PYRIMIDONE COMPOUNDS AS GSK-3 INHIBITORS

This application claims priority to U.S. Provisional Application No. 60/823,267, filed August 23, 2006.

Field of the Invention

The invention relates to pyrimidone derivatives having activity as GSK-3 inhibitors. The invention further relates to pharmaceutical compositions comprising such derivatives, and uses thereof in treating certain disorders.

Background of Invention

Protein kinases regulate the signaling of extracellular events in the cytoplasm and the nucleus, and take part in practically many events relating to the life and death of cells, including mitosis, differentiation and apoptosis. Inhibitors of certain kinases may have utility in the treatment of diseases when the kinase is not misregulated, but is nonetheless essential for maintenance of a disease. In this case, inhibition of the kinase activity would act either as a cure or palliative for these diseases and as such, inhibitors of protein kinases have long been favorable drug targets.

Glycogen synthase kinase-3 (GSK-3), a proline-directed, serine/threonine kinase for which two isoforms, GSK-3α and GSK-3β, have been identified, phosphorylates the rate-limiting enzyme of glycogen synthesis, glycogen synthase (GS). See, for example, Embi, *et al.*, Eur. J. Biochem., 107, 519-527 (1980). GSK-3α and GSK-3β are highly expressed. See, for example, Woodgett, *et al.*, EMBO, 9, 2431-2438 (1990) and Loy, *et al.*, J. Peptide Res., 54, 85-91 (1999). Besides GS, a number of other GSK-3 substrates have been identified, including metabolic, signaling, and structural proteins. Notable among the signaling proteins regulated by GSK-3 are many transcription factors, including activator protein-1; cyclic AMP response element binding protein (CREB); the nuclear factor (NF) of activated T-cells; heat shock factor-1; beta.-catenin; c-Jun; c-Myc; c-Myb; and NF-.sub.KB. See, for example, C. A. Grimes, et al., Prog. Neurobiol., 65, 391-426 (2001), H. Eldar-Finkelman, Trends in Molecular Medicine, 8, 126-132 (2002), and P. Cohen, *et al.*, Nature, 2, 1-8, (2001).

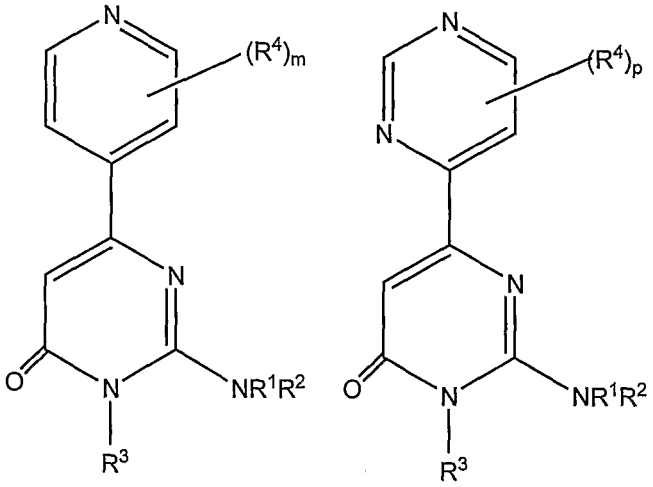
Targeting GSK-3 activity has significant therapeutic potential in the treatment of conditions including Alzheimer's Disease (A. Castro, *et al.*, Exp. Opin. Ther. Pat., 10, 1519-1527 (2000)); asthma (P. J. Barnes, Ann. Rev. Pharmacol. Toxicol., 42, 81-98 (2002)); cancer (Beals, *et al.*, Science, 275, 1930-1933 (1997), L. Kim, *et al.*, Curr. Opin. Genet. Dev., 10, 508-514 (2000), and Q. Eastman, *et al.*, Curr. Opin. Cell Biol., 11, 233 (1999)); diabetes and its related sequelae, for example, Syndrome X and obesity (S. E. Nikoulina, *et al.*, Diabetes, 51, 2190-2198 (2002), Orena, *et al.*, JBC, 15765-15772 (2000), and Summers, *et al.*, J. Biol.

Chem., 274 17934-17940 (1999)); hair loss (S. E. Millar, *et al.*, Dev. Biol., 207, 133-149 (1999) and E. Fuchs, *et al.*, Dev. Cell, 1, 13-25 (2001)); inflammation (P. Cohen, Eur. J. Biochem., 268, 5001-5010 (2001)); mood disorders, such as depression (A. Adnan, *et al.*, Chem. Rev., 101, 2527-2540 (2001) and R. S. B. Williams, *et al.*, Trends Phamacol. Sci., 21, 61-64 (2000)); neuronal cell death and stroke (D. A. E. Cross, *et al.*, J. Neurochem., 77, 94-102 (2001) and C. Sasaki, *et al.*, Neurol. Res., 23, 588-592 (2001)); bipolar disorder (Klein, *et al.*, PNAS, 93, 8455-8459 (1996)); and in cardio-protection (C. Badorff, *et al.*, J. Clin. Invest., 109, 373-381 (2002), S. Haq, *et al.*, J. Cell Biol., 151, 117-129 (2000), and H. Tong, et al., Circulation Res., 90, 377-379 (2002)).

GSK-3 acts as a negative mediator in multiple cellular pathways, including insulin, IGF-I and Wnt signaling cascades controlling muscle cell proliferation and differentiation (Glass, Int. J. Biochem. and Cell Biol., *37*, 1974 (2005); McManus, *et al.*, EMBO J., *24*, 1571 (2005); and Rochat, *et al.*, Mol. Biol. Cell., *15*, 4544 (2004)). The protein level and activity of GSK-3 are increased in muscle atrophic conditions, such as aging and immobilization of in both rats and human (Cosgrove, *et al.*, Frontiers in Myogenesis, p. 71 (2006); and Funai, *et al.* Am. J. Physiol. Regul. Integr. Comp. Physiol., *290*, R1080 (2006); in denervation-induced atrophy, and in Type II diabetic and obese subjects (Frame, *et al.*, Expert Opin. Ther. Targets, *10*, 429 (2006)). GSK-3 inhibition by RNA interference or by small molecules stimulates myotube formation and reduces proteolysis in myocyte cell cultures and in animal models (Van der Velden, *et al.*, Am. J. Physiol. Cell. Physiol., *290*, C453-(2006); Li, *et al.*, Int. J. Biochem. and Cell Biol., *37*, 2207 (2005); Fang, *et al.*, Endocrinology, *146*, 3141 (2005); Evenson, *et al.*, Int. J. Biochem. Cell. Biol., *37*, 2226 (2005)). Therefore, inhibition of GSK-3 activity has therapeutic potential in the treatment of conditions or dysfunctions arising from, or associated with, decreases in muscle mass and function. Such conditions or dysfunctions comprise, for example, genetic or traumatic neurological muscle conditions in the young (*e.g.*, muscular dystrophies); conditions arising from chronic illnesses (*e.g.*, congestive heart failure, chronic renal failure, cancer, stroke, and the like); acute illnesses resulting from extended periods of bed rest; conditions related to decreased physical activity in elderly patients; and/or conditions in those experiencing acute injury/illness resulting in extended periods of immobilization and/or bed rest (*e.g.*, hip replacement, major surgery, etc.).

Summary of the Invention

This invention relates to GSK-3 inhibitors of Formulae I and II, or the pharmaceutical acceptable salts thereof,



I II

wherein R^1 is hydrogen or a C_1-C_6 alkyl group;

R^2 is a -(4-15 membered) heterocycloalkyl, -(5-10 membered) heteroaryl or a C_1-C_6 alkyl group, wherein said alkyl is substituted by a -(4-15 membered) heterocycloalkyl or -(5-10 membered) heteroaryl, and wherein said heterocycloalkyls and heteroaryls of R^2 are optionally substituted by one or more substituents selected from the group R^7;

or $-NR^1R^2$ together may form a (8-15 membered) heterocycloalkyl or -(5-10 membered) heteroaryl, both optionally substituted by one or more substituents selected from the group R^7;

wherein R^3 is hydrogen or C_1-C_6 alkyl;

wherein R^4 is halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl,C_1-C_6 alkoxy or C_1-C_6 haloalkoxy;

wherein each R^7 is independently selected from -OH, halogen, -C_1-C_6 alkyl, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -C_1-C_6 alkoxy, -C_2-C_6 alkenoxy, -C_2-C_6 alkynoxy, -C_1-C_6 hydroxyalkyl, -CN, $-NO_2$, $-NR^8R^9$, $-C(=O)N^8R^9$, $-C(=O)R^8$, $-C(=O)OR^8$, $-S(O)_2NR^8R^9$, $-S(O)_nR^8$, $-NR^9C(=O)R^8$, $-NR^9SO_2R^8$, -(C_{zero}-C_6 alkylene)-C_6-C_{15} aryl, -(C_{zero}-C_6 alkylene)-(5-15 membered) heterocycloalkyl, -(C_{zero}-C_6 alkylene)-(5-15 membered) heteroaryl, -(C_{zero}-C_6 alkylene)-C_6-C_{15} aryloxy and -(C_{zero}-C_6 alkylene)-(5-15 membered) heteroaryloxy, wherein said alkyl, alkenyl, alkynyl, alkoxy, alkenoxy, alkynoxy, hydroxyalkyl, aryl, aryloxy, heteroaryl and heteroaryloxy of R^7 are each optionally independently substituted with one or more subsitutents selected from halogens, -C_1-C_{12} alkyl, -C_1-C_4 alkoxy, $-NR^8R^9$, $-C(=O)N^8R^9$, $-C(=O)R^8$, $-C(=O)OR^8$, $-NR^9C(=O)R^8$, $-NR^9SO_2R^8$,$-S(O)_2NR^8R^9$, $-S(O)_nR^8$ or -OH;

each R^8 and R^9 are independently selected from -H, -C_1-C_{15} alkyl, -C_2-C_{15} alkenyl, -C_2-C_{15} alkynyl, -(C_{zero}-C_4 alkylene)-(C_3-C_{15} cycloalkyl), -(C_{zero}-C_4 alkylene)-(C_4-C_8 cycloalkenyl), (C_{zero}-C_4 alkylene)-((5-15 membered) heterocycloalkyl), -(C_{zero}-C_4 alkylene)-(C_6-C_{15} aryl) and -(C_{zero}-C_4 alkylene)-((5-15 membered) heteroaryl), wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, aryl and heteroaryl of R^8 and R^9 are each

optionally independently substituted with one or more substituents independently selected from -OH, -C_1-C_{12} alkyl, -C_2-C_{12} alkenyl, -C_2-C_{12} alkynyl, -C_1-C_6 alkoxy, -C_2-C_6 alkenoxy, -C_2-C_6 alkynoxy, -C_1-C_6 hydroxyalkyl, halogen, -CN, -NO_2, -CF_3, -NH_2, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, -C(=O)NH_2, -C(=O)NH(C_1-C_6 alkyl), -C(=O)N(C_1-C_6 alkyl)$_2$, -SO_2NH_2, -SO_2NH(C_1-C_6 alkyl), -SO_2N(C_1-C_6 alkyl)$_2$, -C(=O)H, -C(=O)OH and -C(=O)O(C_1-C_6 alkyl);

n is 0, 1 or 2; m is 0, 1, 2, 3 or 4, and p is 0, 1, 2 or 3.

Detailed description of the invention

The present invention provides compounds of Formula I or II shown above, or a pharmaceutical acceptable salt thereof.

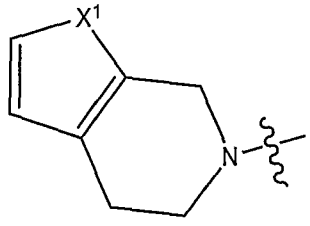
In one embodiment of the present invention for Formulas I or II, R^2 is a -(5-15 membered) heterocycloalkyl or -(5-10 membered) heteroaryl.

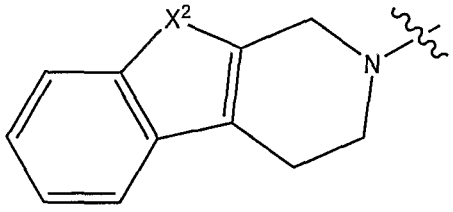
In another embodiment of the present invention for Formulas I or II, R^2 is a -(5-15 membered) heterocycloalkyl.

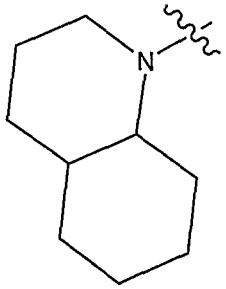
In another embodiment of the present invention for Formulas I or II, R^2 is a C_1-C_6 alkyl group substituted by a -(5-15 membered) heterocycloalkyl or -(5-10 membered) heteroaryl.

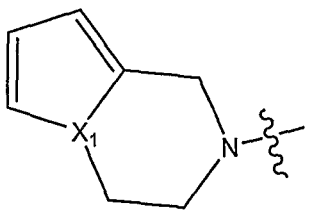
In another embodiment of the present invention for Formulas I or II, -NR^1R^2 together form an 8, 9 or 10 membered heterocycloalkyl. In another embodiment, the 8, 9 or 10 membered heterocycloalkyl is substituted by one or more substituents selected from -OH, halogen, -(C_{zero}-C_4 alkylene)-C_6-C_{15} aryl, -(C_{zero}-C_4 alkylene)-(5-15 membered) heterocycloalkyl, or -(C_{zero}-C_4 alkylene)-(5-15 membered) heteroaryl.

In another embodiment of the present invention for Formulas I or II, -NR^1R^2 taken together is selected from the group consisting of: tetrahydroisoquinolinyl, a bridged azabicyclic group, a bridged diazabicyclic group and a group selected from:









and

wherein X^1 is NR^{13} or S and X^2 is O or NR^{13}, wherein R^{13} is absent, hydrogen or C_1-C_6 alkyl.

In another embodiment, R^2 is a -(5-15 membered) heterocycloalkyl substituted by R^7; wherein R^7 is $-C(=O)R^8$, $-C(=O)OR^8$ or $-S(O)_nR^8$, and R^8 is (C_{zero}-C_6 alkylene)-C_6-C_{15} aryl.

The compounds of Formula I or II may have optical centers and therefore may occur in different enantiomeric and diastereomeric configurations. The present invention includes all enantiomers, diastereomers, and other stereoisomers of such compounds of the Formula I or II, as well as racemic compounds, mixtures, and other mixtures of stereoisomers thereof.

Pharmaceutically acceptable salts of the compounds of Formula I or II include the acid addition and base salts thereof.

Suitable acid addition salts are formed from acids which form non-toxic salts. Examples include, but are not limited to, the acetate, adipate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate/sulphate, borate, camsylate, citrate, cyclamate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mandelates mesylate, methylsulphate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, pyroglutamate, salicylate, saccharate, stearate, succinate, sulfonate, stannate, tartrate, tosylate, trifluoroacetate, and xinofoate salts.

Suitable base salts are formed from bases which form non-toxic salts. Examples include, but are not limited to, the aluminium, arginine, benzathine, calcium, choline, diethylamine, diolamine, glycine, lysine, magnesium, meglumine, olamine, potassium, sodium, tromethamine, and zinc salts.

Hemisalts of acids and bases may also be formed, for example, hemisulphate and hemicalcium salts.

For a review on these and other suitable salts, see Handbook of Pharmaceutical Salts: Properties, Selection, and Use by Stahl and Wermuth (Wiley-VCH, 2002).

Pharmaceutically acceptable salts of compounds of Formulas I or II may be prepared by:

(i) reacting the compound of Formula I or II with the desired acid or base;

(ii) removing an acid- or base-labile protecting group from a suitable precursor of the compound of Formula I or II or by ring-opening a suitable cyclic precursor, for example, a lactone or lactam, using the desired acid or base; or

(iii) converting one salt of the compound of Formula I or II to another by reaction with an appropriate acid or base or by means of a suitable ion exchange column.

Salt forming reactions are typically carried out in solution. The resulting salt may precipitate or be recovered by evaporation of the solvent. The degree of ionization in the resulting salt may vary from completely ionized to almost non-ionized.

The compounds of the invention may exist in a continuum of solid states ranging from fully amorphous to fully crystalline. The term 'amorphous' refers to a state in which the material lacks long range order at the molecular level and, depending upon temperature, may exhibit the physical properties of a solid or a liquid. Typically, such materials do not give distinctive X-ray diffraction patterns and, while exhibiting the properties of a solid, are more formally described as a liquid. Upon heating, a change from solid to liquid properties occurs which is characterized by a change of state, typically second order ('glass transition'). The term 'crystalline' refers to a solid phase in which the material has a regular ordered internal structure at the molecular level and gives a distinctive X-ray diffraction pattern with defined peaks. Such materials when heated sufficiently will also exhibit the properties of a liquid, but the change from solid to liquid is characterized by a phase change, typically first order ('melting point').

The compounds of the invention may also exist in unsolvated and solvated forms. The term 'solvate' is used herein to describe a molecular complex comprising the compound of the invention and one or more pharmaceutically acceptable solvent molecules, for example, ethanol. The term 'hydrate' is employed when said solvent is water.

A currently accepted classification system for organic hydrates is one that defines isolated site, channel, or metal-ion coordinated hydrates. See, for example, Polymorphism in Pharmaceutical Solids; K. R. Morris (Ed. H. G. Brittain, Marcel Dekker, 1995). Isolated site hydrates are ones in which the water molecules are isolated from direct contact with each other by intervening organic molecules. In channel hydrates, the water molecules lie in lattice channels where they are next to other water molecules. In metal-ion coordinated hydrates, the water molecules are bonded to the metal ion.

The compounds of the invention may also exist in a mesomorphic state (mesophase or liquid crystal) when subjected to suitable conditions. The mesomorphic state is intermediate between the true crystalline state and the true liquid state (either melt or solution). Mesomorphism arising as the result of a change in temperature is described as 'thermotropic' and that resulting from the addition of a second component, such as water or another solvent, is described as 'lyotropic'. Compounds that have the potential to form lyotropic mesophases are described as 'amphiphilic' and consist of molecules which possess an ionic (such as $-COO^-Na^+$, $-COO^-K^+$, or $-SO_3^-Na^+$) or non-ionic (such as $-N^-N^+(CH_3)_3$) polar head group. For more information, see Crystals and the Polarizing Microscope; N. H. Hartshorne and A. Stuart, 4th Edition (Edward Arnold, 1970).

The compounds of the invention include compounds of Formula I or II, as hereinbefore defined, including all polymorphs and crystal habits thereof, prodrugs and isomers thereof (including optical, geometric and tautomeric isomers) as hereinafter defined and isotopically-labeled compounds of Formulas I or II.

As indicated, so-called 'prodrugs' of the compounds of Formula I or II are also within the scope of the invention and may be prepared by replacing appropriate functionalities present in the compounds of Formula I or II with certain moieties known to those skilled in the art as 'pro-moieties.' See, for example, Design of Prodrugs by H. Bundgaard (Elsevier, 1985).

Some examples of prodrugs in accordance with the invention include:

(i) compounds of Formula I or II containing a carboxylic acid functionality (-COOH), an ester thereof, for example, a compound wherein the hydrogen of the carboxylic acid functionality of the compound of Formula (I) is replaced by (C_1-C_8)alkyl;

(ii) compounds of Formula I or II containing an alcohol functionality (-OH), an ether thereof, for example, a compound wherein the hydrogen of the alcohol functionality of the compound of Formula I or II is replaced by (C_1-C_6)alkanoyloxymethyl; and

(iii) compounds of Formula I or II containing a primary or secondary amino functionality (-NH_2 or -NHR where R ≠ H), an amide thereof, for example, a compound wherein, as the case may be, one or both hydrogens of the amino functionality of the compound of Formulas I or II is/are replaced by (C_1-C_{10})alkanoyl.

Further examples of replacement groups in accordance with the foregoing examples and examples of other prodrug types may be found in the aforementioned references.

Compounds of Formula I or II containing one or more asymmetric carbon atoms can exist as two or more stereoisomers. Where a compound of Formula I or II contains an alkenyl or alkenylene group, geometric *cis*/*trans* (or Z/E) isomers are possible. Where structural isomers are interconvertible *via* a low energy barrier, tautomeric isomerism ('tautomerism') can occur. This can take the form of proton tautomerism in compounds of Formula I or II containing, for example, an imino, keto, or oxime group, or so-called valence tautomerism in compounds that contain an aromatic moiety. It follows that a single compound may exhibit more than one type of isomerism.

Included within the scope of the present invention are all stereoisomers, geometric isomers and tautomeric forms of the compounds of Formula I or II, including compounds exhibiting more than one type of isomerism, and mixtures of one or more thereof. Also included are acid addition or base salts wherein the counterion is optically active, for example, *d*-lactate or *l*-lysine, or racemic, for example, *dl*-tartrate or *dl*-arginine.

Cis/*trans* isomers may be separated by conventional techniques well known to those skilled in the art, for example, chromatography and fractional crystallization.

Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC).

Alternatively, the racemate (or a racemic precursor) may be reacted with a suitable optically active compound, for example, an alcohol, or, in the case where the compound of Formula I or II contains an acidic or basic moiety, a base or acid such as 1-phenylethylamine or tartaric acid. The resulting diastereomeric mixture may be separated by chromatography and/or fractional crystallization and one or both of the diastereoisomers converted to the corresponding pure enantiomer(s) by means well known to a skilled person.

Chiral compounds of the invention (and chiral precursors thereof) may be obtained in enantiomerically-enriched form using chromatography, typically HPLC, on an asymmetric resin with a mobile phase consisting of a hydrocarbon, typically heptane or hexane, containing from 0 to 50% by volume of isopropanol, typically from 2% to 20%, and from 0 to 5% by volume of an alkylamine, typically 0.1% diethylamine. Concentration of the eluate affords the enriched mixture.

When any racemate crystallizes, crystals of two different types are possible. The first type is the racemic compound (true racemate) referred to above wherein one homogeneous form of crystal is produced containing both enantiomers in equimolar amounts. The second type is the racemic mixture or conglomerate wherein two forms of crystal are produced in equimolar amounts each comprising a single enantiomer.

While both of the crystal forms present in a racemic mixture have identical physical properties, they may have different physical properties compared to the true racemate. Racemic mixtures may be separated by conventional techniques known to those skilled in the art. See, for example, Stereochemistry of Organic Compounds; E. L. Eliel and S. H. Wilen (Wiley, 1994).

The present invention includes all pharmaceutically acceptable isotopically-labelled compounds of Formula I or II wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number which predominates in nature.

Examples of isotopes suitable for inclusion in the compounds of the invention include, but are not limited to, isotopes of hydrogen, such as ^{2}H and ^{3}H, carbon, such as ^{11}C, ^{13}C and ^{14}C, chlorine, such as ^{36}Cl, fluorine, such as ^{18}F, iodine, such as ^{123}I and ^{125}I, nitrogen, such as ^{13}N and ^{15}N, oxygen, such as ^{15}O, ^{17}O and ^{18}O, phosphorus, such as ^{32}P, and sulfur, such as ^{35}S.

Certain isotopically-labelled compounds of Formula I or II, for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, *i.e.* ^{3}H, and carbon-14, *i.e.* ^{14}C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

Isotopically-labeled compounds of Formula I or II can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those

described in the accompanying Examples and Preparations using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

Pharmaceutically acceptable solvates in accordance with the invention include those wherein the solvent of crystallization may be isotopically substituted, *e.g.* D_2O, d_6-acetone, d_6-DMSO.

Specific embodiments of the present invention include the compounds exemplified in the Examples below and their pharmaceutically acceptable salts, complexes, solvates, polymorphs, stereoisomers, metabolites, prodrugs, and other derivatives thereof,

This invention also pertains to a pharmaceutical composition comprising an amount of a compound of Formula I or II effective in treating said disorder or condition.

This invention also pertains to a method of treating a disorder selected from Alzheimer's Disease, cancer, diabetes, Syndrome X, obesity, hair loss, inflammation, mood disorders, neuronal cell death, stroke, bipolar disorder, conditions arising from loss of muscle mass and function, decreased sperm motility and cardio-protection, which method comprises administering an amount of a compound of Formula I or II effective in treating said disorder.

This invention also provides a method of treating a mood disorder or mood episode in a mammal, including a human, comprising administering to said mammal an amount of a compound of Formula I or II effective in treating said disorder or episode.

This invention also provides a method of treating a mood disorder or mood episode in a mammal, including a human, comprising administering to said mammal an amount of a compound of Formula I or II effective in inhibiting PDE10.

Examples of mood disorders and mood episodes that can be treated according to the present invention include, but are not limited to, major depressive episode of the mild, moderate or severe type, a manic or mixed mood episode, a hypomanic mood episode; a depressive episode with atypical features; a depressive episode with melancholic features; a depressive episode with catatonic features; a mood episode with postpartum onset; post-stroke depression; major depressive disorder; dysthymic disorder; minor depressive disorder; premenstrual dysphoric disorder; post-psychotic depressive disorder of schizophrenia; a major depressive disorder superimposed on a psychotic disorder such as delusional disorder or schizophrenia; a bipolar disorder, for example bipolar I disorder, bipolar II disorder, and cyclothymic disorder.

This invention further provides a method of treating a neurodegenerative disorder or condition in a mammal, including a human, which method comprises administering to said mammal an amount of a compound of Formula I or II effective in treating said disorder or condition.

This invention further provides a method of treating a neurodegenerative disorder or condition in a mammal, including a human, which method comprises administering to said mammal an amount of a compound of Formula I or II effective in inhibiting PDE10.

As used herein, and unless otherwise indicated, a "neurodegenerative disorder or condition" refers to a disorder or condition that is caused by the dysfunction and/or death of neurons in the central nervous system. Treatment of these disorders and conditions can be facilitated by administration of an agent which prevents the dysfunction or death of neurons at risk in these disorders or conditions and/or enhances the function of damaged or healthy neurons in such a way as to compensate for the loss of function caused by the dysfunction or death of at-risk neurons. The term "neurotrophic agent" as used herein refers to a substance or agent that has some or all of these properties.

Examples of neurodegenerative disorders and conditions that can be treated according to the present invention include Parkinson's disease; Huntington's disease; dementia, for example Alzheimer's disease, multi-infarct dementia, AIDS-related dementia, and Fronto temperal Dementia; neurodegeneration associated with cerebral trauma; neurodegeneration associated with stroke, neurodegeneration associated with cerebral infarct; hypoglycemia-induced neurodegeneration; neurodegeneration associated with epileptic seizure; neurodegeneration associated with neurotoxin poisoning; and multi-system atrophy.

In one embodiment of the present invention, the neurodegenerative disorder or condition comprises neurodegeneration of striatal medium spiny neurons in a mammal, including a human.

In a further embodiment of the present invention, the neurodegenerative disorder or condition is Huntington's disease.

The term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight or branched moieties. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, and *tert*-butyl.

The term "alkenyl", as used herein, unless otherwise indicated, includes alkyl moieties having at least one carbon-carbon double bond wherein alkyl is as defined above. Examples of alkenyl include ethenyl and propenyl.

The term "alkynyl", as used herein, unless otherwise indicated, includes alkyl moieties having at least one carbon-carbon triple bond wherein alkyl is as defined above. Examples of alkynyl groups include ethynyl and 2-propynyl.

The term "alkoxy", as used herein, unless otherwise indicated, as employed herein alone or as part of another group refers to an alkyl, groups linked to an oxygen atom.

The term "alkylthio" as used herein, unless otherwise indicated, employed herein alone or as part of another group includes any of the above alkyl groups linked through a sulfur atom.

The term "halogen" or "halo" as used herein alone or as part of another group refers to chlorine, bromine, fluorine, or iodine.

The term "haloalkyl" as used herein, unless otherwise indicated, refers to at least one halogen atom linked to an alkyl group. Examples of haloalkyl groups include trifluoromethyl, difluoromethyl, and fluoromethyl groups.

The term "cycloalkyl", as used herein, unless otherwise indicated, includes non-aromatic saturated cyclic alkyl moieties wherein alkyl is as defined above. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl.

The term "aryl", as used herein, unless otherwise indicated, includes an organic radical derived from an aromatic hydrocarbon by removal of a hydrogen atom, such as phenyl, naphthyl, indenyl, and fluorenyl. "Aryl" encompasses fused ring groups wherein at least one ring is aromatic.

The terms "heterocyclic", "heterocycloalkyl", and like terms, as used herein, refer to non-aromatic cyclic groups containing one or more heteroatoms, preferably from one to four heteroatoms, each preferably selected from oxygen, sulfur and nitrogen. The heterocyclic groups of this invention can also include ring systems substituted with one or more oxo moieties. Examples of non-aromatic heterocyclic groups are aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, azepinyl, piperazinyl, 1,2,3,6-tetrahydropyridinyl, oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, tetrahydrothiopyranyl, morpholino, thiomorpholino, thioxanyl, pyrrolinyl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, quinolizinyl, quinuclidinyl, 1,4-dioxaspiro[4.5]decyl, 1,4-dioxaspiro[4.4]nonyl, 1,4-dioxaspiro[4.3]octyl, and 1,4-dioxaspiro[4.2]heptyl.

The term "heteroaryl", as used herein, refers to aromatic groups containing one or more heteroatoms (preferably oxygen, sulfur and nitrogen), preferably from one to four heteroatoms. A multicyclic group containing one or more heteroatoms wherein at least one ring of the group is aromatic is a "heteroaryl" group. The heteroaryl groups of this invention can also include ring systems substituted with one or more oxo moieties. Examples of heteroaryl groups are pyridinyl, pyridazinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, quinolyl, isoquinolyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, triazinyl, isoindolyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzotriazolyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl,

naphthyridinyl, dihydroquinolyl, tetrahydroquinolyl, dihydroisoquinolyl, tetrahydroisoquinolyl, benzofuryl, furopyridinyl, pyrolopyrimidinyl, and azaindolyl.

Unless otherwise indicated, all the foregoing groups derived from hydrocarbons may have up to about 1 to about 20 carbon atoms (*e.g.*, C_1-C_{20} alkyl, C_2-C_{20} alkenyl, C_3-C_{20} cycloalkyl, 3-20 membered heterocycloalkyl; C_6-C_{20} aryl, 5-20 membered heteroaryl, etc.) or 1 to about 15 carbon atoms (*e.g.*, C_1-C_{15} alkyl, C_2-C_{15} alkenyl, C_3-C_{15} cycloalkyl, 3-15 membered heterocycloalkyl, C_6-C_{15} aryl, 5-15 membered heteroaryl, etc.), or 1 to about 12 carbon atoms, or 1 to about 8 carbon atoms, or 1 to about 6 carbon atoms.

Generally preferred GSK-3 inhibitors of the instant invention have K_i values of less than, or about, 10 μM, more preferably less than or about 0.1 μM.

The term "treating", as in "a method of treating a disorder", refers to reversing, alleviating, or inhibiting the progress of the disorder to which such term applies, or one or more symptoms of the disorder. As used herein, the term also encompasses, depending on the condition of the patient, preventing the disorder, including preventing onset of the disorder or of any symptoms associated therewith, as well as reducing the severity of the disorder or any of its symptoms prior to onset. "Treating" as used herein refers also to preventing a recurrence of a disorder.

The term "mammal", as used herein, refers to any member of the class "Mammalia", including humans, dogs, and cats.

The compound of the invention may be administered either alone or in combination with pharmaceutically acceptable carriers, in either single or multiple doses. Suitable pharmaceutical carriers include inert solid diluents or fillers, sterile aqueous solutions and various organic solvents. The pharmaceutical compositions formed thereby can then be readily administered in a variety of dosage forms such as tablets, powders, lozenges, liquid preparations, syrups, injectable solutions and the like. These pharmaceutical compositions can optionally contain additional ingredients such as flavorings, binders, excipients and the like. Thus, the compound of the invention may be formulated for oral, buccal, intranasal, parenteral (*e.g.*, intravenous, intramuscular or subcutaneous), transdermal (*e.g.*, patch) or rectal administration, or in a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (*e.g.*, pregelatinized maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (*e.g.*, lactose, microcrystalline cellulose or calcium phosphate); lubricants (e.g., magnesium stearate, talc or silica); disintegrants (*e.g.*, potato starch or sodium starch glycolate); or wetting agents (*e.g.*, sodium lauryl sulphate). The tablets may be coated by known methods. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they

may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (*e.g.*, sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agents (*e.g.*, lecithin or acacia); non-aqueous vehicles (*e.g.*, almond oil, oily esters or ethyl alcohol); and preservatives (*e.g.*, methyl or propyl p-hydroxybenzoates or sorbic acid).

For buccal administration, the composition may take the form of tablets or lozenges formulated in conventional manner.

The compounds of the invention may be formulated for parenteral administration by injection, including using conventional catheterization techniques or infusion. Formulations for injection may be presented in unit dosage form, *e.g.*, in ampules or in multi-dose containers, with an added preservative. They may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulating agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form for reconstitution with a suitable vehicle, *e.g.*, sterile, pyrogen-free water, before use.

When a product solution is required, it can be made by dissolving the isolated inclusion complex in water (or other aqueous medium) in an amount sufficient to generate a solution of the required strength for oral or parenteral administration to patients. The compounds may be formulated for fast dispersing dosage forms, which are designed to release the active ingredient in the oral cavity. These have often been formulated using rapidly soluble gelatin-based matrices. These dosage forms are well known and can be used to deliver a wide range of drugs. Most fast dispersing dosage forms utilize gelatin as a carrier or structure-forming agent. Typically, gelatin is used to give sufficient strength to the dosage form to prevent breakage during removal from packaging, but once placed in the mouth, the gelatin allows immediate dissolution of the dosage form. Alternatively, various starches are used to the same effect.

The compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases such as cocoa butter or other glycerides.

For intranasal administration or administration by inhalation, the compound of the invention is conveniently delivered in the form of a solution or suspension from a pump spray container that is squeezed or pumped by the patient or as an aerosol spray presentation from a pressurized container or a nebulizer, with the use of a suitable propellant, *e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide, or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurized container or nebulizer may

contain a solution or suspension of the active compound. Capsules and cartridges (made *e.g.*, from gelatin) for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

Aerosol formulations for treatment of the conditions referred to above (e.g. migraine) in the average adult human are preferably arranged so that each metered dose of aerosol contains about 20 mg to about 1,000 mg of the compound of the invention. The overall daily dose with an aerosol will be within the range of about 100 mg to about 10 mg. Administration may be several times daily, e.g. 2, 3, 4 or 8 times, giving for example, 1, 2 or 3 doses each time.

A proposed daily dose of the compound of the invention for oral, parenteral, rectal, or buccal administration to the average adult human may be from about 0.01 mg to about 2,000 mg, preferably from about 0.1 mg to about 200 mg of the active ingredient of Formula I or II per unit dose which could be administered, for example, 1 to 4 times per day.

A proposed daily dose of the compound of the invention for oral, parenteral, rectal or buccal administration to the average adult human may be from about 0.01 mg to about 2,000 mg, preferably from about 0.1 mg to about 200 mg of the active ingredient of Formula I or II per unit dose which could be administered, for example, 1 to 4 times per day.

Assay protocol for GSK-3β (glycogen synthase kinase) whole cell activity in an inducible cell line

Human recombinant GSK-3β and human recombinant Tau were expressed in a CHO Tet-Off cell line. GSK-3β activity was measured using an immunoassay that detects specific phosphorylation of tau at serine 202 and threonine 205 using cellular lysates of the induced cell line. Cells were grown in Minimum Essential Medium Alpha (Invitrogen) supplemented with 10% tetracycline approved FBS (BD Biosciences Clontech) and 400 pg/ml doxycycline (Sigma). Expression of tau and GSK-3β was induced by growth in medium without doxycycline for 72 hours. The cells were incubated with test agent for 90 minutes and then the medium was removed and the cells lysed with a buffer containing 250mM NaCl, 50mM Tris pH 7.5, 5mM EDTA, 0.1% NP40, 5mM DTT, 1mM sodium orthovanadate, 1uM okadaic acid, and 1X Protease Inhibitor (Roche – Complete tablet). Cell lysates were used in a sandwich immunoassay containing 16ng/well of biotinylated antibody HT7 (Pierce), 20 ng/well of ruthenylated antibody AT8, 10 ug/well of streptavidin magnetic beads M-280 (Bioveris) in a buffer containing 0.5% BSA (Roche), 0.5% Tween 20 (Sigma) in PBS (Sigma). Readout of assay signal was performed on an M-8 Analyzer (Bioveris) after overnight incubation at 4°C with shaking.

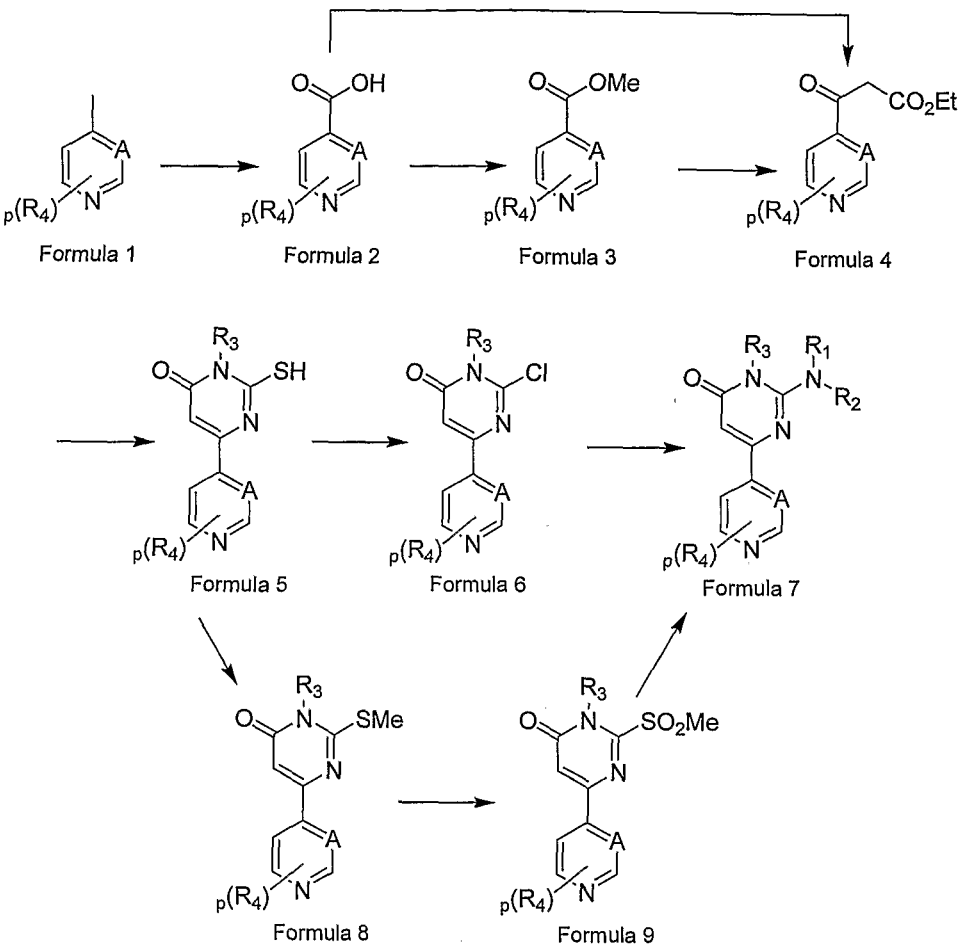
Assay protocol for GSK-3β (glycogen synthase kinase) in a cell free enzyme assay

Recombinant human GSK3β was expressed in SF9/Baculo virus cells. His-tag protein was purified by affinity chromatography to a Ni-NTA Superflow column. Enzyme activity was

assayed as the incorporation of [33P] from the gamma phosphate of [33P]ATP (PerkinElmer) into biotinylated peptide substrate bio-LC-S-R-H-S-S-P-H-Q-pS-E-D-E-E-E-OH (Anaspec). Reactions were carried out in a buffer containing 8 mM MOPS (pH 7.0), 10 mM Magnesium Acetate, 0.2 mM EDTA, 1mM DTT and 2 uM cold ATP. The 33P-ATP was added for 0.025uCi/well (120 uL) and the final concentration of substrate was 1.0 uM. Enzyme was preincubated with test agent for 30 minutes at room temperature followed by initiation of the reaction by the addition of substrate mix. Incubations were carried out at RT for 60 min. Reactions were stopped by addition of 0.66 volume of buffer containing: 12.5mM EDTA, 0.25%Triton-X 100, 125uM ATP, and 6.2 mg/ml streptavidin coated SPA beads (Amersham) in PBS without Ca or Mg. Radioactivity associated with the beads was quantified by scintillation counting of CPM in a Trilux counter (PerkinElmer).

The Schemes below depict various methods of preparing the compounds of the present invention. It should be noted that various substitutents illustrated in the schemes (*e.g*, P, Cap, X1, etc.) are for illustrated purposes only and may be independent of those recited above and in the claims.

The following reaction Schemes are intended to provide an exemplary description of the methodologies employed in the preparation of the Examples. However, it is noted that the compounds prepared according to these Schemes may be modified further to provide new Examples within the scope of this invention. For example, an ester functionality may be reacted further using procedures well known to those skilled in the art to give another ester, an amide, carbinol, or ketone.



Scheme 1

According to Scheme 1, intermediate compounds in Scheme 1, wherein A is a carbon or nitrogen, R^1, R^2, R^3, and R^4 are as described above may be prepared from compounds of Formula 1 and Formula 4, which may be commercially available, or prepared by methods known to those skilled in the art, such as oxidation with selenium dioxide in a solvent such as pyridine.

As shown in Scheme 1, compounds of Formula 3 may be prepared by esterification of compounds of Formula 2 with an acid, such as sulfuric or hydrochloric acid, in a solvent such as methanol (MeOH), ethanol (EtOH), or isopropanol. The preferred solvent is ethanol, with sulfuric acid as the acid, at a temperature between 0°C and 67°C, preferably 20°C to 67°C.

As shown in Scheme 1, compounds of Formula 4 may be prepared by condensation of ethyl acetate (EtOAc) using a base such as sodium hydride, potassium *tert*-butoxide or

metallated hexamethyldisilazine in a polar solvent such as tetrahydrofuran (THF), dimethylformamide (DMF), or EtOAc. The preferred base is potassium *tert*-butoxide, and the preferred solvent is EtOAc/THF at a temperature between 0°C and 67°C, preferably 20°C to 67°C.

Alternatively, compounds of Formula 4 may be prepared by treating compounds of Formula 2 with N,N-carbonyldiimidazole (CDI) in a solvent such as THF to form a reactive intermediate, which can be alkylated with the magnesium salt of ethyl malonate, then heated to afford the decarboxylated product.

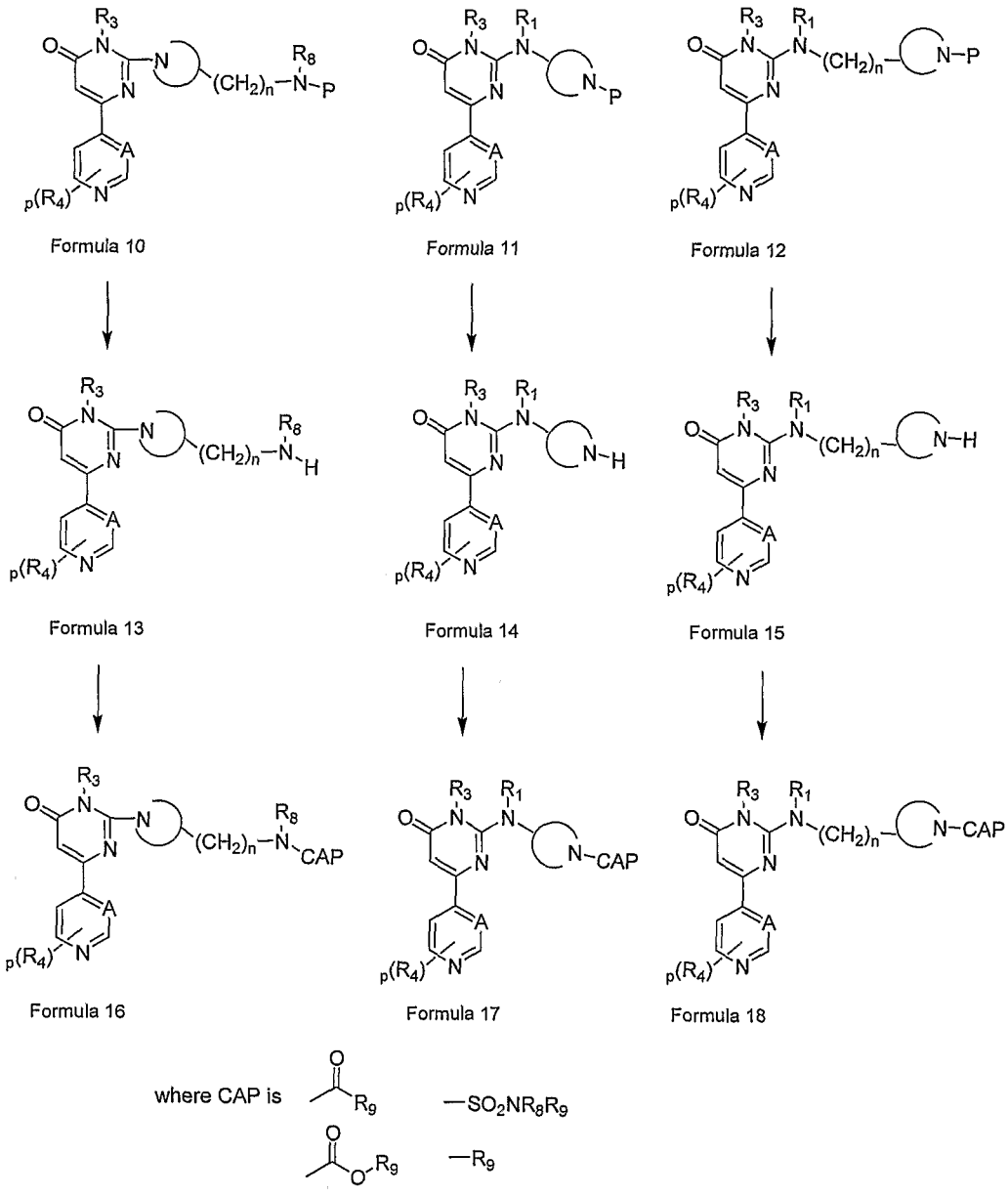
As shown in Scheme 1, compounds of Formula 5 may be prepared by condensation of 1-methyl-2-thiourea in the presence of a base such as sodium hydride, potassium *tert*-butoxide or DBU in a solvent such as MeOH, or EtOH. The preferred solvent is ethanol with DBU as the preferred base at a temperature between 0°C and 80°C, preferably 60°C to 80°C.

As shown in Scheme 1, compounds of Formula 6 may be prepared by chlorination of compounds of Formula 5 using a chlorinating agent such as phosphorous oxychloride or phosphorous pentachloride in a solvent such as DMF or DCE. The preferred solvent is DMF with phosphorous oxychloride as the preferred chlorinating agent at a temperature between 0°C and 110°C, preferably 40°C to 80°C.

As shown in Scheme 1, compounds of Formula 7 may be prepared by nucleophilic amine displacement with an amine of Formula 6 or Formula 9 in the presence of a base such as triethylamine (TEA), diisopropylethylamine (DIPEA), or DBU in a solvent such as DMF, DMSO or NMP. The preferred solvent is DMF, with DBU as the preferred base, at a temperature between 0°C and 110°C, preferably 40°C to 80°C.

As shown in Scheme 1, compounds of Formula 8 may be prepared by displacement of methyl iodide with a compound of Formula 5 in the presence of a base such sodium hydroxide, sodium hydride, potassium-*tert*-butoxide or DBU in a solvent such as THF, water, MeOH, or acetonitrile. The preferred solvent is a mixture of water and THF with sodium hydroxide as the preferred base at a temperature between 0°C and 80°C, preferably 0°C to 40°C.

As shown in Scheme 1, compounds of Formula 9 may be prepared by oxidation of the sulfide in the presence of mCPBA or hydrogen peroxide, in a solvent such as THF or dichloromethane. The preferred solvent is dichloromethane with mCPBA at a temperature between 0°C and 80°C, preferably 0°C to 40°C.



Scheme 2

The compounds of Formulae 10, 11, and 12 refer to compounds of Formula 7, as prepared in Scheme 1, where the $-NR_1R_2$ group of Formula 7 contains an amine group which is protected with a protecting group (*e.g.*, compounds of Formula 10, 11 and 12 where P represents a protecting group such as Boc, Fmoc or CBZ). According to Scheme 2, compounds of Formulae 10, 11, and 12 can be deprotected and then capped to give compounds of Formula 16, 17 or 18. The use of protection/deprotection methods is known to

those skilled in the art. See T.W. Greene; Protective Groups in Organic Synthesis; John Wiley & Sons, New York, 1991.

According to Scheme 2, deprotection of compounds of Formulae 10, 11, and 12 is carried out by known methods to afford compounds of Formula 13, 14 and 15. The preferred protecting group is BOC, which can be removed by known methods, preferably trifluoroacetic acid in DCE at a temperature of –78°C and 67°C preferably 0 to 50°.

According to Scheme 2, desired compounds of Formula 16, 17, and 18, wherein CAP refers to an amide group with side chain R_9, may be prepared by acylation of compounds of Formula 13, 14 and 15 with acid chlorides in the presence of an amine base such as TEA, DIPEA, or pyridine in a solvent such as DMSO, DMF, THF, DCE, or acetonitrile. The preferred solvent is DMSO with TEA as the preferred base at a temperature between 20°C and 120°C preferably between 20°C and 60°C.

Alternatively, compounds of Formula 16, 17, and 18, wherein the CAP group is an amide group R_9 as a side chain, may be prepared by treatment of compounds of Formulae 13, 14 and 15 with the carboxylic acid using a suitable coupling reagent such as DCC, or HATU and a base such as TEA, DIPEA, potassium carbonate, or sodium carbonate. The preferred base is DIPEA in a suitable inert solvent such as DMF, THF, methylene chloride, or dioxane. The preferred coupling agent is HATU. The preferred solvent is DMF at a temperature between -40°C and 40°C, preferably 20 to 40°C.

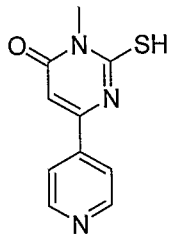
According to reaction Scheme 2, desired compounds of Formulae 16, 17, and 18, wherein CAP group is a carbamate with R_9 as a side chain, may be prepared by reacting compounds of Formula 13, 14 and 15 with the chloroformate in the presence of an amine base such as TEA, DIPEA, or pyridine in a solvent such as DMSO, DMF, THF, DCE, or acetonitrile. The preferred solvent is DCE, with TEA as the preferred amine base, at a temperature between 0°C and 120°C preferably between 0°C and 30°C.

According to reaction Scheme 2, desired compounds of Formula 16, 17, and 18, wherein the CAP is a sulfonamide group with side chain NR_8R_9, may be prepared from compounds of Formulae 13, 14 and 15 with the sulfonychloride in the presence of a base such as TEA, DIPEA, or pyridine in a solvent such as DMSO, DMF, THF, DCE, or acetonitrile. The preferred solvent is DCE, with TEA as the preferred amine base, at a temperature between 0°C and 120°C preferably between 0°C and 30°C.

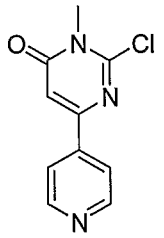
According to Scheme 2, compounds of Formulae 16, 17, and 18, wherein the CAP is described as R_9, may be prepared by reductive amination of compounds of Formulae 13, 14 and 15 by treatment with an aldehyde or ketone, in the presence of a reducing agent such as sodium borohydride, sodium triacetoxyborohydride, or sodium cyanoborohydride, and optional additives such as acetic acid or sodium acetate. The preferred reducing agent is sodium cyanoborohydride in a solvent such as EtOH, THF, methylene chloride, dioxan, or

toluene. The preferred solvent is EtOH at a temperature of –78°C and 67°C, preferably 0 to 50°C.

Preparation 1: 2-Chloro-3-methyl-6-pyridin-4-yl-3H-pyrimidin-4-one



Step A: 2-Mercapto-3-methyl-6-pyridin-4-yl-3H-pyrimidin-4-one: A mixture of ethyl isonicotinoylacetate (Acros) (40.6 g, 210 mmol), 1-methyl-2-thiourea (56.8 g, 630 mmol), DBU (31.4 ml, 31.9 g, 210 mmol) and EtOH (400 ml) was heated at reflux for 4 hr. After cooling in an ice-water bath, a solution of methanesulfonic acid (13.6 ml, 20.2 g, 210 mmol) in water (70 ml) was added slowly and the thick precipitate collected by filtration and washed with water. The solid was air-dried overnight to give the title compound (32.6g). Crystals from the mother liquors were collected, washed and dried as above to give more title compound (1.45g). Total yield = 34.03 g (74%) of off-white solid. ^{1}H-NMR(DMSO): δ ppm 12.88 (s, 1 H), 8.69 - 8.72 (m, 2 H), 7.68 - 7.71 (m, 2 H), 6.37 (s, 1 H), 3.55 (s, 3 H).

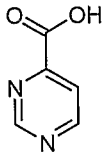


Step B: 2-Chloro-3-methyl-6-pyridin-4-yl-3H-pyrimidin-4-one:

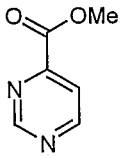
Freshly distilled $POCl_3$ (21.8 ml, 35.8 g, 0.23 mol) was added to DMF (245 ml) with stirring under a nitrogen atmosphere and the mixture stirred for 20 min. The product of Preparation 1, Step A (33.2 g, 0.15 mol), was added portionwise and the resulting mixture stirred at room temperature for 5 min., then heated at 70°C for 4 hr. After cooling (4°C) overnight, the mixture was sealed under nitrogen and EtOAc (865 ml) was added with stirring. After stirring for 30 min., the precipitate was collected, washed with EtOAc and dried. The solid was dissolved in water (550 ml) and the pH adjusted to 10 with 15% aqueous sodium hydroxide. The precipitate was collected and washed with water. The solid was dried at the pump and then in a vacuum oven over phosphorus pentoxide at 45-50°C for 4 days to give a crude product (27.4 g). This solid was recrystallized (hot filtration) from EtOAc (final volume approx 170 ml) to give the title compound (21.0 g) as a light-beige solid, m.p. = 147.8 - 148°C.

Evaporation of the mother liquor afforded more product (5.60 g). Total yield (26.6 g, 79%). ^{1}H-NMR(DMSO): δ ppm 8.65 - 8.72 (m, 18 H), 7.89 - 7.96 (m, 21 H), 7.25 (s, 1 H), 3.56 (s, 3 H).

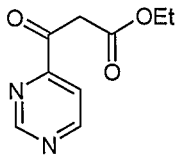
Preparation 2: 2-Chloro-1-methyl-1H-[4,4']bipyrimidinyl-6-one



Step A: Preparation of Pyrimidine-4-carboxylic acid: To a solution of 4-methyl pyrimidine (Aldrich) (10 g, 0.10 mmol) in pyridine (100 ml) was added SeO_2 (17.8 g, 0.16 mmol). The mixture was heated to 55°C for 2 hr., then 85°C for 3.5 hr. The reaction was allowed to cool to RT and stirred for 36 hr. The solids were filtered through diatomaceous earth. The solvent was evaporated and the residue diluted in 100 ml MeOH. The precipitate was collected to give the title compound as a brown solid (9.7 g, 78%). ^{1}H-NMR(DMSO-d_6): δ ppm 13.4-14.0(broad, 1H), 9.34 (s, 1H), 9.04 (d, *J*=4.98 Hz, 1H) and 8.02((d, *J*=4.98 Hz, 1H). Mass: (M+1) 125 calculated for $C_5H_4N_2O_2$.

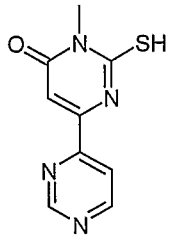


Step B: Preparation of Pyrimidine-4-carboxylic acid methyl ester: A solution of the product of Preparation 2, Step A (6.17 g, 49.7 mmol), in MeOH (60 ml) was added to sulfuric acid (0.3 ml) and heated to refluxed for 16 hr. Excess solvent was removed under vacuum to obtain a residue, which was dissolved in 10% MeOH/$CHCl_3$ (100 ml) and adsorbed onto silica gel. The crude material was purified by column chromatography over silica gel eluting with $CHCl_3$ then 10% MeOH/$CHCl_3$ to obtain the title compound as a yellow solid (5.8 g, 85%). ^{1}H-NMR(DMSO): δ 9.4(s, 1H), 9.0(d, J=4.9 Hz, 1H), 8.0(d, J=4.9 Hz, 1H) and 4.0(s, 3H). Mass: (M+H) 140 calculated for $C_6H_7N_2O_2$.

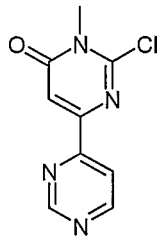


Step C: 3-Oxo-3-pyrimidin-4-yl-propionic acid ethyl ester : To a solution of the product of Preparation 2, Step B (5.8 g, 42 mmol), in EtOAc (180 ml) was added 1M potassium *tert*-butoxide in THF (85 ml, 85 mmol) in four portions, with mechanical stirring. The reaction was refluxed for 40 hr. Water (200 ml) was added and layers separated. The aqueous was washed with EtOAc (2 X 100 ml). The aqueous was acidified with conc. HCl to pH 2-3 then extracted with $CHCl_3$ (3 X 100 ml). The organics were combined, washed with

brine, dried over sodium sulfate, and concentrated to give the title compound as an orange solid (7.07g 86%). (Mixture of keto and enol form) Keto: ^{1}H-NMR(CDCl3) δ ppm 12.22 (s, 1 H), 9.23(s, 1H), 8.89 (d, *J*=4.98 Hz, 1 H), 7.83 - 7.85 (m, 1 H), 7.26(s, 1H), 6.46(s, 1H), 4.30 (q, *J*=7.05 Hz, 2 H), 1.34 (t, *J*=7.26 Hz, 3 H).

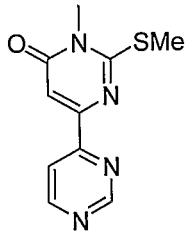


Step D: 2-Mercapto-1-methyl-1H-[4,4']bipyrimidinyl-6-one : To a solution of the product of Preparation 2, Step C (8 g, 41.2371 mmol), in EtOH (70 ml) were added N-methyl thiourea (7.43 g, 82.47 mmol) and DBU (6.27 g, 41.29 mmol) at RT. The mixture was heated to 70°C and stirred for 4 hr. The mixture was concentrated and the crude residue purified by column chromatography over 60-120 mesh silica gel column using 40% EtOAc in DCM as eluting solvent to give the title compound as yellow crystalline solid (6 g, 66%). ^{1}H-NMR (DMSO): δ ppm10.5-10.8(broad, 1H), 9.4(s, 1H), 9.0(d, *J*=5 Hz, 1 H), 7.8(d, *J*=5 Hz, 1 H), 6.6(s, 1H) and 3.75(s, 3H). Mass: (M+H) 221 calculated for $C_9H_8N_4OS$.

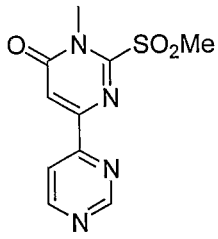


Step E: 2-Chloro-1-methyl-1H-[4,4']bipyrimidinyl-6-one : To DMF (50 ml) cooled in an ice bath was added $POCl_3$ (11 ml). The mixture was stirred for 30 min., and then the product of Preparation 2, Step C (5 g, 22.7 mmol) was added in one portion. The reaction mixture was heated in a 50°C oil bath and stirred for 1hr. The reaction mixture was cooled to RT and poured onto ice water (~200 ml) and stirred until mixture warmed to RT. The solution was neutralized to pH ~ 7 with solid sodium bicarbonate. The formed solid was collected to yield (3.42g) of brown solid. The crude residue was redissolved in EtOAc and washed with 1N NaOH (2x100ml) then brine, dried over sodium sulfate, and concentrated to give the title compound as a tan solid (1.44g). The neutralized aqueous was extracted with EtOAc (3X). The organics were washed with 1N NaOH (100 ml) then brine, dried over sodium sulfate, and concentrated to give the title compound as a tan solid (0.933 g). Total yield was 2.37 g, 47%. ^{1}H-NMR(DMSO): δ ppm 9.32(s, 1H), 9.01 (d, *J*=5 Hz, 1 H), 8.14 (d, *J*=5 Hz, 1 H), 7.30 (s, 1H) and 3.57 (s, 3H).

Preparation 3: 3-Methyl-2-(methylsulfonyl)-6-pyridin-4-yl-3H-pyrimidin-4-one

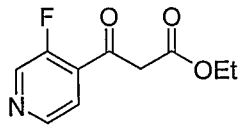


Step A: 3-Methyl-2-(methylthio)-6-pyridin-4-yl-3H-pyrimidin-4-one: To a suspension of the product of Preparation 2, Step D (250 mg, 1.1 mmol), in THF (3 ml) was added MeI (0.08 ml, 1.2 mmol) then 1N NaOH (1.4 ml, 1.4 mmol). The suspension was stirred for 30 min. The mixture was diluted with water then extracted with $CHCl_3$ (3X). The organics were combined, washed with brine, dried over sodium sulfate, and concentrated to give the title compound as a yellow crystalline solid (277 mg, 100%). ^{1}H-NMR (DMSO-d_6): δ ppm 9.30 (s, 1 H), 9.02 (d, *J*=5 Hz, 1 H), 8.31 (d, *J*=5 Hz, 1 H), 7.09 (s, 1 H), 3.45 (s, 3 H), 2.70 (s, 3 H).



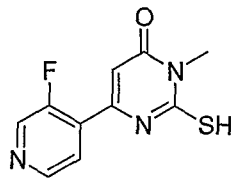
Step B: 3-Methyl-2-(methylsulfonyl)-6-pyridin-4-yl-3H-pyrimidin-4-one: To a solution of the product of Preparation 3, Step A (550 mg, 2.3 mmol), in THF (55 ml) was added mCPBA (1.0 g, 5.8 mmol) and stirred for 16 hr. The solvent was removed and the residue redissolved in $CHCl_3$ and adsorbed onto silica gel. The residue was purified by column chromatography over 60-120 mesh silica gel column eluting with 50% EtOAc in hexane to give a white solid (625 mg, 54%). ^{1}H-NMR(DMSO-d_6): δ ppm 9.35 (s, 1 H), 9.06 (d, *J*=5 Hz, 1 H), 8.31 (d, *J*=5 Hz, 1 H), 7.09 (s, 1 H), 3.76 (s, 3 H), 3.71 (s, 3 H).

Preparation 4: 2-Chloro-6-(3-fluoropyridin-4-yl)-3-methylpyrimidin-4(3H)-one

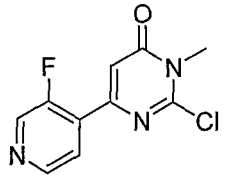


Step A: Ethyl 3-(3-fluoropyridin-4-yl)-3-oxopropanoate: To a suspension of 3-fluoroisonicotinic acid (3 g, 21.3 mmol) in THF (50 ml) was added CDI (3.6 g, 22.4 mmol). The mixture was heated at 50°C for about 16 to 18 hr. In a separate flask, potassium ethyl malonate (4.7g, 27.7 mmol) and magnesium chloride (3.2 g, 33.2 mmol) was suspended in THF and stirred at 35°C for 1 hr. To this mixture was added the anhydride

mixture from the previous step. The combined mixture was heated at reflux for 1 hr. and then at 50°C for 16-18 hr. The mixture was cooled to RT and acidified with aq. HCl (1 N) to pH ~5. After addition of water (5 ml), the organic layer was separated. The aqueous layer was further extracted with EtOAc (3 X 30 ml) and the combined organic layer was dried (sodium sulfate), and evaporated to a crude oil. Addition of MeOH precipitated the title product as a white solid, 3.9 g (86.4%): ^{1}H-NMR(DMSO-d6) δ 8.52 (d, 1H), 8.41(q, 1H), 7.63 (m, 1H), 5.13 (s, 1H), 4.00 (q, 2H), 3.32 (s, 2H), 1.16 (t, 3H); LCMS 212.2 (M+H).

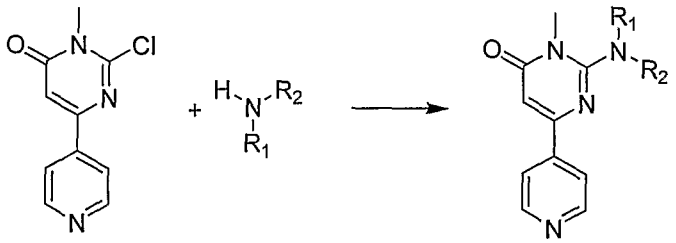


Step B: 6-(3-Fluoropyridin-4-yl)-2-mercapto-3-methylpyrimidin-4(3H)-one: To a suspension of the product of Preparation 4, Step A (3.9 g, 18.4 mmol), in toluene (40 ml) was added N-methylthiourea (5.6 g, 62.6 mmol) and DBU (3.0 ml, 20.3 mmol) and the mixture heated at 100°C for 48 hr. 30 ml of EtOH was added and the reaction heated at 100°C for ~18 hr. The reaction was cooled to RT and water (18 ml) and methanesulfonic acid (2 ml) was added and stirred for 1 hr. The aqueous layer was concentrated to a small volume and the formed precipitate was collected to provide 2.4 g (55%) of yellow solid. ^{1}H-NMR (MeOH-d_4) δ 8.65 (d, 1H), 8.55(d, 1H), 7.63 (q, 1H), 6.17 (s, 1H), 3.69 (s, 3H); LCMS 238.2 (M+H).



Step C: Preparation of 2-Chloro-6-(3-fluoropyridin-4-yl)-3-methylpyrimidin-4(3H)-one: Phosphorous oxychloride (0.41 ml, 4.43 mmol) was added to DMF (5 ml) and stirred at RT for 30 min. To this mixture was added the product of Preparation 4, Step B (700mg, 2.95 mmol), portionwise and the mixture was heated at 62°C for 2 hr. After cooling and concentration, water was added slowly. The mixture was extracted with dichloromethane (5 X 30 ml), dried (sodium sulfate), and concentrated to give the title product (365 mg, 52%) as yellow solid. ^{1}H-NMR($CDCl_3$) δ 8.68 (d, 1H), 8.57(q, 1H), 7.99 (q, 1H), 7.12 (s, 1H), 3.72 (s, 3H); LCMS 240.3 (M+H).

General Procedure for Examples 1-35

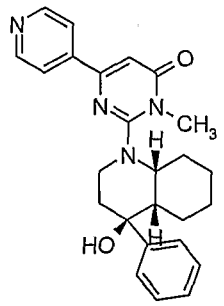
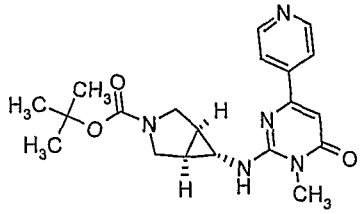


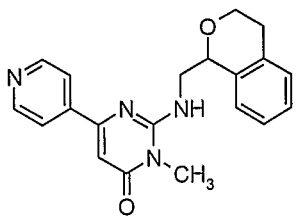
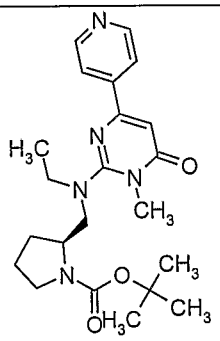
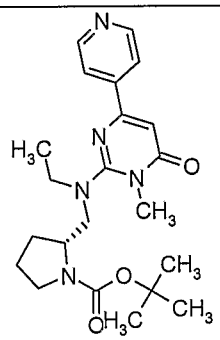
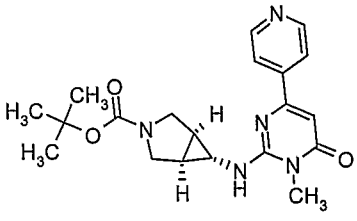
Preparation 1 **Examples 1-35**

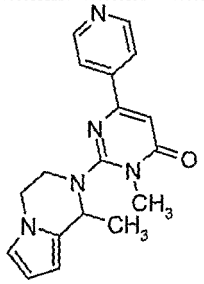
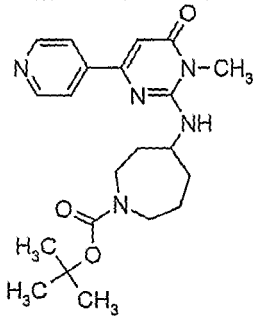
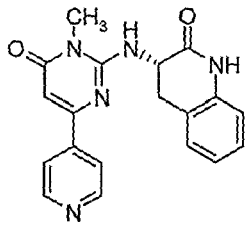
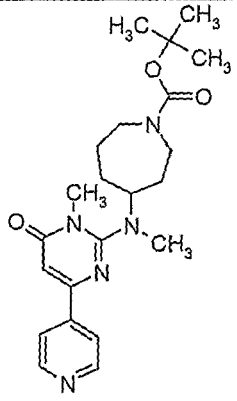
To the amine (80 μmol) was added a solution of the product of Preparation 1 (15.5 mg, 70 μmol) and TEA (16 mg, 160 μmol) in DMF (400 μl). The mixture was sealed and heated to 80°C for 12 hr. with shaking. The mixture was diluted with EtOAc (2 ml) and water (2 ml), then shaken. The organic layer was transferred to tarred vials and aqueous layer extracted with EtOAc (2 ml). The organic layer was transferred to tarred vials. The organics were evaporated and vials weighed for crude mass. The residues were dissolved in DMSO (930 μl) and heated to 60C for 1hr. Products were purified by Prep HPLC.

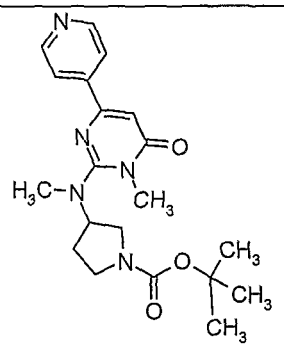
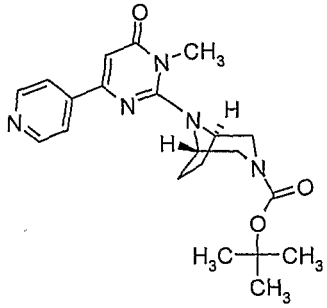
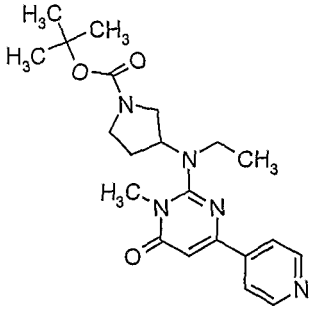
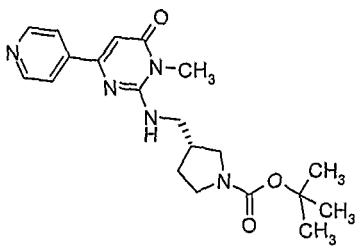
EXAMPLES

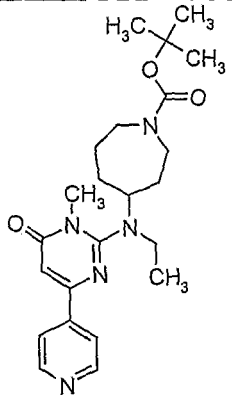
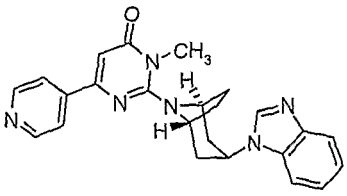
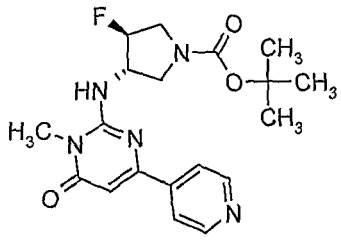
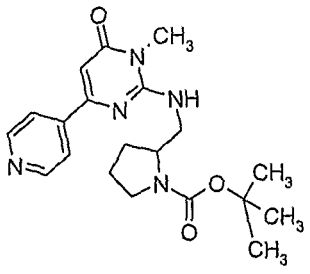
The following Examples 1 to 35 were prepared according to the General Procedure described above.

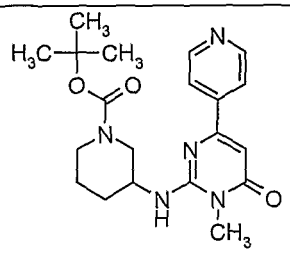
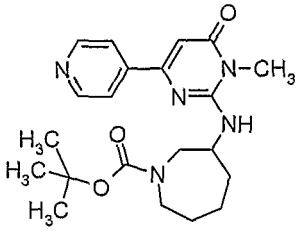
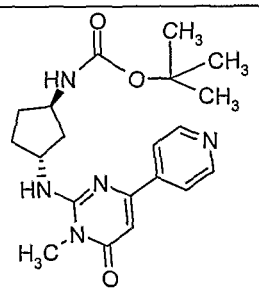
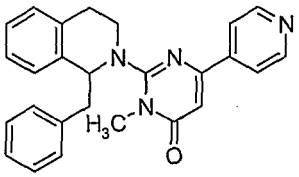
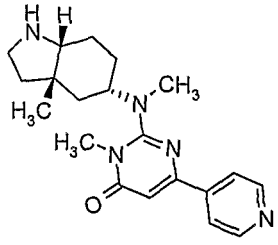
Ex.	Structure	Name	Observed Mass (MH+)	Enzyme IC_{50} (nM)
1		2-[(4S,4aS,8aR)-4-Hydroxy-4-phenyloctahydroquinolin-1(2H)-yl]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	417.1	0.7
2		*tert*-butyl (1R,5S,6s)-6-[(1-Methyl-6-oxo-4-pyridin-4-yl-1,6-dihydropyrimidin-2-yl)amino]-3-azabicyclo[3.1.0]hexane-3-carboxylate	384.1	2.2

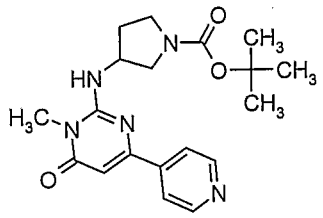
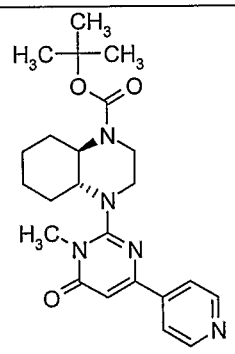
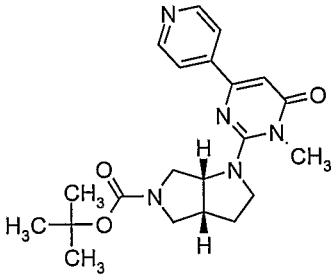
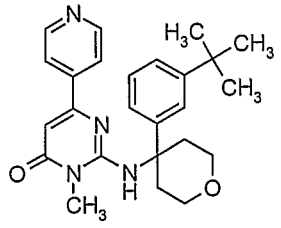
Ex.	Structure	Name	Observed Mass (MH+)	Enzyme IC_{50} (nM)
3		2-[(3,4-dihydro-1H-Isochromen-1-ylmethyl)amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	349.1	23
4		*tert*-butyl (2S)-2-{[Ethyl(1-methyl-6-oxo-4-pyridin-4-yl-1,6-dihydropyrimidin-2-yl)amino]methyl}pyrrolidine-1-carboxylate	414.1	4.2
5		*tert*-butyl (2R)-2-{[Ethyl(1-methyl-6-oxo-4-pyridin-4-yl-1,6-dihydropyrimidin-2-yl)amino]methyl}pyrrolidine-1-carboxylate	414.1	2.1
6		*tert*-butyl (1R,5S,6s)-6-[(1-Methyl-6-oxo-4-pyridin-4-yl-1,6-dihydropyrimidin-2-yl)amino]-3-azabicyclo[3.1.0]hexane-3-carboxylate	384.2	2.8

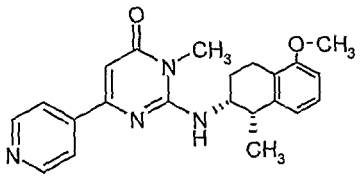
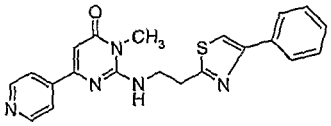
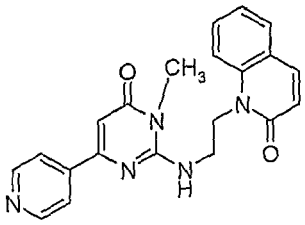
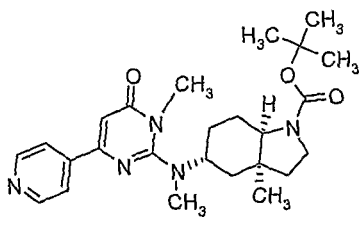
Ex.	Structure	Name	Observed Mass (MH+)	Enzyme IC_{50} (nM)
7		3-Methyl-2-(1-methyl-3,4-dihydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-6-pyridin-4-ylpyrimidin-4(3H)-one	322.1	10.7
8		*tert*-butyl 4-[(1-Methyl-6-oxo-4-pyridin-4-yl-1,6-dihydropyrimidin-2-yl)amino]azepane-1-carboxylate	400.1	9.1
9		(3S)-3-[(1-Methyl-6-oxo-4-pyridin-4-yl-1,6-dihydropyrimidin-2-yl)amino]-3,4-dihydroquinolin-2(1H)-one	348.1	30
10		*tert*-butyl 4-[Methyl(1-methyl-6-oxo-4-pyridin-4-yl-1,6-dihydropyrimidin-2-yl)amino]azepane-1-carboxylate	414.1	14.4

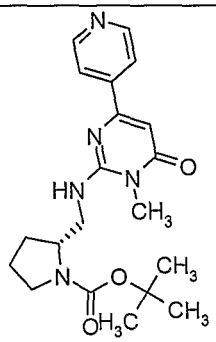
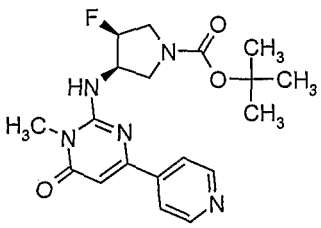
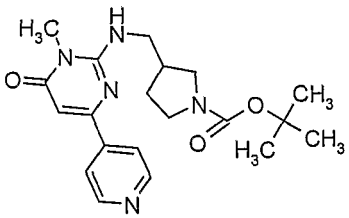
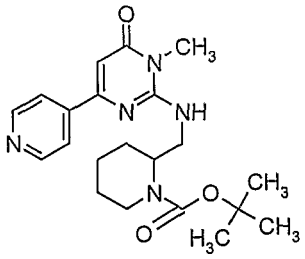
Ex.	Structure	Name	Observed Mass (MH+)	Enzyme IC_{50} (nM)
11		*tert*-butyl 3-[Methyl(1-methyl-6-oxo-4-pyridin-4-yl-1,6-dihydropyrimidin-2-yl)amino]pyrrolidine-1-carboxylate	386.1	17.7
12		*tert*-butyl (1R,5S)-8-(1-Methyl-6-oxo-4-pyridin-4-yl-1,6-dihydropyrimidin-2-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate	398.1	32.4
13		*tert*-butyl 3-[Ethyl(1-methyl-6-oxo-4-pyridin-4-yl-1,6-dihydropyrimidin-2-yl)amino]pyrrolidine-1-carboxylate	400.1	16.5
14		*tert*-butyl (3R)-3-{[(1-Methyl-6-oxo-4-pyridin-4-yl-1,6-dihydropyrimidin-2-yl)amino]methyl}pyrrolidine-1-carboxylate	386.1	74

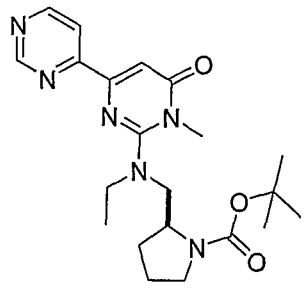
Ex.	Structure	Name	Observed Mass (MH+)	Enzyme IC_{50} (nM)
15		*tert*-butyl 4-[Ethyl(1-methyl-6-oxo-4-pyridin-4-yl-1,6-dihydropyrimidin-2-yl)amino]azepane-1-carboxylate	428.2	31
16		2-[(1R,5S)-3-(1H-Benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	413.1	20.5
17		*tert*-butyl (3S,4S)-3-Fluoro-4-[(1-methyl-6-oxo-4-pyridin-4-yl-1,6-dihydropyrimidin-2-yl)amino]pyrrolidine-1-carboxylate	390.1	26.3
18		*tert*-butyl 2-{[(1-Methyl-6-oxo-4-pyridin-4-yl-1,6-dihydropyrimidin-2-yl)amino]methyl}pyrrolidine-1-carboxylate	386.1	107.5

Ex.	Structure	Name	Observed Mass (MH+)	Enzyme IC_{50} (nM)
19		*tert*-butyl 3-[(1-Methyl-6-oxo-4-pyridin-4-yl-1,6-dihydropyrimidin-2-yl)amino]piperidine-1-carboxylate	386.1	42
20		*tert*-butyl 3-[(1-Methyl-6-oxo-4-pyridin-4-yl-1,6-dihydropyrimidin-2-yl)amino]azepane-1-carboxylate	400.1	24.1
21		*tert*-butyl {(1R,3R)-3-[(1-Methyl-6-oxo-4-pyridin-4-yl-1,6-dihydropyrimidin-2-yl)amino]cyclopentyl}carbamate	386.1	52.5
22		2-(1-Benzyl-3,4-dihydroisoquinolin-2(1H)-yl)-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	409.1	37
23		3-methyl-2-{Methyl[(3aS,5S,7aR)-3a-methyloctahydro-1H-indol-5-yl]amino}-6-pyridin-4-ylpyrimidin-4(3H)-one	354.2	47

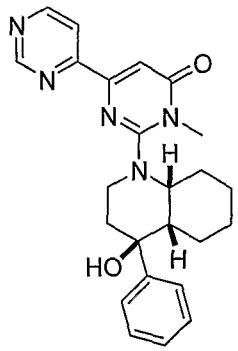
Ex.	Structure	Name	Observed Mass (MH+)	Enzyme IC_{50} (nM)
24		*tert*-butyl 3-[(1-Methyl-6-oxo-4-pyridin-4-yl-1,6-dihydropyrimidin-2-yl)amino]pyrrolidine-1-carboxylate	372.1	43
25		*tert*-butyl (4aR,8aR)-4-(1-Methyl-6-oxo-4-pyridin-4-yl-1,6-dihydropyrimidin-2-yl)octahydroquinoxaline-1(2H)-carboxylate	426.1	40
26		*tert*-butyl (3aR,6aR)-1-(1-Methyl-6-oxo-4-pyridin-4-yl-1,6-dihydropyrimidin-2-yl)hexahydropyrrolo[3,4-b]pyrrole-5(1H)-carboxylate	398.1	97
27		2-{[4-(3-*tert*-Butylphenyl)tetrahydro-2H-pyran-4-yl]amino}-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	419.1	12

Ex.	Structure	Name	Observed Mass (MH+)	Enzyme IC_{50} (nM)
28		2-{[(1S,2R)-5-Methoxy-1-methyl-1,2,3,4-tetrahydronaphthalen-2-yl]amino}-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	377.1	3.9
29		3-Methyl-2-{[2-(4-phenyl-1,3-thiazol-2-yl)ethyl]amino}-6-pyridin-4-ylpyrimidin-4(3H)-one	390	16
30		1-{2-[(1-Methyl-6-oxo-4-pyridin-4-yl-1,6-dihydropyrimidin-2-yl)amino]ethyl}quinolin-2(1H)-one	374.1	25
31		*tert*-butyl (3aS,5R,7aR)-3a-Methyl-5-[methyl(1-methyl-6-oxo-4-pyridin-4-yl-1,6-dihydropyrimidin-2-yl)amino]octahydro-1H-indole-1-carboxylate	454.2	30.1

Ex.	Structure	Name	Observed Mass (MH+)	Enzyme IC_{50} (nM)
32		*tert*-butyl (2R)-2-{[(1-Methyl-6-oxo-4-pyridin-4-yl-1,6-dihydropyrimidin-2-yl)amino]methyl}pyrrolidine-1-carboxylate	386.1	71
33		*tert*-butyl (3S,4R)-3-Fluoro-4-[(1-methyl-6-oxo-4-pyridin-4-yl-1,6-dihydropyrimidin-2-yl)amino]pyrrolidine-1-carboxylate	390.1	77
34		*tert*-butyl 3-{[(1-Methyl-6-oxo-4-pyridin-4-yl-1,6-dihydropyrimidin-2-yl)amino]methyl}pyrrolidine-1-carboxylate	386.1	113.5
35		*tert*-butyl 2-{[(1-Methyl-6-oxo-4-pyridin-4-yl-1,6-dihydropyrimidin-2-yl)amino]methyl}piperidine-1-carboxylate	400.1	168.5

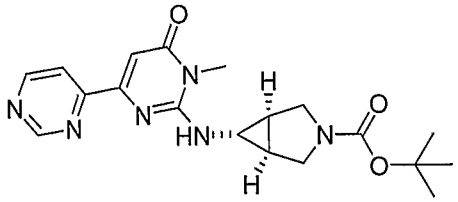


Example 36: *tert*-butyl (2S)-2-{[Ethyl(1-methyl-6-oxo-4-pyrimidin-4-yl-1,6-dihydropyrimidin-2-yl)amino]methyl}pyrrolidine-1-carboxylate: To a solution of the product of Preparation 2 (67 mg, 0.30 mmol) in DMF (1.5 ml) was added (S)-*tert*-butyl-2-((ethylamino)methyl)pyrrolidine-1-carboxylate (82 mg, 0.36 mmol), then TEA (0.1 ml, 0.7 mmol). The reaction was heated to 80°C for 16 hr. The reaction was partitioned between EtOAc and water and the organic layer was separated and adsorbed onto silica gel. The crude residue was purified by column chromatography over 60-120 mesh silica gel eluting with a gradient of 50-100% EtOAc in hexanes to give the title compound as a yellow semi-solid (104 mg, 83%). ^{1}H-NMR($CDCl_3$): δ ppm 9.22(s, 1H) 8.90 (d, *J*=5 Hz, 1 H), 8.51 (d, *J*=5 Hz, 1 H), 7.18(s, 1H), 4.19(m, 1H), 3.68(m, 1H), 3.47-3.29(m, 5H), 2.00-1.70(m, 4H), 1.42(s, 9H), 1.25(t, *J*=7 Hz, 3H), Calc MW: 414.5, Found: 415.4 (MH+).

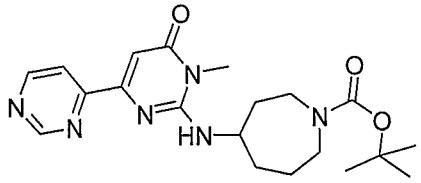


Example 37: 2-[(4S,4aS,8aR)-4-Hydroxy-4-phenyloctahydroquinolin-1(2H)-yl]-3-methyl-6-pyrimidin-4-ylpyrimidin-4(3H)-one: To a solution of the product of Preparation 2 (67 mg, 0.30 mmols) in DMF (1.5 ml) was added (4S,4aS,8aR)-4-phenyl-decahydroquinolin-4-ol (8 2mg, 0.36 mmol), then TEA (0.1 ml, 0.7 mmol). The reaction was heated to 80°C for 16 hr. The reaction was partitioned between EtOAc and water and the organic was separated and adsorbed onto silica gel. The crude residue was purified by column chromatography over 60-120 mesh silica gel eluting with a gradient of 50-100% EtOAc in hexanes to give the title compound as a yellow semi-solid (47 mg, 37%). ^{1}H-NMR($CDCl_3$): δ ppm 9.32(s, 1H), 9.05 (d, *J*=5 Hz, 1 H), 8.2 (d, *J*=5 Hz, 1 H), 7.49 (d, *J*=7.5 Hz, 1 H), 7.32 (t, *J*=7.5 Hz, 1 H), 7.20 (t,

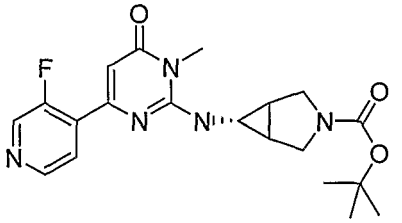
J=7.5 Hz, 1 H), 4.95(s, 1H), 3.49(m, 1H), 3.29(s, 3H), 3.22-3.06(m, 2H), 2.26(m, 1H), 2.05(m, 1H), 1.88(m, 1H), 1.66-1.49(m, 3H), 1.29-0.97(m, 5H). Calc MW: 417.5, Found: 418.5 (MH+).



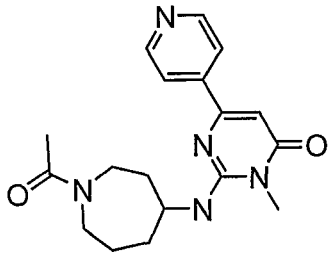
Example 38: *tert*-butyl (1R,5S,6s)-6-[(1-Methyl-6-oxo-4- pyrimidin -4-yl-1,6-dihydropyrimidin-2-yl)amino]-3-azabicyclo[3.1.0]hexane-3-carboxylate: To a solution of the product of Preparation 3 (20 mg, 0.07mmol) in DMF (0.5 ml) was added (1R,5S,6s)-*tert*-butyl 6-amino-3-aza-bicyclo[3.1.0]hexane-3-carboxylate (20 mg, 0.10 mmol), followed by the addition of TEA (0.1 ml, 0.7 mmol). The reaction was heated to 80°C for 16 hr., cooled and diluted with DMSO (0.5 ml). The crude mixture was purified on prep. HPLC eluting with mixture of acetonitrile and water, with 0.01% ammonium hydroxide modifier, to give the title compound as a yellow semi-solid (19.9 mg, 68%). ^{1}H-NMR($CDCl_3$): δ ppm 9.22(s, 1H), 8.93 (d, *J*=5 Hz, 1 H), 8.34 (d, *J*=5 Hz, 1 H), 6.99(s, 1H), 3.75(m, 2H), 3.63(m, 1H), 3.51(m, 2H), 3.40(s, 3H), 2.55(m, 1H), 1.97(m, 1H), 1.89(m, 1H), 1.48(s, 1H). Calc MW: 384.4, Found 385.4 (MH+).



Example 39: *tert*-butyl 4-[(1-Methyl-6-oxo-4-pyrimidin-4-yl-1,6-dihydropyrimidin-2-yl)amino]azepane-1-carboxylate: To a solution of product of Preparation 3 (80 mg, 0.30 mmol) in DMF (1.0ml) was added *tert*-butyl 4-aminoazepane-1-carboxylate (75 mg, 0.35 mmol), followed by the addition of TEA (0.15 ml, 1.1 mmol). The reaction was then heated to 80°C for 16 hr., and cooled to RT. The reaction was diluted with DMSO (1.5 ml) and purified on prep. HPLC eluting with mixture of acetonitrile and water, with 0.01% ammonium hydroxide modifier, to give a yellow semi-solid (23.2 mg, 19%). ^{1}H-NMR($CDCl_3$): δ ppm 9.21(s, 1H), 8.91 (d, *J*=5 Hz, 1 H), 8.32 (d, *J*=5 Hz, 1 H), 8.27 (d, *J*=5 Hz, 1 H), 6.94(s, 1H), 4.27(m, 1H), 3.68-3.36(m, 7H), 2.23(m, 1H), 2.09(m, 1H), 1.99-1.64(m, 4H), 1.49 (d, *J*=5 Hz, 9 H). Calc MW: 400.4, Found: 401.4 (MH+).



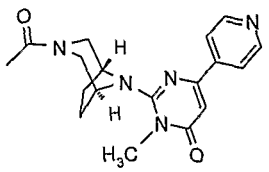
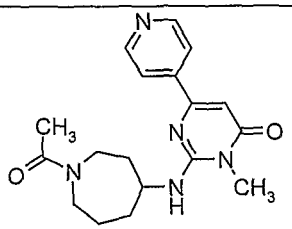
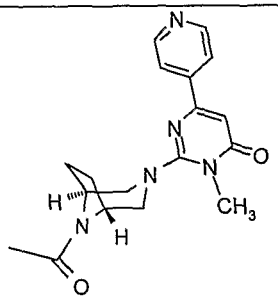
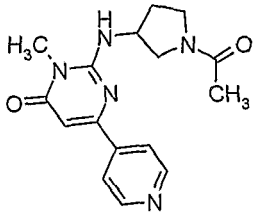
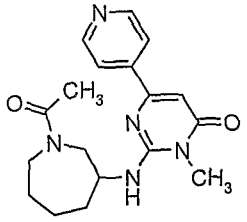
Example 40: 2-(6-Amino 3-aza-bicyclo[3.1.0]hexane-3-tert-butyl carboxylate)-6-(3-fluoropyridin-4-yl)-3-methylpyrimidin-4(3H)-one: To a solution of the product of Preparation 4, Step C (50 mg, 0.21 mmol), TEA (58 mg, 0.42 mol), and (1R,5S,6s)-*tert*-butyl 6-amino-3-aza-bicyclo[3.1.0]hexane-3-carboxylate (50 mg, 0.25 mmol) in DMF (0.5 ml) was heated in a microwave (Biotage) at 150 °C for 5 min. Addition of water (5 ml) resulted in a precipitate, which was extracted with EtOAc (2 X 5 ml). The crude residue was purified with prep. TLC using 100% EtOAc as mobile phase to give a white solid (31 mg, 37%). ^{1}H-NMR (500 MHz, CD3OD): δ ppm 8.57(d, 1H), 8.51 (d, 1 H), 8.16 (q, 1 H), 6.52 (s, 1 H), 3.71 (m, 2H), 3.48 (m, 2H), 3.39 (s, 3H), 2.5 (t, H), 1.9 (m, 2H), 1.46 (s, 9 H). Calc. MW: 401.4, Found: 402.5 (MH+).

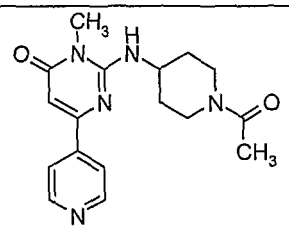
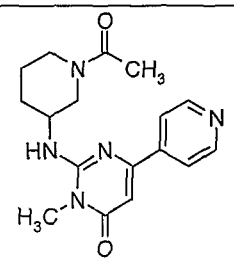
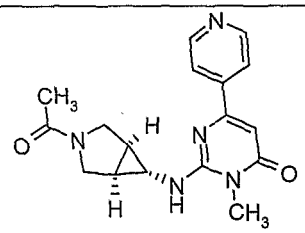
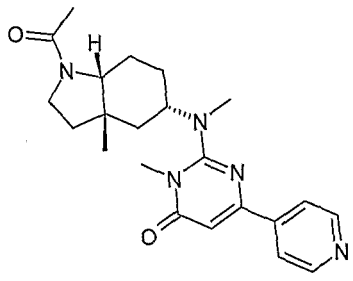


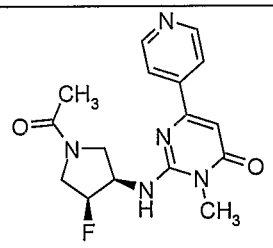
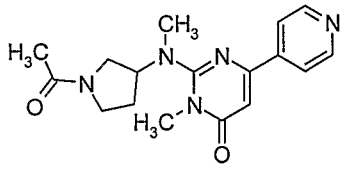
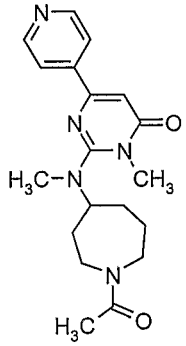
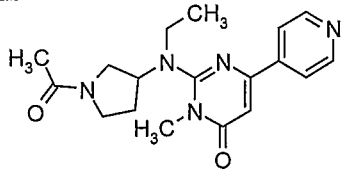
Example 41: 2-(1-Acetylazepan-4-ylamino)-3-methyl-6-(pyridin-4-yl)pyrimidin-4(3H)-one: To the product of Example 8 (80 μmol) was added a soln. of TFA (2 ml) in DCE (2 ml). The reaction was shaken for 4 hr. The solvent was evaporated to give a crude residue, which was dissolved in DMF (500 μl). TEA (160 μmol) in DMF (0.2 ml) was added followed by 1-hydroxybenzotrazole/dimethylsulfoxide-N-methylpyrrolidinone (HBTU) (80 μmol) in DMF (0.2 ml). To this was added acetic acid (80 μmol) in DMF (0.1 ml). The reaction was shaken at room temperature for 16 hr. The crude mixture was evaporated, dissolved in DMSO, and purified by prep. HPLC to give the title compound (1.9 mg). Calc. MW: 341.2, Found: 342 (MH+), Retention time 1.37 min.

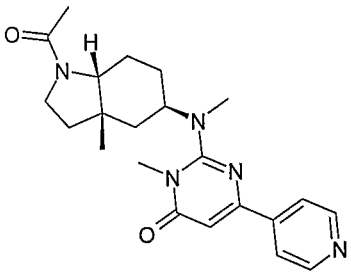
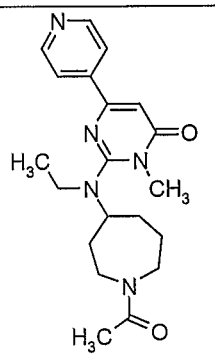
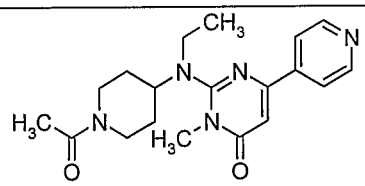
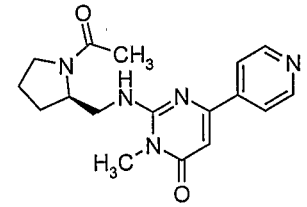
General Procedure for Examples 42 to 60

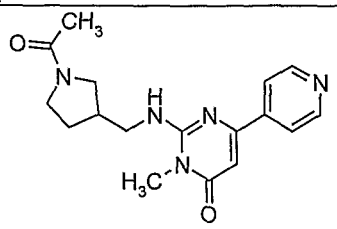
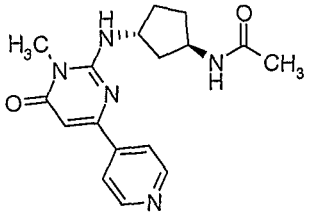
Examples 42 to 60 were prepared using the analogous procedure described to prepare Example 41, substituting the appropriate starting material (Examples 1 to 35) and coupling with the appropriate acid. The assay protocol used is the percent inhibition at 1 μM for GSK-3β in the cell free enzyme assay described above.

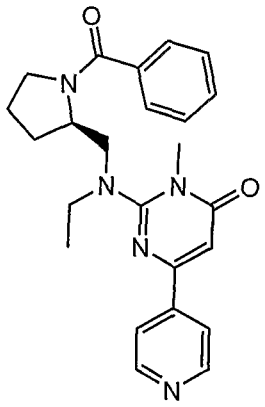
Ex	Structure	Name	Observed Mass (MH+)	Percent inhibition at 1 μM
42		2-[(1R,5S)-8-Acetyl-38-diazabicyclo[3.2.1]oct-3-yl]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	340	74
43		2-[(1-Acetylazepan-4-yl)amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	342	84
44		2-[(1R,5S)-3-Acetyl-38-diazabicyclo[3.2.1]oct-8-yl]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	340	72
45		2-[(1-Acetylpyrrolidin-3-yl)amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	314	39
46		2-[(1-Acetylazepan-3-yl)amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	482	51

Ex	Structure	Name	Observed Mass (MH+)	Percent inhibition at 1 μM
47		2-[(1-Acetylpiperidin-4-yl)amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	328	44
48		2-[(1-Acetylpiperidin-3-yl)amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	328	55
49		2-{[(1R,5S,6s)-3-Acetyl-3-azabicyclo[3.1.0]hex-6-yl]amino}-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	326	75
50		2-{[(3a,S5,S7,aR)-1-Acetyl-3a-methyloctahydro-1H-indol-5-yl](methyl)amino}-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	342	82

Ex	Structure	Name	Observed Mass (MH+)	Percent inhibition at 1 μM
51		2-{[(3R,4S)-1-Acetyl-4-fluoropyrrolidin-3-yl]amino}-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	332	78
52		2-[(1-Acetylpyrrolidin-3-yl)(methyl)amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	328	51
53		2-[(1-Acetylazepan-4-yl)(methyl)amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	356	79
54		2-[(1-Acetylpyrrolidin-3-yl)(ethyl)amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	342	64

Ex	Structure	Name	Observed Mass (MH+)	Percent inhibition at 1 μM
55		2-{[(3a,S5,R7,aR)-1-Acetyl-3a-methyloctahydro-1H-indol-5-yl](methyl)amino}-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	396	71
56		2-[(1-Acetylazepan-4-yl)(ethyl)amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	370	85
57		2-[(1-Acetylpiperidin-4-yl)(ethyl)amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	356	93
58		2-({[(2R)-1-Acetylpyrrolidin-2-yl]methyl}amino)-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	328	64

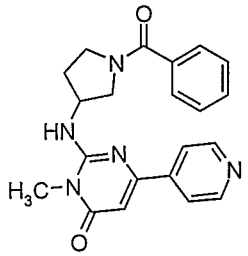
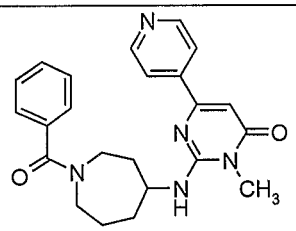
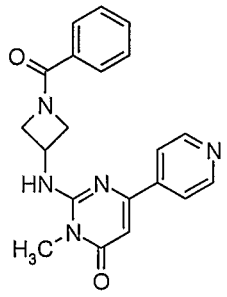
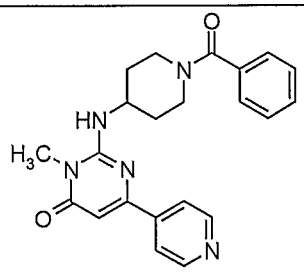
Ex	Structure	Name	Observed Mass (MH+)	Percent inhibition at 1 μM
59		2-{[(1-Acetylpyrrolidin-3-yl)methyl]amino}-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	328	37
60		N-{(1R,3R)-3-[(1-Methyl-6-oxo-4-pyridin-4-yl-16-dihydropyrimidin-2-yl)amino]cyclopentyl}acetamide	328	77

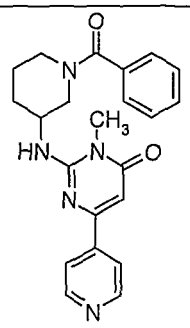
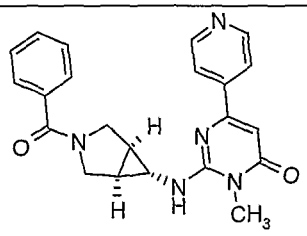
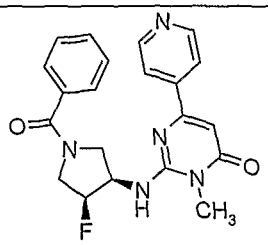
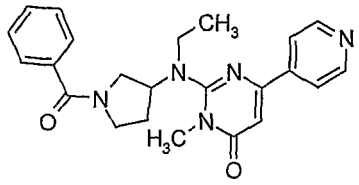
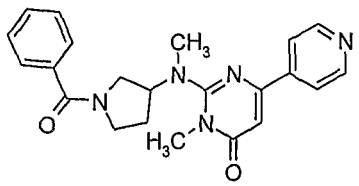


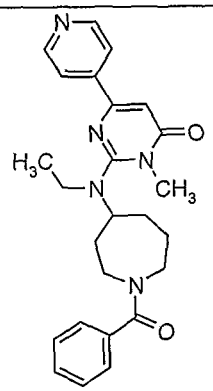
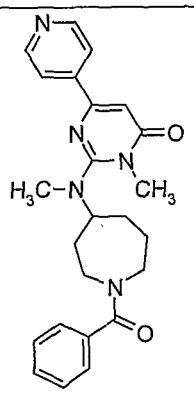
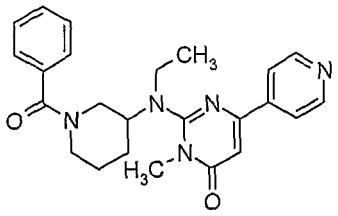
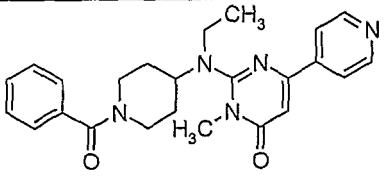
Example 61: (R)-2-(((1-Benzoylpyrrolidin-2-yl)methyl)(ethyl)amino)-3-methyl-6-(pyridin-4-yl)pyrimidin-4(3H)-one: To the product of Example 4 (80 μmol) was added TFA (2 ml) in DCE (2 ml) and the mixture was shaken for 4 hr. The solvent was removed and the residue was dissolved in DMF (500 μl). TEA (160 μmol) in DMF (0.2 ml) was added followed by benzoylchloride (80 μmol) in DMF (0.2 ml). The reaction was shaken at RT for 16 hr. The crude mixture was evaporated, then dissolved in DMSO and purified by prep. HPLC to give the title compound (4.0 mg). Calc. MW: 417.5, Found: 418 (MH+), Retention time: 1.89 min.

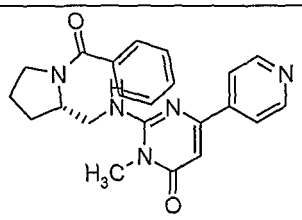
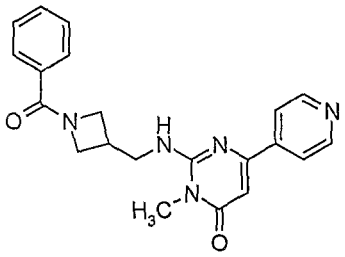
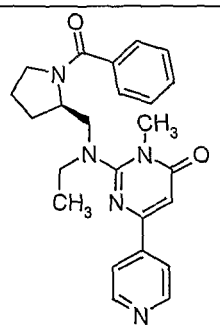
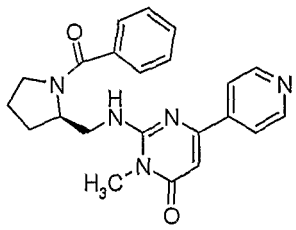
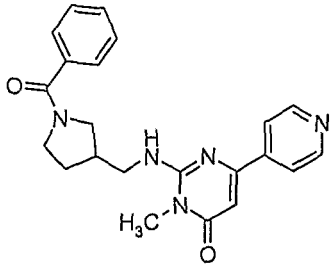
General Procedure for Examples 62 to 155

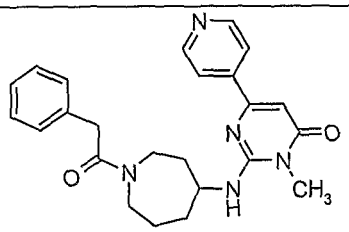
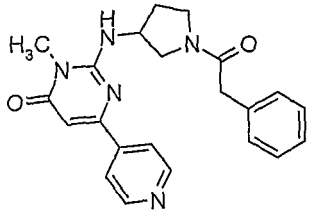
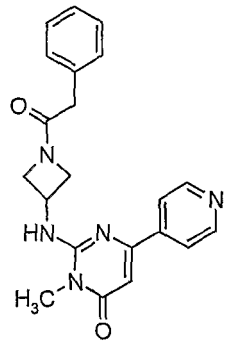
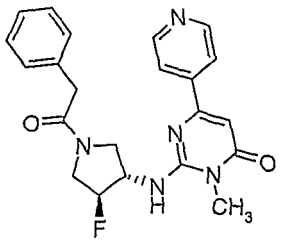
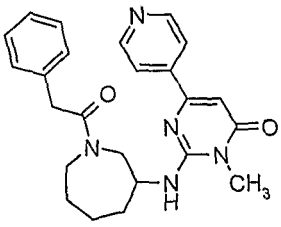
Examples 62 to 155 were prepared by using the analogous procedure described to prepare Example 61, substituting the appropriate starting material (Examples 1 to 35) and coupling with the appropriate acid chloride.

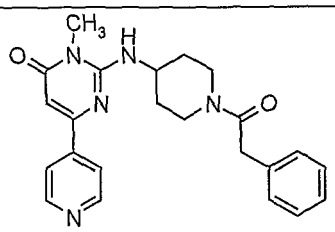
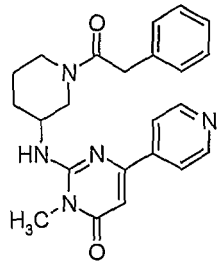
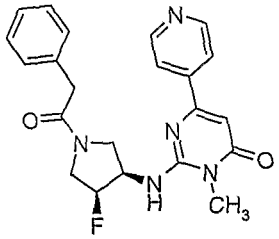
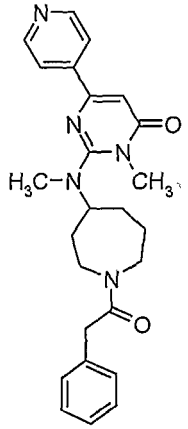
Ex.	Structure	Name	Observed Mass (MH+)	Enzyme IC_{50} (nM)
62		2-[(1-Benzoylpyrrolidin-3-yl)amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	376	77.5
63		2-[(1-Benzoylazepan-4-yl)amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	404	12.4
64		2-[(1-Benzoylazetidin-3-yl)amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	362	367
65		2-[(1-Benzoylpiperidin-4-yl)amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	390	202

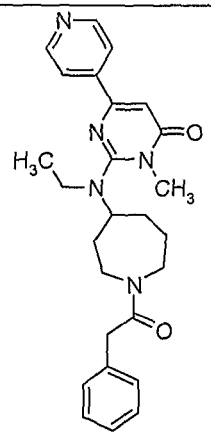
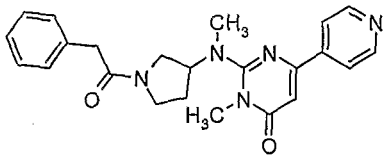
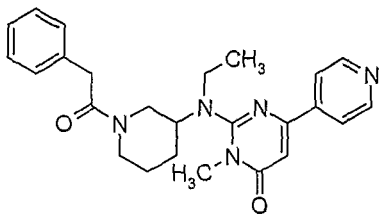
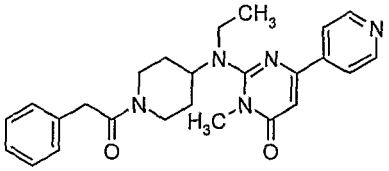
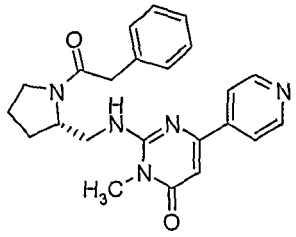
Ex.	Structure	Name	Observed Mass (MH+)	Enzyme IC_{50} (nM)
66		2-[(1-Benzoylpiperidin-3-yl)amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	390	1,000
67		2-{[(1R,5S,6s)-3-Benzoyl-3-azabicyclo[3.1.0]hex-6-yl]amino}-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	388	2.00
68		2-{[(3R,4S)-1-Benzoyl-4-fluoropyrrolidin-3-yl]amino}-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	394	56.0
69		2-[(1-Benzoylpyrrolidin-3-yl)(ethyl)amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	404	96.1
70		2-[(1-Benzoylpyrrolidin-3-yl)(methyl)amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	390	170.3

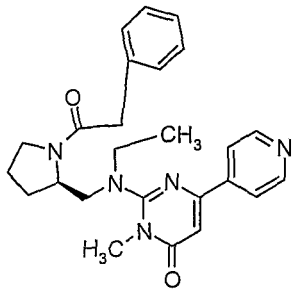
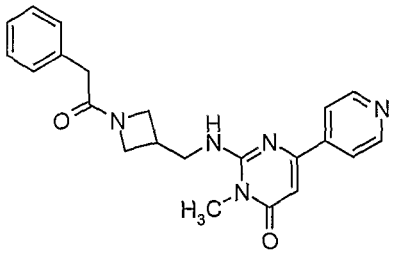
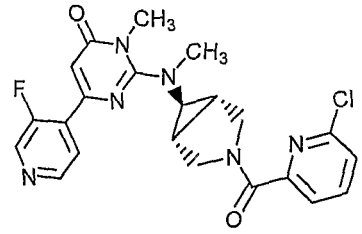
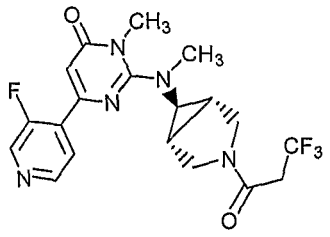
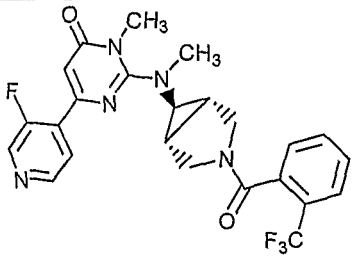
Ex.	Structure	Name	Observed Mass (MH+)	Enzyme IC_{50} (nM)
71		2-[(1-Benzoylazepan-4-yl)(ethyl)amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	432	36.3
72		2-[(1-Benzoylazepan-4-yl)(methyl)amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	418	61.5
73		2-[(1-Benzoylpiperidin-3-yl)(ethyl)amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	418	345
74		2-[(1-Benzoylpiperidin-4-yl)(ethyl)amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	418	143.9

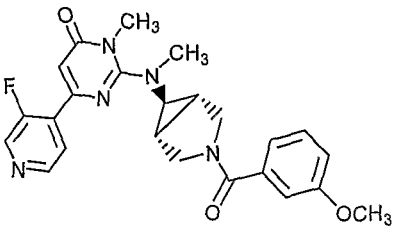
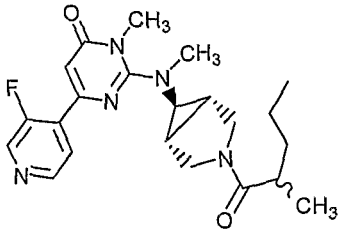
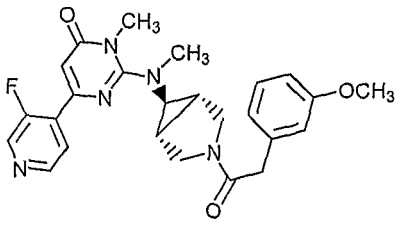
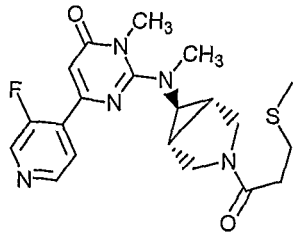
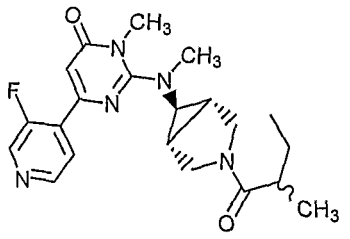
Ex.	Structure	Name	Observed Mass (MH+)	Enzyme IC_{50} (nM)
75		2-({[(2S)-1-Benzoylpyrrolidin-2-yl]methyl}amino)-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	390	183
76		2-{[(1-Benzoylazetidin-3-yl)methyl]amino}-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	376	72.4
77		2-[{[(2R)-1-Benzoylpyrrolidin-2-yl]methyl}(ethyl)amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	418	29.5
78		2-({[(2R)-1-Benzoylpyrrolidin-2-yl]methyl}amino)-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	390	277
79		2-{[(1-Benzoylpyrrolidin-3-yl)methyl]amino}-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	390	69.9

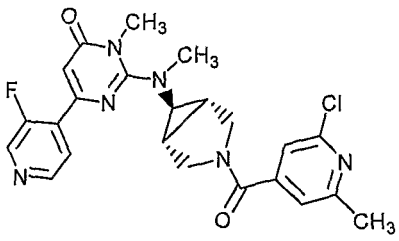
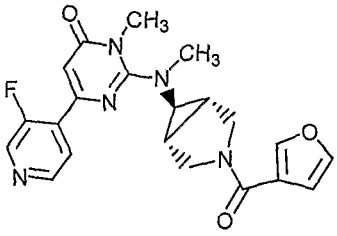
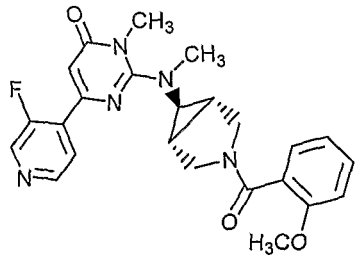
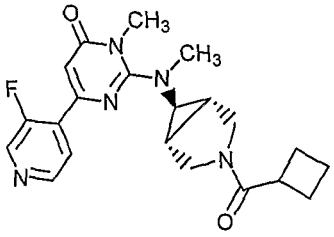
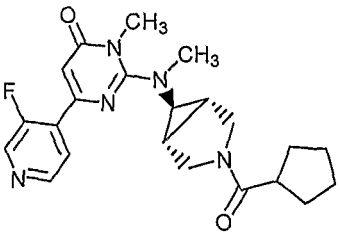
Ex.	Structure	Name	Observed Mass (MH+)	Enzyme IC_{50} (nM)
80		3-Methyl-2-{[1-(phenylacetyl)azepan-4-yl]amino}-6-pyridin-4-ylpyrimidin-4(3H)-one	418	53.8
81		3-Methyl-2-{[1-(phenylacetyl)pyrrolidin-3-yl]amino}-6-pyridin-4-ylpyrimidin-4(3H)-one	390	111.4
82		3-Methyl-2-{[1-(phenylacetyl)azetidin-3-yl]amino}-6-pyridin-4-ylpyrimidin-4(3H)-one	376	818
83		2-{[(3S,4S)-4-Fluoro-1-(phenylacetyl)pyrrolidin-3-yl]amino}-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	408	39
84		3-Methyl-2-{[1-(phenylacetyl)azepan-3-yl]amino}-6-pyridin-4-ylpyrimidin-4(3H)-one	418	674

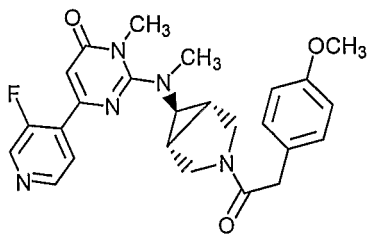
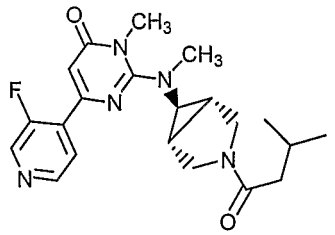
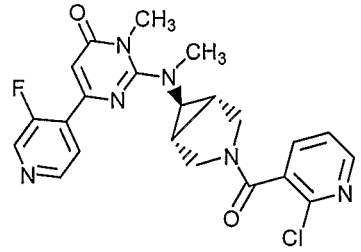
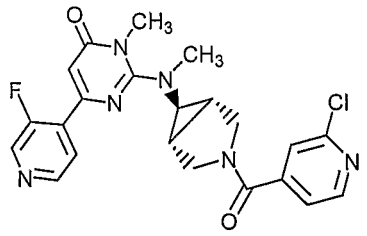
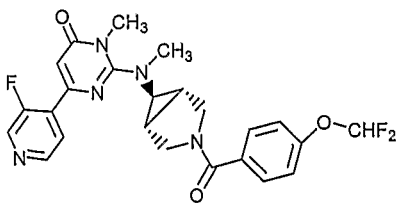
Ex.	Structure	Name	Observed Mass (MH+)	Enzyme IC_{50} (nM)
85		3-Methyl-2-{[1-(phenylacetyl)piperidin-4-yl]amino}-6-pyridin-4-ylpyrimidin-4(3H)-one	404	333
86		3-Methyl-2-{[1-(phenylacetyl)piperidin-3-yl]amino}-6-pyridin-4-ylpyrimidin-4(3H)-one	404	136
87		2-{[(3R,4S)-4-Fluoro-1-(phenylacetyl)pyrrolidin-3-yl]amino}-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	408	285
88		3-Methyl-2-{methyl[1-(phenylacetyl)azepan-4-yl]amino}-6-pyridin-4-ylpyrimidin-4(3H)-one	432	102

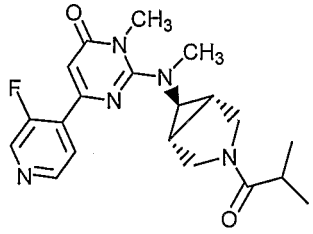
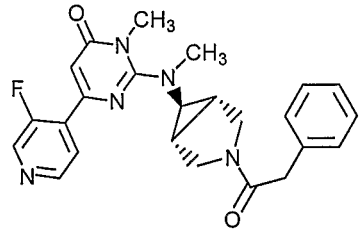
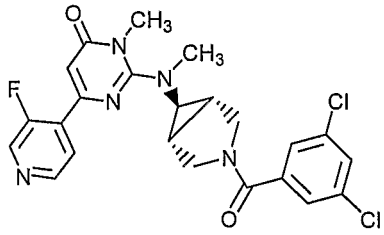
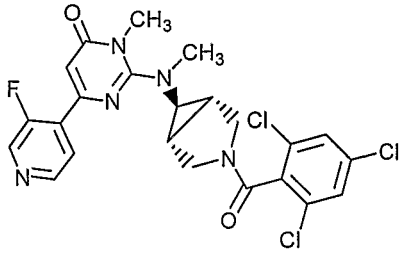
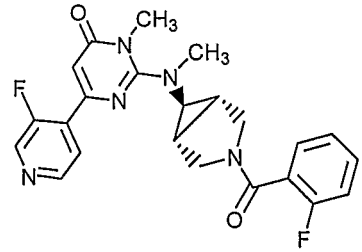
Ex.	Structure	Name	Observed Mass (MH+)	Enzyme IC_{50} (nM)
89		2-{Ethyl[1-(phenylacetyl)azepan-4-yl]amino}-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	446	64.6
90		3-Methyl-2-{methyl[1-(phenylacetyl)pyrrolidin-3-yl]amino}-6-pyridin-4-ylpyrimidin-4(3H)-one	404	132.6
91		2-{Ethyl[1-(phenylacetyl)piperidin-3-yl]amino}-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	432	147
92		2-{Ethyl[1-(phenylacetyl)piperidin-4-yl]amino}-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	432	105
93		3-Methyl-2-({[(2S)-1-(phenylacetyl)pyrrolidin-2-yl]methyl}amino)-6-pyridin-4-ylpyrimidin-4(3H)-one	404	878

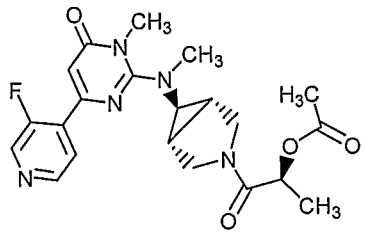
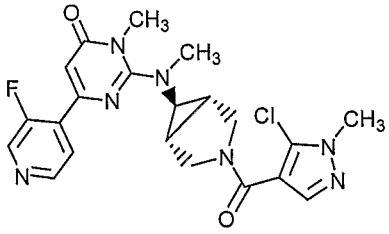
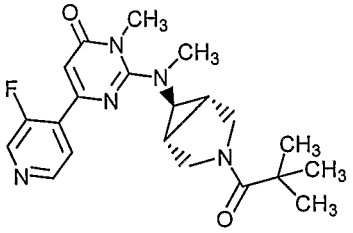
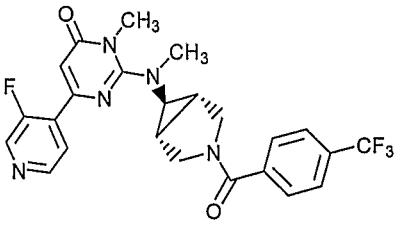
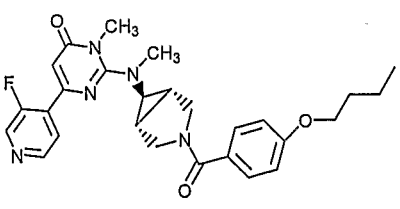
Ex.	Structure	Name	Observed Mass (MH+)	Enzyme IC_{50} (nM)
94		2-(Ethyl{[(2R)-1-(phenylacetyl)pyrrolidin-2-yl]methyl}amino)-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	432	18.2
95		3-Methyl-2-({[1-(phenylacetyl)azetidin-3-yl]methyl}amino)-6-pyridin-4-ylpyrimidin-4(3H)-one	390	1,381
96		2-[{(1R,5S,6s)-3-[(6-Chloropyridin-2-yl)carbonyl]-3-azabicyclo[3.1.0]hex-6-yl}(methyl)amino]-6-(3-fluoropyridin-4-yl)-3-methylpyrimidin-4(3H)-one	455	3.92
97		6-(3-Fluoropyridin-4-yl)-3-methyl-2-{methyl[(1R,5S,6s)-3-(3,3,3-trifluoropropanoyl)-3-azabicyclo[3.1.0]hex-6-yl]amino}pyrimidin-4(3H)-one	426	55.4
98		6-(3-Fluoropyridin-4-yl)-3-methyl-2-(methyl{(1R,5S,6s)-3-[2-(trifluoromethyl)benzoyl]-3-azabicyclo[3.1.0]hex-6-yl}amino)pyrimidin-4(3H)-one	488	4.39

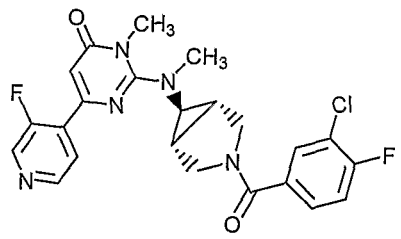
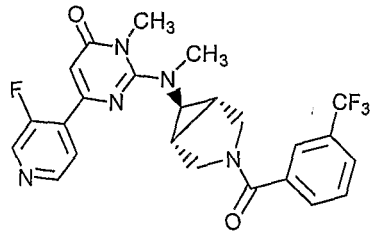
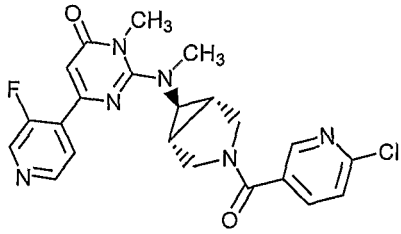
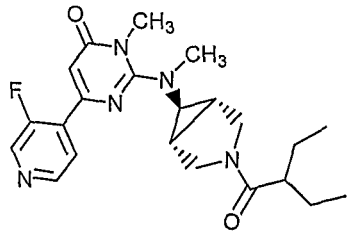
Ex.	Structure	Name	Observed Mass (MH+)	Enzyme IC_{50} (nM)
99		6-(3-Fluoropyridin-4-yl)-2-{[(1R,5S,6s)-3-(3-methoxybenzoyl)-3-azabicyclo[3.1.0]hex-6-yl](methyl)amino}-3-methylpyrimidin-4(3H)-one	450	1.46
100		6-(3-Fluoropyridin-4-yl)-3-methyl-2-{methyl[(1R,5S,6s)-3-(2-methylpentanoyl)-3-azabicyclo[3.1.0]hex-6-yl]amino}pyrimidin-4(3H)-one	414	9.02
101		6-(3-Fluoropyridin-4-yl)-2-[{(1R,5S,6s)-3-[(3-methoxyphenyl)acetyl]-3-azabicyclo[3.1.0]hex-6-yl}(methyl)amino]-3-methylpyrimidin-4(3H)-one	464	13.6
102		6-(3-Fluoropyridin-4-yl)-3-methyl-2-(methyl{(1R,5S,6s)-3-[3-(methylthio)propanoyl]-3-azabicyclo[3.1.0]hex-6-yl}amino)pyrimidin-4(3H)-one	418	16.0
103		6-(3-Fluoropyridin-4-yl)-3-methyl-2-{methyl[(1R,5S,6s)-3-(2-methylbutanoyl)-3-azabicyclo[3.1.0]hex-6-yl]amino}pyrimidin-4(3H)-one	400	2.77

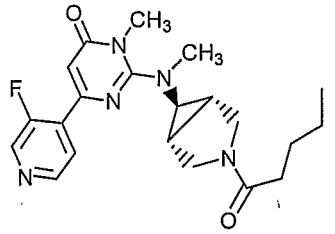
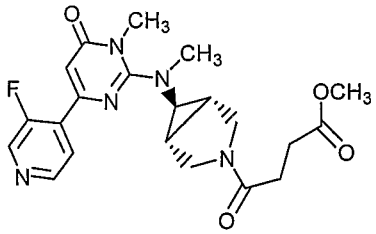
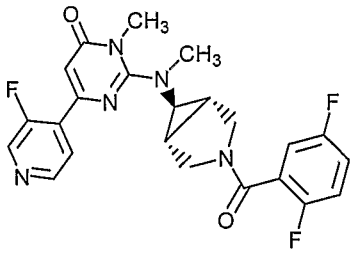
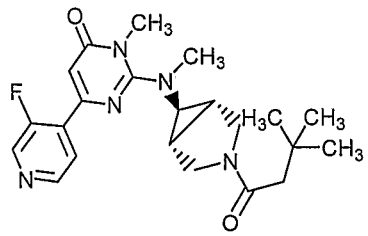
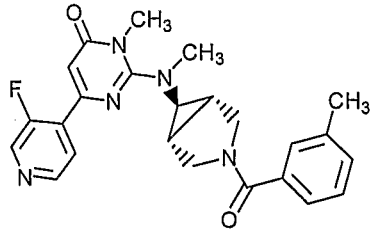
Ex.	Structure	Name	Observed Mass (MH+)	Enzyme IC_{50} (nM)
104		2-{[(1R,5S,6s)-3-(2-Chloro-6-methylisonicotinoyl)-3-azabicyclo[3.1.0]hex-6-yl](methyl)amino}-6-(3-fluoropyridin-4-yl)-3-methylpyrimidin-4(3H)-one	469	16.1
105		6-(3-Fluoropyridin-4-yl)-2-{[(1R,5S,6s)-3-(3-furoyl)-3-azabicyclo[3.1.0]hex-6-yl](methyl)amino}-3-methylpyrimidin-4(3H)-one	410	8.81
106		6-(3-Fluoropyridin-4-yl)-2-{[(1R,5S,6s)-3-(2-methoxybenzoyl)-3-azabicyclo[3.1.0]hex-6-yl](methyl)amino}-3-methylpyrimidin-4(3H)-one	450	0.91
107		2-{[(1R,5S,6s)-3-(Cyclobutylcarbonyl)-3-azabicyclo[3.1.0]hex-6-yl](methyl)amino}-6-(3-fluoropyridin-4-yl)-3-methylpyrimidin-4(3H)-one	398	18.4
108		2-{[(1R,5S,6s)-3-(Cyclopentylcarbonyl)-3-azabicyclo[3.1.0]hex-6-yl](methyl)amino}-6-(3-fluoropyridin-4-yl)-3-methylpyrimidin-4(3H)-one	412	6.39

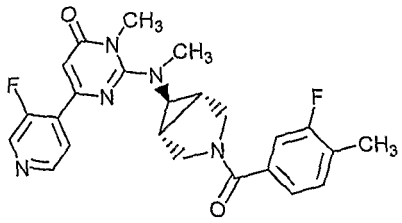
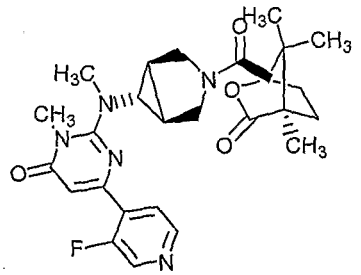
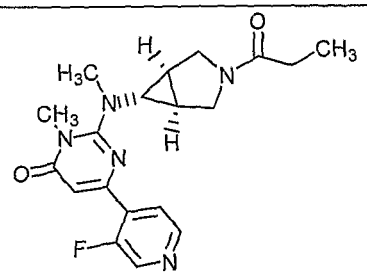
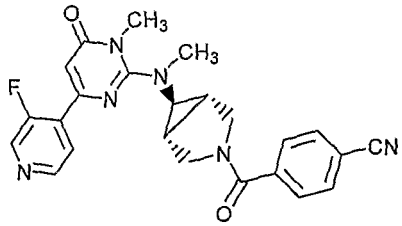
Ex.	Structure	Name	Observed Mass (MH+)	Enzyme IC_{50} (nM)
109		6-(3-Fluoropyridin-4-yl)-2-[{(1R,5S,6s)-3-[(4-methoxyphenyl)acetyl]-3-azabicyclo[3.1.0]hex-6-yl}(methyl)amino]-3-methylpyrimidin-4(3H)-one	464	4.03
110		6-(3-Fluoropyridin-4-yl)-3-methyl-2-{methyl[(1R,5S,6s)-3-(3-methylbutanoyl)-3-azabicyclo[3.1.0]hex-6-yl]amino}pyrimidin-4(3H)-one	400	18.3
111		2-[{(1R,5S,6s)-3-[(2-Chloropyridin-3-yl)carbonyl]-3-azabicyclo[3.1.0]hex-6-yl}(methyl)amino]-6-(3-fluoropyridin-4-yl)-3-methylpyrimidin-4(3H)-one	455	2.20
112		2-{[(1R,5S,6s)-3-(2-Chloroisonicotinoyl)-3-azabicyclo[3.1.0]hex-6-yl](methyl)amino}-6-(3-fluoropyridin-4-yl)-3-methylpyrimidin-4(3H)-one	455	2.63
113		2-[{(1R,5S,6s)-3-[4-(Difluoromethoxy)benzoyl]-3-azabicyclo[3.1.0]hex-6-yl}(methyl)amino]-6-(3-fluoropyridin-4-yl)-3-methylpyrimidin-4(3H)-one	486	8.57

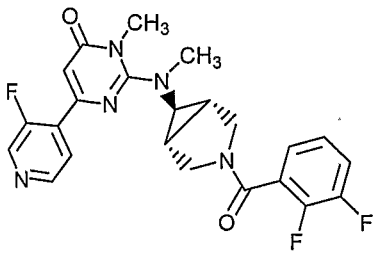
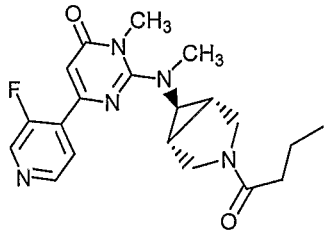
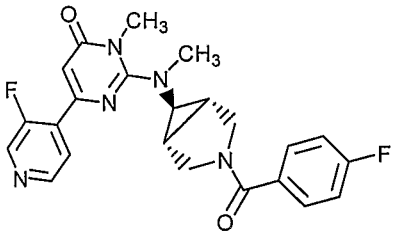
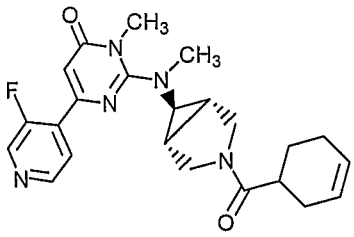
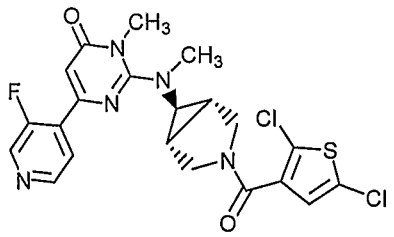
Ex.	Structure	Name	Observed Mass (MH+)	Enzyme IC_{50} (nM)
114		6-(3-Fluoropyridin-4-yl)-2-{[(1R,5S,6s)-3-isobutyryl-3-azabicyclo[3.1.0]hex-6-yl](methyl)amino}-3-methylpyrimidin-4(3H)-one	386	15.3
115		6-(3-Fluoropyridin-4-yl)-3-methyl-2-{methyl[(1R,5S,6s)-3-(phenylacetyl)-3-azabicyclo[3.1.0]hex-6-yl]amino}pyrimidin-4(3H)-one	434	14.2
116		2-{[(1R,5S,6s)-3-(3,5-Dichlorobenzoyl)-3-azabicyclo[3.1.0]hex-6-yl](methyl)amino}-6-(3-fluoropyridin-4-yl)-3-methylpyrimidin-4(3H)-one	488	4.40
117		6-(3-Fluoropyridin-4-yl)-3-methyl-2-{methyl[(1R,5S,6s)-3-(2,4,6-trifluorobenzoyl)-3-azabicyclo[3.1.0]hex-6-yl]amino}pyrimidin-4(3H)-one	474	1.84
118		2-{[(1R,5S,6s)-3-(2-Fluorobenzoyl)-3-azabicyclo[3.1.0]hex-6-yl](methyl)amino}-6-(3-fluoropyridin-4-yl)-3-methylpyrimidin-4(3H)-one	438	1.11

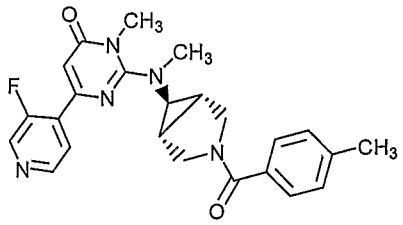
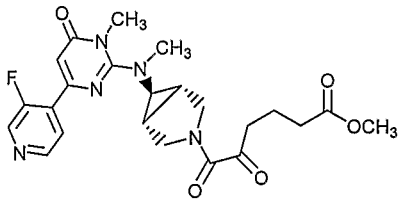
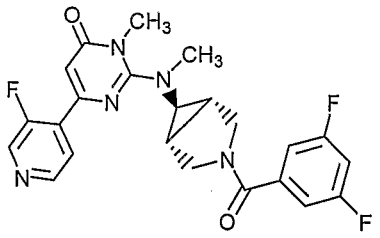
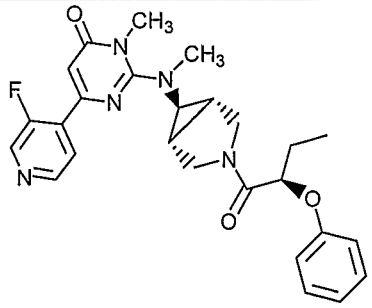
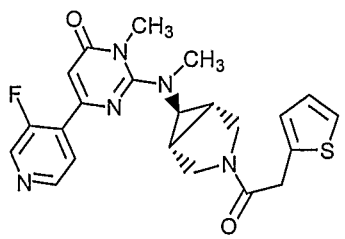
Ex.	Structure	Name	Observed Mass (MH+)	Enzyme IC_{50} (nM)
119		(1S)-2-[(1R,5S,6R)-6-{[4-(3-Fluoropyridin-4-yl)-1-methyl-6-oxo-1,6-dihydropyrimidin-2-yl](methyl)amino}-3-azabicyclo[3.1.0]hex-3-yl]-1-methyl-2-oxoethyl acetate	430	32.9
120		2-[{(1R,5S,6s)-3-[(5-Chloro-1-methyl-1H-pyrazol-4-yl)carbonyl]-3-azabicyclo[3.1.0]hex-6-yl}(methyl)amino]-6-(3-fluoropyridin-4-yl)-3-methylpyrimidin-4(3H)-one	458	4.52
121		2-{[(1R,5S,6s)-3-(2,2-Dimethylpropanoyl)-3-azabicyclo[3.1.0]hex-6-yl](methyl)amino}-6-(3-fluoropyridin-4-yl)-3-methylpyrimidin-4(3H)-one	400	1.41
122		6-(3-Fluoropyridin-4-yl)-3-methyl-2-(methyl{(1R,5S,6s)-3-[4-(trifluoromethyl)benzoyl]-3-azabicyclo[3.1.0]hex-6-yl}amino)pyrimidin-4(3H)-one	488	15.1
123		2-{[(1R,5S,6s)-3-(4-Butoxybenzoyl)-3-azabicyclo[3.1.0]hex-6-yl](methyl)amino}-6-(3-fluoropyridin-4-yl)-3-methylpyrimidin-4(3H)-one	492	13.6

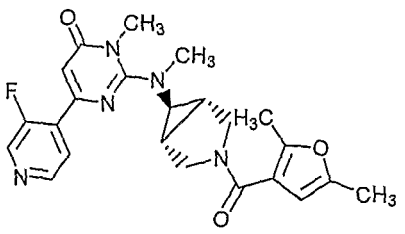
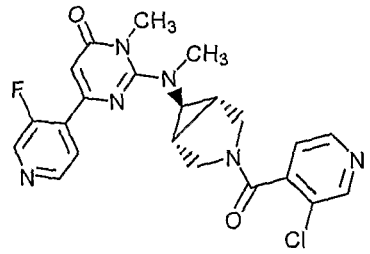
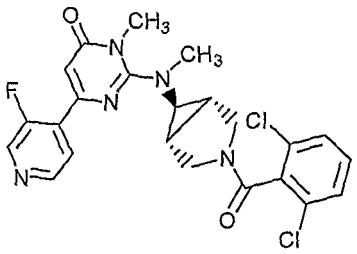
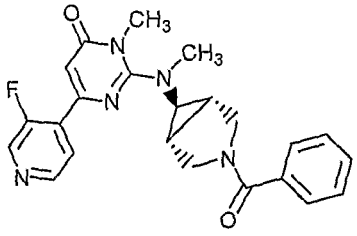
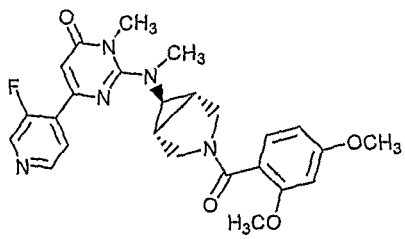
Ex.	Structure	Name	Observed Mass (MH+)	Enzyme IC_{50} (nM)
124		2-{[(1R,5S,6s)-3-(3-Chloro-4-fluorobenzoyl)-3-azabicyclo[3.1.0]hex-6-yl](methyl)amino}-6-(3-fluoropyridin-4-yl)-3-methylpyrimidin-4(3H)-one	472	4.58
125		6-(3-Fluoropyridin-4-yl)-3-methyl-2-(methyl{(1R,5S,6s)-3-[3-(trifluoromethyl)benzoyl]-3-azabicyclo[3.1.0]hex-6-yl}amino)pyrimidin-4(3H)-one	488	2.11
126		2-[{(1R,5S,6s)-3-[(6-Chloropyridin-3-yl)carbonyl]-3-azabicyclo[3.1.0]hex-6-yl}(methyl)amino]-6-(3-fluoropyridin-4-yl)-3-methylpyrimidin-4(3H)-one	455	6.98
127		2-{[(1R,5S,6s)-3-(2-Ethylbutanoyl)-3-azabicyclo[3.1.0]hex-6-yl](methyl)amino}-6-(3-fluoropyridin-4-yl)-3-methylpyrimidin-4(3H)-one	414	4.41

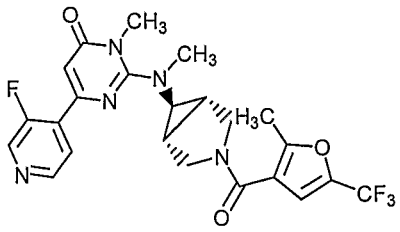
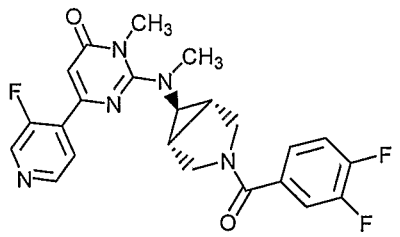
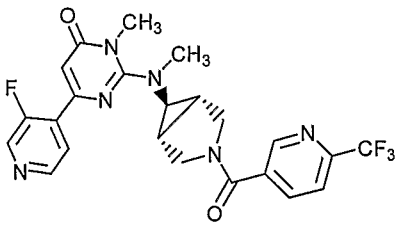
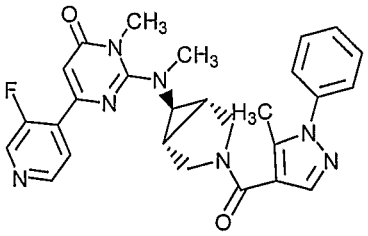
Ex.	Structure	Name	Observed Mass (MH+)	Enzyme IC_{50} (nM)
128		6-(3-Fluoropyridin-4-yl)-3-methyl-2-{methyl[(1R,5S,6s)-3-pentanoyl-3-azabicyclo[3.1.0]hex-6-yl]amino}pyrimidin-4(3H)-one	400	16.4
129		Methyl 4-[(1R,5S,6s)-6-{[4-(3-fluoropyridin-4-yl)-1-methyl-6-oxo-1,6-dihydropyrimidin-2-yl](methyl)amino}-3-azabicyclo[3.1.0]hex-3-yl]-4-oxobutanoate	430	84.4
130		2-{[(1R,5S,6s)-3-(2,5-Difluorobenzoyl)-3-azabicyclo[3.1.0]hex-6-yl](methyl)amino}-6-(3-fluoropyridin-4-yl)-3-methylpyrimidin-4(3H)-one	456	1.69
131		2-{[(1R,5S,6s)-3-(3,3-Dimethylbutanoyl)-3-azabicyclo[3.1.0]hex-6-yl](methyl)amino}-6-(3-fluoropyridin-4-yl)-3-methylpyrimidin-4(3H)-one	414	1.57
132		6-(3-Fluoropyridin-4-yl)-3-methyl-2-{methyl[(1R,5S,6s)-3-(3-methylbenzoyl)-3-azabicyclo[3.1.0]hex-6-yl]amino}pyrimidin-4(3H)-one	434	1.05

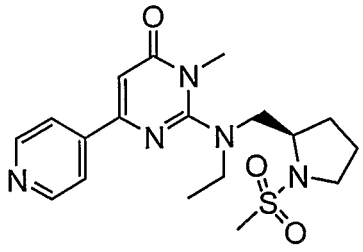
Ex.	Structure	Name	Observed Mass (MH+)	Enzyme IC_{50} (nM)
133		2-{[(1R,5S,6s)-3-(3-Fluoro-4-methylbenzoyl)-3-azabicyclo[3.1.0]hex-6-yl](methyl)amino}-6-(3-fluoropyridin-4-yl)-3-methylpyrimidin-4(3H)-one	452	2.91
134		6-(3-Fluoropyridin-4-yl)-3-methyl-2-{methyl[(1R,5S,6R)-3-{[(1S,4R)-4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]hept-1-yl]carbonyl}-3-azabicyclo[3.1.0]hex-6-yl]amino}pyrimidin-4(3H)-one	496	65.7
135		6-(3-Fluoropyridin-4-yl)-3-methyl-2-{methyl[(1R,5S,6s)-3-propionyl-3-azabicyclo[3.1.0]hex-6-yl]amino}pyrimidin-4(3H)-one	372	5.46
136		4-{[(1R,5S,6s)-6-{[4-(3-Fluoropyridin-4-yl)-1-methyl-6-oxo-1,6-dihydropyrimidin-2-yl](methyl)amino}-3-azabicyclo[3.1.0]hex-3-yl]carbonyl}benzonitrile	445	42.6

Ex.	Structure	Name	Observed Mass (MH+)	Enzyme IC_{50} (nM)
137		2-{[(1R,5S,6s)-3-(2,3-Difluorobenzoyl)-3-azabicyclo[3.1.0]hex-6-yl](methyl)amino}-6-(3-fluoropyridin-4-yl)-3-methylpyrimidin-4(3H)-one	456	3.29
138		2-{[(1R,5S,6s)-3-Butyryl-3-azabicyclo[3.1.0]hex-6-yl](methyl)amino}-6-(3-fluoropyridin-4-yl)-3-methylpyrimidin-4(3H)-one	386	13.8
139		2-{[(1R,5S,6s)-3-(4-Fluorobenzoyl)-3-azabicyclo[3.1.0]hex-6-yl](methyl)amino}-6-(3-fluoropyridin-4-yl)-3-methylpyrimidin-4(3H)-one	438	5.67
140		2-{[(1R,5S,6s)-3-(Cyclohex-3-en-1-ylcarbonyl)-3-azabicyclo[3.1.0]hex-6-yl](methyl)amino}-6-(3-fluoropyridin-4-yl)-3-methylpyrimidin-4(3H)-one	424	8.72
141		2-[{(1R,5S,6s)-3-[(2,5-Dichloro-3-thienyl)carbonyl]-3-azabicyclo[3.1.0]hex-6-yl}(methyl)amino]-6-(3-fluoropyridin-4-yl)-3-methylpyrimidin-4(3H)-one	494	1.04

Ex.	Structure	Name	Observed Mass (MH+)	Enzyme IC_{50} (nM)
142		6-(3-Fluoropyridin-4-yl)-3-methyl-2-{methyl[(1R,5S,6s)-3-(4-methylbenzoyl)-3-azabicyclo[3.1.0]hex-6-yl]amino}pyrimidin-4(3H)-one	434	3.51
143		Methyl 5-[(1R,5S,6s)-6-{[4-(3-fluoropyridin-4-yl)-1-methyl-6-oxo-1,6-dihydropyrimidin-2-yl](methyl)amino}-3-azabicyclo[3.1.0]hex-3-yl]-5-oxopentanoate	444	57.4
144		2-{[(1R,5S,6s)-3-(3,5-Difluorobenzoyl)-3-azabicyclo[3.1.0]hex-6-yl](methyl)amino}-6-(3-fluoropyridin-4-yl)-3-methylpyrimidin-4(3H)-one	456	4.09
145		6-(3-Fluoropyridin-4-yl)-3-methyl-2-{methyl[(1R,5S,6s)-3-(2-phenoxybutanoyl)-3-azabicyclo[3.1.0]hex-6-yl]amino}pyrimidin-4(3H)-one	478	13.2
146		6-(3-Fluoropyridin-4-yl)-3-methyl-2-{methyl[(1R,5S,6s)-3-(2-thienylacetyl)-3-azabicyclo[3.1.0]hex-6-yl]amino}pyrimidin-4(3H)-one	440	6.16

Ex.	Structure	Name	Observed Mass (MH+)	Enzyme IC_{50} (nM)
147		2-{[(1R,5S,6s)-3-(2,5-Dimethyl-3-furoyl)-3-azabicyclo[3.1.0]hex-6-yl](methyl)amino}-6-(3-fluoropyridin-4-yl)-3-methylpyrimidin-4(3H)-one	438	3.70
148		2-{[(1R,5S,6s)-3-(3-Chloroisonicotinoyl)-3-azabicyclo[3.1.0]hex-6-yl](methyl)amino}-6-(3-fluoropyridin-4-yl)-3-methylpyrimidin-4(3H)-one	455	36.1
149		2-{[(1R,5S,6s)-3-(2,6-Dichlorobenzoyl)-3-azabicyclo[3.1.0]hex-6-yl](methyl)amino}-6-(3-fluoropyridin-4-yl)-3-methylpyrimidin-4(3H)-one	488	3.81
150		2-{[(1R,5S,6s)-3-Benzoyl-3-azabicyclo[3.1.0]hex-6-yl](methyl)amino}-6-(3-fluoropyridin-4-yl)-3-methylpyrimidin-4(3H)-one	420	1.51
151		2-{[(1R,5S,6s)-3-(2,4-Dimethoxybenzoyl)-3-azabicyclo[3.1.0]hex-6-yl](methyl)amino}-6-(3-fluoropyridin-4-yl)-3-methylpyrimidin-4(3H)-one	480	1.22

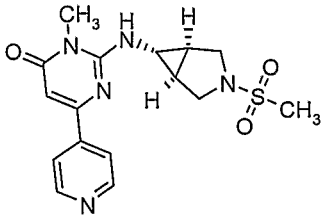
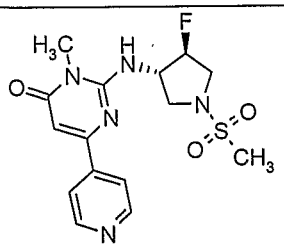
Ex.	Structure	Name	Observed Mass (MH+)	Enzyme IC_{50} (nM)
152		6-(3-Fluoropyridin-4-yl)-3-methyl-2-(methyl{(1R,5S,6s)-3-[5-methyl-2-(trifluoromethyl)-3-furoyl]-3-azabicyclo[3.1.0]hex-6-yl}amino)pyrimidin-4(3H)-one	492	11.9
153		2-{[(1R,5S,6s)-3-(3,4-Difluorobenzoyl)-3-azabicyclo[3.1.0]hex-6-yl](methyl)amino}-6-(3-fluoropyridin-4-yl)-3-methylpyrimidin-4(3H)-one	456	7.23
154		6-(3-Fluoropyridin-4-yl)-3-methyl-2-{methyl[(1R,5S,6s)-3-{[6-(trifluoromethyl)pyridin-3-yl]carbonyl}-3-azabicyclo[3.1.0]hex-6-yl]amino}pyrimidin-4(3H)-one	489	26.4
155		6-(3-Fluoropyridin-4-yl)-3-methyl-2-(methyl{(1R,5S,6s)-3-[(5-methyl-1-phenyl-1H-pyrazol-4-yl)carbonyl]-3-azabicyclo[3.1.0]hex-6-yl}amino)pyrimidin-4(3H)-one	500	102

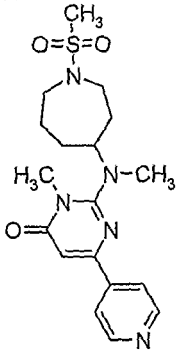
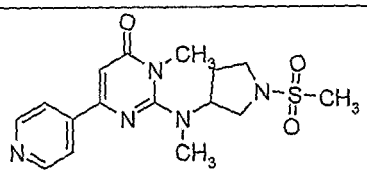
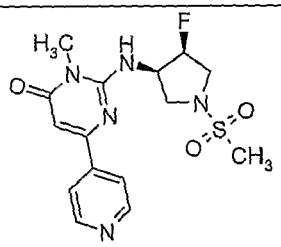
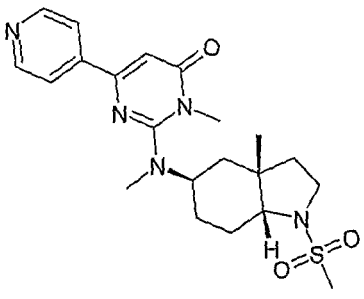


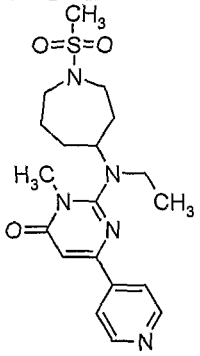
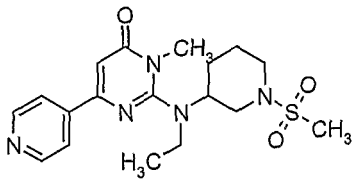
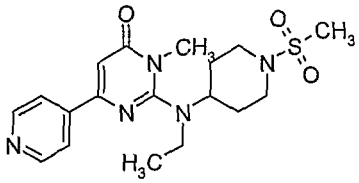
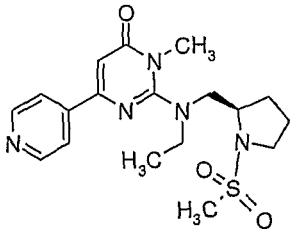
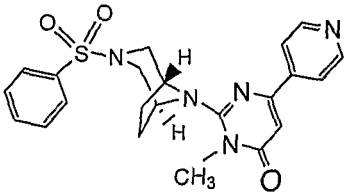
Example 156: (R)-2-(Ethyl((1-(methylsulfonyl)pyrrolidin-2-yl)methyl)amino)-3-methyl-6-(pyridin-4-yl)pyrimidin-4(3H)-one: To the product of Example 32 (80 μmol) was added a soln. of TFA (2 ml) in DCE (2 ml) and the mixture was shaken for 4 hr. The solvent was removed to give a residue, which was dissolved in DCE (500 μl). TEA (160 μmol) in DCE (0.2 ml) was added followed by methanesulfonylchloride (80 μmol) in DCE (0.2 ml). The reaction was shaken at RT for 16 hr. The mixture evaporated, then dissolved in DMSO and purified by prep. HPLC to give the title compound (8.9 mg). Calc. MW: 391.5, Found: 392 (MH+), Retention time: 2.41min.

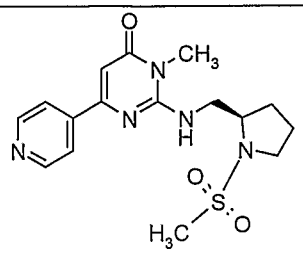
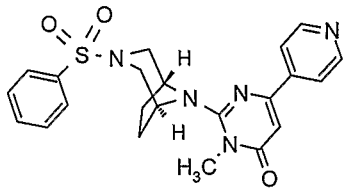
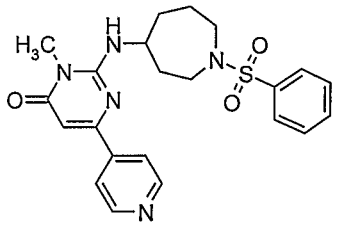
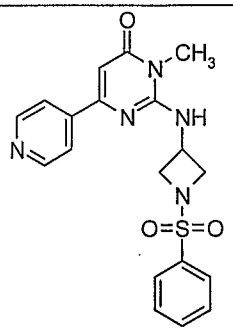
General Procedure for Examples 157 to 199

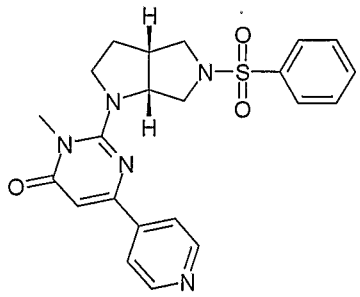
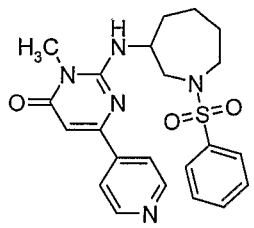
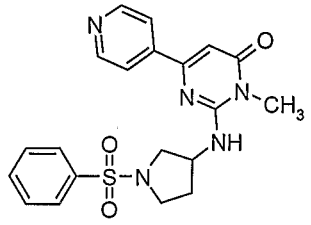
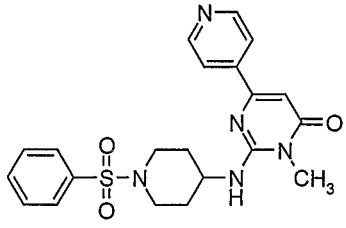
Examples 157 to 199 were prepared by using the analogous procedure described to prepare Example 156 substituting the appropriate starting material (Examples 1 to 35) and coupling with the appropriate sulfonyl chloride.

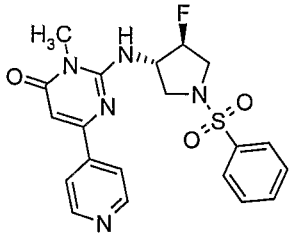
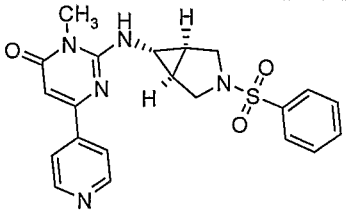
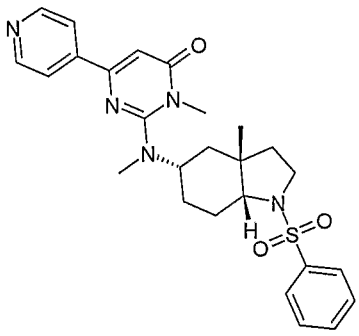
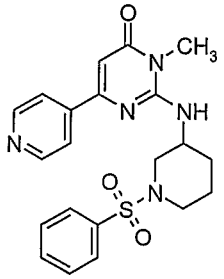
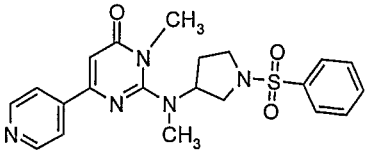
Ex.	Structure	Name	Observed Mass (MH+)	Percent inhibition at 1 μM
157		3-Methyl-2-{[(1R,5S,6s)-3-(methylsulfonyl)-3-azabicyclo[3.1.0]hex-6-yl]amino}-6-pyridin-4-ylpyrimidin-4(3H)-one	362	61
158		2-{[(3S,4S)-4-Fluoro-1-(methylsulfonyl)pyrrolidin-3-yl]amino}-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	368	74

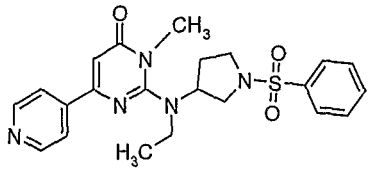
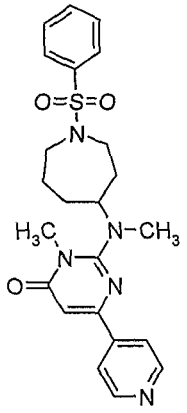
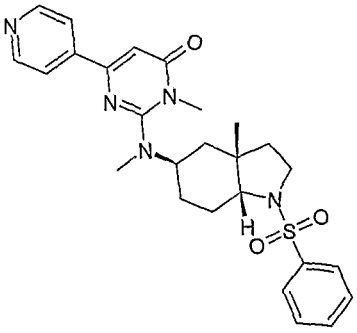
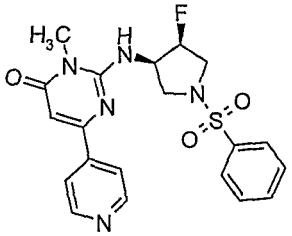
Ex.	Structure	Name	Observed Mass (MH+)	Percent inhibition at 1 μM
159		3-Methyl-2-{methyl[1-(methylsulfonyl)azepan-4-yl]amino}-6-pyridin-4-ylpyrimidin-4(3H)-one	392	100
160		3-Methyl-2-{methyl[1-(methylsulfonyl)pyrrolidin-3-yl]amino}-6-pyridin-4-ylpyrimidin-4(3H)-one	364	79
161		2-{[(3R,4S)-4-Fluoro-1-(methylsulfonyl)pyrrolidin-3-yl]amino}-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	368	93
162		3-Methyl-2-{methyl[(3a,S5,R7,aR)-3a-methyl-1-(methylsulfonyl)octahydro-1H-indol-5-yl]amino}-6-pyridin-4-ylpyrimidin-4(3H)-one	432	84

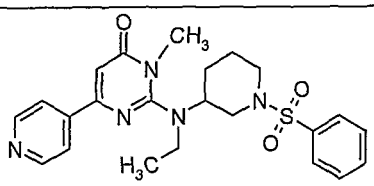
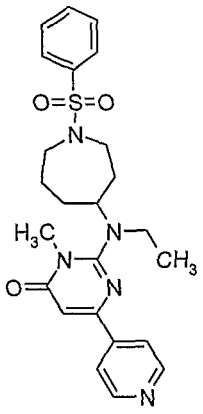
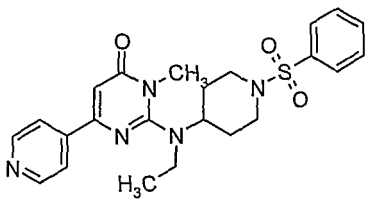
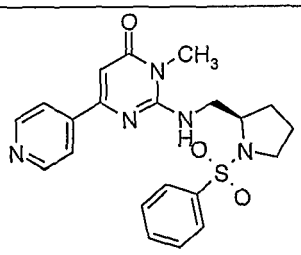
Ex.	Structure	Name	Observed Mass (MH+)	Percent inhibition at 1 μM
163		2-{Ethyl[1-(methylsulfonyl)azepan-4-yl]amino}-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	406	100
164		2-{Ethyl[1-(methylsulfonyl)piperidin-3-yl]amino}-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	392	82
165		2-{Ethyl[1-(methylsulfonyl)piperidin-4-yl]amino}-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	392	80
166		2-(Ethyl{[(2R)-1-(methylsulfonyl)pyrrolidin-2-yl]methyl}amino)-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	392	74
167		3-Methyl-2-[(1R,5S)-8-(phenylsulfonyl)-38-diazabicyclo[3.2.1]oct-3-yl]-6-pyridin-4-ylpyrimidin-4(3H)-one	438	98

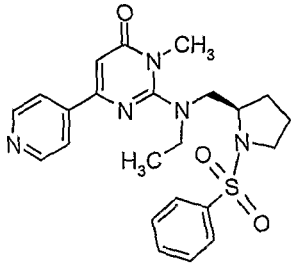
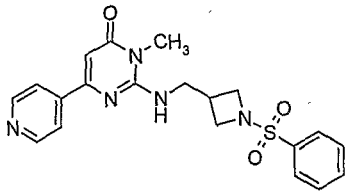
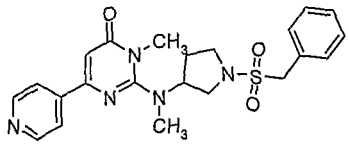
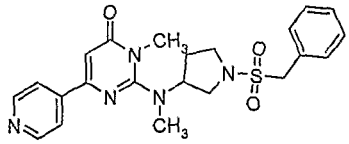
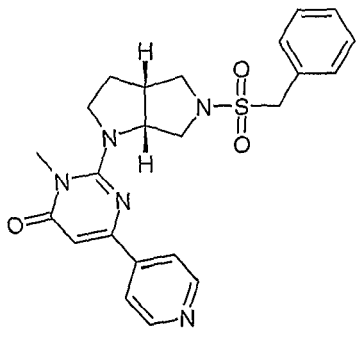
Ex.	Structure	Name	Observed Mass (MH+)	Percent inhibition at 1 μM
168		3-Methyl-2-({[(2R)-1-(methylsulfonyl)pyrrolidin-2-yl]methyl}amino)-6-pyridin-4-ylpyrimidin-4(3H)-one	364	78
169		3-Methyl-2-[(1R,5S)-3-(phenylsulfonyl)-38-diazabicyclo[3.2.1]oct-8-yl]-6-pyridin-4-ylpyrimidin-4(3H)-one	438	92
170		3-Methyl-2-{[1-(phenylsulfonyl)azepan-4-yl]amino}-6-pyridin-4-ylpyrimidin-4(3H)-one	440	99
171		3-Methyl-2-{[1-(phenylsulfonyl)azetidin-3-yl]amino}-6-pyridin-4-ylpyrimidin-4(3H)-one	398	61

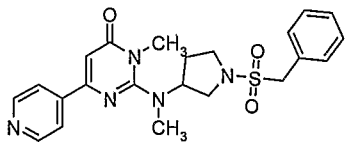
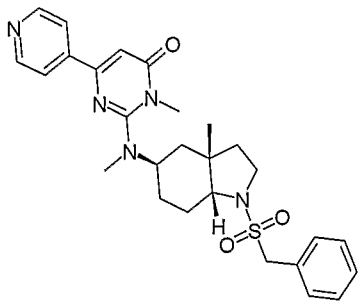
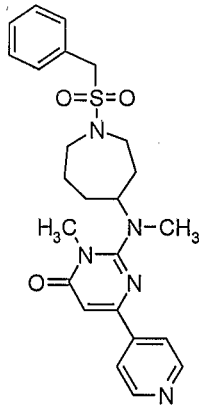
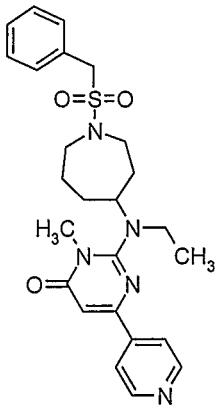
Ex.	Structure	Name	Observed Mass (MH+)	Percent inhibition at 1 μM
172		3-Methyl-2-[(3a,R6,aR)-5-(phenylsulfonyl)hexahydropyrrolo[34-b]pyrrol-1(2H)-yl]-6-pyridin-4-ylpyrimidin-4(3H)-one	438	81
173		3-Methyl-2-{[1-(phenylsulfonyl)azepan-3-yl]amino}-6-pyridin-4-ylpyrimidin-4(3H)-one	440	51
174		3-Methyl-2-{[1-(phenylsulfonyl)pyrrolidin-3-yl]amino}-6-pyridin-4-ylpyrimidin-4(3H)-one	412	95
175		3-Methyl-2-{[1-(phenylsulfonyl)piperidin-4-yl]amino}-6-pyridin-4-ylpyrimidin-4(3H)-one	426	49

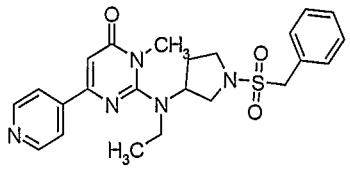
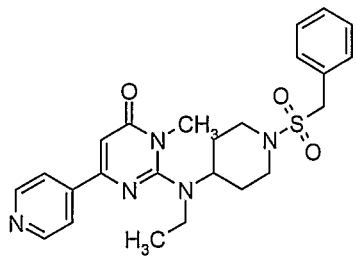
Ex.	Structure	Name	Observed Mass (MH+)	Percent inhibition at 1 μM
176		2-{[(3S,4S)-4-Fluoro-1-(phenylsulfonyl)pyrrolidin-3-yl]amino}-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	430	96
177		3-Methyl-2-{[(1R,5S,6s)-3-(phenylsulfonyl)-3-azabicyclo[3.1.0]hex-6-yl]amino}-6-pyridin-4-ylpyrimidin-4(3H)-one	424	97
178		3-Methyl-2-{methyl[(3a,S5,S7,aR)-3a-methyl-1-(phenylsulfonyl)octahydro-1H-indol-5-yl]amino}-6-pyridin-4-ylpyrimidin-4(3H)-one	494	100
179		3-Methyl-2-{[1-(phenylsulfonyl)piperidin-3-yl]amino}-6-pyridin-4-ylpyrimidin-4(3H)-one	426	93
180		3-Methyl-2-{methyl[1-(phenylsulfonyl)pyrrolidin-3-yl]amino}-6-pyridin-4-ylpyrimidin-4(3H)-one	426	93

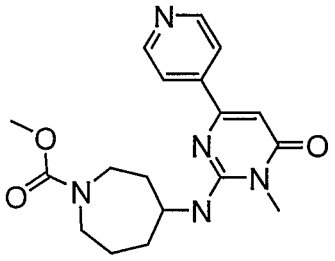
Ex.	Structure	Name	Observed Mass (MH+)	Percent inhibition at 1 μM
181		3-Methyl-2-{methyl[1-(phenylsulfonyl)azepan-4-yl]amino}-6-pyridin-4-ylpyrimidin-4(3H)-one	454	96
182		3-Methyl-2-{methyl[1-(phenylsulfonyl)azepan-4-yl]amino}-6-pyridin-4-ylpyrimidin-4(3H)-one	454	96
183		3-Methyl-2-{methyl[(3,aS5,R7,aR)-3a-methyl-1-(phenylsulfonyl)octahydro-1H-indol-5-yl]amino}-6-pyridin-4-ylpyrimidin-4(3H)-one	494	100
184		2-{[(3R,4S)-4-Fluoro-1-(phenylsulfonyl)pyrrolidin-3-yl]amino}-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	430	100

Ex.	Structure	Name	Observed Mass (MH+)	Percent inhibition at 1 μM
185		2-{Ethyl[1-(phenylsulfonyl)piperidin-3-yl]amino}-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	454	101
186		2-{Ethyl[1-(phenylsulfonyl)azepan-4-yl]amino}-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	468	101
187		2-{Ethyl[1-(phenylsulfonyl)piperidin-4-yl]amino}-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	454	102
188		3-Methyl-2-({[(2R)-1-(phenylsulfonyl)pyrrolidin-2-yl]methyl}amino)-6-pyridin-4-ylpyrimidin-4(3H)-one	426	94

Ex.	Structure	Name	Observed Mass (MH+)	Percent inhibition at 1 μM
189		2-(Ethyl{[(2R)-1-(phenylsulfonyl)pyrrolidin-2-yl]methyl}amino)-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	454	95
190		3-Methyl-2-({[1-(phenylsulfonyl)azetidin-3-yl]methyl}amino)-6-pyridin-4-ylpyrimidin-4(3H)-one	412	35
191		3-Methyl-2-({[1-(phenylsulfonyl)pyrrolidin-3-yl]methyl}amino)-6-pyridin-4-ylpyrimidin-4(3H)-one	426	76
192		2-{[1-(Benzylsulfonyl)azepan-4-yl]amino}-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	454	81
193		2-[(3a,R6,aR)-5-(Benzylsulfonyl)hexahydropyrrolo[34-b]pyrrol-1(2H)-yl]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	452	80

Ex.	Structure	Name	Observed Mass (MH+)	Percent inhibition at 1 μM
194		2-{[1-(Benzylsulfonyl)pyrrolidin-3-yl](methyl)amino}-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	440	90
195		2-{[(3,aS5,R7,aR)-1-(Benzylsulfonyl)-3a-methyloctahydro-1H-indol-5-yl](methyl)amino}-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	508	92
196		2-{[1-(Benzylsulfonyl)azepan-4-yl](methyl)amino}-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	468	94
197		2-{[1-(Benzylsulfonyl)azepan-4-yl](ethyl)amino}-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	344	93

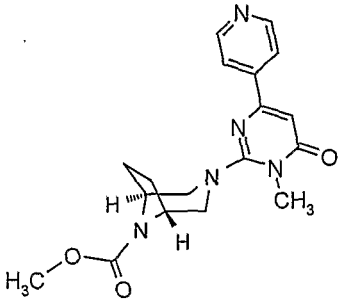
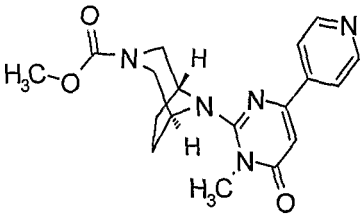
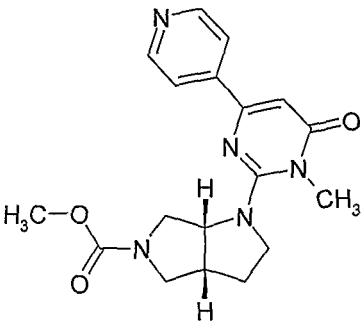
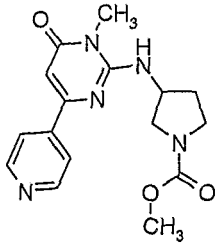
Ex.	Structure	Name	Observed Mass (MH+)	Percent inhibition at 1 μM
198		2-{[1-(Benzylsulfonyl)pyrrolidin-3-yl](ethyl)amino}-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	454	97
199		2-{[1-(Benzylsulfonyl)piperidin-4-yl](ethyl)amino}-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	468	89

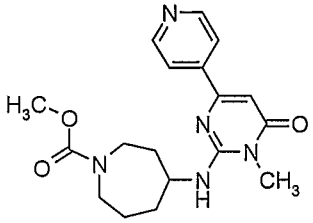
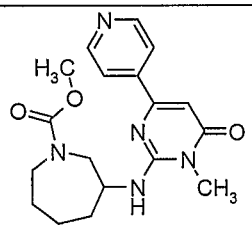
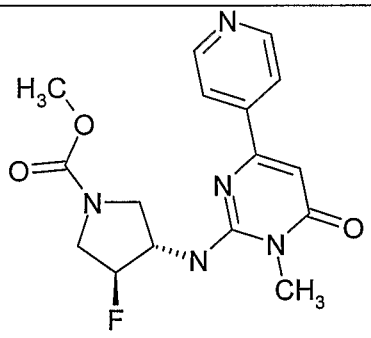
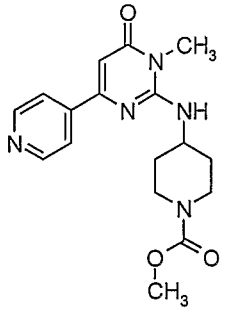


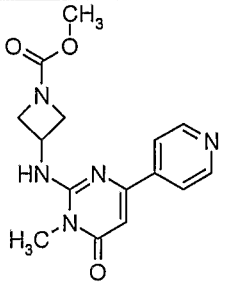
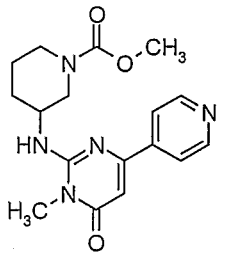
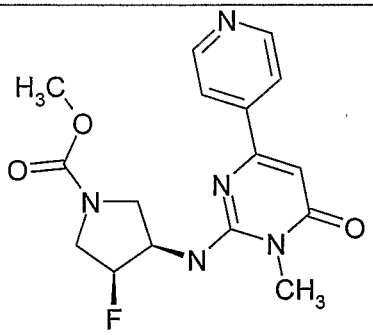
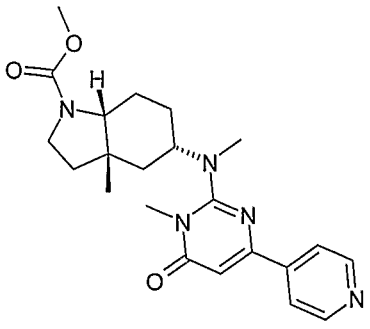
Example 200: (R)-2-(Ehyl((1-(methylsulfonyl)pyrrolidin-2-yl)methyl)amino)-3-methyl-6-(pyridin-4-yl)pyrimidin-4(3H)-one: To the product of Example 8 (80 μmol) was added a soln. of TFA (2 ml) in DCE (2 ml) and the mixture was shaken for 4 hr. The solvent was removed to give a crude residue, which was dissolved in DCE (500 ml). TEA (160 μmol) in DCE (0.2 ml) was added followed by methylchloroformate (80 μmol) in DCE (0.2 ml). The reaction was shaken at RT for 16 hr. The crude mixture was evaporated, then dissolved in DMSO and purified by prep. HPLC to give the title compound (3.9 mg). Calc. MW: 357.4, Found: 358 (MH+), Retention time: 1.7min.

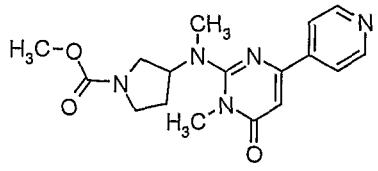
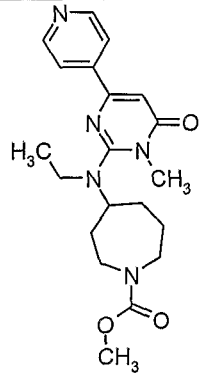
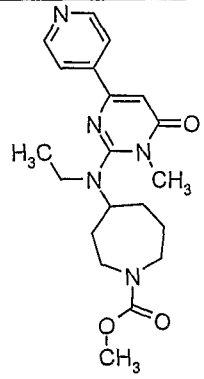
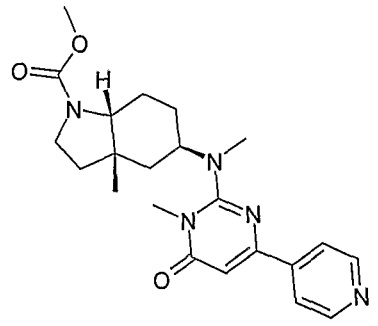
General Procedure for Examples 201 to 221

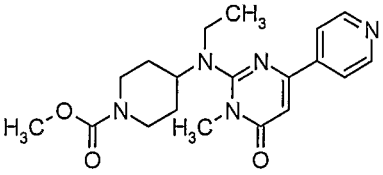
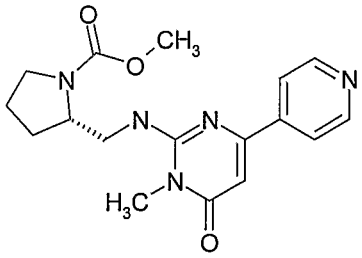
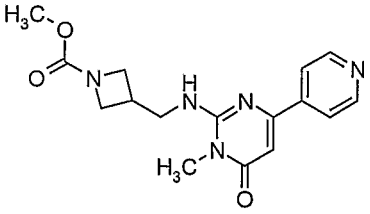
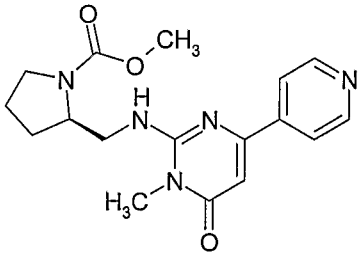
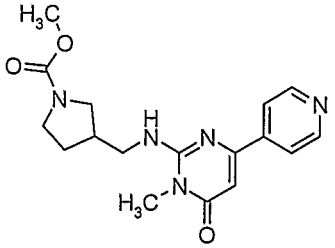
Examples 201 to 221 were prepared by using the analogous procedure described to prepare Example 200, substituting the appropriate starting material (Examples 1 to 35) and coupling with the appropriate chloroformate.

Ex.	Structure	Name	Observed Mass (MH+)	Percent inhibition at 1 μM
201		Methyl (1R,5S)-3-(1-methyl-6-oxo-4-pyridin-4-yl-16-dihydropyrimidin-2-yl)-38-diazabicyclo[3.2.1]octane-8-carboxylate	314	89
202		Methyl (1R,5S)-8-(1-methyl-6-oxo-4-pyridin-4-yl-16-dihydropyrimidin-2-yl)-38-diazabicyclo[3.2.1]octane-3-carboxylate	314	93
203		Methyl (3a,R6,aR)-1-(1-methyl-6-oxo-4-pyridin-4-yl-16-dihydropyrimidin-2-yl)hexahydropyrrolo[34-b]pyrrole-5(1H)-carboxylate	356	32
204		Methyl 3-[(1-methyl-6-oxo-4-pyridin-4-yl-16-dihydropyrimidin-2-yl)amino]pyrrolidine-1-carboxylate	330	82

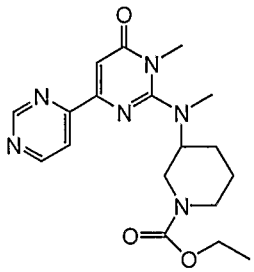
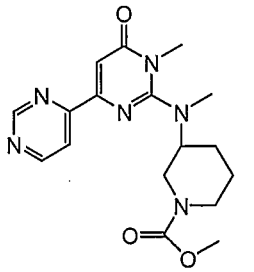
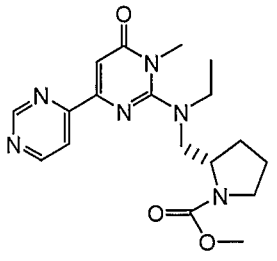
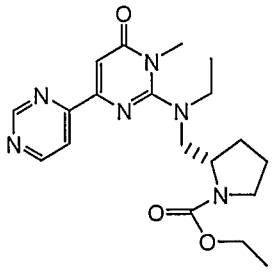
Ex.	Structure	Name	Observed Mass (MH+)	Percent inhibition at 1 μM
205		Methyl 4-[(1-methyl-6-oxo-4-pyridin-4-yl-16-dihydropyrimidin-2-yl)amino]azepane-1-carboxylate	358	86
206		Methyl 3-[(1-methyl-6-oxo-4-pyridin-4-yl-16-dihydropyrimidin-2-yl)amino]azepane-1-carboxylate	358	94
207		Methyl (3S,4S)-3-fluoro-4-[(1-methyl-6-oxo-4-pyridin-4-yl-16-dihydropyrimidin-2-yl)amino]pyrrolidine-1-carboxylate	348	74
208		Methyl 4-[(1-methyl-6-oxo-4-pyridin-4-yl-16-dihydropyrimidin-2-yl)amino]piperidine-1-carboxylate	344	77

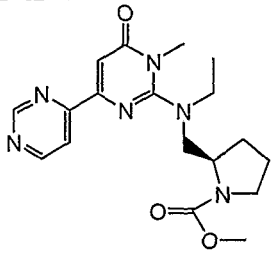
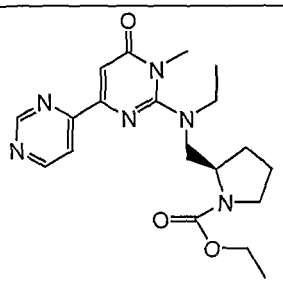
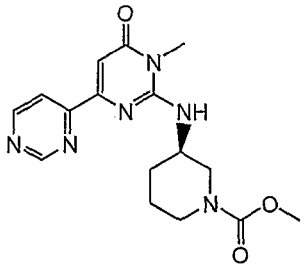
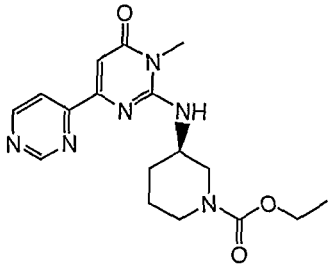
Ex.	Structure	Name	Observed Mass (MH+)	Percent inhibition at 1 μM
209		Methyl 3-[(1-methyl-6-oxo-4-pyridin-4-yl-16-dihydropyrimidin-2-yl)amino]azetidine-1-carboxylate	356	80
210		Methyl 3-[(1-methyl-6-oxo-4-pyridin-4-yl-16-dihydropyrimidin-2-yl)amino]piperidine-1-carboxylate	344	99
211		Methyl (3S,4R)-3-fluoro-4-[(1-methyl-6-oxo-4-pyridin-4-yl-16-dihydropyrimidin-2-yl)amino]pyrrolidine-1-carboxylate	348	67
212		Methyl (3a,S5,S7,aR)-3a-methyl-5-[methyl(1-methyl-6-oxo-4-pyridin-4-yl-16-dihydropyrimidin-2-yl)amino]octahydro-1H-indole-1-carboxylate	356	93

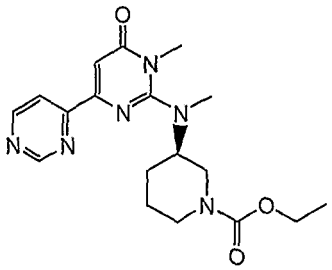
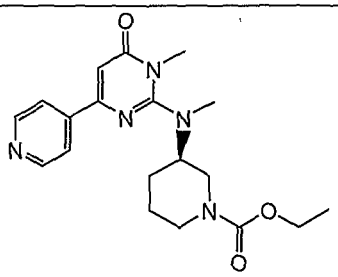
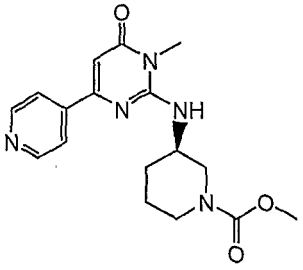
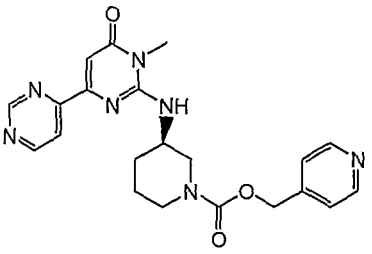
Ex.	Structure	Name	Observed Mass (MH+)	Percent inhibition at 1 μM
213		Methyl 3-[methyl(1-methyl-6-oxo-4-pyridin-4-yl-16-dihydropyrimidin-2-yl)amino]pyrrolidine-1-carboxylate	344	95
214		Methyl 4-[methyl(1-methyl-6-oxo-4-pyridin-4-yl-16-dihydropyrimidin-2-yl)amino]azepane-1-carboxylate	372	99
215		Methyl 4-[ethyl(1-methyl-6-oxo-4-pyridin-4-yl-16-dihydropyrimidin-2-yl)amino]azepane-1-carboxylate	386	93
216		Methyl (3a,S5,R7,aR)-3a-methyl-5-[methyl(1-methyl-6-oxo-4-pyridin-4-yl-16-dihydropyrimidin-2-yl)amino]octahydro-1H-indole-1-carboxylate	412	88

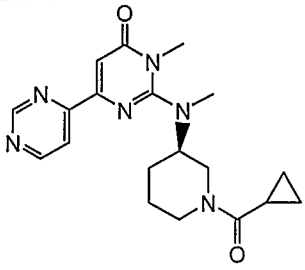
Ex.	Structure	Name	Observed Mass (MH+)	Percent inhibition at 1 μM
217		Methyl 4-[ethyl(1-methyl-6-oxo-4-pyridin-4-yl-16-dihydropyrimidin-2-yl)amino]piperidine-1-carboxylate	372	84
218		Methyl (2S)-2-{[(1-methyl-6-oxo-4-pyridin-4-yl-16-dihydropyrimidin-2-yl)amino]methyl}pyrrolidine-1-carboxylate	344	68
219		Methyl 3-{[(1-methyl-6-oxo-4-pyridin-4-yl-16-dihydropyrimidin-2-yl)amino]methyl}azetidine-1-carboxylate	330	72
220		Methyl (2R)-2-{[(1-methyl-6-oxo-4-pyridin-4-yl-16-dihydropyrimidin-2-yl)amino]methyl}pyrrolidine-1-carboxylate	344	91
221		Methyl 3-{[(1-methyl-6-oxo-4-pyridin-4-yl-16-dihydropyrimidin-2-yl)amino]methyl}pyrrolidine-1-carboxylate	344	71

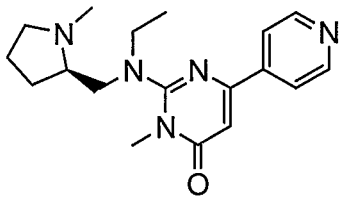
Examples 222 to 234 were prepared by using the analogous procedure described to prepare Example 200, substituting the appropriate starting material (Examples 1 to 35) and coupling with the appropriate chloroformate.

Ex.	Structure	Name	Observed Mass (MH+)	Enzyme IC_{50} (nM)
222		Ethyl 3-[methyl(1-methyl-6-oxo-1,6-dihydro-4,4'-bipyrimidin-2-yl)amino]piperidine-1-carboxylate	372	1.14
223		Methyl 3-[methyl(1-methyl-6-oxo-1,6-dihydro-4,4'-bipyrimidin-2-yl)amino]piperidine-1-carboxylate	358	1.04
224		Methyl (2S)-2-{[ethyl(1-methyl-6-oxo-1,6-dihydro-4,4'-bipyrimidin-2-yl)amino]methyl}pyrrolidine-1-carboxylate	372	1.11
225		Ethyl (2S)-2-{[ethyl(1-methyl-6-oxo-1,6-dihydro-4,4'-bipyrimidin-2-yl)amino]methyl}pyrrolidine-1-carboxylate	386	0.755

Ex.	Structure	Name	Observed Mass (MH+)	Enzyme IC_{50} (nM)
226		Methyl (2R)-2-{[ethyl(1-methyl-6-oxo-1,6-dihydro-4,4'-bipyrimidin-2-yl)amino]methyl}pyrrolidine-1-carboxylate	372	1.00
227		Ethyl (2R)-2-{[ethyl(1-methyl-6-oxo-1,6-dihydro-4,4'-bipyrimidin-2-yl)amino]methyl}pyrrolidine-1-carboxylate	386	0.825
228		Methyl (3R)-3-[(1-methyl-6-oxo-1,6-dihydro-4,4'-bipyrimidin-2-yl)amino]piperidine-1-carboxylate	344	0.994
229		Ethyl (3R)-3-[(1-methyl-6-oxo-1,6-dihydro-4,4'-bipyrimidin-2-yl)amino]piperidine-1-carboxylate	359	1.99

Ex.	Structure	Name	Observed Mass (MH+)	Enzyme IC_{50} (nM)
230		Ethyl (3R)-3-[methyl(1-methyl-6-oxo-1,6-dihydro-4,4'-bipyrimidin-2-yl)amino]piperidine-1-carboxylate	373	0.95
231		Ethyl (3R)-3-[methyl(1-methyl-6-oxo-4-pyridin-4-yl-1,6-dihydropyrimidin-2-yl)amino]piperidine-1-carboxylate	372	1.15
232		Methyl (3R)-3-[(1-methyl-6-oxo-4-pyridin-4-yl-1,6-dihydropyrimidin-2-yl)amino]piperidine-1-carboxylate	344	0.854
233		Pyridin-4-ylmethyl (3R)-3-[(1-methyl-6-oxo-1,6-dihydro-4,4'-bipyrimidin-2-yl)amino]piperidine-1-carboxylate	422	5.00

Ex.	Structure	Name	Observed Mass (MH+)	Enzyme IC_{50} (nM)
234		2-{[(3R)-1-(Cyclopropylcarbonyl)piperidin-3-yl](methyl)amino}-1-methyl-4,4'-bipyrimidin-6(1H)-one	369	1.68

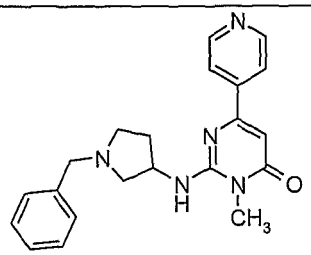
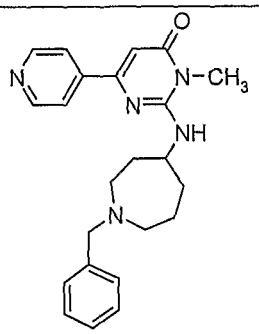
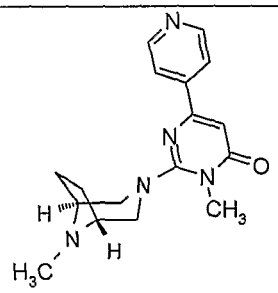
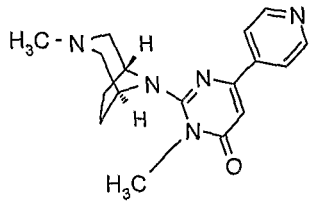
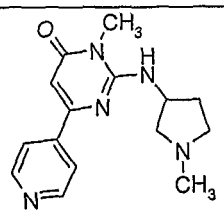


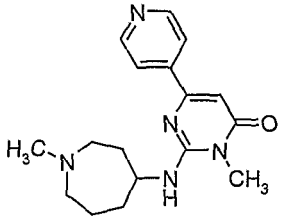
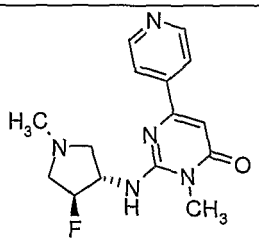
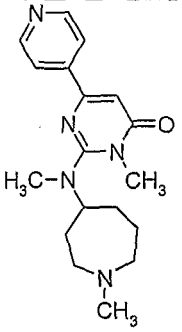
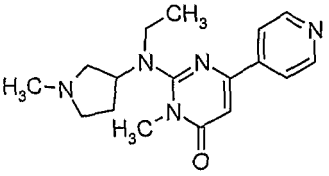
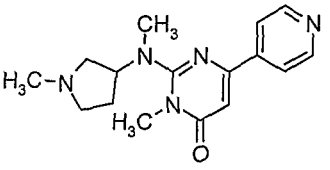
Example 235: (R)-2-(Ethyl((1-methylpyrrolidin-2-yl)methyl)amino)-3-methyl-6-(pyridin-4-yl)pyrimidin-4(3H)-one: To the product of Example 4 (80 μmol) was added a soln. of TFA (2 ml) in DCE (2 ml) and the mixture was shaken for 4 hr. The solvent was removed to give a residue, which was dissolved in MeOH (0.5 ml). TEA (160 μmol) in MeOH (0.2 ml) was added, followed by formaldehyde (80 μmol) in MeOH (0.2 ml). Sodium cyanoborohydride (100 umol) was added, dissolved in MeOH (0.5 ml). The reaction was shaken at RT for 16 hr. The mixture was evaporated, dissolved in DMSO, and purified by prep. HPLC to give the title compound (5.0 mg). Calc. MW: 327.4, Found: 328 (MH+), Retention time: 2.13 min.

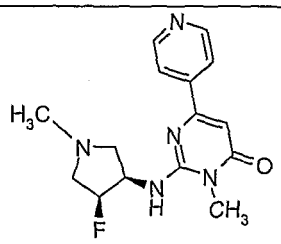
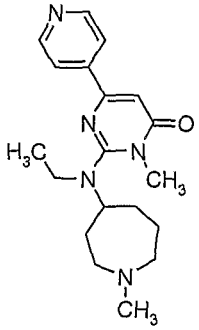
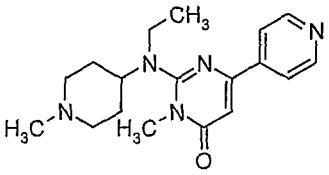
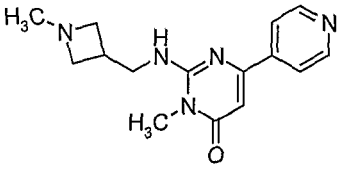
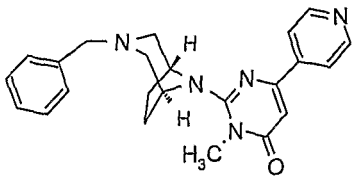
General Procedure for Examples 236 to 262

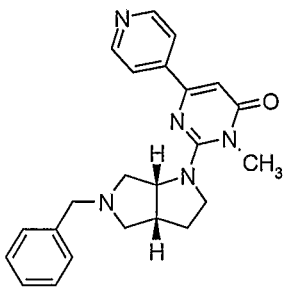
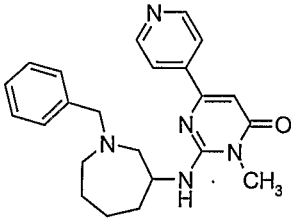
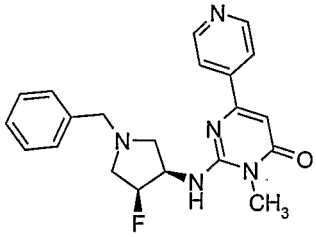
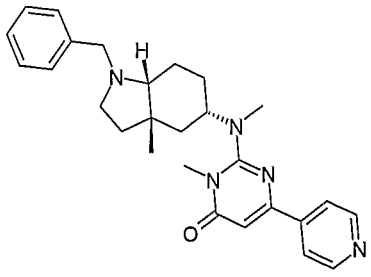
Examples 236 to 262 may be prepared by using the analogous procedure described to prepare Example 235, substituting the appropriate starting material (Examples 1 to 35) and coupling with the appropriate aldehyde.

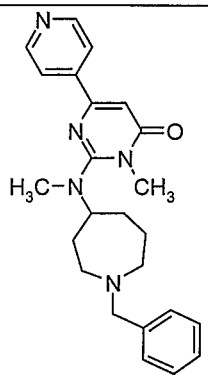
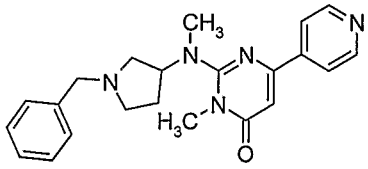
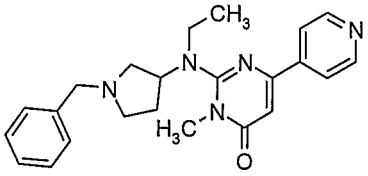
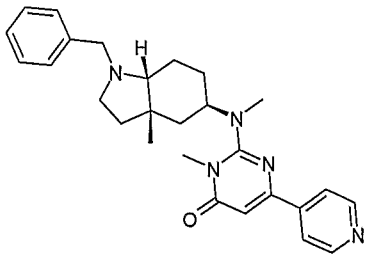
Ex.	Structure	Name	Observed MW	Percent inhibition at 1 μM

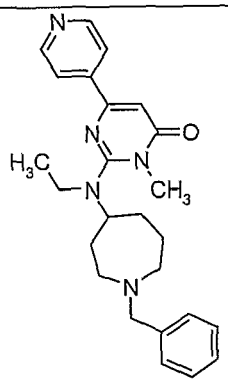
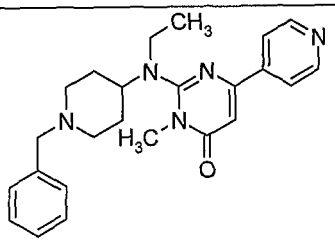
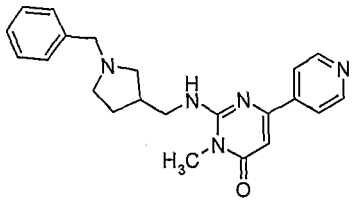
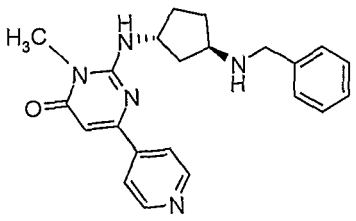
Ex.	Structure	Name	Observed MW	Percent inhibition at 1 μM
236		2-[(1-Benzylpyrrolidin-3-yl)amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	362	63
237		2-[(1-Benzylazepan-4-yl)amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	390	84
238		3-Methyl-2-[(1R,5S)-8-methyl-38-diazabicyclo[3.2.1]oct-3-yl]-6-pyridin-4-ylpyrimidin-4(3H)-one	312	47
239		3-Methyl-2-[(1R,5S)-3-methyl-38-diazabicyclo[3.2.1]oct-8-yl]-6-pyridin-4-ylpyrimidin-4(3H)-one	312	57
240		3-Methyl-2-[(1-methylpyrrolidin-3-yl)amino]-6-pyridin-4-ylpyrimidin-4(3H)-one	286	49

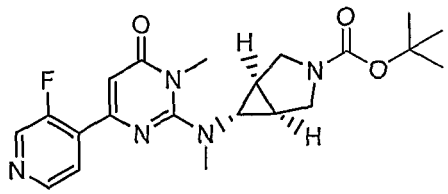
Ex.	Structure	Name	Observed MW	Percent inhibition at 1 μM
241		3-Methyl-2-[(1-methylazepan-4-yl)amino]-6-pyridin-4-ylpyrimidin-4(3H)-one	314	72
242		2-{[(3S,4S)-4-Fluoro-1-methylpyrrolidin-3-yl]amino}-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	304	43
243		3-Methyl-2-[methyl(1-methylazepan-4-yl)amino]-6-pyridin-4-ylpyrimidin-4(3H)-one	328	60
244		2-[ethyl(1-Methylpyrrolidin-3-yl)amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	314	60
245		3-Methyl-2-[methyl(1-methylpyrrolidin-3-yl)amino]-6-pyridin-4-ylpyrimidin-4(3H)-one	300	52

Ex.	Structure	Name	Observed MW	Percent inhibition at 1 μM
246		2-{[(3R,4S)-4-Fluoro-1-methylpyrrolidin-3-yl]amino}-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	304	67
247		2-[Ethyl(1-methylazepan-4-yl)amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	342	78
248		2-[Ethyl(1-methylpiperidin-4-yl)amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	328	39
249		3-Methyl-2-{[(1-methylazetidin-3-yl)methyl]amino}-6-pyridin-4-ylpyrimidin-4(3H)-one	286	33
250		2-[(1R,5S)-3-Benzyl-38-diazabicyclo[3.2.1]oct-8-yl]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	300	69

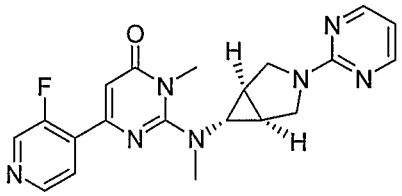
Ex.	Structure	Name	Observed MW	Percent inhibition at 1 μM
251		2-[(3a,R6,aR)-5-Benzylhexahydropyrrolo[34-b]pyrrol-1(2H)-yl]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	388	47
252		2-[(1-Benzylazepan-3-yl)amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	390	74
253		2-{[(3R,4S)-1-Benzyl-4-fluoropyrrolidin-3-yl]amino}-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	380	91
254		2-{[(3a,S5,S7,aR)-1-Benzyl-3a-methyloctahydro-1H-indol-5-yl](methyl)amino}-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	444	47

Ex.	Structure	Name	Observed MW	Percent inhibition at 1 μM
255		2-[(1-Benzylazepan-4-yl)(methyl)amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	404	76
256		2-[(1-Benzylpyrrolidin-3-yl)(methyl)amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	376	83
257		2-[(1-Benzylpyrrolidin-3-yl)(ethyl)amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	390	71
258		2-{[(3a,S5,R7,aR)-1-Benzyl-3a-methyloctahydro-1H-indol-5-yl](methyl)amino}-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	444	43

Ex.	Structure	Name	Observed MW	Percent inhibition at 1 μM
259		2-[(1-Benzylazepan-4-yl)(ethyl)amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	418	83
260		2-[(1-Benzylpiperidin-4-yl)(ethyl)amino]-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	404	44
261		2-{[(1-Benzylpyrrolidin-3-yl)methyl]amino}-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	376	70
262		2-{[(1R,3R)-3-(Benzylamino)cyclopentyl]amino}-3-methyl-6-pyridin-4-ylpyrimidin-4(3H)-one	376	48



Example 263: (1S,5R,6s)-*tert*-butyl 6-((4-(3-Fluoropyridin-4-yl)-1-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)(methyl)amino)-3-aza-bicyclo[3.1.0]hexane-3-carboxylate: To a solution of (1S,5R,6s)-*tert*-butyl-6-(4-(3-fluoropyridin-4-yl)-1-methyl-6-oxo-1,6-dihydropyrimidin-2-ylamino)-3-aza-bicyclo[3.1.0]hexane-3-carboxylate (1.2 g, 3 mmol) in DMF (15 ml) was added 60% NaH (956 mg, 6 mmol) and the mixture was stirred at RT for 10 min. To the mixture was added a solution of 0.4 ml MeI in 2 ml DMF and the mixture was stirred at room temperature for 2 hr. The mixture was partitioned between EtOAc and water and the organic layer was separated and dried over magnesium sulfate. The residue was purified by column chromatography eluting with a gradient of 5-100% EtOAc in hexanes to give the title compound as a white solid (864 mg, 72%).

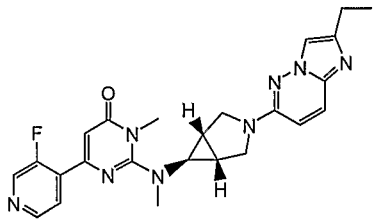
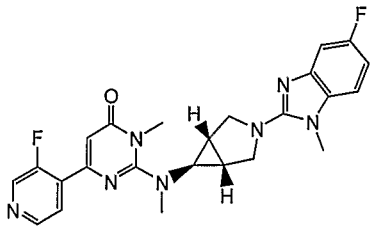
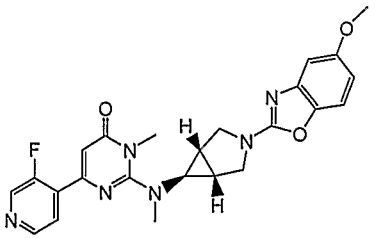


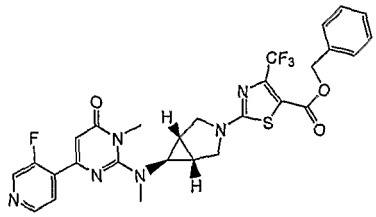
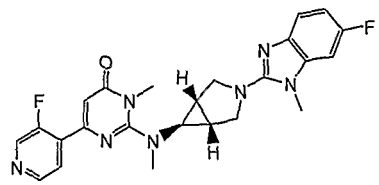
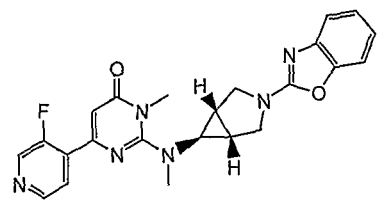
Example 264: 6-(3-Fluoropyridin-4-yl)-3-methyl-2-(methyl((1S,5R,6s)-3-(pyrimidin-2-yl)-3-aza-bicyclo[3.1.0]hexan-6-yl)amino)pyrimidin-4(3H)-one: To the product of Example 274 was added a solution of TFA (5 ml) in DCM (5 ml) and the mixture was shaken for 1 hr. The solvents were evaporated to give a crude residue (35 mg, 85 μmol), which was dissolved in DMF (1 ml) followed by addition of TEA (90 μl, 510 μmol), then 2-chloropyrimidine (19 mg, 166 μmol). The reaction was carried out at 170°C in Biotage Microwave Reactor for 10 min. The reaction was partitioned between EtOAc and water and the organic layer was separated and dried over magnesium sulfate. The residue was purified by column chromatography using a gradient of 100% EtOAc to 10% MeOH in EtOAc as eluting solvent to give the title compound (5 mg, 11%). ^{1}H-NMR($CDCl_3$): δ ppm 8.48 (d, 1H), 8.46 (d, 1H), 8.28 (d, 2H), 7.95 (t, 1H), 6.77 (s, 1H), 6.53 (t, 1H), 3.94 (d, 2H), 3.60 (d, 2H), 3.49 (s, 3H), 3.01 (s, 3H), 2.68 (t, 1H), 1.88 (m, 1H); LCMS 394.3 (M+H).

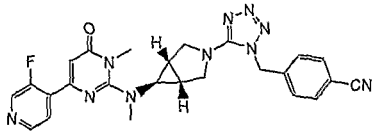
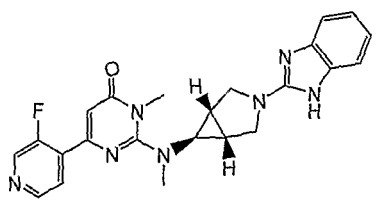
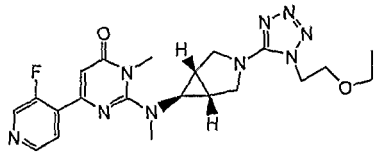
General Procedure for Examples 265 to 291

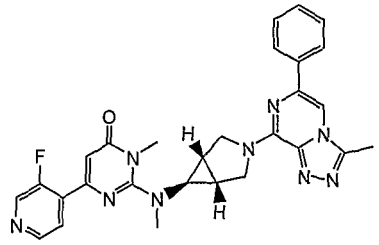
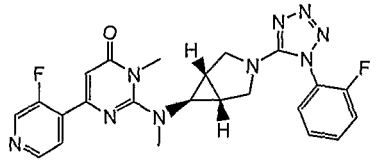
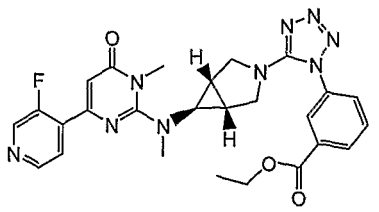
Examples 265 to 291 were prepared by using the analogous procedure described to prepare Examples 263 and 264, substituting the appropriate starting material and coupling with the appropriate reagent.

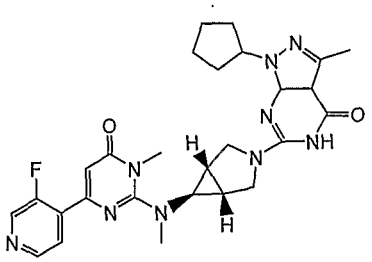
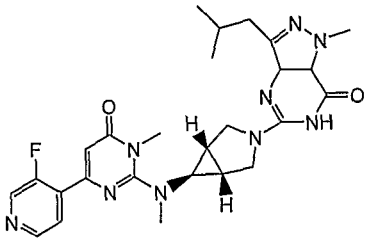
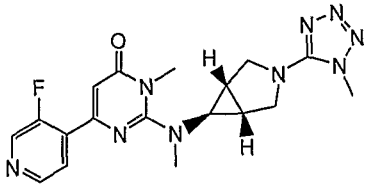
Ex.	Structure	Name	Observed MW	Enzyme IC_{50} (nM)

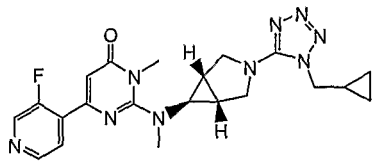
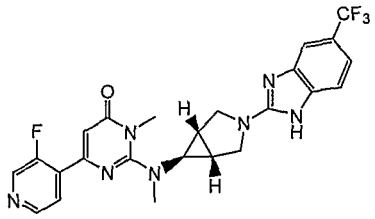
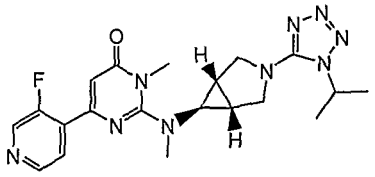
Ex.	Structure	Name	Observed MW	Enzyme IC_{50} (nM)
265		2-{[(1R,5S,6s)-3-(2-Ethylimidazo[1,2-b]pyridazin-6-yl)-3-azabicyclo[3.1.0]hex-6-yl](methyl)amino}-6-(3-fluoropyridin-4-yl)-3-methylpyrimidin-4(3H)-one	460	52.4
266		2-{[(1R,5S,6s)-3-(5-Fluoro-1-methyl-1H-benzimidazol-2-yl)-3-azabicyclo[3.1.0]hex-6-yl](methyl)amino}-6-(3-fluoropyridin-4-yl)-3-methylpyrimidin-4(3H)-one	463	16.7
267		6-(3-Fluoropyridin-4-yl)-2-{[(1R,5S,6s)-3-(5-methoxy-1,3-benzoxazol-2-yl)-3-azabicyclo[3.1.0]hex-6-yl](methyl)amino}-3-methylpyrimidin-4(3H)-one	462	14.2

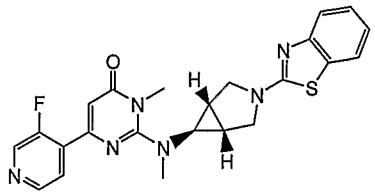
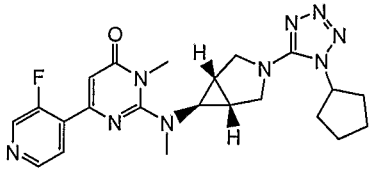
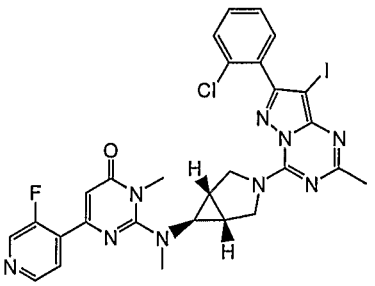
Ex.	Structure	Name	Observed MW	Enzyme IC_{50} (nM)
268		Benzyl 2-[(1R,5S,6s)-6-{[4-(3-fluoropyridin-4-yl)-1-methyl-6-oxo-1,6-dihydropyrimidin-2-yl](methyl)amino}-3-azabicyclo[3.1.0]hex-3-yl]-4-(trifluoromethyl)-1,3-thiazole-5-carboxylate	600	126
269		2-{[(1R,5S,6s)-3-(6-Fluoro-1-methyl-1H-benzimidazol-2-yl)-3-azabicyclo[3.1.0]hex-6-yl](methyl)amino}-6-(3-fluoropyridin-4-yl)-3-methylpyrimidin-4(3H)-one	463	18.8
270		2-{[(1R,5S,6s)-3-(1,3-Benzoxazol-2-yl)-3-azabicyclo[3.1.0]hex-6-yl](methyl)amino}-6-(3-fluoropyridin-4-yl)-3-methylpyrimidin-4(3H)-one	432	24.6

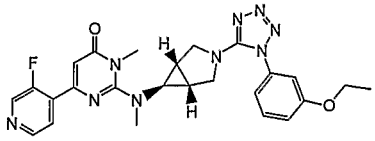
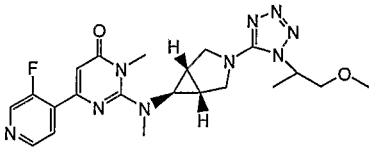
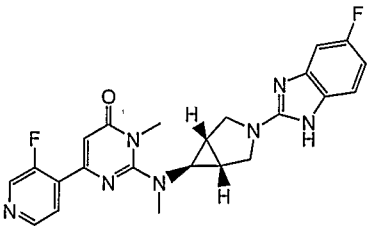
Ex.	Structure	Name	Observed MW	Enzyme IC_{50} (nM)
271		4-({5-[(1R,5S,6s)-6-{[4-(3-Fluoropyridin-4-yl)-1-methyl-6-oxo-1,6-dihydropyrimidin-2-yl](methyl)amino}-3-azabicyclo[3.1.0]hex-3-yl]-1H-tetrazol-1-yl}methyl)benzonitrile	499	8.8
272		2-{[(1R,5S,6s)-3-(1H-Benzimidazol-2-yl)-3-azabicyclo[3.1.0]hex-6-yl](methyl)amino}-6-(3-fluoropyridin-4-yl)-3-methylpyrimidin-4(3H)-one	431	76.1
273		2-[{(1R,5S,6s)-3-[1-(2-Ethoxyethyl)-1H-tetrazol-5-yl]-3-azabicyclo[3.1.0]hex-6-yl}(methyl)amino]-6-(3-fluoropyridin-4-yl)-3-methylpyrimidin-4(3H)-one	455	29.0

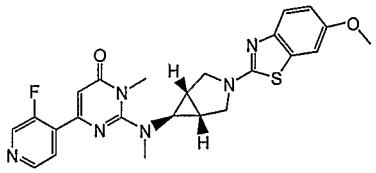
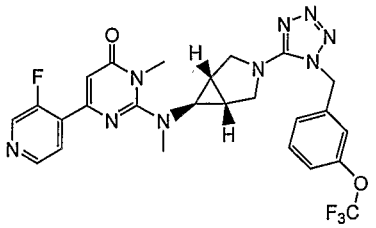
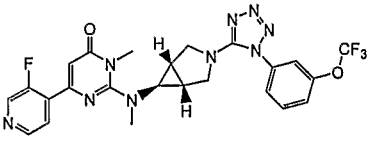
Ex.	Structure	Name	Observed MW	Enzyme IC_{50} (nM)
274		6-(3-Fluoropyridin-4-yl)-3-methyl-2-{methyl[(1R,5S,6s)-3-(3-methyl-6-phenyl[1,2,4]triazolo[4,3-a]pyrazin-8-yl)-3-azabicyclo[3.1.0]hex-6-yl]amino}pyrimidin-4(3H)-one	524	234
275		2-[{(1R,5S,6s)-3-[1-(2-Fluorophenyl)-1H-tetrazol-5-yl]-3-azabicyclo[3.1.0]hex-6-yl}(methyl)amino]-6-(3-fluoropyridin-4-yl)-3-methylpyrimidin-4(3H)-one	477	1.12
276		Ethyl 3-{5-[(1R,5S,6s)-6-{[4-(3-fluoropyridin-4-yl)-1-methyl-6-oxo-1,6-dihydropyrimidin-2-yl](methyl)amino}-3-azabicyclo[3.1.0]hex-3-yl]-1H-tetrazol-1-yl}benzoate	532	6.21

Ex.	Structure	Name	Observed MW	Enzyme IC_{50} (nM)
277		1-Cyclopentyl-6-[(1R,5S,6s)-6-{[4-(3-fluoropyridin-4-yl)-1-methyl-6-oxo-1,6-dihydropyrimidin-2-yl](methyl)amino}-3-azabicyclo[3.1.0]hex-3-yl]-3-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	532	51.7
278		5-[(1R,5S,6s)-6-{[4-(3-Fluoropyridin-4-yl)-1-methyl-6-oxo-1,6-dihydropyrimidin-2-yl](methyl)amino}-3-azabicyclo[3.1.0]hex-3-yl]-3-isobutyl-1-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one	520	109
279		6-(3-Fluoropyridin-4-yl)-3-methyl-2-{methyl[(1R,5S,6s)-3-(1-methyl-1H-tetrazol-5-yl)-3-azabicyclo[3.1.0]hex-6-yl]amino}pyrimidin-4(3H)-one	397	58.6

Ex.	Structure	Name	Observed MW	Enzyme IC_{50} (nM)
280		2-[{(1R,5S,6s)-3-[1-(Cyclopropylmethyl)-1H-tetrazol-5-yl]-3-azabicyclo[3.1.0]hex-6-yl}(methyl)amino]-6-(3-fluoropyridin-4-yl)-3-methylpyrimidin-4(3H)-one	437	4.48
281		6-(3-Fluoropyridin-4-yl)-3-methyl-2-(methyl{(1R,5S,6s)-3-[5-(trifluoromethyl)-1H-benzimidazol-2-yl]-3-azabicyclo[3.1.0]hex-6-yl}amino)pyrimidin-4(3H)-one	499	36.3
282		6-(3-Fluoropyridin-4-yl)-2-{[(1R,5S,6s)-3-(1-isopropyl-1H-tetrazol-5-yl)-3-azabicyclo[3.1.0]hex-6-yl](methyl)amino}-3-methylpyrimidin-4(3H)-one	426	3.25

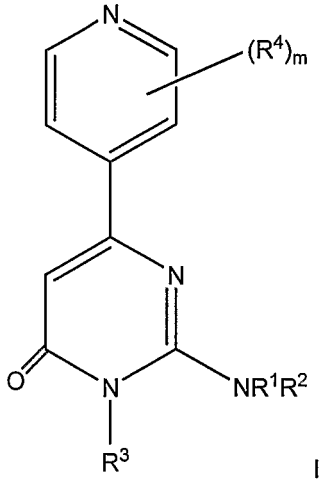
Ex.	Structure	Name	Observed MW	Enzyme IC_{50} (nM)
283		2-{[(1R,5S,6s)-3-(1,3-Benzothiazol-2-yl)-3-azabicyclo[3.1.0]hex-6-yl](methyl)amino}-6-(3-fluoropyridin-4-yl)-3-methylpyrimidin-4(3H)-one	448	55.7
284		2-{[(1R,5S,6s)-3-(1-Cyclopentyl-1H-tetrazol-5-yl)-3-azabicyclo[3.1.0]hex-6-yl](methyl)amino}-6-(3-fluoropyridin-4-yl)-3-methylpyrimidin-4(3H)-one	451	12.5
285		2-[{(1R,5S,6s)-3-[7-(2-Chlorophenyl)-8-iodo-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-3-azabicyclo[3.1.0]hex-6-yl}(methyl)amino]-6-(3-fluoropyridin-4-yl)-3-methylpyrimidin-4(3H)-one	683	5666

Ex.	Structure	Name	Observed MW	Enzyme IC_{50} (nM)
286		2-[{(1R,5S,6s)-3-[1-(3-Ethoxyphenyl)-1H-tetrazol-5-yl]-3-azabicyclo[3.1.0]hex-6-yl}(methyl)amino]-6-(3-fluoropyridin-4-yl)-3-methylpyrimidin-4(3H)-one	504	3.20
287		6-(3-Fluoropyridin-4-yl)-2-[{(1R,5S,6s)-3-[1-(2-methoxy-1-methylethyl)-1H-tetrazol-5-yl]-3-azabicyclo[3.1.0]hex-6-yl}(methyl)amino]-3-methylpyrimidin-4(3H)-one	455	3.06
288		2-{[(1R,5S,6s)-3-(5-Fluoro-1H-benzimidazol-2-yl)-3-azabicyclo[3.1.0]hex-6-yl](methyl)amino}-6-(3-fluoropyridin-4-yl)-3-methylpyrimidin-4(3H)-one	449	116

Ex.	Structure	Name	Observed MW	Enzyme IC_{50} (nM)
289		6-(3-Fluoropyridin-4-yl)-2-{[(1R,5S,6s)-3-(6-methoxy-1,3-benzothiazol-2-yl)-3-azabicyclo[3.1.0]hex-6-yl](methyl)amino}-3-methylpyrimidin-4(3H)-one	478	25.1
290		6-(3-Fluoropyridin-4-yl)-3-methyl-2-{methyl[(1R,5S,6s)-3-{1-[3-(trifluoromethoxy)benzyl]-1H-tetrazol-5-yl}-3-azabicyclo[3.1.0]hex-6-yl]amino}pyrimidin-4(3H)-one	558	27.7
291		6-(3-Fluoropyridin-4-yl)-3-methyl-2-{methyl[(1R,5S,6s)-3-{1-[3-(trifluoromethoxy)phenyl]-1H-tetrazol-5-yl}-3-azabicyclo[3.1.0]hex-6-yl]amino}pyrimidin-4(3H)-one	543	5.99

CLAIMS

1. A compound of Formula I,



I,

or a pharmaceutical acceptable salt thereof, wherein:

R^1 is hydrogen or a C_1-C_6 alkyl group;

R^2 is a -(4-15 membered) heterocycloalkyl, -(5-10 membered) heteroaryl or a C_1-C_6 alkyl group, wherein said alkyl is substituted by a -(4-15 membered) heterocycloalkyl or -(5-10 membered) heteroaryl, and wherein said heterocycloalkyls and heteroaryls of R^2 are optionally substituted by one or more substituents selected from the group R^7;

or $-NR^1R^2$ together may form a (8-15 membered) heterocycloalkyl or -(5-10 membered) heteroaryl, both optionally substituted by one or more substituents selected from the group R^7;

wherein R^3 is hydrogen or C_1-C_6 alkyl;

wherein R^4 is halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl,C_1-C_6 alkoxy or C_1-C_6 haloalkoxy;

wherein each R^7 is independently selected from -OH, halogen, -C_1-C_6 alkyl, -C_3-C_8 cycloalkyl, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -C_1-C_6 alkoxy, -C_2-C_6 alkenoxy, -C_2-C_6 alkynoxy, -C_1-C_6 hydroxyalkyl, -CN, $-NO_2$, $-NR^8R^9$, $-C(=O)N^8R^9$, $-C(=O)R^8$, $-C(=O)OR^8$, $-S(O)_2NR^8R^9$, $-S(O)_nR^8$, $-NR^9C(=O)R^8$, $-NR^9SO_2R^8$, -(C_{zero}-C_6 alkylene)-C_6-C_{15} aryl, -(C_{zero}-C_6 alkylene)-(5-15 membered) heterocycloalkyl, -(C_{zero}-C_6 alkylene)-(5-15 membered) heteroaryl, -(C_{zero}-C_6 alkylene)-C_6-C_{15} aryloxy and -(C_{zero}-C_6 alkylene)-(5-15 membered) heteroaryloxy, wherein said alkyl, alkenyl, alkynyl, alkoxy, alkenoxy, alkynoxy, hydroxyalkyl, aryl, aryloxy, heteroaryl and heteroaryloxy of R^7 are each optionally independently substituted with one or more subsitutents selected from halogens, -C_1-C_{12} alkyl, -C_1-C_4 alkoxy, $-NR^8R^9$, $-C(=O)N^8R^9$, $-C(=O)R^8$, $-C(=O)OR^8$, $-NR^9C(=O)R^8$, $-NR^9SO_2R^8$, $-S(O)_2NR^8R^9$, $-S(O)_nR^8$ or -OH;

each R^8 and R^9 are independently selected from –H, -C_1-C_{15} alkyl, -C_2-C_{15} alkenyl, -C_2-C_{15} alkynyl, -(C_{zero}-C_4 alkylene)-(C_3-C_{15} cycloalkyl), -(C_{zero}-C_4 alkylene)-(C_4-C_8

cycloalkenyl), -(C_{zero}-C_4 alkylene)-((5-15 membered) heterocycloalkyl), -(C_{zero}-C_4 alkylene)-(C_6-C_{15} aryl) and -(C_{zero}-C_4 alkylene)-((5-15 membered) heteroaryl), wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, aryl and heteroaryl of R^8 and R^9 are each optionally independently substituted with one or more substituents independently selected from -OH, -C_1-C_{12} alkyl, -C_2-C_{12} alkenyl, -C_2-C_{12} alkynyl, C_1-C_6 alkoxy, -C_2-C_6 alkenoxy, -C_2-C_6 alkynoxy, -C_1-C_6 hydroxyalkyl, halogen, -CN, -NO_2, -CF_3, -NH_2, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, -C(=O)NH_2, -C(=O)NH(C_1-C_6 alkyl), -C(=O)N(C_1-C_6 alkyl)$_2$, -SO_2NH_2, -SO_2NH(C_1-C_6 alkyl), -SO_2N(C_1-C_6 alkyl)$_2$, -C(=O)H, -C(=O)OH and -C(=O)O(C_1-C_6 alkyl);

n is 0, 1 or 2; and m is 0, 1, 2, 3 or 4.

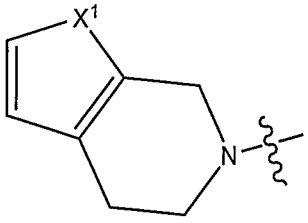
2. The compound of claim 1, wherein R^2 is a -(5-15 membered) heterocycloalkyl or -(5-10 membered) heteroaryl.

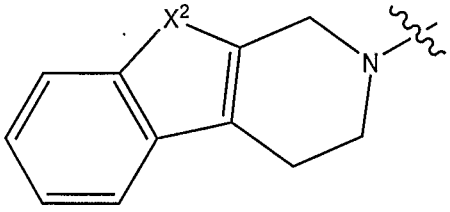
3. The compound of claim 2, wherein R^2 is a -(5-15 membered) heterocycloalkyl.

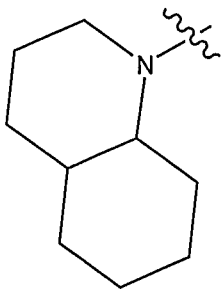
4. The compound of claim 1, wherein R^2 is a C_1-C_6 alkyl group substituted by a -(5-15 membered) heterocycloalkyl or -(5-10 membered) heteroaryl.

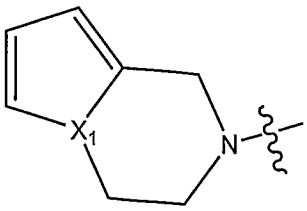
5. The compound of claim 1, wherein -NR^1R^2 together form an 8-, 9-, or 10-membered heterocycloalkyl.

6. The compound of claim 1, wherein -NR^1R^2 taken together is selected from: tetrahydroisoquinolinyl, a bridged azabicyclic group, a bridged diazabicyclic group, and a group selected from:









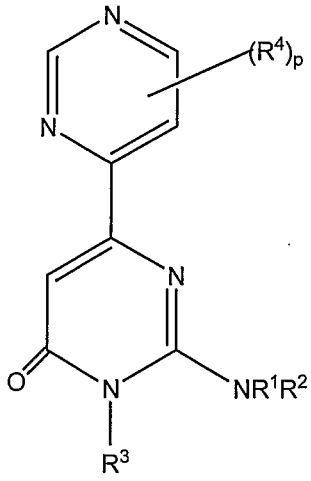
and

wherein X^1 is NR^{13} or S, and X^2 is O or NR^{13}, wherein R^{13} is absent, hydrogen or C_1-C_6 alkyl.

7. The compound of claim 5, wherein said 8-, 9-, or 10-membered heterocycloalkyl is substituted by one or more substituents selected from -OH, halogen, -(C_{zero}-C_4 alkylene)-C_6-C_{15} aryl, -(C_{zero}-C_4 alkylene)-(5-15 membered) heterocycloalkyl,or -(C_{zero}-C_4 alkylene)-(5-15 membered) heteroaryl.

8. The compound of claim 1, wherein R^2 is a -(5-15 membered) heterocycloalkyl substituted by R^7; wherein R^7 is -C(=O)R^8, -C(=O)OR^8 or -S(O)$_n$$R^8$, and R^8 is -(C_{zero}-C_6 alkylene)-C_6-C_{15} aryl.

9. A compound of Formula II,



II,

or a pharmaceutical acceptable salt thereof, wherein:

R^1 is hydrogen or a C_1-C_6 alkyl group;

R^2 is a -(4-15 membered) heterocycloalkyl, -(5-10 membered) heteroaryl or a C_1-C_6 alkyl group, wherein said alkyl is substituted by a -(4-15 membered) heterocycloalkyl or -(5-10 membered) heteroaryl, and wherein said heterocycloalkyls and heteroaryls of R^2 are optionally substituted by one or more substituents selected from the group R^7;

or -NR^1R^2 together may form a (8-15 membered) heterocycloalkyl or -(5-10 membered) heteroaryl, both optionally substituted by one or more substituents selected from the group R^7;

wherein R^3 is hydrogen or C_1-C_6 alkyl;

wherein R^4 is halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl,C_1-C_6 alkoxy or C_1-C_6 haloalkoxy;

wherein each R^7 is independently selected from -OH, halogen, -C_1-C_6 alkyl, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -C_1-C_6 alkoxy, -C_2-C_6 alkenoxy, -C_2-C_6 alkynoxy, -C_1-C_6 hydroxyalkyl,

-CN, $-NO_2$, $-NR^8R^9$, $-C(=O)N^8R^9$, $-C(=O)R^8$, $-C(=O)OR^8$, $-S(O)_2NR^8R^9$, $-S(O)_nR^8$, $-NR^9C(=O)R^8$, $-NR^9SO_2R^8$, $-(C_{zero}-C_6$ alkylene)-C_6-C_{15} aryl, $-(C_{zero}-C_6$ alkylene)-(5-15 membered) heterocycloalkyl, $-(C_{zero}-C_6$ alkylene)-(5-15 membered) heteroaryl, $-(C_{zero}-C_6$ alkylene)-C_6-C_{15} aryloxy and $-(C_{zero}-C_6$ alkylene)-(5-15 membered) heteroaryloxy, wherein said alkyl, alkenyl, alkynyl, alkoxy, alkenoxy, alkynoxy, hydroxyalkyl, aryl, aryloxy, heteroaryl and heteroaryloxy of R^7 are each optionally independently substituted with one or more subsitutents selected from halogens, $-C_1-C_{12}$ alkyl, $-C_1-C_4$ alkoxy, $-NR^8R^9$, $-C(=O)NR^8R^9$, --$C(=O)R^8$, $-C(=O)OR^8$, $-NR^9C(=O)R^8$, $-NR^9SO_2R^8$, $-S(O)_2NR^8R^9$, $-S(O)_nR^8$ or -OH;

each R^8 and R^9 are independently selected from -H, $-C_1-C_{15}$ alkyl, $-C_2-C_{15}$ alkenyl, $-C_2-C_{15}$ alkynyl, $-(C_{zero}-C_4$ alkylene)-$(C_3-C_{15}$ cycloalkyl), $-(C_{zero}-C_4$ alkylene)-$(C_4-C_8$ cycloalkenyl), $-(C_{zero}-C_4$ alkylene)-((5-15 membered) heterocycloalkyl), $-(C_{zero}-C_4$ alkylene)-$(C_6-C_{15}$ aryl) and $-(C_{zero}-C_4$ alkylene)-((5-15 membered) heteroaryl), wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, aryl and heteroaryl of R^8 and R^9 are each optionally independently substituted with one or more substituents independently selected from -OH, $-C_1-C_{12}$ alkyl, $-C_2-C_{12}$ alkenyl, $-C_2-C_{12}$ alkynyl, $-C_1-C_6$ alkoxy, $-C_2-C_6$ alkenoxy, $-C_2-C_6$ alkynoxy, $-C_1-C_6$ hydroxyalkyl, halogen, -CN, $-NO_2$, $-CF_3$, $-NH_2$, $-NH(C_1-C_6$ alkyl), $-N(C_1-C_6$ alkyl)$_2$, $-C(=O)NH_2$, $-C(=O)NH(C_1-C_6$ alkyl), $-C(=O)N(C_1-C_6$ alkyl)$_2$, $-SO_2NH_2$, $-SO_2NH(C_1-C_6$ alkyl), $-SO_2N(C_1-C_6$ alkyl)$_2$, -C(=O)H, -C(=O)OH and $-C(=O)O(C_1-C_6$ alkyl);

n is 0, 1 or 2; and p 0, 1, 2, or 3.

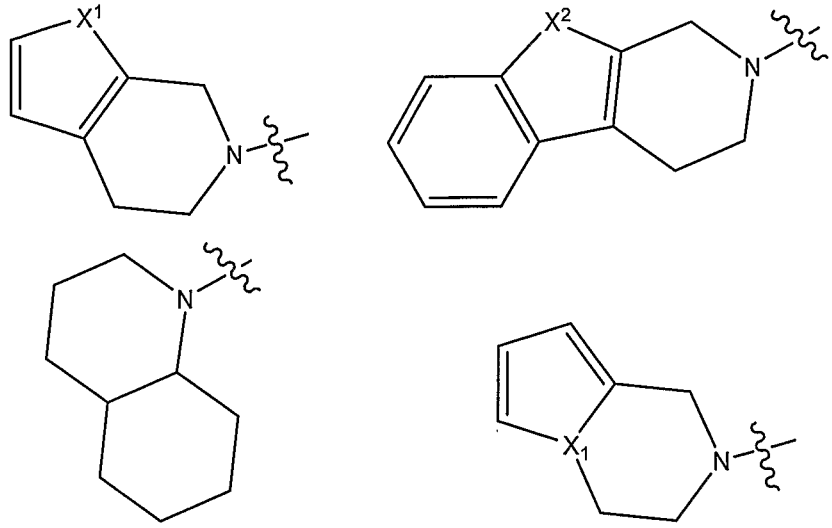
10. The compound of claim 9, wherein R^2 is a -(5-15 membered) heterocycloalkyl or -(5-10 membered) heteroaryl.

11. The compound of claim 10, wherein R^2 is a -(5-15 membered) heterocycloalkyl.

12 The compound of claim 9, wherein R^2 is a C_1-C_6 alkyl group substituted by a -(5-15 membered) heterocycloalkyl or -(5-10 membered) heteroaryl.

13. The compound of claim 9, wherein $-NR^1R^2$ together form an 8-, 9-, or 10-membered heterocycloalkyl.

14. The compound of claim 9, wherein $-NR^1R^2$ taken together is selected from: tetrahydroisoquinolinyl, a bridged azabicyclic group, a bridged diazabicyclic group, and a group selected from:



and

wherein X^1 is NR^{13} or S, and X^2 is O or NR^{13}, wherein R^{13} is absent, hydrogen or C_1-C_6 alkyl.

15. The compound of claim 13, wherein said 8-, 9-, or 10-membered heterocycloalkyl is substituted by one or more substituents selected from -OH, halogen, -(C_{zero}-C_4 alkylene)-C_6-C_{15} aryl, -(C_{zero}-C_4 alkylene)-(5-15 membered) heterocycloalkyl,or -(C_{zero}-C_4 alkylene)-(5-15 membered) heteroaryl.

16. The compound of claim 9, wherein R^2 is a -(5-15 membered) heterocycloalkyl substituted by R^7; wherein R^7 is $-C(=O)R^8$, $-C(=O)OR^8$ or $-S(O)_nR^8$, and R^8 is -(C_{zero}-C_6 alkylene)-C_6-C_{15} aryl.

17. A pharmaceutical composition comprising an amount of a compound of claim 1, or claim 9, and a pharmaceutically acceptable carrier, vehicle or diluent.

18. A method of treating a disorder selected from: Alzheimer's Disease, cancer, diabetes, Syndrome X, obesity, hair loss, inflammation, mood disorders, neuronal cell death, stroke, bipolar disorder, conditions arising from loss of muscle mass and function, frailty, and cardio-protection, which method comprises administering an amount of a compound of claim 1, or claim 9, effective in treating said disorder.