkenyl-N-C_3-C_7 cycloalkenylaminocarbonyl which may be substituted,
a N-C_3-C_6 alkenyl- N-C_6-C_{10} arylaminocarbonyl which may be substituted,
a N-C_3-C_6 alkenyl- N-heterocycle-aminocarbonyl which may be substituted,
a N,N-di-C_3-C_6 alkynylaminocarbonyl which may be substituted,

a N-C_3-C_6 alkynyl-N-C_3-C_7 cycloalkylaminocarbonyl which may be substituted,
a N-C_3-C_6 alkynyl-N-C_3-C_7 cycloalkenylaminocarbonyl which may be substituted,
a N-C_3-C_6 alkynyl-N-C_6-C_{10} arylaminocarbonyl which may be substituted,
a N-C_3-C_6 alkynyl-N-heterocycle-aminocarbonyl which may be substituted,
a N,N-di-C_3-C_7 cycloalkylaminocarbonyl which may be substituted,
a N-C_3-C_7 cycloalkyl-N-C_3-C_7 cycloalkenylaminocarbonyl which may be substituted,
a N-C_3-C_7 cycloalkyl-N-C_6-C_{10} arylaminocarbonyl which may be substituted,
a N-C_3-C_7 cycloalkyl-N-heterocycle-aminocarbonyl which may be substituted,
a N,N-di-C_3-C_7 cycloalkenylaminocarbonyl which may be substituted,
a N-C_3-C_7 cycloalkenyl-N-C_6-C_{10} arylaminocarbonyl which may be substituted,
a N-C_3-C_7 cycloalkenyl-N-heterocycle-aminocarbonyl which may be substituted,
a N,N-di-C_6-C_{10} arylaminocarbonyl which may be substituted,
a N-C_6-C_{10} aryl-N-heterocycle-aminocarbonyl which may be substituted, or
a N,N-di-heterocycle-aminocarbonyl which may be substituted, aminothiocarbonyl,
a C_1-C_6 alkylaminothiocarbonyl which may be substituted,
a C_3-C_6 alkenylaminothiocarbonyl which may be substituted,
a C_3-C_6 alkynylaminothiocarbonyl which may be substituted,
a C_3-C_7 cycloalkylaminothiocarbonyl which may be substituted,
a C_3-C_7 cycloalkenylaminothiocarbonyl which may be substituted,
a C_6-C_{10} arylaminothiocarbonyl which may be substituted,
a heterocycle-aminothiocarbonyl which may be substituted,
a N,N-di-C_1-C_6 alkylaminothiocarbonyl which may be substituted,
a N-C_1-C_6 alkyl-N-C_3-C_7 alkenylaminothiocarbonyl which may be substituted,
a N-C_1-C_6 alkyl-N-C_3-C_7 alkynylaminothiocarbonyl which may be substituted,
a N-C_1-C_6 alkyl-N-C_3-C_7 cycloalkylaminothiocarbonyl which may be substituted,
a N-C_1-C_6 alkyl-N-C_3-C_7 cycloalkenylaminothiocarbonyl which may be substituted,
a N-C_1-C_6 alkyl-N-C_6-C_{10} arylaminothiocarbonyl which may be substituted,
a N-C_1-C_6 alkyl-N-heterocycle-aminothiocarbonyl which may be substituted,
a N,N-di-C_3-C_6 alkenylaminothiocarbonyl which may be substituted,
a N-C_3-C_6 alkenyl-N-C_3-C_6 alkynylaminothiocarbonyl which may be substituted,
a N-C_3-C_6 alkenyl-N-C_3-C_7 cycloalkylaminothiocarbonyl which may be substituted,
a N-C_3-C_6 alkenyl-N-C_3-C_7 cycloalkenylaminothiocarbonyl which may be substituted,
a N-C_3-C_6 alkenyl- N-C_6-C_{10} arylaminothiocarbonyl which may be substituted,
a N-C_3-C_6 alkenyl- N-heterocycle-aminothiocarbonyl which may be substituted,
a N,N-di-C_3-C_6 alkynylaminothiocarbonyl which may be substituted,
a N-C_3-C_6 alkynyl-N-C_3-C_7 cycloalkylaminothiocarbonyl which may be substituted,
a N-C_3-C_6 alkynyl-N-C_3-C_7 cycloalkenylaminothiocarbonyl which may be substituted,
a N-C_3-C_6 alkynyl-N-C_6-C_{10} arylaminothiocarbonyl which may be substituted,
a N-C_3-C_6 alkynyl-N-heterocycle-aminothiocarbonyl which may be substituted,
a N,N-di-C_3-C_7 cycloalkylaminothiocarbonyl which may be substituted,
a N-C_3-C_7 cycloalkyl-N-C_3-C_7 cycloalkenylaminothiocarbonyl which may be substituted,
a N-C_3-C_7 cycloalkyl-N-C_6-C_{10} arylaminothiocarbonyl which may be substituted,
a N-C_3-C_7 cycloalkyl-N-heterocycle-aminothiocarbonyl which may be substituted,
a N,N-di-C_3-C_7 cycloalkenylaminothiocarbonyl which may be substituted,
a N-C_3-C_7 cycloalkenyl-N-C_6-C_{10} arylaminothiocarbonyl which may be substituted,
a N-C_3-C_7 cycloalkenyl-N-heterocycle-aminothiocarbonyl which may be substituted,
a N,N-di-C_6-C_{10} arylaminothiocarbonyl which may be substituted,
a N-C_6-C_{10} aryl-N-heterocycle-aminothiocarbonyl which may be substituted, or
a N,N-di-heterocycle-aminothiocarbonyl which may be substituted, or

R^5 and R^6 may combine to each other to form a 3 to 7-membered nitrogen-containing heterocyclic ring which may further contain oxygen and/or sulfur atom and may be substituted, or
R^5 and R^3 may combine to each other to form a 5 to 7-membered nitrogen-containing heterocyclic ring which may further contain oxygen and/or sulfur atom and may be substituted,
each of r and s represents 0 or an integer of 1 to 5, provided that sum of r and s is 5 or less;
X represents oxygen atom, or
a group represented by the following formula (IV):



(IV)

2. The compound, an optically active isomer thereof, or a pharmaceutically acceptable salt thereof according to claim 1, wherein R^1 is a C_1-C_6 alkyl.

3. The compound, an optically active isomer thereof, or a pharmaceutically acceptable salt thereof according to claim 1, wherein R^1 is methyl group.

4. The compound, an optically active isomer thereof, or a pharmaceutically acceptable salt thereof according to any one of the claims 1 to 3, wherein A is phenyl group.

5. The compound, an optically active isomer thereof, or a pharmaceutically acceptable salt thereof according to any one of the claims 1 to 4, wherein X is oxygen atom.

6. The compound, an optically active isomer thereof, or a pharmaceutically acceptable salt thereof according to any one of the claims 1 to 4, wherein X is a group represented by the formula (IV).

7. A compound according to claim 1 selected from the group consisting of:

6-(3-Fluoro-pyridin-4-yl)-3-methyl-2-((3S)-3-(4-morpholin-4-yl-phenyl)-piperazin-1-yl)-3H-pyrimidin-4-one;
2-((2S)-2-(4-((3R)-3-Dimethylamino-pyrrolidin-1-yl)-phenyl)-morpholin-4-yl)-6-(3-fluoro-pyridin-4-yl)-3-methyl-3H-pyrimidin-4-one;
6-(3-Fluoro-pyridin-4-yl)-3-methyl-2-((3S)-3-(4-piperidin-1-yl-phenyl)-piperazin-1-yl)-3H-pyrimidin-4-one;
6-(3-Fluoro-pyridin-4-yl)-3-methyl-2-((2S)-2-(4-(4-pyrrolidin-1-yl-piperidin-1-yl)-phenyl(-morpholin-4-yl)-3H-pyrimidin-4-one;
2-((2S)-2-(4-(4-Dimethylamino-piperidin-1-yl)-phenyl)-morpholin-4-yl)-6-(3-fluoro-pyridin-4-yl)-3-methyl-3H-pyrimidin-4-one;
6-(3-Fluoro-pyridin-4-yl)-3-methyl-2-((3S)-3-(4-(4-methyl-piperazin-1-yl)-phenyl)-piperazin-1-yl)-3H-pyrimidin-4-one;
6-(3-Fluoro-pyridin-4-yl)-2-(3S)-3-(4-(4-hydroxy-piperidin-1-yl)-phenyl)-piperazin-1-yl)-3-methyl-3H-pyrimidin-4-one;
6-(3-Fluoro-pyridin-4-yl)-2-((3S)-3-(4-((3R)-3-hydroxy-pyrrolidin-1-yl)-phenyl)-piperazin-1-yl)-3-methyl-3H-pyrimidin-4-one;
2-((2S)-2-(4-((3S,5R)-3,5-Dimethyl-piperazin-1-yl)-phenyl)-morpholin-4-yl)-6-(3-fluoro-pyridin-4-yl)-3-methyl-3H-pyrimidin-4-one;
6-(3-Fluoro-pyridin-4-yl)-3-methyl-2-((2S)-2-(4-(4-methyl-piperazin-1-yl)-phenyl)-morpholin-4-yl)-3H-pyrimidin-4-one;
2-((2S)-2-(4-((3S)-3-Dimethylamino-pyrrolidin-1-yl)-phenyl)-morpholin-4-yl)-6-(3-fluoro-pyridin-4-yl)-3-methyl-3H-pyrimidin-4-one;
6-(3-Fluoro-pyridin-4-yl)-2-((2S)-2-(4-(4-isopropyl-piperazin-1-yl)-phenyl)-morpholin-4-yl)-3-methyl-3H-pyrimidin-4-one;
6-(3-Fluoro-pyridin-4-yl)-2-((2S)-2-(4-(4-(2-hydroxyethyl)-piperazin-1-yl)-phenyl)-morpholin-4-yl)-3-methyl-3H-pyrimidin-4-one;
6-(3-fluoro-pyridin-4-yl)-3-methyl-2-((3S)-3-(4-((3S)-3-(pyrrolidin-1-yl)-pyrrolidin-1-yl)-phenyl)-piperazin-1-yl)-3H-pyrimidin-4-one;
6-(3-Fluoro-pyridin-4-yl)-3-methyl-2-((3S)-3-(4-(5-methyl-(1,2,4)oxadiazol-3-yl)-phenyl)-piperazin-1-yl)-3H-pyrimidin-4-one;
2-((2S)-2-(4-Cyclopentylamino-phenyl)-morpholin-4-yl)-6-(3-fluoro-pyridin-4-yl)-3-methyl-3H-pyrimidin-4-one;
6-(3-Fluoro-pyridin-4-yl)-2-((2S)-2-(4-(3-hydroxy-azetidin-1-yl)-phenyl)-morpholin-4- yl)-3-methyl-3H-pyrimidin-4-one;
N-(4-((2S)-4-((4-(3-Fluoro-pyridin-4-yl)-1-methyl-6-oxo-1,6-dihydro-pyrimidin-2-yl)-morpholin-2-yl)-phenyl)-acetamide;
2-((2S)-2-(4-Cyclopentyloxy-phenyl)-morpholin-4-yl)-6-(3-fluoro-pyridin-4-yl)-3-methyl-3H-pyrimidin-4-one;
2-((2S)-2-(4-Cyclopropylmethoxy-phenyl)-morpholin-4-yl)-6-(3-fluoro-pyridin-4-yl)-3- methyl-3H-pyrimidin-

4-one;
2-((2S)-2-(4-(2-Dimethylamino-ethoxy)-phenyl)-morpholin-4-yl)-6-(3-fluoro-pyridin-4- yl)-3-methyl-3H-pyrimidin-4-one;
2-((2S)-2-(4-Amino-phenyl)-morpholin-4-yl)-6-(3-fluoro-pyridin-4-yl)-3-methyl-3H-pyrimidin-4-one;
Cyclopropanecarboxylic acid (4-((2S)-4-(4-(3-fluoro-pyridin-4-yl)-1-methyl-6-oxo-1,6- dihydro-pyrimidin-2-yl)-morpholin-2-yl)-phenyl)-amide;
N-(4-((2S)-4-(4-(3-Fluoro-pyridin-4-yl)-1-methyl-6-oxo-1,6-dihydro-pyrimidin-2-yl)-morpholin-2-yl)-phenyl)-2,2-dimethyl-propionamide;
6-(3-Fluoro-pyridin-4-yl)-3-methyl-2-((2S)-2-(4-(methyl-((3R)-tetrahydro-furan-3-yl)- amino)-phenyl)-morpholin-4-yl)-3H-pyrimidin-4-one;
6-(3-Fluoro-pyridin-4-yl)-3-methyl-2-((2S)-2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-morpholin-4-yl)-3H-pyrimidin-4-one;
6-(3-Fluoro-pyridin-4-yl)-2-((2S)-2-(4-hydroxy-phenyl)-morpholin-4-yl)-3-methyl-3H-pyrimidin-4-one;
2-((2S)-2-(4-(2-Diethylamino-ethoxy)-phenyl)-morpholin-4-yl)-6-(3-fluoro-pyridin-4-yl)-3-methyl-3H-pyrimidin-4-one;
6-(3-Fluoro-pyridin-4-yl)-3-methyl-2-((2S)-2-(4-(2-piperidin-1-yl-ethoxy)-phenyl)-morpholin-4-yl)-3H-pyrimidin-4-one;
6-(3-Fluoro-pyridin-4-yl)-3-methyl-2-((2S)-2-(4-(2-(4-methyl-piperazin-1-yl)-ethoxy)- phenyl)-morpholin-4-yl)-3H-pyrimidin-4-one;
N^2,N^2-Dimethyl-N^1-(4-((2S)-4-(3-methyl-4-oxo-3,4-dihydro-6-(3-fluoropyridin-4-yl pyrimidin-2-yl)morpholin-2-yl)phenyl)glycinamide;
Methyl (4-((2S)-4-(6-(3-fluoropyridin-4-yl)-3-methyl-4-oxo-3H-pyrimidin- 2-yl)morpholin-2-yl)phenyl)carbamate;
N'-(4-((2S)-4-(6-(3-Fluoropyridin-4-yl)-3-methyl-4-oxo-3H-pyrimidin-2-yl)morpholin-2-yl)phenyl)-N,N-dimethylurea;
6-{4-[4-(3-Fluoropyridin-4-yl)-1-methyl-6-oxo-1,6-dihydropyrimidin-2-yl]morpholin-2- yl}-3,4-dihydroquinolin-2(1H)-one;
6-(3-Fluoro-pyridin-4-yl)-3-methyl-2-{(2S)-2-[4-morpholine-4-carbonyl]-phenyl}-morpholin-4-yl}-3H-pyrimidin-4-one;
N-(3-{(2S)-4-[4-(3-Fluoropyridin-4-yl)-1-methyl-6-oxo-1,6-dihydropyrimidin-2-yl]-morpholin-2-yl}-4-methoxyphenyl)acetamide;
N-(3-{(2S)-4-[4-(3-Fluoropyridin-4-yl)-1-methyl-6-oxo-1,6-dihydropyrimidin-2-yl]-morpholin-2-yl}phenyl)acetamide; and
6-(3-Fluoropyridin-4-yl)-3-methyl-2-((3S)-3-(4-([1,2,4]oxadiazol-3-yl)phenyl)piperazin- 1-yl)-3H-pyrimidin-4-one,

an optically active isomer thereof, or a pharmaceutically acceptable salt thereof.

8. A medicament comprising as an active ingredient a substance selected from the group consisting of the compound represented by the formula (I) and an optically active isomer thereof, or a pharmaceutically acceptable salt thereof according to claim 1.

9. The medicament according to claim 8 which is used for preventive and/or therapeutic treatment of a disease caused by tau protein kinase 1 hyperactivity to suppress the neurotoxicity of beta amyloid protein and the formation of the paired helical filament and to inhibit the death of nerve cells..

10. The medicament according to claim 8 which is used for preventive and/or therapeutic treatment of a neurodegenerative disease

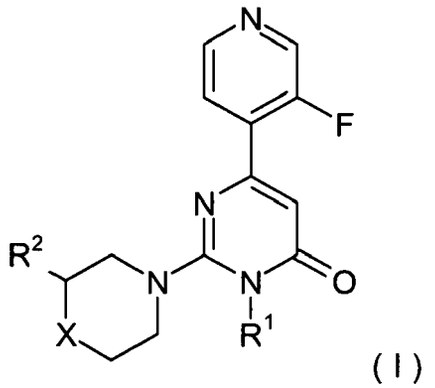
11. The medicament according to claim 10, wherein the disease is selected from the group consisting of Alzheimer disease, ischemic cerebrovascular accidents, Down syndrome, cerebral bleeding due to cerebral amyloid angiopathy, progressive supranuclear palsy, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, Guam parkinsonism-dementia complex, Lewy body disease, Pick's disease, corticobasal degeneration, frontotemporal dementia, vascular dementia, traumatic injuries, brain and spinal cord trauma, peripheral neuropathies, retinopathies and glaucoma.

12. The medicament according to claim 8, which is used for preventive and/or therapeutic treatment of a disease selected from the group consisting of non-insulin dependent diabetes, obesity, manic depressive illness, schizophrenia, alopecia, breast cancer, non-small cell lung carcinoma, thyroid cancer, T or B-cell leukemia, and a virus-induced

tumor.

Patentansprüche

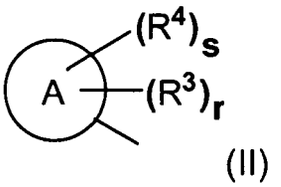
1. Verbindung, wiedergegeben durch die Formel (I), ein optisch aktives Isomer derselben oder ein pharmazeutisch akzeptables Salz derselben:



(I)

worin jedes Symbol wie unten definiert ist:

R^1 bedeutet ein C_1-C_{12}-Alkyl;
R^2 bedeutet eine Gruppe wiedergegeben durch die folgende Formel (II):



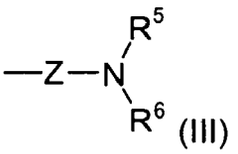
(II)

worin A ein C_6-C_{10}-Aryl oder einen Heterocyclus bedeutet, ausgewählt aus der Gruppe bestehend aus Benzofuran, Dihydrobenzofuran, Isobenzofuran, Chromen, Indol, Indolin, Isoindol, Benzoxazolinon, Tetrahydroisochinolin, Chroman, Isochroman, Benzothiophen, Isoindolin, Indazol, Benzimidazol, Benzotriazol, Benzothiazolinon, Chinolin, Phthalazin, Chinoxalin, Chinazolin, Cinnolin, Benzothiazol, Benzodioxol, Benzodioxan, Phthalimid;
R^3 gleich oder unterschiedlich sein kann und
ein Wasserstoffatom,
Hydroxyl,
ein Halogen,
Nitro,
Cyano
ein C_1-C_6-Alkyl, das substituiert sein kann,
ein C_2-C_6-Alkenyl, das substituiert sein kann,
ein C_2-C_6-Alkinyl, das substituiert sein kann,
ein C_3-C_7-Cycloalkyl, das substituiert sein kann,
ein C_3-C_7-Cycloalkenyl, das substituiert sein kann,
ein C_6-C_{10}-Aryl, das substituiert sein kann,
ein Heterocyclus, der substituiert sein kann,
ein C_1-C_6-Alkyloxy, das substituiert sein kann,
ein C_3-C_6-Alkenyloxy, das substituiert sein kann,
ein C_3-C_6-Alkinyloxy, das substituiert sein kann,
ein C_3-C_7-Cycloalkyloxy, das substituiert sein kann,
ein C_3-C_7-Cycloalkenyloxy, das substituiert sein kann,

ein C_6-C_{10}-Aryloxy, das substituiert sein kann,
eine Heterocyclus-Oxy-Gruppe, die substituiert sein kann, Mercapto,
ein C_1-C_6-Alkylthio, das substituiert sein kann,
ein C_3-C_6-Alkenylthio, das substituiert sein kann,
ein C_3-C_6-Alkinylthio, das substituiert sein kann,
ein C_3-C_7-Cycloalkylthio, das substituiert sein kann,
ein C_3-C_7-Cycloalkenylthio, das substituiert sein kann,
ein C_6-C_{10}-Arylthio, das substituiert sein kann,
eine Heterocyclus-Thio-Gruppe, die substituiert sein kann, Amino,
ein C_1-C_6-Alkylamino, das substituiert sein kann,
ein C_3-C_6-Alkenylamino, das substituiert sein kann,
ein C_3-C_6-Alkinylamino, das substituiert sein kann,
ein C_3-C_7-Cycloalkylamino, das substituiert sein kann,
ein C_3-C_7-Cycloalkenylamino, das substituiert sein kann,
ein C_6-C_{10}-Arylamino, das substituiert sein kann,
ein Heterocyclus-Amino, das substituiert sein kann,
ein N,N-Di-C_1-C_6-alkylamino, das substituiert sein kann,
ein N-C_1-C_6-Alkyl-N-C_3-C_6-alkenylamino, das substituiert sein kann,
ein N-C_1-C_6-Alkyl-N-C_3-C_6-alkinylamino, das substituiert sein kann,
ein N-C_1-C_6-Alkyl-N-C_3-C_7-cycloalkylamino, das substituiert sein kann,
ein N-C_1-C_6-Alkyl-N-C_3-C_7-cycloalkenylamino, das substituiert sein kann,
ein N-C_1-C_6-Alkyl-N-C_6-C_{10}-arylamino, das substituiert sein kann,
ein N-C_1-C_6-Alkyl-N-Heterocyclus-Amino, das substituiert sein kann,
ein N,N-Di-C_3-C_6-alkenylamino, das substituiert sein kann,
ein N-C_3-C_6-Alkenyl-N-C_3-C_6-alkinylamino, das substituiert sein kann,
ein N-C_3-C_6-Alkenyl-N-C_3-C_7-cycloalkylamino, das substituiert sein kann,
ein N-C_3-C_6-Alkenyl-N-C_3-C_7-cycloalkenylamino, das substituiert sein kann,
ein N-C_3-C_6-Alkenyl-N-C_6-C_{10}-arylamino, das substituiert sein kann,
ein N-C_3-C_6-Alkenyl-N-Heterocyclus-Amino, das substituiert sein kann,
ein N,N-Di-C_3-C_6-alkinylamino, das substituiert sein kann,
ein N-C_3-C_6-Alkinyl-N-C_3-C_7-cycloalkylamino, das substituiert sein kann,
ein N-C_3-C_6-Alkinyl-N-C_3-C_7-cycloalkenylamino, das substituiert sein kann,
ein N-C_3-C_6-Alkinyl-N-C_6-C_{10}-arylamino, das substituiert sein kann,
ein N-C_3-C_6-Alkinyl-N-Heterocyclus-Amino, das substituiert sein kann,
ein N,N-Di-C_3-C_7-cycloalkylamino, das substituiert sein kann,
ein N-C_3-C_7-Cycloalkyl-N-C_3-C_7-cycloalkenylamino, das substituiert sein kann,
ein N-C_3-C_7-Cycloalkyl-N-C_6-C_{10}-arylamino, das substituiert sein kann,
ein N-C_3-C_7-Cycloalkyl-N-Heterocyclus-Amino, das substituiert sein kann,
ein N,N-Di-C_3-C_7-cycloalkenylamino, das substituiert sein kann,
ein N-C_3-C_7-Cycloalkenyl-N-C_6-C_{10}-arylamino, das substituiert sein kann,
ein N-C_3-C_7-Cycloalkenyl-N-Heterocyclus-Amino, das substituiert sein kann,
ein N,N-Di-C_6-C_{10}-arylamino, das substituiert sein kann,
ein N-C_6-C_{10}-Aryl-N-Heterocyclus-Amino, das substituiert sein kann,
ein N,N-Diheterocyclus-Amino, das substituiert sein kann,
ein C_1-C_6-Alkylcarbonyl, das substituiert sein kann,
ein C_2-C_6-Alkenylcarbonyl, das substituiert sein kann,
ein C_2-C_6-Alkinylcarbonyl, das substituiert sein kann,
ein C_3-C_7-Cycloalkylcarbonyl, das substituiert sein kann,
ein C_3-C_7-Cycloalkenylcarbonyl, das substituiert sein kann,
ein C_6-C_{10}-Arylcarbonyl, das substituiert sein kann,
ein Heterocyclus-Carbonyl, das substituiert sein kann,
ein C_1-C_6-Alkylsulfonyl, das substituiert sein kann,
ein C_3-C_6-Alkenylsulfonyl, das substituiert sein kann,
ein C_3-C_6-Alkinylsulfonyl, das substituiert sein kann,
ein C_3-C_7-Cycloalkylsulfonyl, das substituiert sein kann,
ein C_3-C_7-Cycloalkenylsulfonyl, das substituiert sein kann,
ein C_6-C_{10}-Arylsulfonyl, das substituiert sein kann,
ein Heterocyclus-Sulfonyl, das substituiert sein kann,

Carboxyl,
ein C_1-C_6-Alkyloxycarbonyl, das substituiert sein kann,
ein C_3-C_6-Alkenyloxycarbonyl, das substituiert sein kann,
ein C_3-C_6-Alkinyloxycarbonyl, das substituiert sein kann,
ein C_3-C_7-Cycloalkyloxycarbonyl, das substituiert sein kann,
ein C_3-C_7-Cycloalkenyloxycarbonyl, das substituiert sein kann,
ein C_6-C_{10}-Aryloxycarbonyl das substituiert sein kann,
ein Heterocyclus-Oxycarbonyl, das substituiert sein kann, Aminocarbonyl,
ein C_1-C_6-Alkylaminocarbonyl, das substituiert sein kann,
ein C_3-C_6-Alkenylaminocarbonyl, das substituiert sein kann,
ein C_3-C_6-Alkinylaminocarbonyl, das substituiert sein kann,
ein C_3-C_7-Cycloalkylaminocarbonyl, das substituiert sein kann,
ein C_3-C_7-Cycloalkenylaminocarbonyl, das substituiert sein kann,
ein C_6-C_{10}-Arylaminocarbony, das substituiert sein kann,
ein Heterocyclus-Aminocarbonyl, das substituiert sein kann,
ein N,N-Di-C_1-C_6-alkylaminocarbonyl, das substituiert sein kann,
ein N-C_1-C_6-Alkyl-N-C_3-C_7-alkenylaminocarbonyl, das substituiert sein kann,
ein N-C_1-C_6-Alkyl-N-C_3-C_7-alkinylaminocarbonyl, das substituiert sein kann,
ein N-C_1-C_6-Alkyl-N-C_3-C_7-cycloalkylaminocarbonyl, das substituiert sein kann,
ein N-C_1-C_6-Alkyl-N-C_3-C_7-cycloalkenylaminocarbonyl, das substituiert sein kann,
ein N-C_1-C_6-Alkyl-N-C_6-C_{10}-arylaminocarbonyl, das substituiert sein kann,
ein N-C_1-C_6-Alkyl-N-Heterocyclus-Aminocarbonyl, das substituiert sein kann,
ein N,N-Di-C_3-C_6-alkenylaminocarbonyl, das substituiert sein kann,
ein N-C_3-C_6-Alkenyl-N-C_3-C_6-alkinylaminocarbonyl, das substituiert sein kann,
ein N-C_3-C_6-Alkenyl-N-C_3-C_7-cycloalkylaminocarbonyl, das substituiert sein kann,
ein N-C_3-C_6-Alkenyl-N-C_3-C_7-cycloalkenylaminocarbonyl, das substituiert sein kann,
ein N-C_3-C_6-Alkenyl-N-C_6-C_{10}-arylaminocarbonyl, das substituiert sein kann,
ein N-C_3-C_6-Alkenyl-N-Heterocyclus-Aminocarbonyl, das substituiert sein kann,
ein N,N-Di-C_3-C_6-alkinylaminocarbonyl, das substituiert sein kann,
ein N-C_3-C_6-Alkinyl-N-C_3-C_7-cycloalkylaminocarbonyl, das substituiert sein kann,
ein N-C_3-C_6-Alkinyl-N-C_3-C_7-cycloalkenylaminocarbonyl, das substituiert sein kann,
ein N-C_3-C_6-Alkinyl-N-C_6-C_{10}-arylaminocarbonyl, das substituiert sein kann,
ein N-C_3-C_6-Alkinyl-N-Heterocyclus-Aminocarbonyl, das substituiert sein kann,
ein N,N-Di-C_3-C_7-cycloalkylaminocarbonyl, das substituiert sein kann,
ein N-C_3-C_7-Cycloalkyl-N-C_3-C_7-cycloalkenylaminocarbonyl, das substituiert sein kann,
ein N-C_3-C_7-Cycloalkyl-N-C_6-C_{10}-arylaminocarbonyl, das substituiert sein kann,
ein N-C_3-C_7-Cycloalkyl-N-Heterocyclus-Aminocarbonyl, das substituiert sein kann,
ein N,N-Di-C_3-C_7-cycloalkenylaminocarbonyl, das substituiert sein kann,
ein N-C_3-C_7-Cycloalkenyl-N-C_6-C_{10}-arylaminocarbonyl, das substituiert sein kann,
ein N-C_3-C_7-Cycloalkenyl-N-Heterocyclus-Aminocarbonyl, das substituiert sein kann,
ein N,N-Di-C_6-C_{10}-arylaminocarbonyl, das substituiert sein kann,
ein N-C_6-C_{10}-Aryl-N-Heterocyclus-Aminocarbonyl, das substituiert sein kann, oder
ein N,N-Diheterocyclus-Aminocarbonyl, das substituiert sein kann, Aminothiocarbonyl,
ein C_1-C_6-Alkylaminothiocarbonyl, das substituiert sein kann,
ein C_3-C_6-Alkenylaminothiocarbonyl, das substituiert sein kann,
ein C_3-C_6-Alkinylaminothiocarbonyl, das substituiert sein kann,
ein C_3-C_7-Cycloalkylaminothiocarbonyl, das substituiert sein kann,
ein C_3-C_7-Cycloalkenylaminothiocarbonyl, das substituiert sein kann,
ein C_6-C_{10}-Arylaminothiocarbonyl, das substituiert sein kann,
ein Heterocyclus-Aminothiocarbonyl, das substituiert sein kann,
ein N,N-Di-C_1-C_6-alkylaminothiocarbonyl, das substituiert sein kann,
ein N-C_1-C_6-Alkyl-N-C_3-C_7-alkenylaminothiocarbonyl, das substituiert sein kann,
ein N-C_1-C_6-Alkyl-N-C_3-C_7-alkinylaminothiocarbonyl, das substituiert sein kann,
ein N-C_1-C_6-Alkyl-N-C_3-C_7-cycloalkylaminothiocarbonyl, das substituiert sein kann,
ein N-C_1-C_6-Alkyl-N-C_3-C_7-cycloalkenylaminothiocarbonyl, das substituiert sein kann,
ein N-C_1-C_6-Alkyl-N-C_6-C_{10}-arylaminothiocarbonyl, das substituiert sein kann,
ein N-C_1-C_6-Alkyl-N-Heterocyclus-Aminothiocarbonyl, das substituiert sein kann,
ein N,N-Di-C_3-C_6-alkenylaminothiocarbonyl, das substituiert sein kann,

ein N-C_3-C_6-Alkenyl-N-C_3-C_6-alkinylaminothiocarbonyl, das substituiert sein kann,
ein N-C_3-C_6-Alkenyl-N-C_3-C_7-cycloalkylaminothiocarbonyl, das substituiert sein kann,
ein N-C_3-C_6-Alkenyl-N-C_3-C_7-cycloalkenylaminothiocarbonyl, das substituiert sein kann,
ein N-C_3-C_6-Alkenyl-N-C_6-C_{10}-arylaminothiocarbonyl, das substituiert sein kann,
ein N-C_3-C_6-Alkenyl-N-Heterocydus-Aminothiocarbonyl, das substituiert sein kann
ein N,N-Di-C_3-C_6-alkinylaminothiocarbonyl, das substituiert sein kann,
ein N-C_3-C_6-Alkinyl-N-C_3-C_7-cycloalkylaminothiocarbonyl, das substituiert sein kann,
ein N-C_3-C_6-Alkinyl-N-C_3-C_7-cycloalkenylaminothiocarbonyl, das substituiert sein kann,
ein N-C_3-C_6-Alkinyl-N-C_6-C_{10}-arylaminothiocarbonyl, das substituiert sein kann,
ein N-C_3-C_6-Alkinyl-N-Heterocyclus-Aminothiocarbonyl, das substituiert sein kann,
ein N,N-Di-C_3-C_7-cycloalkylaminothiocarbonyl, das substituiert sein kann,
ein N-C_3-C_7-Cycloalkyl-N-C_3-C_7-cycloalkenylaminothiocarbonyl, das substituiert sein kann,
ein N-C_3-C_7-Cycloalkyl-N-C_6-C_{10}-arylaminothiocarbonyl, das substituiert sein kann,
ein N-C_3-C_7-Cycloalkyl-N-Heterocyclus-Aminothiocarbonyl, das substituiert sein kann,
ein N,N-Di-C_3-C_7-cycloalkenylaminothiocarbonyl, das substituiert sein kann,
ein N-C_3-C_7-Cycloalkenyl-N-C_6-C_{10}-arylaminothiocarbonyl, das substituiert sein kann,
ein N-C_3-C_7-Cycloalkenyl-N-Heterocyclus-Aminothiocarbonyl, das substituiert sein kann,
ein N,N-Di-C_6-C_{10}-arylaminothiocarbonyl, das substituiert sein kann,
ein N-C_6-C_{10}-Aryl-N-Heterocyclus-Aminothiocarbonyl, das substituiert sein kann, oder
ein N,N-Diheterocyclus-Aminothiocarbonyl, das substituiert sein kann, bedeutet;
R^4 ein Wasserstoffatom oder
eine Gruppe bedeutet, wiedergegeben durch die folgende Formel (III):

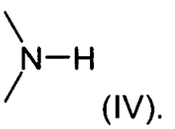


(III)

worin Z eine Bindung, Carbonyl oder Sulfonyl bedeutet, R^5 und R^6 jeweils unabhängig voneinander
ein Wasserstoffatom,
ein C_1-C_6-Alkyl, das substituiert sein kann,
ein C_2-C_6-Alkenyl, das substituiert sein kann,
ein C_2-C_6-Alkinyl, das substituiert sein kann,
ein C_3-C_7-Cycloalkyl, das substituiert sein kann,
ein C_3-C_7-Cycloalkenyl, das substituiert sein kann,
ein C_6-C_{10}-Aryl, das substituiert sein kann,
ein Heterocyclus, der substituiert sein kann,
ein C_1-C_6-Alkylcarbonyl, das substituiert sein kann,
ein C_2-C_6-Alkenylcarbonyl, das substituiert sein kann,
ein C_2-C_6-Alkinylcarbonyl, das substituiert sein kann,
ein C_3-C_7-Cycloalkylcarbonyl, das substituiert sein kann,
ein C_3-C_7-Cycloalkenylcarbonyl, das substituiert sein kann,
ein C_6-C_{10}-Arylcarbonyl, das substituiert sein kann,
ein Heterocyclus-Carbonyl, das substituiert sein kann,
ein C_1-C_6-Alkylsulfonyl, das substituiert sein kann,
ein C_3-C_6-Alkenylsulfonyl, das substituiert sein kann,
ein C_3-C_6-Alkinylsulfonyl, das substituiert sein kann,
ein C_3-C_7-Cycloalkylsulfonyl, das substituiert sein kann,
ein C_3-C_7-Cycloalkenylsulfonyl, das substituiert sein kann,
ein C_6-C_{10}-Arylsulfonyl, das substituiert sein kann,
ein Heterocyclus-Sulfonyl, das substituiert sein kann, Carboxyl,
ein C_1-C_6-Alkyloxycarbonyl, das substituiert sein kann,
ein C_3-C_6-Alkenyloxycarbonyl, das substituiert sein kann,
ein C_3-C_6-Alkinyloxycarbonyl, das substituiert sein kann,
ein C_3-C_7-Cycloalkyloxycarbonyl, das substituiert sein kann,
ein C_3-C_7-Cycloalkenyloxycarbonyl, das substituiert sein kann,

ein C_6-C_{10}-Aryloxycarbonyl, das substituiert sein kann,
ein Heterocyclus-Oxycarbonyl, das substituiert sein kann, Aminocarbonyl,
ein C_1-C_6-Alkylaminocarbonyl, das substituiert sein kann,
ein C_3-C_6-Alkenylaminocarbonyl, das substituiert sein kann,
ein C_3-C_6-Alkinylaminocarbonyl, das substituiert sein kann,
ein C_3-C_7-Cycloalkylaminocarbonyl, das substituiert sein kann,
ein C_3-C_7-Cycloalkenylaminocarbonyl, das substituiert sein kann,
ein C_6-C_{10}-Arylaminocarbonyl, das substituiert sein kann,
ein Heterocyclus-Aminocarbonyl, das substituiert sein kann,
ein N,N-Di-C_1-C_6-alkylaminocarbonyl, das substituiert sein kann,
ein N-C_1-C_6-Alkyl-N-C_3-C_7-alkenylaminocarbonyl, das substituiert sein kann,
ein N-C_1-C_6-Alkyl-N-C_3-C_7-alkinylaminocarbonyl, das substituiert sein kann,
ein N-C_1-C_6-Alkyl-N-C_3-C_7-cycloalkylaminocarbonyl, das substituiert sein kann,
ein N-C_1-C_6-Alkyl-N-C_3-C_7-cycloalkenylaminocarbonyl, das substituiert sein kann,
ein N-C_1-C_6-Alkyl-N-C_6-C_{10}-arylaminocarbonyl, das substituiert sein kann,
ein N-C_1-C_6-Alkyl-N-Heterocyclus-Aminocarbonyl, das substituiert sein kann,
ein N,N-Di-C_3-C_6-alkenylaminocarbonyl, das substituiert sein kann,
ein N-C_3-C_6-Alkenyl-N-C_3-C_6-alkinylaminocarbonyl, das substituiert sein kann,
ein N-C_3-C_6-Alkenyl-N-C_3-C_7-cycloalkylaminocarbonyl, das substituiert sein kann,
ein N-C_3-C_6-Alkenyl-N-C_3-C_7-cydoalkenylaminocarbonyl, das substituiert sein kann,
ein N-C_3-C_6-Alkenyl-N-C_6-C_{10}-arylaminocarbonyl, das substituiert sein kann,
ein N-C_3-C_6-Alkenyl-N-Heterocyclus-Aminocarbonyl, das substituiert sein kann,
ein N,N-Di-C_3-C_6-alkinylaminocarbonyl, das substituiert sein kann,
ein N-C_3-C_6-Alkinyl-N-C_3-C_7-cycloalkylaminocarbonyl, das substituiert sein kann,
ein N-C_3-C_6-Alkinyl-N-C_3-C_7-cycloalkenylaminocarbonyl, das substituiert sein kann,
ein N-C_3-C_6-Alkinyl-N-C_6-C_{10}-arylaminocarbonyl, das substituiert sein kann,
ein N-C_3-C_6-Alkinyl-N-Heterocyclus-Aminocarbonyl, das substituiert sein kann,
ein N,N-Di-C3-C7-cycloalkylaminocarbonyl, das substituiert sein kann,
ein N-C_3-C_7-Cycloalkyl-N-C_3-C_7-cydoalkenylaminocarbonyl, das substituiert sein kann,
ein N-C_3-C_7-Cycloalkyl-N-C_6-C_{io}-arylaminocarbonyl, das substituiert sein kann,
ein N-C_3-C_7-Cycloalkyl-N-Heterocyclus-Aminocarbonyl, das substituiert sein kann,
ein N,N-Di-C_3-C_7-cycloalkenylaminocarbonyl, das substituiert sein kann,
ein N-C_3-C_7-Cycloalkenyl-N-C_6-C_{10}-arylaminocarbonyl, das substituiert sein kann,
ein N-C_3-C_7-Cycloalkenyl-N-Heterocyclus-Aminocarbonyl, das substituiert sein kann,
ein N,N-Di-C_6-C_{10}-arylaminocarbonyl, das substituiert sein kann,
ein N-C_6-C_{10}-Aryl-N-Heterocyclus-Aminocarbonyl, das substituiert sein kann, oder
ein N,N-Diheterocyclus-Aminocarbonyl, das substituiert sein kann, Aminothiocarbonyl,
ein C_1-C_6-Alkylaminothiocarbonyl, das substituiert sein kann,
ein C_3-C_6-Alkenylaminothiocarbonyl, das substituiert sein kann,
ein C_3-C_6-Alkinylaminothiocarbonyl, das substituiert sein kann,
ein C_3-C_7-Cycloalkylaminothiocarbonyl, das substituiert sein kann,
ein C_3-C_7-Cycloalkenylaminothiocarbonyl, das substituiert sein kann,
ein C_6-C_{10}-Arylaminothiocarbonyl, das substituiert sein kann,
ein Heterocyclus-Aminothiocarbonyl, das substituiert sein kann,
ein N,N-Di-C_1-C_6-alkylaminothiocarbonyl, das substituiert sein kann,
ein N-C_1-C_6-Alkyl-N-C_3-C_7-alkenylaminothiocarbonyl, das substituiert sein kann,
ein N-C_1-C_6-Alkyl-N-C_3-C_7-alkinylaminothiocarbonyl, das substituiert sein kann,
ein N-C_1-C_6-Alkyl-N-C_3-C_7-cycloalkylaminothiocarbonyl, das substituiert sein kann,
ein N-C_1-C_6-Alkyl-N-C_3-C_7-cycloalkenylaminothiocarbonyl, das substituiert sein kann,
ein N-C_1-C_6-Alkyl-N-C_6-C_{10}-arylaminothiocarbonyl, das substituiert sein kann,
ein N-C_1-C_6-Alkyl-N-Heterocyclus-Aminothiocarbonyl, das substituiert sein kann,
ein N,N-Di-C_3-C_6-alkenylaminothiocarbonyl, das substituiert sein kann,
ein N-C_3-C_6-Alkenyl-N-C_3-C_6-alkinylaminothiocarbonyl, das substituiert sein kann,
ein N-C_3-C_6-Alkenyl-N-C_3-C_7-cycloalkylaminothiocarbonyl, das substituiert sein kann,
ein N-C_3-C_6-Alkenyl-N-C_3-C_7-cydoalkenylaminothiocarbonyl, das substituiert sein kann,
ein N-C_3-C_6-Alkenyl-N-C_6-C_{10}-arylaminothiocarbonyl, das substituiert sein kann,
ein N-C_3-C_6-Alkenyl-N-Heterocyclus-Aminothiocarbonyl, das substituiert sein kann,
ein N,N-Di-C_3-C_6-alkinylaminothiocarbonyl, das substituiert sein kann,

ein N-C_3-C_6-Alkinyl-N-C_3-C_7-cycloalkylaminothiocarbonyl, das substituiert sein kann,
ein N-C_3-C_6-Alkinyl-N-C_3-C_7-cycloalkenylaminothiocarbonyl, das substituiert sein kann,
ein N-C_3-C_6-Alkinyl-N-C_6-C_{10}-arylaminothiocarbonyl, das substituiert sein kann,
ein N-C_3-C_6-Alkinyl-N-Heterocyclus-Aminothiocarbonyl, das substituiert sein kann,
ein N,N-Di-C_3-C_7-cycloalkylaminothiocarbonyl, das substituiert sein kann,
ein N-C_3-C_7-Cycloalkyl-N-C_3-C_7-cycloalkenylaminothiocarbonyl, das substituiert sein kann,
ein N-C_3-C_7-Cycloalkyl-N-C_6-C_{10}-arylaminothiocarbonyl, das substituiert sein kann,
ein N-C_3-C_7-Cycloalkyl-N-Heterocyclus-Aminothiocarbonyl, das substituiert sein kann,
ein N,N-Di-C_3-C_7-cycloalkenylaminothiocarbonyl, das substituiert sein kann,
ein N-C_3-C_7-Cycloalkenyl-N-C_6-C_{10}-arylaminothiocarbonyl, das substituiert sein kann,
ein N-C_3-C_7-Cycloalkenyl-N-Heterocyclus-Aminothiocarbonyl, das substituiert sein kann,
ein N,N-Di-C_6-C_{10}-arylaminothiocarbonyl, das substituiert sein kann,
ein N-C_6-C_{10}-Aryl-N-Heterocyclus-Aminothiocarbonyl, das substituiert sein kann, oder
ein N,N-Diheterocyclus-Aminothiocarbonyl, das substituiert sein kann, bedeuten oder
R^5 und R^6 miteinander verbunden sein können, um einen 3 bis 7-gliedrigen stickstoffhaltigen heterocyclisches Ring zu bilden, der ferner ein Sauerstoff-und/oder Schwefelatom enthalten kann und substituiert sein kann, oder
R^5 und R^3 miteinander verbunden sein können, um einen 5 bis 7-gliedrigen stickstoffhaltigen heterocyclisches Ring zu bilden, der ferner ein Sauerstoff-und/oder Schwefelatom enthalten kann und substituiert sein kann,
jedes von r und s null oder eine ganze Zahl von 1 bis 5 darstellt, vorausgesetzt, dass die Summe von r und s 5 oder weniger beträgt;
X bedeutet ein Sauerstoffatom oder
eine Gruppe wiedergegeben durch die folgende Formel (IV):



(IV).

2. Verbindung, ein optisch aktives Isomer derselben oder ein pharmazeutisch akzeptables Salz derselben gemäß Anspruch 1, worin R^1 ein C_1-C_6-Alkyl ist.

3. Verbindung, ein optisch aktives Isomer derselben oder ein pharmazeutisch akzeptables Salz derselben gemäß Anspruch 1, worin R^1 eine Methylgruppe ist.

4. Verbindung, ein optisch aktives Isomer derselben oder ein pharmazeutisch akzeptables Salz derselben gemäß einem der Ansprüche 1 bis 3, worin A eine Phenylgruppe ist.

5. Verbindung, ein optisch aktives Isomer derselben oder ein pharmazeutisch akzeptables Salz derselben gemäß einem der Ansprüche 1 bis 4, worin X ein Sauerstoffatom ist.

6. Verbindung, ein optisch aktives Isomer derselben oder ein pharmazeutisch akzeptables Salz derselben gemäß einem der Ansprüche 1 bis 4, worin X ein eine Gruppe ist, die durch Formel (IV) wiedergegeben wird.

7. Verbindung gemäß Anspruch 1, ausgewählt aus der Gruppe bestehend aus:

6-(3-Fluor-pyridin-4-yl)-3-methyl-2-((3S)-3-(4-morpholin-4-yl-phenyl)-piperazin-1-yl)-3H-pyrimidin-4-on;
2-((2S)-2-(4-((3R)-3-Dimethylamino-pyrrolidin-1-yl)-phenyl)-morpholin-4-yl)-6-(3-fluor-pyridin-4-yl)-3-methyl-3H-pyrimidin-4-on;
6-(3-Fluor-pyridin-4-yl)-3-methyl-2-((3S)-3-(4-piperidin-1-yl-phenyl)-piperazin-1-yl)-3H-pyrimidin-4-on;
6-(3-Fluor-pyrid in-4-yl)-3-methyl-2-((2S)-2-(4-(4-pyrrolidin-1-yl-piperidin-1-yl)-phenyl(-morpholin-4-yl)-3H-pyrimidin-4-on;
2-((2S)-2-(4-(4-Dimethylamino-piperidin-1-yl)-phenyl)-morpholin-4-yl)-6-(3-fluor-pyridin-4-yl)-3-methyl-3H-pyrimidin-4-on;
6-(3-Fluor-pyridin-4-yl)-3-methyl-2-((3S)-3-(4-(4-methyl-piperazin-1-yl)-phenyl)-piperazin-1-yl)-3H-pyrimidin-4-on;
6-(3-Fluor-pyridin-4-yl)-2-(3S)-3-(4-(4-hydroxy-piperidin-1-yl)-phenyl)-piperazin-1-yl)-3-methyl-3H-pyrimidin-4-on;

6-(3-Fluor-pyridin-4-yl)-2-((3S)-3-(4-((3R)-3-hydroxy-pyrrolidin-1-yl)-phenyl)-piperazin-1-yl)-3-methyl-3H-pyrimidin-4-on;
2-((2S)-2-(4-((3S,5R)-3,5-Dimethyl-piperazin-1-yl)-phenyl)-morpholin-4-yl)-6-(3-fluor-pyridin-4-yl)-3-methyl-3H-pyrimidin-4-on;
6-(3-Fluor-pyridin-4-yl)-3-methyl-2-((2S)-2-(4-(4-methyl-piperazin-1-yl)-phenyl)-morpholin-4-yl)-3H-pyrimidin-4-on;
2-((2S)-2-(4-((3S)-3-Dimethylamino-pyrrolidin-1-yl)-phenyl)-morpholin-4-yl)-6-(3-fluor-pyridin-4-yl)-3-methyl-3H-pyrimidin-4-on;
6-(3-Fluor-pyridin-4-yl)-2-((2S)-2-(4-(4-isopropyl-piperazin-1-yl)-phenyl)-morpholin-4-yl)-3-methyl-3H-pyrimidin-4-on;
6-(3-Fluor-pyridin-4-yl)-2-((2S)-2-(4-(4-(2-hydroxyethyl)-piperazin-1-yl)-phenyl)-morpholin-4-yl)-3-methyl-3H-pyrimidin-4-on;
6-(3-Fluor-pyridin-4-yl)-3-methyl-2-((3S)-3-(4-((3S)-3-(pyrrolidin-1-yl)-pyrrolidin-1-yl)-phenyl)-piperazin-1-yl)-3H-pyrimidin-4-on;
6-(3-Fluor-pyridin-4-yl)-3-methyl-2-((3S)-3-(4-(5-methyl-(1,2,4)oxadiazol-3-yl)-phenyl)-piperazin-1-yl)-3H-pyrimidin-4-on;
2-((2S)-2-(4-Cyclopentylamino-phenyl)-morpholin-4-yl)-6-(3-fluor-pyridin-4-yl)-3- methyl-3H-pyrimidin-4-on;
6-(3-Fluor-pyridin-4-yl)-2-((2S)-2-(4-(3-hydroxy-azetidin-1-yl)-phenyl)-morpholin-4-yl)-3-methyl-3H-pyrimidin-4-on;
N-(4-((2S)-4-((4-(3-Fluor-pyridin-4-yl)-1-methyl-6-oxo-1,6-dihydro-pyrimidin-2-yl)-morpholin-2-yl)-phenyl)-acetamid;
2-((2S)-2-(4-Cyclopentyloxy-phenyl)-morpholin-4-yl)-6-(3-fluor-pyridin-4-yl)-3-methyl-3H-pyrimidin-4-on;
2-((2S)-2-(4-Cyclopropylmethoxy-phenyl)-morpholin-4-yl)-6-(3-fluor-pyridin-4-yl)-3-methyl-3H-pyrimidin-4-on;
2-((2S)-2-(4-(2-Dimethylamino-ethoxy)-phenyl)-morpholin-4-yl)-6-(3-fluor-pyridin-4-yl)-3-methyl-3H-pyrimidin-4-on;
2-((2S)-2-(4-Amino-phenyl)-morpholin-4-yl)-6-(3-fluor-pyridin-4-yl)-3-methyl-3H-pyrimidin-4-on;
Cyclopropancarbonsäure (4-((25)-4-(4-(3-fluor-pyridin-4-yl)-1-methyl-6-oxo-1,6-dihydro-pyrimidin-2-yl)-morpholin-2-yl)-phenyl)-amid;
N-(4-((2S)-4-(4-(3-Fluor-pyridin-4-yl)-1-methyl-6-oxo-1,6-dihydro-pyrimidin-2-yl)-morpholin-2-yl)-phenyl)-2,2-dimethyl-propionamid;
6-(3-Fluor-pyridin-4-yl)-3-methyl-2-((2S)-2-(4-(methyl-((3R)-tetrahydrofuran-3-yl)-amino)-phenyl)-morpholin-4-yl)-3H-pyrimidin-4-on;
6-(3-Fluor-pyridin-4-yl)-3-methyl-2-((2S)-2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-morpholin-4-yl)-3H-pyrimidin-4-on;
6-(3-Fluor-pyridin-4-yl)-2-((2S)-2-(4-hydroxy-phenyl)-morpholin-4-yl)-3-methyl-3H-pyrimidin-4-on;
2-((2S)-2-(4-(2-Diethylamino-ethoxy)-phenyl)-morpholin-4-yl)-6-(3-fluor-pyridin-4-yl)-3-methyl-3H-pyrimidin-4-on;
6-(3-Fluor-pyrid in-4-yl)-3-methyl-2-((2S)-2-(4-(2-piperid in-1-yl-ethoxy)-phenyl)-morpholin-4-yl)-3H-pyrimidin-4-on;
6-(3-Fluor-pyrid in-4-yl)-3-methyl-2-((2S)-2-(4-(2-(4-methyl-piperazin-1-yl)-ethoxy)-phenyl)-morpholin-4-yl)-3H-pyrimidin-4-on;
N^2,N^2-Dimethyl-N^1-(4-((2S)-4-(3-methyl-4-oxo-3,4-dihydro-6-(3-fluorpyridin-4-yl)pyrimidin-2-yl)morpholin-2-yl)phenyl)glycinamid;
Methyl(4-((2S)-4-(6-(3-fluorpyridin-4-yl)-3-methyl-4-oxo-3H-pyrimidin-2-yl)morpholin-2-yl)phenyl)carbamat;
N'-(4-((2S)-4-(6-(3-Fluorpyridin-4-yl)-3-methyl-4-oxo-3H-pyrimidin-2-yl)morpholin-2-yl)phenyl)-N,N-dimethylharnstoff;
6-{4-[4-(3-Fluorpyridin-4-yl)-1-methyl-6-oxo-1,6-dihydropyrimidin-2-yl]morpholin-2-yl}-3,4-dihydrochinolin-2(1H)-on;
6-(3-Fluor-pyridin-4-yl)-3-methyl-2-{(2S)-2-[4-morpholin-4-carbonyl]-phenyl}-morpholin-4-yl}-3H-pyrimidin-4-on;
N-(3-{(2S)-4-[4-(3-Fluorpyridin-4-yl)-1-methyl-6-oxo-1,6-dihydropyrimidin-2-yl]-morpholin-2-yl}-4-methoxyphenyl)acetamid;
N-(3-{(2S)-4-[4-(3-Fluorpyridin-4-yl)-1-methyl-6-oxo-1,6-dihydropyrimidin-2-yl]-morpholin-2-yl}phenyl)acetamid und
6-(3-Fluorpyridin-4-yl)-3-methyl-2-((3S)-3-(4-([1,2,4]oxadiazol-3-yl)phenyl)piperazin-1-yl)-3H-pyrimidin-4-on,

ein optisch aktives Isomer derselben oder ein pharmazeutisch akzeptables Salz derselben.

8. Arzneimittel, das als einen aktiven Bestandteil eine Substanz enthält, ausgewählt aus der Gruppe bestehend aus der Verbindung wiedergegeben durch die Formel (I) und eines optisch aktiven Isomers derselben oder eines pharmazeutisch akzeptablen Salzes derselben gemäß Anspruch 1.

9. Arzneimittel gemäß Anspruch 8, das zur präventiven und/oder therapeutischen Behandlung einer Krankheit verwendet wird, die durch tau-Proteinkinase-I-Hyperaktivität verursacht wird, um die Neurotoxizität von β-Amyloid-Protein und die Bildung des gepaarten Filaments zu unterdrücken und den Tod von Nervenzellen zu hemmen.

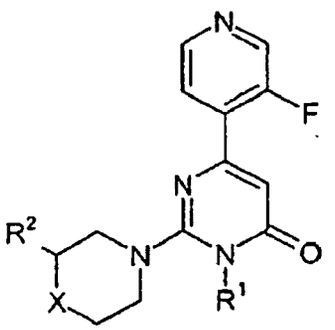
10. Arzneimittel gemäß Anspruch 8, das zur präventiven und/oder therapeutischen Behandlung einer neurodegenerativen Krankheit verwendet wird.

11. Arzneimittel gemäß Anspruch 10, wobei die Krankheit ausgewählt ist aus der Gruppe bestehend aus of Alzheimer-Krankheit, ischämisch zerebrovaskulären Insulten, Down-Syndrom, Gehirnblutung infolge von zerebraler Amyloidangiopathie, progressiver supranukleärer Blickparese (PSP), subakutem sklerosierendem panenzephalitischem Parkinsonismus, postenzephalitischem Parkinsonismus, Dementia Pugilistica, Parkinsonismus-Dementia-Komplex von Guam, Lewy-Körper-Demenz, Pick-Krankheit, kortikobasaler Degeneration, frontotemporaler Demenz, vaskulärer Demenz, traumatischen Verletzungen, Gehirn- und Rückenmarksverletzungen, Neuropathien, Retinopathien und Glaukom.

12. Arzneimittel gemäß Anspruch 8, das zur präventiven und/oder therapeutischen Behandlung einer Krankheit verwendet wird, die ausgewählt ist aus der Gruppe bestehend aus Diabetes mellitus Typ II (nicht-insulinabhängig (NIDDM)), Adipositas, manisch-depressiver Erkrankung, Schizophrenie, Alopezie, Brustkrebs, nicht-kleinzelligem Bronchialkarzinom (NSCLC), Schilddrüsenkrebs, T- oder B-Zell-Leukämie und virusinduziertem Tumor.

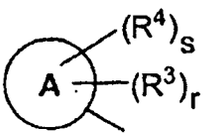
Revendications

1. Composé représenté par la formule (I), isomère optiquement actif de celui-ci, ou sel pharmaceutiquement acceptable de celui-ci :



(I)

dans laquelle chaque symbole est tel que défini ci-dessous. R^1 représente un alkyle en C_1 à C_{12} ;
R^2 représente
un groupe représenté par la formule (II) suivante :

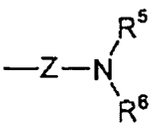


dans laquelle A représente un aryle en C_6 à C_{10} ou un hétérocycle choisi dans le groupe constitué par le benzofurane, le dihydrobenzofurane, l'isobenzofurane, le chromène, l'indole, l'indoline, l'isoindole, la benzoxazolinone, la tétrahydroisoquinoline, le chromane, l'isochromane, le benzothiophène, l'isoindoline, l'indazole, le benzimidazole, le benzotriazole, la benzothiazolinone, la quinoline, la phtalazine, la quinoxaline, la quinazoline, la cinnoline, le ben-

zothiazole, le benzodioxole, le benzodioxane, le phtalimide ;
les R^3 peuvent être identiques ou différents et représentent un atome d'hydrogène,
hydroxyle,
un halogène,
nitro,
cyano,
un alkyle en C_1 à C_6 éventuellement substitué,
un alcényle en C_2 à C_6 éventuellement substitué,
un alcynyle en C_2 à C_6 éventuellement substitué,
un cycloalkyle en C_3 à C_7 éventuellement substitué,
un cycloalcényle en C_3 à C_7 éventuellement substitué,
un aryle en C_6 à C_{10} éventuellement substitué,
un hétérocycle éventuellement substitué,
un alkyloxy en C_1 à C_6 éventuellement substitué,
un alcényloxy en C_3 à C_6 éventuellement substitué,
un alcynyloxy en C_3 à C_6 éventuellement substitué,
un cycloalkyloxy en C_3 à C_7 éventuellement substitué,
un cycloalcényloxy en C_3 à C_7 éventuellement substitué,
un aryloxy en C_6 à C_{10} éventuellement substitué,
un groupe hétérocyclo-oxy éventuellement substitué, mercapto,
un alkylthio en C_1 à C_6 éventuellement substitué,
un alcénylthio en C_3 à C_6 éventuellement substitué,
un alcynylthio en C_3 à C_6 éventuellement substitué,
un cycloalkylthio en C_3 à C_7 éventuellement substitué,
un cycloalcénylthio en C_3 à C_7 éventuellement substitué,
un arylthio en C_6 à C_{10} éventuellement substitué,
un groupe hétérocyclo-thio éventuellement substitué, amino,
un alkylamino en C_1 à C_6 éventuellement substitué,
un alcénylamino en C_3 à C_6 éventuellement substitué,
un alcynylamino en C_3 à C_6 éventuellement substitué,
un cycloalkylamino en C_3 à C_7 éventuellement substitué,
un cycloalcénylamino en C_3 à C_7 éventuellement substitué,
un arylamino en C_6 à C_{10} éventuellement substitué,
un hétérocyclo-amino éventuellement substitué,
un N,N-di(alkyl en C_1 à C_6) amino éventuellement substitué,
un N-(alkyl en C_1 à C_6)-N-(alcénylamino en C_3 à C_6) éventuellement substitué,
un N-(alkyl en C_1 à C_6)-N-(alcynylamino en C_3 à C_6) éventuellement substitué,
un N-(alkyl en C_1 à C_6) -N- (cycloalkylamino en C_3 à C_7) éventuellement substitué,
un N-(alkyl en C_1 à C_6)-N-(cycloalcénylamino en C_3 à C_7) éventuellement substitué,
un N-(alkyl en C_1 à C_6)-N-(arylamino en C_6 à C_{10}) éventuellement substitué,
un N-(alkyl en C_1 à C_6)-N-hétérocyclo-amino éventuellement substitué,
un N,N-di(alcényl en C_3 à C_6)amino éventuellement substitué,
un N- (alcényl en C_3 à C_6)-N-(alcynylamino en C_3 à C_6) éventuellement substitué,
un N-(alcényl en C_3 à C_6)-N-(cycloalkylamino en C_3 à C_7) éventuellement substitué,
un N-(alcényl en C_3 à C_6)-N-(cycloalcénylamino en C_3 à C_7) éventuellement substitué,
un N-(alcényl en C_3 à C_6)-N-(arylamino en C_6 à C_{10}) éventuellement substitué,
un N-(alcényl en C_3 à C_6)-N-hétérocyclo-amino éventuellement substitué,
un N,N-di(alcynyl en C_3 à C_6)amino éventuellement substitué,
un N-(alcynyl en C_3 à C_6)-N-(cycloalkylamino en C_3 à C_7) éventuellement substitué,
un N-(alcynyl en C_3 à C_6)-N-(cycloalcénylamino en C_3 à C_7) éventuellement substitué,
un N-(alcynyl en C_3 à C_6)-N-(arylamino en C_6 à C_{10}) éventuellement substitué,
un N-(alcynyl en C_3 à C_6)-N-hétérocyclo-amino éventuellement substitué,
un N,N-di(cycloalkyl en C_3 à C_7) amino éventuellement substitué,
un N-(cycloalkyl en C_3 à C_7)-N-(cycloalcénylamino en C_3 à C_7) éventuellement substitué,
un N-(cycloalkyl en C_3 à C_7)-N-(arylamino en C_6 à C_{10}) éventuellement substitué,
un N-(cycloalkyl en C_3 à C_7)-N-hétérocyclo-amino éventuellement substitué,
un N,N-di(cycloalcényl en C_3 à C_7)amino éventuellement substitué,
un N-(cycloalcényl en C_3 à C_7)-N-(arylamino en C_6 à C_{10}) éventuellement substitué,

un N-(cycloalcényl en C_3 à C_7)-N-hétérocyclo-amino éventuellement substitué,
un N,N-di(aryl en C_6 à C_{10})amino éventuellement substitué,
un N-(aryl en C_6 à C_{10})-N-hétérocyclo-amino éventuellement substitué,
un N,N-dihétérocyclo-amino éventuellement substitué,
un (alkyl en C_1 à C_6)carbonyle éventuellement substitué,
un (alcényl en C_2 à C_6)carbonyle éventuellement substitué,
un (alcynyl en C_2 à C_6)carbonyle éventuellement substitué,
un (cycloalkyl en C_3 à C_7)carbonyle éventuellement substitué,
un (cycloalcényl en C_3 à C_7)carbonyle éventuellement substitué,
un (aryl en C_6 à C_{10})carbonyle éventuellement substitué,
un hétérocyclocarbonyle éventuellement substitué,
un alkylsulfonyle en C_1 à C_6 éventuellement substitué,
un alcénylsulfonyle en C_3 à C_6 éventuellement substitué,
un alcynylsulfonyle en C_3 à C_6 éventuellement substitué,
un cycloalkylsulfonyle en C_3 à C_7 éventuellement substitué,
un cycloalcénylsulfonyle en C_3 à C_7 éventuellement substitué,
un arylsulfonyle en C_6 à C_{10} éventuellement substitué,
un hétérocyclosulfonyle éventuellement substitué, carboxyle,
un (alkyl en C1 à C_6)oxycarbonyle éventuellement substitué,
un (alcényl en C_3 à C_6)oxycarbonyle éventuellement substitué,
un (alcynyl en C_3 à C_6)oxycarbonyle éventuellement substitué,
un (cycloalkyl en C_3 à C_7)oxycarbonyle éventuellement substitué,
un (cycloalcényl en C_3 à C_7)oxycarbonyle éventuellement substitué,
un (aryl en C_6 à C_{10})oxycarbonyle éventuellement substitué,
un hétérocyclo-oxycarbonyle éventuellement substitué, aminocarbonyle,
un (alkyl en C_1 à C_6)aminocarbonyle éventuellement substitué,
un (alcényl en C_3 à C_6)aminocarbonyle éventuellement substitué,
un (alcynyl en C_3 à C_6)aminocarbonyle éventuellement substitué,
un (cycloalkyl en C_3 à C_7)aminocarbonyle éventuellement substitué,
un (cycloalcényl en C_3 à C_7)aminocarbonyle éventuellement substitué,
un (aryl en C_6 à C_{10})aminocarbonyle éventuellement substitué,
un hétérocyclo-aminocarbonyle éventuellement substitué,
un N,N-di(alkyl en C_1 à C_6)aminocarbonyle éventuellement substitué,
un N-(alkyl en C_1 à C_6)-N-(alcényl en C_3 à C_7)amino-carbonyle éventuellement substitué,
un N-(alkyl en C_1 à C_6)-N-(alcynyl en C_3 à C_7)amino-carbonyle éventuellement substitué,
un N-(alkyl en C_1 à C_6)-N-(cycloalkyl en C_3 à C_7)amino-carbonyle éventuellement substitué,
un N-(alkyl en C_1 à C_6)-N-(cycloalcényl en C_3 à C_7)aminocarbonyle éventuellement substitué,
un N-(alkyl en C_1 à C_6)-N-(aryl en C_6 à C_{10})aminocarbonyle éventuellement substitué,
un N-(alkyl en C_1 à C_6)-N-hétérocyclo-aminocarbonyle éventuellement substitué,
un N,N-di(alcényl en C_3 à C_6)aminocarbonyle éventuellement substitué,
un N-(alcényl en C_3 à C_6)-N-(alcynyl en C_3 à C_6)amino-carbonyle éventuellement substitué,
un N-(alcényl en C_3 à C_6)-N-(cycloalkyl en C_3 à C_7)aminocarbonyle éventuellement substitué,
un N-(alcényl en C_3 à C_6)-N-(cycloalcényl en C_3 à C_7)aminocarbonyle éventuellement substitué,
un N-(alcényl en C_3 à C_6)-N-(aryl en C_6 à C_{10})amino-carbonyle éventuellement substitué,
un N-(alcényl en C_3 à C_6)-N-hétérocyclo-aminocarbonyle éventuellement substitué,
un N,N-di(alcynyl en C_3 à C_6)aminocarbonyle éventuellement substitué,
un N-(alcynyl en C_3 à C_6)-N-(cycloalkyl en C_3 à C_7)aminocarbonyle éventuellement substitué,
un N-(alcynyl en C_3 à C_6)-N-(cycloalcényl en C_3 à C_7)aminocarbonyle éventuellement substitué,
un N-(alcynyl en C_3 à C_6)-N-(aryl en C_6 à C_{10})amino-carbonyle éventuellement substitué,
un N-(alcynyl en C_3 à C_6)-N-hétérocyclo-aminocarbonyle éventuellement substitué,
un N,N-di(cycloalkyl en C_3 à C_6)aminocarbonyle éventuellement substitué,
un N-(cycloalkyl en C_3 à C_7)-N-(cycloalcényl en C_3 à C_7)aminocarbonyle éventuellement substitué,
un N-(cycloalkyl en C_3 à C_7)-N-(aryl en C_6 à C_{10})amino-carbonyle éventuellement substitué,
un N-(cycloalkyl en C_3 à C)-N-hétérocyclo-aminocarbonyle éventuellement substitué,
un N,N-di(cycloalcényl en C_3 à C_7)aminocarbonyle éventuellement substitué,
un N-(cycloalcényl en C_3 à C_7)-N-(aryl en C_6 à C_{10})aminocarbonyle éventuellement substitué,
un N-(cycloalcényl en C_3 à C_7)-N-hétérocyclo-amino-carbonyle éventuellement substitué,
un N,N-di(aryl en C_6 à C_{10})aminocarbonyle éventuellement substitué,

un N-(aryl en C_6 à C_{10})-N-hétérocyclo-aminocarbonyle éventuellement substitué, ou
un N,N-dihétérocyclo-aminocarbonyle éventuellement substitué, aminothiocarbonyle,
un (alkyl en C_1 à C_6)aminothiocarbonyle éventuellement substitué,
un (alcényl en C_3 à C_6)aminothiocarbonyle éventuellement substitué,
un (alcynyl en C_3 à C_6)aminothiocarbonyle éventuellement substitué,
un (cycloalkyl en C_3 à C_7)aminothiocarbonyle éventuellement substitué,
un (cycloalcényl en C_3 à C_7)aminothiocarbonyle éventuellement substitué,
un (aryl en C_6 à C_{10})aminothiocarbonyle éventuellement substitué,
un hétérocyclo-aminothiocarbonyle éventuellement substitué,
un N,N-di(alkyl en C_1 à C_6)aminothiocarbonyle éventuellement substitué,
un N-(alkyl en C_1 à C_6)-N-(alcényl en C_3 à C_7)aminothiocarbonyle éventuellement substitué,
un N-(alkyl en C_1 à C_6)-N-(alcynyl en C_3 à C_7)aminothiocarbonyle éventuellement substitué,
un N-(alkyl en C_1 à C_6)-N-(cycloalkyl en C_3 à C_7)aminothiocarbonyle éventuellement substitué,
un N-(alkyl en C_1 à C_6)-N-(cycloalcényl en C_3 à C_7)aminothiocarbonyle éventuellement substitué,
un N-(alkyl en C_1 à C_6)-N-(aryl en C_6 à C_{10})amino-thiocarbonyle éventuellement substitué,
un N-(alkyl en C_1 à C_6)-N-hétérocyclo-aminothiocarbonyle éventuellement substitué,
un N,N-di(alcényl en C_3 à C_6)aminothiocarbonyle éventuellement substitué,
un N-(alcényl en C_3 à C_6)-N-(alcynyl en C_3 à C_6)aminothiocarbonyle éventuellement substitué,
un N-(alcényl en C_3 à C_6)-N-(cycloalkyl en C_3 à C_7)aminothiocarbonyle éventuellement substitué,
un N-(alcényl en C_3 à C_6)-N-(cycloalcényl en C_3 à C_7)aminothiocarbonyle éventuellement substitué,
un N-(alcényl en C_3 à C_6)-N-(aryl en C_6 à C_{10})aminothiocarbonyle éventuellement substitué,
un N-(alcényl en C_3 à C_6)-N-hétérocyclo-aminothiocarbonyle éventuellement substitué,
un N,N-di(alcynyl en C_3 à C_6)aminothiocarbonyle éventuellement substitué,
un N-(alcynyl en C_3 à C_6)-N-(cycloalkyl en C_3 à C_7)aminothiocarbonyle éventuellement substitué,
un N-(alcynyl en C_3 à C_6)-N-(cycloalcényl en C_3 à C_7)aminothiocarbonyle éventuellement substitué,
un N-(alcynyl en C_3 à C_6)-N-(aryl en C_6 à C_{10})aminothiocarbonyle éventuellement substitué,
un N-(alcynyl en C_3 à C_6)-N-hétérocyclo-aminothiocarbonyle éventuellement substitué,
un N,N-di(cycloalkyl en C_3 à C_6)aminothiocarbonyle éventuellement substitué,
un N-(cycloalkyl en C_3 à C_7)-N-(cycloalcényl en C_3 à C_7)aminothiocarbonyle éventuellement substitué,
un N-(cycloalkyl en C_3 à C_7)-N-(aryl en C_6 à C_{10})aminothiocarbonyle éventuellement substitué,
un N-(cycloalkyl en C_3 à C_7)-N-hétérocyclo-amino-thiocarbonyle éventuellement substitué,
un N,N-di(cycloalcényl en C_3 à C_7)aminothiocarbonyle éventuellement substitué,
un N-(cycloalcényl en C_3 à C_7)-N-(aryl en C_6 à C_{10})aminothiocarbonyle éventuellement substitué,
un N-(cycloalcényl en C_3 à C_7)-N-hétérocyclo-aminothiocarbonyle éventuellement substitué,
un N,N-di(aryl en C_6 à C_{10})aminothiocarbonyle éventuellement substitué,
un N-(aryl en C_6 à C_{10})-N-hétérocyclo-aminothiocarbonyle éventuellement substitué, ou
un N,N-dihétérocyclo-aminothiocarbonyle éventuellement substitué,
R^4 représente un atome d'hydrogène, ou
un groupe représenté par la formule (III) suivante :

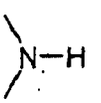


(III)

dans laquelle Z représente une liaison, un carbonyle ou un sulfonyle,
chacun de R^5 et R^6 représente indépendamment
un atome d'hydrogène,
un alkyle en C_1 à C_6 éventuellement substitué,
un alcényle en C_2 à C_6 éventuellement substitué,
un alcynyle en C_2 à C_6 éventuellement substitué,
un cycloalkyle en C_3 à C_7 éventuellement substitué,
un cycloalcényle en C_3 à C_7 éventuellement substitué,
un aryle en C_6 à C_{10} éventuellement substitué,
un hétérocycle éventuellement substitué,
un (alkyl en C_1 à C_6)carbonyle éventuellement substitué,

un (alcényl en C_2 à C_6)carbonyle éventuellement substitué,
un (alcynyl en C_2 à C_6)carbonyle éventuellement substitué,
un (cycloalkyl en C_3 à C_7)carbonyle éventuellement substitué,
un (cycloalcényl en C_3 à C_7)carbonyle éventuellement substitué,
un (aryl en C_6 à C_{10})carbonyle éventuellement substitué,
un hétérocyclocarbonyle éventuellement substitué,
un alkylsulfonyle en C_1 à C_6 éventuellement substitué,
un alcénylsulfonyle en C_3 à C_6 éventuellement substitué,
un alcynylsulfonyle en C_3 à C_6 éventuellement substitué,
un cycloalkylsulfonyle en C_3 à C_7 éventuellement substitué,
un cycloalcénylsulfonyle en C_3 à C_7 éventuellement substitué,
un arylsulfonyle en C_6 à C_{10} éventuellement substitué,
un hétérocyclosulfonyle éventuellement substitué, carboxyle,
un (alkyl en C_1 à C_6)oxycarbonyle éventuellement substitué,
un (alcényl en C_3 à C_6)oxycarbonyle éventuellement substitué,
un (alcynyl en C_3 à C_6)oxycarbonyle éventuellement substitué,
un (cycloalkyl en C_3 à C_7)oxycarbonyle éventuellement substitué,
un (cycloalcényl en C_3 à C_7)oxycarbonyle éventuellement substitué,
un (aryl en C_6 à C_{10})oxycarbonyle éventuellement substitué,
un hétérocyclo-oxycarbonyle éventuellement substitué, aminocarbonyle,
un (alkyl en C_1 à C_6)aminocarbonyle éventuellement substitué,
un (alcényl en C_3 à C_6)aminocarbonyle éventuellement substitué,
un (alcynyl en C_3 à C_6)aminocarbonyle éventuellement substitué,
un (cycloalkyl en C_3 à C_7)aminocarbonyle éventuellement substitué,
un (cycloalcényl en C_3 à C_7)aminocarbonyle éventuellement substitué,
un (aryl en C_6 à C_{10})aminocarbonyle éventuellement substitué,
un hétérocyclo-aminocarbonyle éventuellement substitué,
un N,N-di(alkyl en C_1 à C_6)aminocarbonyle éventuellement substitué,
un N-(alkyl en C_1 à C_6)-N-(alcényl en C_3 à C_7)amino-carbonyle éventuellement substitué,
un N-(alkyl en C_1 à C_6)-N-(alcynyl en C_3 à C_7)amino-carbonyle éventuellement substitué,
un N-(alkyl en C_1 à C_6)-N-(cycloalkyl en C_3 à C_7)amino-carbonyle éventuellement substitué,
un N-(alkyl en C_1 à C_6)-N-(cycloalcényl en C_3 à C_7)aminocarbonyle éventuellement substitué,
un N-(alkyl en C_1 à C_6)-N-(aryl en C_6 à C_{10})aminocarbonyle éventuellement substitué,
un N-(alkyl en C_1 à C_6)-N-hétérocyclo-aminocarbonyle éventuellement substitué,
un N,N-di(alcényl en C_3 à C_6)aminocarbonyle éventuellement substitué,
un N-(alcényl en C_3 à C_6)-N-(alcynyl en C_3 à C_6)amino-carbonyle éventuellement substitué,
un N-(alcényl en C_3 à C_6)-N-(cycloalkyl en C_3 à C_7)aminocarbonyle éventuellement substitué,
un N-(alcényl en C_3 à C_6)-N-(cycloalcényl en C_3 à C_7)aminocarbonyle éventuellement substitué,
un N-(alcényl en C_3 à C_6)-N-(aryl en C_6 à C_{10})amino-carbonyle éventuellement substitué,
un N-(alcényl en C_3 à C_6)-N-hétérocyclo-aminocarbonyle éventuellement substitué,
un N,N-di(alcynyl en C_3 à C_6)aminocarbonyle éventuellement substitué,
un N-(alcynyl en C_3 à C_6)-N-(cycloalkyl en C_3 à C_7)aminocarbonyle éventuellement substitué,
un N-(alcynyl en C_3 à C_6)-N-(cycloalcényl en C_3 à C_7)aminocarbonyle éventuellement substitué,
un N-(alcynyl en C_3 à C_6)-N-(aryl en C_6 à C_{10})amino-carbonyle éventuellement substitué,
un N-(alcynyl en C_3 à C_6)-N-hétérocyclo-aminocarbonyle éventuellement substitué,
un N,N-di(cycloalkyl en C_3 à C_6)aminocarbonyle éventuellement substitué,
un N-(cycloalkyl en C_3 à C_7)-N-(cycloalcényl en C_3 à C_7)aminocarbonyle éventuellement substitué,
un N-(cycloalkyl en C_3 à C_7)-N-(aryl en C_6 à C_{10})amino-carbonyle éventuellement substitué,
un N-(cycloalkyl en C_3 à C_7)-N-hétérocyclo-aminocarbonyle éventuellement substitué,
un N,N-di(cycloalcényl en C_3 à C_7)aminocarbonyle éventuellement substitué,
un N-(cycloalcényl en C_3 à C_7)-N-(aryl en C_6 à C_{10}) aminocarbonyle éventuellement substitué,
un N-(cycloalcényl en C_3 à C_7)-N-hétérocyclo-amino-carbonyle éventuellement substitué,
un N,N-di(aryl en C_6 à C_{10})aminocarbonyle éventuellement substitué,
un N-(aryl en C_6 à C_{10})-N-hétérocyclo-aminocarbonyle éventuellement substitué, ou
un N,N-dihétérocyclo-aminocarbonyle éventuellement substitué, aminothiocarbonyle,
un (alkyl en C_1 à C_6)aminothiocarbonyle éventuellement substitué,
un (alcényl en C_3 à C_6)aminothiocarbonyle éventuellement substitué,
un (alcynyl en C_3 à C_6)aminothiocarbonyle éventuellement substitué,

un (cycloalkyl en C_3 à C_7)aminothiocarbonyle éventuellement substitué,
un (cycloalcényl en C_3 à C_7)aminothiocarbonyle éventuellement substitué,
un (aryl en C_6 à C_{10})aminothiocarbonyle éventuellement substitué,
un hétérocyclo-aminothiocarbonyle éventuellement substitué,
un N,N-di(alkyl en C_1 à C_6)aminothiocarbonyle éventuellement substitué,
un N-(alkyl en C_1 à C_6)-N-(alcényl en C_3 à C_7)aminothiocarbonyle éventuellement substitué,
un N-(alkyl en C_1 à C_6)-N-(alcynyl en C_3 à C_7)aminothiocarbonyle éventuellement substitué,
un N-(alkyl en C_1 à C_6)-N-(cycloalkyl en C_3 à C_7)aminothiocarbonyle éventuellement substitué,
un N-(alkyl en C_1 à C_6)-N-(cycloalcényl en C_3 à C_7)aminothiocarbonyle éventuellement substitué,
un N-(alkyl en C_1 à C_6)-N-(aryl en C_6 à C_{10})amino-thiocarbonyle éventuellement substitué,
un N-(alkyl en C_1 à C_6)-N-hétérocyclo-aminothiocarbonyle éventuellement substitué,
un N,N-di(alcényl en C_3 à C_6)aminothiocarbonyle éventuellement substitué,
un N-(alcényl en C_3 à C_6)-N-(alcynyl en C_3 à C_6)aminothiocarbonyle éventuellement substitué,
un N-(alcényl en C_3 à C_6)-N-(cycloalkyl en C_3 à C_7)aminothiocarbonyle éventuellement substitué,
un N-(alcényl en C_3 à C_6)-N-(cycloalcényl en C_3 à C_7)aminothiocarbonyle éventuellement substitué,
un N-(alcényl en C_3 à C_6)-N-(aryl en C_6 à C_{10})aminothiocarbonyle éventuellement substitué,
un N-(alcényl en C_3 à C_6)-N-hétérocyclo-aminothiocarbonyle éventuellement substitué,
un N,N-di(alcynyl en C_3 à C_6)aminothiocarbonyle éventuellement substitué,
un N-(alcynyl en C_3 à C_6)-N-(cycloalkyl en C_3 à C_7)aminothiocarbonyle éventuellement substitué,
un N-(alcynyl en C_3 à C_6)-N-(cycloalcényl en C_3 à C_7)aminothiocarbonyle éventuellement substitué,
un N-(alcynyl en C_3 à C_6)-N-(aryl en C_6 à C_{10})aminothiocarbonyle éventuellement substitué,
un N-(alcynyl en C_3 à C_6)-N-hétérocyclo-aminothiocarbonyle éventuellement substitué,
un N,N-di(cycloalkyl en C_3 à C_6)aminothiocarbonyle éventuellement substitué,
un N-(cycloalkyl en C_3 à C_7)-N-(cycloalcényl en C_3 à C_7)aminothiocarbonyle éventuellement substitué,
un N-(cycloalkyl en C_3 à C_7)-N-(aryl en C_6 à C_{10})aminothiocarbonyle éventuellement substitué,
un N-(cycloalkyl en C_3 à C_7)-N-hétérocyclo-amino-thiocarbonyle éventuellement substitué,
un N,N-di(cycloalcényl en C_3 à C_7)aminothiocarbonyle éventuellement substitué,
un N-(cycloalcényl en C_3 à C_7)-N-(aryl en C_6 à C_{10})aminothiocarbonyle éventuellement substitué,
un N-(cycloalcényl en C_3 à C_7)-N-hétérocyclo-aminothiocarbonyle éventuellement substitué,
un N,N-di(aryl en C_6 à C_{10})aminothiocarbonyle éventuellement substitué,
un N-(aryl en C_6 à C_{10})-N-hétérocyclo-aminothiocarbonyle éventuellement substitué, ou
un N,N-dihétérocyclo-aminothiocarbonyle éventuellement substitué,
R^5 et R^6 peuvent se combiner l'un l'autre pour former un hétérocycle azoté à 3 à 7 chaînons qui peut en outre contenir un atome d'oxygène et/ou un atome de soufre et qui peut être substitué, ou
R^5 et R^3 peuvent se combiner l'un l'autre pour former un hétérocycle azoté à 5 à 7 chaînons qui peut en outre contenir un atome d'oxygène et/ou un atome de soufre et qui peut être substitué,
chacun de r et s vaut 0 ou est un entier de 1 à 5, du moment que la somme de r et s vaut 5 ou moins ;
X représente un atome d'oxygène, ou
un groupe représenté par la formule (IV) suivante :



(IV)

2. Composé, isomère optiquement actif de celui-ci, ou sel pharmaceutiquement acceptable de celui-ci, selon la revendication 1, dans lequel R^1 est un alkyle en C_1 à C_6.

3. Composé, isomère optiquement actif de celui-ci, ou sel pharmaceutiquement acceptable de celui-ci, selon la revendication 1, dans lequel R^1 est un groupe méthyle.

4. Composé, isomère optiquement actif de celui-ci, ou sel pharmaceutiquement acceptable de celui-ci, selon l'une quelconque des revendications 1 à 3, dans lequel A est un groupe phényle.

5. Composé, isomère optiquement actif de celui-ci, ou sel pharmaceutiquement acceptable de celui-ci, selon l'une quelconque des revendications 1 à 4, dans lequel X est un atome d'oxygène.

6. Composé, isomère optiquement actif de celui-ci, ou sel pharmaceutiquement acceptable de celui-ci, selon l'une quelconque des revendications 1 à 4, dans lequel X est un groupe représenté par la formule (IV).

7. Composé selon la revendication 1 choisi dans le groupe constitué par les suivants :

6-(3-fluoro-pyridin-4-yl)-3-méthyl-2-((3S)-3-(4-morpholin-4-yl-phényl)-pipérazin-1-yl)-3H-pyrimidin-4-one ;
2-((2S)-2-(4-((3R)-3-diméthylamino-pyrrolidin-1-yl)-phényl)-morpholin-4-yl)-6-(3-fluoro-pyridin-4-yl)-3-méthyl-3H-pyrimidin-4-one ;
6-(3-fluoro-pyridin-4-yl)-3-méthyl-2-((3S)-3-(4-pipéridin-1-yl-phényl)-pipérazin-1-yl)-3H-pyrimidin-4-one ;
6-(3-fluoro-pyridin-4-yl)-3-méthyl-2-((2S)-2-(4-(4-pyrrolidin-1-yl-pipéridin-1-yl)-phényl(-morpholin-4-yl)-3H-pyrimidin-4-one ;
2-((2S)-2-(4-(4-diméthylamino-pipéridin-1-yl)-phényl)-morpholin-4-yl)-6-(3-fluoro-pyridin-4-yl)-3-méthyl-3H-pyrimidin-4-one ;
6-(3-fluoro-pyridin-4-yl)-3-méthyl-2-((3S)-3-(4-(4-méthyl-pipérazin-1-yl)-phényl)-pipérazin-1-yl)-3H-pyrimidin-4-one ;
6-(3-fluoro-pyridin-4-yl)-2-(3S)-3-(4-(4-hydroxy-pipéridin-1-yl)-phényl)-pipérazin-1-yl)-3-méthyl-3H-pyrimidin-4-one ;
6-(3-fluoro-pyridin-4-yl)-2-((3S)-3-(4-((3R)-3-hydroxy-pyrrolidin-1-yl)-phényl)-pipérazin-1-yl)-3-méthyl-3H-pyrimidin-4-one ;
2-((2S)-2-(4-((3S,5R)-3,5-diméthyl-pipérazin-l-yl)-phényl)-morpholin-4-yl)-6-(3-fluoro-pyridin-4-yl)-3-méthyl-3H-pyrimidin-4-one ;
6-(3-fluoro-pyridin-4-yl)-3-méthyl-2-((2S)-2-(4-(4-méthyl-pipérazin-1-yl)-phényl)-morpholin-4-yl)-3H-pyrimidin-4-one ;
2-((2S)-2-(4-((3S)-3-diméthylamino-pyrrolidin-l-yl)-phényl)-morpholin-4-yl)-6-(3-fluoro-pyridin-4-yl)-3-méthyl-3H-pyrimidin-4-one ;
6-(3-fluoro-pyridin-4-yl)-2-((2S)-2-(4-(4-isopropyl-pipérazin-1-yl)-phényl)-morpholin-4-yl)-3-méthyl-3H-pyrimidin-4-one ;
6-(3-fluoro-pyridin-4-yl)-2-((2S)-2-(4-(4-(2-hydroxyéthyl)-pipérazin-1-yl)-phényl)-morpholin-4-yl)-3-méthyl-3H-pyrimidin-4-one ;
6-(3-fluoro-pyridin-4-yl)-3-méthyl-2-((3S)-3-(4-((3S)-3-(pyrrolidin-1-yl)-pyrrolidin-1-yl)-phényl)-pipérazin-1-yl)-3H-pyrimidin-4-one ;
6-(3-fluoro-pyridin-4-yl)-3-méthyl-2-((3S)-3-(4-(5-méthyl-(1,2,4)oxadiazol-3-yl)-phényl)-pipérazin-1-yl)-3H-pyrimidin-4-one ;
2-((2S)-2-(4-cyclopentylamino-phényl)-morpholin-4-yl)-6-(3-fluoro-pyridin-4-yl)-3-méthyl-3H-pyrimidin-4-one ;
6-(3-fluoro-pyridin-4-yl)-2-((2S)-2-(4-(3-hydroxy-azétidin-1-yl)-phényl)-morpholin-4-yl)-3-méthyl-3H-pyrimidin-4-one ;
N-(4-((2S)-4-((4-(3-fluoro-pyridin-4-yl)-1-méthyl-6-oxo-1,6-dihydro-pyrimidin-2-yl)-morpholin-2-yl)-phényl)-acétamide ;
2-((2S)-2-(4-cyclopentyloxy-phényl)-morpholin-4-yl)-6-(3-fluoro-pyridin-4-yl)-3-méthyl-3H-pyrimidin-4-one ;
2-((2S)-2-(4-cyclopropylméthoxy-phényl)-morpholin-4-yl)-6-(3-fluoro-pyridin-4-yl)-3-méthyl-3H-pyrimidin-4-one ;
2-((2S)-2-(4-(2-diméthylamino-éthoxy)-phényl)-morpholin-4-yl)-6-(3-fluoro-pyridin-4-yl)-3-méthyl-3H-pyrimidin-4-one ;
2-((2S)-2-(4-amino-phényl)-morpholin-4-yl)-6-(3-fluoro-pyridin-4-yl)-3-méthyl-3H-pyrimidin-4-one ;
(4-((2S)-4-(4-(3-fluoro-pyridin-4-yl)-1-méthyl-6-oxo-1,6-dihydro-pyrimidin-2-yl)-morpholin-2-yl)-phényl)-amide d'acide cyclopropanecarboxylique ;
N-(4-((2S)-4-(4-(3-fluoro-pyridin-4-yl)-1-méthyl-6-oxo-1,6-dihydro-pyrimidin-2-yl)-morpholin-2-yl)-phényl)-2,2-diméthyl-propionamide ;
6-(3-fluoro-pyridin-4-yl)-3-méthyl-2-((2S)-2-(4-(méthyl-((3R)-tétrahydro-furan-3-yl)-amino)-phényl)-morpholin-4-yl)-3H-pyrimidin-4-one ;
6-(3-fluoro-pyridin-4-yl)-3-méthyl-2-((2S)-2-[4-(2-pyrrolidin-1-yl-éthoxy)-phényl]-morpholin-4-yl)-3H-pyrimidin-4-one ;
6-(3-fluoro-pyridin-4-yl)-2-((2S)-2-(4-hydroxy-phényl)-morpholin-4-yl)-3-méthyl-3H-pyrimidin-4-one ;
2-((2S)-2-(4-(2-diéthylamino-éthoxy)-phényl)-morpholin-4-yl)-6-(3-fluoro-pyridin-4-yl)-3-méthyl-3H-pyrimidin-4-one ;
6-(3-fluoro-pyridin-4-yl)-3-méthyl-2-((2S)-2-(4-(2-pipéridin-1-yl-éthoxy)-phényl)-morpholin-4-yl)-3H-pyrimidin-4-one ;
6-(3-fluoro-pyridin-4-yl)-3-méthyl-2-((2S)-2-(4-(2-(4-méthyl-pipérazin-1-yl)-éthoxy)-phényl)-morpholin-4-

yl)-3H-pyrimidin-4-one ;
N^2,N^2-diméthyl-N^1-(4-((2S)-4-(3-méthyl-4-oxo-3,4-dihydro-6-(3-fluoropyridin-4-yl)pyrimidin-2-yl)morpholin-2-yl)phényl)glycinamide ;
(4-((2S)-4-(6-(3-fluoropyridin-4-yl)-3-méthyl-4-oxo-3H-pyrimidin-2-yl)morpholin-2-yl)phényl)carbamate de méthyle ;
N'-(4-((2S)-4-(6-(3-fluoropyridin-4-yl)-3-méthyl-4-oxo-3H-pyrimidin-2-yl)morpholin-2-yl)phényl)-N,N-diméthylurée ;
6-{4-[4-(3-fluoropyridin-4-yl)-1-méthyl-6-oxo-1,6-dihydropyrimidin-2-yl]morpholin-2-yl}-3,4-dihydroquinolin-2(1H)-one ;
6-(3-fluoro-pyridin-4-yl)-3-méthyl-2-{(2S)-2-[4-morpholine-4-carbonyl]-phényl}-morpholin-4-yl}-3H-pyrimidin-4-one ;
N-(3-{(2S)-4-[4-(3-fluoropyridin-4-yl)-1-méthyl-6-oxo-1,6-dihydropyrimidin-2-yl]-morpholin-2-yl}-4-méthoxyphényl)acétamide ;
N-(3-{(2S)-4-[4-(3-fluoropyridin-4-yl)-1-méthyl-6-oxo-1,6-dihydropyrimidin-2-yl]-morpholin-2-yl}phényl)acétamide ; et
6-(3-fluoropyridin-4-yl)-3-méthyl-2-((3S)-3-(4-([1,2,4]oxadiazol-3-yl)phényl)pipérazin-1-yl)-3H-pyrimidin-4-one,

un isomère optiquement actif de ceux-ci, ou un sel pharmaceutiquement acceptable de ceux-ci.

8. Médicament comprenant, à titre d'ingrédient actif, une substance choisie dans le groupe constitué par le composé représenté par la formule (I) et un isomère optiquement actif de celui-ci, ou un sel pharmaceutiquement acceptable de celui-ci, selon la revendication 1.

9. Médicament selon la revendication 8, qui est utilisé pour le traitement prophylactique et/ou thérapeutique d'une maladie provoquée par une hyperactivité de tau protéine kinase 1 afin de supprimer la neurotoxicité de la protéine bêta amyloïde et la formation du filament hélicoïdal apparié et afin d'inhiber la mort de cellules nerveuses.

10. Médicament selon la revendication 8, qui est utilisé pour le traitement prophylactique et/ou thérapeutique d'une maladie neurodégénérative.

11. Médicament selon la revendication 10, dans lequel la maladie est choisie dans le groupe constitué par la maladie d'Alzheimer, les accidents cérébro-vasculaires ischémiques, le syndrome de Down, une hémorragie cérébrale due à une angiopathie amyloïde cérébrale, une ophtalmoplégie supranucléaire progressive, un parkinsonisme panencéphalitique sclérosant subaigu, un parkinsonisme post-encéphalitique, une encéphalite des pugilistes, le complexe de parkinsonisme-démence de Guam, une maladie des corps de Lewy, la maladie de Pick, une dégénérescence cortico-basale, une démence frontotemporale, une démence vasculaire, des lésions traumatiques, un traumatisme du cerveau et de la moelle épinière, des neuropathies périphériques, des rétinopathies et un glaucome.

12. Médicament selon la revendication 8, qui est utilisé pour le traitement prophylactique et/ou thérapeutique d'une maladie choisie dans le groupe constitué par le diabète non insulinodépendant, l'obésité, la psychose maniacodépressive, la schizophrénie, l'alopécie, le cancer du sein, le carcinome du poumon non à petites cellules, le cancer de la thyroïde, la leucémie à cellules T ou B, et une tumeur induite par un virus.

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