US 20110301141A1

(19) United States

(12) Patent Application Publication

Baker-Glenn et al.

(10) Pub. No.: US 2011/0301141 A1

(43) Pub. Date: Dec. 8, 2011

(54) **AMINOPYRIMIDINE DERIVATIVES AS LRRK2 INHIBITORS**

(75) Inventors: **Charles Baker-Glenn**, Puckeridge (GB); **Daniel Jon Burdick**, Burlingame, CA (US); **Mark Chambers**, St. Neots (GB); **Bryan K. Chan**, Burlingame, CA (US); **Huifen Chen**, Burlingame, CA (US); **Anthony Estrada**, San Carlos, CA (US); **Janet Gunzner-Toste**, Piedmont, CA (US); **Daniel Shore**, San Francisco, CA (US); **Zachary Sweeney**, Redwood City, CA (US); **Shumei Wang**, Foster City, CA (US); **Guiling Zhao**, San Mateo, CA (US)

(73) Assignee: **Genentech, Inc.**, South San Francisco, CA (US)

(21) Appl. No.: **13/150,929**

(22) Filed: **Jun. 1, 2011**

Related U.S. Application Data

(60) Provisional application No. 61/482,455, filed on May 4, 2011, provisional application No. 61/351,530, filed on Jun. 4, 2010.

Publication Classification

(51) **Int. Cl.**

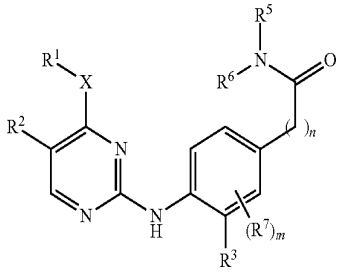
A61K 31/5377	(2006.01)
C07D 401/12	(2006.01)
C07D 401/14	(2006.01)
A61P 25/16	(2006.01)
A61K 31/506	(2006.01)
A61K 31/5386	(2006.01)
A61K 31/553	(2006.01)
C07D 413/12	(2006.01)
C07D 403/12	(2006.01)

(52) **U.S. Cl.** **514/210.16**; 544/122; 544/323; 544/295; 544/105; 540/544; 544/123; 544/330; 514/235.8; 514/275; 514/249; 514/210.18; 514/252.14; 514/230.5; 514/252.2; 514/211.15

(57) **ABSTRACT**

Compounds of the formula I:

I



or pharmaceutically acceptable salts thereof, wherein m, n. X, R^1, R^2, R^3, R^5, R^6 and R^7 are as defined herein. Also disclosed are methods of making the compounds and using the compounds for treatment of diseases associated with LRRK2 receptor, such as Parkinson's disease.

AMINOPYRIMIDINE DERIVATIVES AS LRRK2 INHIBITORS

FIELD OF THE INVENTION

[0001] This invention pertains to compounds that modulate the function of LRRK2 and are useful for treatment of LRRK2-mediated diseases and conditions such as Parkinson's disease.

BACKGROUND OF THE INVENTION

[0002] Neurodegenerative diseases such as Parkinson's disease, Lewy body dementia and Huntington's disease affect millions of individuals. Parkinson's disease is a chronic, progressive motor system disorder that afflicts approximately one out of every 1000 people, with hereditary Parkinson's disease accounting for 5-10% of all of patients. Parkinson's disease is caused by progressive loss of mid-brain dopamine neurons, leaving patients with impaired ability to direct and control their movements. The primary Parkinson's disease symptoms are trembling, rigidity, slowness of movement, and impaired balance. Many Parkinson's disease patients also experience other symptoms such as emotional changes, memory loss, speech problems, and sleeping disorders.

[0003] The gene encoding the leucine-rich repeat kinase 2 protein (LRRK2) has been identified in association with hereditary Parkinson's disease (Paisan-Ruiz et al., *Neuron,* Vol. 44(4), 2004, pp 595-600; Zimprich et al., *Neuron, Vol.* 44(4), 2004, 601-607). In-vitro studies show that Parkinson's disease—associated mutation leads to increased LRRK2 kinase activity and decreased rate of GTP hydrolysis compared to wild-type (Guo et al., *Experimental Cell Research, Vol.* 313(16), 2007, pp. 3658-3670. Anti-LRRK2 antibodies have been used to label brainstem Lewy bodies associated with Parkinson's disease and cortical antibodies associated with Lewis body dementia suggesting that LRRK2 may play an important role in Lewie body formation and pathogenesis associated with these diseases (Zhou et al., *Molecular Degeneration,* 2006, 1:17 doi:10.1186/1750-1326-1-17). LRRK2 has also been identified as a gene potentially associated with increased susceptibility to Crohn's disease and susceptibility to leprosy (Zhang et al., *New England J. Med.* Vol. 361 (2009) pp. 2609-2618.

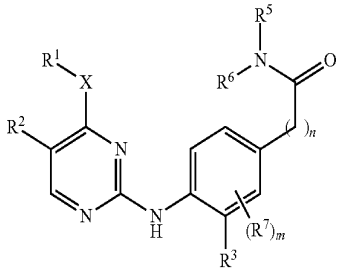
[0004] LRRK2 has also been associated with the transition of mild cognitive impairment to Alzheimer's disease (WO2007/149789); L-Dopa induced dyskinesia (Hurley et al., *Eur. J. Neurosci.,* Vol. 26, 2007, pp. 171-177; CNS disorders associated with neuronal progenitor differentiation (Milosevic et al., *Neurodegen.,* Vol. 4, 2009, p. 25); cancers such as kidney, breast, prostate, blood and lung cancers and acute myelogenous leukemia (WO2011/038572); papillary renal and thyroid carcinomas (Looyenga et al., www.pnas.org/cgi/doi/10.1073/pnas.1012500108); multiple myeloma (Chapman et al., *Nature* Vol. 471, 2011, pp. 467-472); amyotrophic lateral sclerosis (Shtilbans et al., *Amyotrophic Lateral Sclerosis* "Early Online 2011, pp. 1-7); rheumatoid arthritis (Nakamura et al., *DNA Res.* Vol. 13(4), 2006, pp. 169-183); and ankylosing spondylytis (Danoy et al., *PLoS Genetics,* Vol. 6(12), 2010, e1001195, pp. 1-5).

[0005] Accordingly, compounds and compositions effective at modulating LRRK2 activity may provide a treatment for neurodegenerative diseases such as Parkinson's disease and Lewie body dementia, for CNS disorders such as Alzheimer's disease and L-Dopa induced dyskinesia, for cancers such as kidney, breast, prostate, blood, papillary and lung cancers, acute myelogenous leukemia and multiple myeloma, and for inflammatory diseases such as leprosy, Crohn's disease, amyotrophic lateral sclerosis, rheumatoid arthritis, and ankylosing spondylytis. Particularly, there is a need for compounds with LRRK2 affinity that are selective for LRRK2 over other kinases, such as JAK2, and which can provide effective drugs for treatment of neurodegenerative disorders such as Parkinson's disease.

SUMMARY OF THE INVENTION

[0006] The invention provides compounds of the formula I:

I



or pharmaceutically acceptable salts thereof,

wherein:

[0007] m is from 0 to 3;

[0008] X is: —NR^a—; —O—; or —$S(O)_r$— wherein r is from 0 to 2 and R^a is hydrogen or C_{1-6}alkyl;

[0009] R^1 is: C_{1-6}alkyl; C_{2-6}alkenyl; C_{2-6}alkynyl; halo-C_{1-6}alkyl; C_{1-6}alkoxy-C_{1-6}alkyl; hydroxy-C_{1-6}alkyl; amino-C_{1-6}alkyl; C_{1-6}alkylsulfonyl-C_{1-6}alkyl; C_{3-6}cycloalkyl optionally substituted with C_{1-6}alkyl; C_{3-6}cycloalkyl-C_{1-6}alkyl wherein the C_{3-6}cycloalkyl portion is optionally substituted with C_{1-6}alkyl; tetrahydropyranyl; tetrahydrofuranyl; tetrahydrofuranyl-C_{1-6}alkyl; oxetanyl; or oxetan-C_{1-6}alkyl;

[0010] or R^1 and R^a together with the atoms to which they are attached may form a three to six membered ring that may optionally include an additional heteroatom selected from O, N and S, and which is substituted with oxo, halo or C_{1-6}alkyl;

[0011] R^2 is: halo; C_{1-6}alkoxy; cyano; C_{2-6}alkynyl; C_{2-6}alkenyl; halo-C_{1-6}alkyl; halo-C_{1-6}alkoxy; C_{3-6}cycloalkyl wherein the C_{3-6}cycloalkyl portion is optionally substituted with C_{1-6}alkyl; C_{3-6}cycloalkyl-C_{1-6}alkyl wherein the C_{3-6}cycloalkyl portion is optionally substituted with C_{1-6}alkyl; tetrahydrofuranyl; tetrahydrofuranyl-C_{1-6}alkyl; acetyl; oxetanyl; or oxetan-C_{1-6}alkyl;

[0012] R^3 is: —OR^4; halo; cyano; C_{1-6}alkyl; halo-C_{1-6}alkyl; C_{3-6}cycloalkyl optionally substituted with C_{1-6}alkyl; C_{3-6}cycloalkyl-C_{1-6}alkyl wherein the C_{3-6}cycloalkyl portion is optionally substituted with C_{1-6}alkyl; tetrahydrofuranyl; tetrahydrofuranyl-C_{1-6}alkyl; oxetanyl; or oxetan-C_{1-6}alkyl;

[0013] R^4 is: hydrogen; C_{1-6}alkyl; halo-C_{1-6}alkyl; C_{1-6}alkoxy-C_{1-6}alkyl; C_{3-6}cycloalkyl optionally substituted with C_{1-6}alkyl or halo; C_{3-6}cycloalkyl-C_{1-6}alkyl wherein the C_{3-6}cycloalkyl portion is optionally substituted with C_{1-6}alkyl or halo; tetrahydrofuranyl; tetrahydrofuranyl-C_{1-6}alkyl; oxetanyl; or oxetan-C_{1-6}alkyl;

[0014] R^5 is: hydrogen; or C_{1-6}alkyl;

[0015] n is 0 or 1;

[0016] R^6 is: hydrogen; C_{1-6}alkyl; C_{1-6}alkoxy-C_{1-6}alkyl; hydroxy-C_{1-6}alkyl; amino-C_{1-6}alkyl; C_{3-6}cycloalkyl; C_{3-6}cy-

cloalkyl-C_{1-6}alkyl; heterocyclyl; or heterocyclyl-C_{1-6}alkyl; wherein the C_{3-6}cycloalkyl, C_{3-6}cycloalkyl-C_{1-6}alkyl, heterocyclyl and heterocyclyl-C_{1-6}alkyl each may be optionally substituted with one, two, three or four groups groups independently selected from: C_{1-6}alkyl; halo-C_{1-6}alkyl; C_{1-6}alkoxy; halo-C_{1-6}alkoxy; hydroxy; hydroxy-C_{1-6}alkyl; halo; nitrile; C_{1-6}alkyl-carbonyl; C_{1-6}alkyl-sulfonyl; C_{3-6}cycloalkyl; C_{3-6}cycloalkyl-C_{1-6}alkyl; C_{3-6}cycloalkyl-carbonyl; amino; or heterocyclyl; or two of the groups together with the atoms to which they are attached may form a five or six-membered ring;

[0017] or R^5 and R^6 together with the nitrogen atom to which they are attached form a three- to seven-membered ring that optionally includes an additional heteroatom selected from O, N and $S(O)_n$, and which is optionally substituted with one, two, three or four groups independently selected from: C_{1-6}alkyl; halo-C_{1-6}alkyl; C_{1-6}alkoxy; halo-C_{1-6}alkoxy; hydroxy; C_{1-6}alkoxy-C_{1-6}alkyl; hydroxy-C_{1-6}alkyl; halo, nitrile; C_{1-6}alkyl-carbonyl; C_{1-6}alkyl-sulfonyl; C_{3-6}cycloalkyl; C_{3-6}cycloalkyl-C_{1-6}alkyl; C_{3-6}cycloalkyl-carbonyl; amino; or heterocyclyl; or two of the groups together with the atoms to which they are attached may form a five or six-membered ring; and

[0018] R^7 is: halo; C_{1-6}alkyl; C_{1-6}alkoxy; halo-C_{1-6}alkyl; or halo-C_{1-6}alkoxy.

[0019] The invention also provides and pharmaceutical compositions comprising the compounds, methods of using the compounds, and methods of preparing the compounds.

DETAILED DESCRIPTION OF THE INVENTION

[0020] Definitions

[0021] Unless otherwise stated, the following terms used in this Application, including the specification and claims, have the definitions given below. It must be noted that, as used in the specification and the appended claims, the singular forms "a", "an," and "the" include plural referents unless the context clearly dictates otherwise.

[0022] "Alkyl" means the monovalent linear or branched saturated hydrocarbon moiety, consisting solely of carbon and hydrogen atoms, having from one to twelve carbon atoms. "Lower alkyl" refers to an alkyl group of one to six carbon atoms, i.e. C_1-C_6alkyl. Examples of alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, isobutyl, sec-butyl, tert-butyl, pentyl, n-hexyl, octyl, dodecyl, and the like.

[0023] "Alkenyl" means a linear monovalent hydrocarbon radical of two to six carbon atoms or a branched monovalent hydrocarbon radical of three to six carbon atoms, containing at least one double bond, e.g., ethenyl, propenyl, and the like.

[0024] "Alkynyl" means a linear monovalent hydrocarbon radical of two to six carbon atoms or a branched monovalent hydrocarbon radical of three to six carbon atoms, containing at least one triple bond, e.g., ethynyl, propynyl, and the like.

[0025] "Alkylene" means a linear saturated divalent hydrocarbon radical of one to six carbon atoms or a branched saturated divalent hydrocarbon radical of three to six carbon atoms, e.g., methylene, ethylene, 2,2-dimethylethylene, propylene, 2-methylpropylene, butylene, pentylene, and the like.

[0026] "Alkoxy" and "alkyloxy", which may be used interchangeably, mean a moiety of the formula —OR, wherein R is an alkyl moiety as defined herein. Examples of alkoxy moieties include, but are not limited to, methoxy, ethoxy, isopropoxy, and the like.

[0027] "Alkoxyalkyl" means a moiety of the formula R^a—O—R^b—, where R^a is alkyl and R^b is alkylene as defined herein. Exemplary alkoxyalkyl groups include, by way of example, 2-methoxyethyl, 3-methoxypropyl, 1-methyl-2-methoxyethyl, 1-(2-methoxyethyl)-3-methoxypropyl, and 1-(2-methoxyethyl)-3-methoxypropyl.

[0028] "Alkoxyalkoxy" means a group of the formula —O—R—R' wherein R is alkylene and R' is alkoxy as defined herein.

[0029] "Alkylcarbonyl" means a moiety of the formula —C(O)—R, wherein R is alkyl as defined herein.

[0030] "Alkoxycarbonyl" means a group of the formula —C(O)—R wherein R is alkoxy as defined herein.

[0031] "Alkylcarbonylalkyl" means a group of the formula —R—C(O)—R wherein R is alkylene and R' is alkyl as defined herein.

[0032] "Alkoxycarbonylalkyl" means a group of the formula —R—C(O)—R wherein R is alkylene and R' is alkoxy as defined herein.

[0033] "Alkoxycarbonylalkoxy"means a group of the formula —O—R—C(O)—R' wherein R is alkylene and R' is alkoxy as defined herein.

[0034] "Hydroxycarbonylalkoxy" means a group of the formula —O—R—C(O)—OH wherein R is alkylene as defined herein.

[0035] "Alkylaminocarbonylalkoxy" means a group of the formula —O—R—C(O)—NHR' wherein R is alkylene and R' is alkyl as defined herein.

[0036] "Dialkylaminocarbonylalkoxy" means a group of the formula —O—R—C(O)—NR'R" wherein R is alkylene and R' and R" are alkyl as defined herein.

[0037] "Alkylaminoalkoxy" means a group of the formula —O—R—NHR' wherein R is alkylene and R' is alkyl as defined herein.

[0038] "Dialkylaminoalkoxy" means a group of the formula —O—R—NR'R' wherein R is alkylene and R' and R" are alkyl as defined herein.

[0039] "Alkylsulfonyl" means a moiety of the formula —SO_2—R, wherein R is alkyl as defined herein.

[0040] "Alkylsulfonylalkyl means a moiety of the formula —R'—SO_2—R" where where R' is alkylene and R" is alkyl as defined herein.

[0041] "Alkylsulfonylalkoxy" means a group of the formula —O—R—SO_2—R' wherein R is alkylene and R' is alkyl as defined herein.

[0042] "Amino means a moiety of the formula —NRR' wherein R and R' each independently is hyrdogen or alkyl as defined herein. "Amino thus includes "alkylamino (where one of R and R' is alkyl and the other is hydrogen) and "dialkylamino (where R and R' are both alkyl.

[0043] "Aminocarbonyl" means a group of the formula —C(O)—R wherein R is amino as defined herein.

[0044] "Alkoxyamino" means a moiety of the formula —NR—OR' wherein R is hydrogen or alkyl and R' is alkyl as defined herein.

[0045] "Alkylsulfanyl" means a moiety of the formula —SR wherein R is alkyl as defined herein.

[0046] "Aminoalkyl" means a group —R—R' wherein R' is amino and R is alkylene as defined herein. "Aminoalkyl" includes aminomethyl, aminoethyl, 1-aminopropyl, 2-aminopropyl, and the like. The amino moiety of "aminoalkyl" may be substituted once or twice with alkyl to provide "alkylaminoalkyl" and "dialkylaminoalkyl" respectively. "Alkylaminoalkyl" includes methylaminomethyl, methylaminoet-

hyl, methylaminopropyl, ethylaminoethyl and the like. "Dialkylaminoalkyl" includes dimethylaminomethyl, dimethylaminoethyl, dimethylaminopropyl, N-methyl-N-ethylaminoethyl, and the like.

[0047] "Aminoalkoxy" means a group —OR—R' wherein R' is amino and R is alkylene as defined herein.

[0048] "Alkylsulfonylamido" means a moiety of the formula —NR'SO_2—R wherein R is alkyl and R' is hydrogen or alkyl.

[0049] "Aminocarbonyloxyalkyl" or "carbamylalkyl" means a group of the formula —R—O—C(O)—NR'R" wherein R is alkylene and R', R" each independently is hydrogen or alkyl as defined herein.

[0050] "Alkynylalkoxy" means a group of the formula —O—R—R' wherein R is alkylene and R' is alkynyl as defined herein.

[0051] "Aryl" means a monovalent cyclic aromatic hydrocarbon moiety consisting of a mono-, bi- or tricyclic aromatic ring. The aryl group can be optionally substituted as defined herein. Examples of aryl moieties include, but are not limited to, phenyl, naphthyl, phenanthryl, fluorenyl, indenyl, pentalenyl, azulenyl, oxydiphenyl, biphenyl, methylenediphenyl, aminodiphenyl, diphenylsulfidyl, diphenylsulfonyl, diphenylisopropylidenyl, benzodioxanyl, benzofuranyl, benzodioxylyl, benzopyranyl, benzoxazinyl, benzoxazinonyl, benzopiperadinyl, benzopiperazinyl, benzopyrrolidinyl, benzomorpholinyl, methylenedioxyphenyl, ethylenedioxyphenyl, and the like, of which may be optionally substituted as defined herein.

[0052] "Arylalkyl" and "Aralkyl", which may be used interchangeably, mean a radical-R^aR^b where R^a is an alkylene group and R^b is an aryl group as defined herein; e.g., phenylalkyls such as benzyl, phenylethyl, 3-(3-chlorophenyl)-2-methylpentyl, and the like are examples of arylalkyl.

[0053] "Arylsulfonyl means a group of the formula —SO_2—R wherein R is aryl as defined herein.

[0054] "Aryloxy" means a group of the formula —O—R wherein R is aryl as defined herein.

[0055] "Aralkyloxy" means a group of the formula —O—R—R" wherein R is alkylene and R' is aryl as defined herein.

[0056] "Carboxy" or "hydroxycarbonyl", which may be used interchangeably, means a group of the formula —C(O)—OH.

[0057] "Cyanoalkyl" " means a moiety of the formula —R'—R", where R' is alkylene as defined herein and R" is cyano or nitrile.

[0058] "Cycloalkyl" means a monovalent saturated carbocyclic moiety consisting of mono- or bicyclic rings. Particular cycloalkyl are unsubstituted or substituted with alkyl. Cycloalkyl can optionally be substituted as defined herein. Unless defined otherwise, cycloalkyl may be optionally substitued with one or more substituents, wherein each substituent is independently hydroxy, alkyl, alkoxy, halo, haloalkyl, amino, monoalkylamino, or dialkylamino Examples of cycloalkyl moieties include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and the like, including partially unsaturated (cycloalkenyl) derivatives thereof.

[0059] "Cycloalkylalkyl" means a moiety of the formula —R'—R", where R' is alkylene and R" is cycloalkyl as defined herein.

[0060] "Cycloalkylalkoxy" means a group of the formula —O—R—R' wherein R is alkylene and R' is cycloalkyl as defined herein.

[0061] "Heteroaryl" means a monocyclic or bicyclic radical of 5 to 12 ring atoms having at least one aromatic ring containing one, two, or three ring heteroatoms selected from N, O, or S, the remaining ring atoms being C, with the understanding that the attachment point of the heteroaryl radical will be on an aromatic ring. The heteroaryl ring may be optionally substituted as defined herein. Examples of heteroaryl moieties include, but are not limited to, optionally substituted imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, pyrazinyl, thienyl, benzothienyl, thiophenyl, furanyl, pyranyl, pyridyl, pyrrolyl, pyrazolyl, pyrimidyl, quinolinyl, isoquinolinyl, benzofuryl, benzothiophenyl, benzothiopyranyl, benzimidazolyl, benzooxazolyl, benzooxadiazolyl, benzothiazolyl, benzothiadiazolyl, benzopyranyl, indolyl, isoindolyl, triazolyl, triazinyl, quinoxalinyl, purinyl, quinazolinyl, quinolizinyl, naphthyridinyl, pteridinyl, carbazolyl, azepinyl, diazepinyl, acridinyl and the like, each of which may be optionally substituted as defined herein.

[0062] Heteroarylalkyl" or "heteroaralkyl" means a group of the formula —R—R' wherein R is alkylene and R' is heteroaryl as defined herein.

[0063] "Heteroarylsulfonyl means a group of the formula —SO_2—R wherein R is heteroaryl as defined herein.

[0064] "Heteroaryloxy" means a group of the formula —O—R wherein R is heteroaryl as defined herein.

[0065] "Heteroaralkyloxy" means a group of the formula —O—R—R" wherein R is alkylene and R' is heteroaryl as defined herein.

[0066] The terms "halo", "halogen" and "halide", which may be used interchangeably, refer to a substituent fluoro, chloro, bromo, or iodo.

[0067] "Haloalkyl" means alkyl as defined herein in which one or more hydrogen has been replaced with same or different halogen. Exemplary haloalkyls include —CH_2Cl, —CH_2CF_3, —CH_2CCl_3, perfluoroalkyl (e.g., —CF_3), and the like.

[0068] "Haloalkoxy" means a moiety of the formula —OR, wherein R is a haloalkyl moiety as defined herein. An exemplary haloalkoxy is difluoromethoxy.

[0069] "Heterocycloamino" means a saturated ring wherein at least one ring atom is N, NH or N-alkyl and the remaining ring atoms form an alkylene group.

[0070] "Heterocyclyl" means a monovalent saturated moiety, consisting of one to three rings, incorporating one, two, or three or four heteroatoms (chosen from nitrogen, oxygen or sulfur). The heterocyclyl ring may be optionally substituted as defined herein. Examples of heterocyclyl moieties include, but are not limited to, optionally substituted piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, azepinyl, pyrrolidinyl, azetidinyl, tetrahydropyranyl, tetrahydrofuranyl, oxetanyl and the like. Such heterocyclyl may be optionally substituted as defined herein.

[0071] "Heterocyclylalkyl" means a moiety of the formula —R—R' wherein R is alkylene and R' is heterocyclyl as defined herein.

[0072] "Heterocyclyloxy" means a moiety of the formula —OR wherein R is heterocyclyl as defined herein.

[0073] "Heterocyclylalkoxy" means a moiety of the formula —OR—R' wherein R is alkylene and R' is heterocyclyl as defined herein.

[0074] "Hydroxyalkoxy" means a moiety of the formula —OR wherein R is hydroxyalkyl as defined herein.

[0075] "Hydroxyalkylamino" means a moiety of the formula —NR—R' wherein R is hydrogen or alkyl and R' is hydroxyalkyl as defined herein.

[0076] "Hydroxyalkylaminoalkyl" means a moiety of the formula —R—NR'—R" wherein R is alkylene, R' is hydrogen or alkyl, and R" is hydroxyalkyl as defined herein.

[0077] "Hydroxycarbonylalkyl" or "carboxyalkyl" means a group of the formula —R—(CO)—OH where R is alkylene as defined herein.

[0078] "Hydroxycarbonylalkoxy" means a group of the formula —O—R—C(O)—OH wherein R is alkylene as defined herein.

[0079] "Hydroxyalkyloxycarbonylalkyl" or "hydroxyalkoxycarbonylalkyl" means a group of the formula —R—C(O)—O—R—OH wherein each R is alkylene and may be the same or different.

[0080] "Hydroxyalkyl" means an alkyl moiety as defined herein, substituted with one or more, for example, one, two or three hydroxy groups, provided that the same carbon atom does not carry more than one hydroxy group. Representative examples include, but are not limited to, hydroxymethyl, 2-hydroxyethyl, 2-hydroxypropyl, 3-hydroxypropyl, 1-(hydroxymethyl)-2-methylpropyl, 2-hydroxybutyl, 3-hydroxybutyl, 4-hydroxybutyl, 2,3-dihydroxypropyl, 2-hydroxy-1-hydroxymethylethyl, 2,3-dihydroxybutyl, 3,4-dihydroxybutyl and 2-(hydroxymethyl)-3-hydroxypropyl

[0081] "Hydroxycycloalkyl" means a cycloalkyl moiety as defined herein wherein one, two or three hydrogen atoms in the cycloalkyl radical have been replaced with a hydroxy substituent. Representative examples include, but are not limited to, 2-, 3-, or 4-hydroxycyclohexyl, and the like.

[0082] "Alkoxy hydroxyalkyl" and "hydroxy alkoxyalkyl", which may be used interchangeably, means an alkyl as defined herein that is substituted at least once with hydroxy and at least once with alkoxy. "Alkoxy hydroxyalkyl" and "hydroxy alkoxyalkyl" thus encompass, for example, 2-hydroxy-3-methoxy-propan-1-yl and the like.

[0083] "Urea"or "ureido" means a group of the formula —NR'—C(O)—NR"R'" wherein R', R" and R'" each independently is hydrogen or alkyl.

[0084] "Carbamate" means a group of the formula —O—C(O)—NR'R" wherein R' and R" each independently is hydrogen or alkyl.

[0085] "Carboxy" means a group of the formula —O—C(O)—OH.

[0086] "Sulfonamido" means a group of the formula —SO_2—NR'R" wherein R', R" and R'" each independently is hydrogen or alkyl.

[0087] "Optionally substituted" when used in association with an "aryl", phenyl", "heteroaryl" "cycloalkyl" or "heterocyclyl" moiety means that such moiety may be unsubstituted (i.e., all open valencies are occupied by a hydrogen atom) or substituted with specific groups as related herein.

[0088] "Leaving group" means the group with the meaning conventionally associated with it in synthetic organic chemistry, i.e., an atom or group displaceable under substitution reaction conditions. Examples of leaving groups include, but are not limited to, halogen, alkane- or arylenesulfonyloxy, such as methanesulfonyloxy, ethanesulfonyloxy, thiomethyl, benzenesulfonyloxy, tosyloxy, and thienyloxy, dihalophosphinoyloxy, optionally substituted benzyloxy, isopropyloxy, acyloxy, and the like.

[0089] "Modulator" means a molecule that interacts with a target. The interactions include, but are not limited to, agonist, antagonist, and the like, as defined herein.

[0090] "Optional" or "optionally" means that the subsequently described event or circumstance may but need not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not.

[0091] "Disease" and "Disease state" means any disease, condition, symptom, disorder or indication.

[0092] "Inert organic solvent" or "inert solvent" means the solvent is inert under the conditions of the reaction being described in conjunction therewith, including for example, benzene, toluene, acetonitrile, tetrahydrofuran, N,N-dimethylformamide, chloroform, methylene chloride or dichloromethane, dichloroethane, diethyl ether, ethyl acetate, acetone, methyl ethyl ketone, methanol, ethanol, propanol, isopropanol, tent-butanol, dioxane, pyridine, and the like. Unless specified to the contrary, the solvents used in the reactions of the present invention are inert solvents.

[0093] "Pharmaceutically acceptable" means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic, and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary as well as human pharmaceutical use.

[0094] "Pharmaceutically acceptable salts" of a compound means salts that are pharmaceutically acceptable, as defined herein, and that possess the desired pharmacological activity of the parent compound.

[0095] It should be understood that all references to pharmaceutically acceptable salts include solvent addition forms (solvates) or crystal forms (polymorphs) as defined herein, of the same acid addition salt.

[0096] "Protective group" or "protecting group" means the group which selectively blocks one reactive site in a multifunctional compound such that a chemical reaction can be carried out selectively at another unprotected reactive site in the meaning conventionally associated with it in synthetic chemistry. Certain processes of this invention rely upon the protective groups to block reactive nitrogen and/or oxygen atoms present in the reactants. For example, the terms "amino-protecting group" and "nitrogen protecting group" are used interchangeably herein and refer to those organic groups intended to protect the nitrogen atom against undesirable reactions during synthetic procedures. Exemplary nitrogen protecting groups include, but are not limited to, trifluoroacetyl, acetamido, benzyl (Bn), benzyloxycarbonyl (carbobenzyloxy, CBZ), p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, tert-butoxycarbonyl (BOC), and the like. The artisan in the art will know how to chose a group for the ease of removal and for the ability to withstand the following reactions.

[0097] "Solvates" means solvent additions forms that contain either stoichiometric or non stoichiometric amounts of solvent. Some compounds have a tendency to trap a fixed molar ratio of solvent molecules in the crystalline solid state, thus forming a solvate. If the solvent is water the solvate formed is a hydrate, when the solvent is alcohol, the solvate formed is an alcoholate. Hydrates are formed by the combination of one or more molecules of water with one of the substances in which the water retains its molecular state as H_2O, such combination being able to form one or more hydrate.

[0098] "Parkinson's disease" means a degenerative disorder of the central nervous system that impairs motor skills, speech, and/or cognitive function. Symptoms of Parkinson's disease may include, for example, muscle rigidity, tremor, slowing of physical movement (bradykinesia) and loss of physical movement (akinesia).

[0099] "Lewie body disease" also called "Lewie body demntia", diffuse Lewy body disease", cortical Lewie body disease", means a neurogenerative disorder characterized anatomically by the presence of Lewie bodies in the brain.

[0100] "Subject" means mammals and non-mammals. Mammals means any member of the mammalia class including, but not limited to, humans; non-human primates such as chimpanzees and other apes and monkey species; farm animals such as cattle, horses, sheep, goats, and swine; domestic animals such as rabbits, dogs, and cats; laboratory animals including rodents, such as rats, mice, and guinea pigs; and the like. Examples of non-mammals include, but are not limited to, birds, and the like. The term "subject" does not denote a particular age or sex.

[0101] "Therapeutically effective amount" means an amount of a compound that, when administered to a subject for treating a disease state, is sufficient to effect such treatment for the disease state. The "therapeutically effective amount" will vary depending on the compound, disease state being treated, the severity or the disease treated, the age and relative health of the subject, the route and form of administration, the judgment of the attending medical or veterinary practitioner, and other factors.

[0102] The terms "those defined above" and "those defined herein" when referring to a variable incorporates by reference the broad definition of the variable as well as particular definitions, if any.

[0103] "Treating" or "treatment" of a disease state includes, inter alia, inhibiting the disease state, i.e., arresting the development of the disease state or its clinical symptoms, and/or relieving the disease state, i.e., causing temporary or permanent regression of the disease state or its clinical symptoms.

[0104] The terms "treating", "contacting" and "reacting" when referring to a chemical reaction means adding or mixing two or more reagents under appropriate conditions to produce the indicated and/or the desired product. It should be appreciated that the reaction which produces the indicated and/or the desired product may not necessarily result directly from the combination of two reagents which were initially added, i.e., there may be one or more intermediates which are produced in the mixture which ultimately leads to the formation of the indicated and/or the desired product.

Nomenclature and Structures

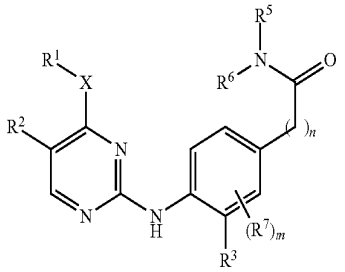
[0105] In general, the nomenclature and chemical names used in this Application are based on ChembioOffice™ by CambridgeSoft™. Any open valency appearing on a carbon, oxygen sulfur or nitrogen atom in the structures herein indicates the presence of a hydrogen atom unless indicated otherwise. Where a nitrogen-containing heteroaryl ring is shown with an open valency on a nitrogen atom, and variables such as R^a, R^b or R_c are shown on the heteroaryl ring, such variables may be bound or joined to the open valency nitrogen. Where a chiral center exists in a structure but no specific stereochemistry is shown for the chiral center, both enantiomers associated with the chiral center are encompassed by the structure. Where a structure shown herein may exist in multiple tautomeric forms, all such tautomers are encompassed by the structure. The atoms represented in the structures herein are intended to encompass all naturally occurring isotopes of such atoms. Thus, for example, the hydrogen atoms represented herein are meant to include deuterium and tritium, and the carbon atoms are meant to include C^{13} and C^{14} isotopes.

[0106] All patents and publications identified herein are incorporated herein by reference in their entirety.

Compounds of the Invention

[0107] The invention provides compounds of the formula I:

I



or pharmaceutically acceptable salts thereof,

wherein:

[0108] m is from 0 to 3;

[0109] X is: —NR^a—; —O—; or —$S(O)_r$— wherein r is from 0 to 2 and R^a is hydrogen or C_{1-6}alkyl;

[0110] R^1 is: C_{1-6}alkyl; C_{2-6}alkenyl; C_{2-6}alkynyl; halo-C_{1-6}alkyl; C_{1-6}alkoxy-C_{1-6}alkyl; hydroxy-C_{1-6}alkyl; amino-C_{1-6}alkyl; C_{1-6}alkylsulfonyl-C_{1-6}alkyl; C_{3-6}cycloalkyl optionally substituted with C_{1-6}alkyl; C_{3-6}cycloalkyl-C_{1-6}alkyl wherein the C_{3-6}cycloalkyl portion is optionally substituted with C_{1-6}alkyl; tetrahydropyranyl; tetrahydrofuranyl; tetrahydrofuranyl-C_{1-6}alkyl; oxetanyl; or oxetan-C_{1-6}alkyl;

[0111] or R^1 and R^a together with the atoms to which they are attached may form a three to six membered ring that may optionally include an additional heteroatom selected from O, N and S, and which is substituted with oxo, halo or C_{1-6}alkyl;

[0112] R^2 is: halo; C_{1-6}alkoxy; cyano; C_{2-6}alkynyl; C_{2-6}alkenyl; halo-C_{1-6}alkyl; halo-C_{1-6}alkoxy; C_{3-6}cycloalkyl wherein the C_{3-6}cycloalkyl portion is optionally substituted with C_{1-6}alkyl; C_{3-6}cycloalkyl-C_{1-6}alkyl wherein the C_{3-6}cycloalkyl portion is optionally substituted with C_{1-6}alkyl; tetrahydrofuranyl; tetrahydrofuranyl-C_{1-6}alkyl; acetyl; oxetanyl; or oxetan-C_{1-6}alkyl;

[0113] R^3 is: —OR^4; halo; cyano; C_{1-6}alkyl; halo-C_{1-6}alkyl; C_{3-6}cycloalkyl optionally substituted with C_{1-6}alkyl; C_{3-6}cycloalkyl-C_{1-6}alkyl wherein the C_{3-6}cycloalkyl portion is optionally substituted with C_{1-6}alkyl; tetrahydrofuranyl; tetrahydrofuranyl-C_{1-6}alkyl; oxetanyl; or oxetan-C_{1-6}alkyl;

[0114] R^4 is: hydrogen; C_{1-6}alkyl; halo-C_{1-6}alkyl; C_{1-6}alkoxy-C_{1-6}alkyl; C_{3-6}cycloalkyl optionally substituted with C_{1-6}alkyl or halo; C_{3-6}cycloalkyl-C_{1-6}alkyl wherein the C_{3-6}cycloalkyl portion is optionally substituted with

C_{1-6}alkyl or halo; tetrahydrofuranyl; tetrahydrofuranyl-C_{1-6}alkyl; oxetanyl; or oxetan-C_{1-6}alkyl;

[0115] R^5 is: hydrogen; or C_{1-6}alkyl;

[0116] n is 0 or 1;

[0117] R^6 is: hydrogen; C_{1-6}alkyl; C_{1-6}alkoxy-C_{1-6}alkyl; hydroxy-C_{1-6}alkyl; amino-C_{1-6}alkyl; C_{3-6}cycloalkyl; C_{3-6}cycloalkyl-C_{1-6}alkyl; heterocyclyl; or heterocyclyl-C_{1-6}alkyl; wherein the C_{3-6}cycloalkyl, C_{3-6}cycloalkyl-C_{1-6}alkyl, heterocyclyl and heterocyclyl-C_{1-6}alkyl each may be optionally substituted with one, two, three or four groups groups independently selected from: C_{1-6}alkyl; halo-C_{1-6}alkyl; C_{1-6}alkoxy; halo-C_{1-6}alkoxy; hydroxy; hydroxy-C_{1-6}alkyl; halo; nitrile; C_{1-6}alkyl-carbonyl; C_{1-6}alkyl-sulfonyl; C_{3-6}cycloalkyl; C_{3-6}cycloalkyl-C_{1-6}alkyl; C_{3-6}cycloalkyl-carbonyl; amino; or heterocyclyl; or two of the groups together with the atoms to which they are attached may form a five or six-membered ring;

[0118] or R^5 and R^6 together with the nitrogen atom to which they are attached form a three- to seven-membered ring that optionally includes an additional heteroatom selected from O, N and $S(O)_n$, and which is optionally substituted with one, two, three or four groups independently selected from: C_{1-6}alkyl; halo-C_{1-6}alkyl; C_{1-6}alkoxy; halo-C_{1-6}alkoxy; hydroxy; C_{1-6}alkoxy-C_{1-6}alkyl; hydroxy-C_{1-6}alkyl; halo, nitrile; C_{1-6}alkyl-carbonyl; C_{1-6}alkyl-sulfonyl; C_{3-6}cycloalkyl; C_{3-6}cycloalkyl-C_{1-6}alkyl; C_{3-6}cycloalkyl-carbonyl; amino; or heterocyclyl; or two of the groups together with the atoms to which they are attached may form a five or six-membered ring; and

[0119] R^7 is: halo; C_{1-6}alkyl; C_{1-6}alkoxy; halo-C_{1-6}alkyl; or halo-C_{1-6}alkoxy.

[0120] In certain embodiments of formula I, n is 0.

[0121] In certain embodiments of formula I, n is 1.

[0122] In certain embodiments of formula I, R^1 and R^a together with the atoms to which they are attached may form a three to six membered ring that may optionally include an additional heteroatom selected from O, N and S, and which may be optionally substituted with oxo, halo or C_{1-6}alkyl.

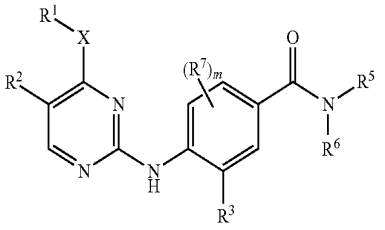
[0123] In certain embodiments of formula I, R^1 and R^a together with the atoms to which they are attached form a five or six membered ring.

[0124] In certain embodiments of formula I, R^1 and R^a together with the atoms to which they are attached form a pyrolidinyl, piperidinyl or oxazoladinonyl group.

[0125] In certain embodiments of formula I, R^2 is acetyl.

[0126] In certain embodiments the subject compounds are of formula II:

II

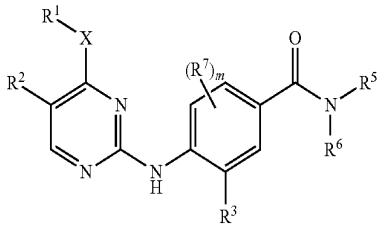


or pharmaceutically acceptable salts thereof,

wherein X, m, R^1, R^2, R^3, R^5 and R^7 are as defined in formula I.

[0127] In certain embodiments the subject compounds are of formula II:

II



or pharmaceutically acceptable salts thereof,

wherein:

[0128] m is from 0 to 3;

[0129] X is: —NR^a—; —O—; or —$S(O)_r$— wherein r is from 0 to 2 and R^a is hydrogen or C_{1-6}alkyl;

[0130] R^1 is: C_{1-6}alkyl; C_{2-6}alkenyl; C_{2-6}alkynyl; halo-C_{1-6}alkyl; C_{1-6}alkoxy-C_{1-6}alkyl; hydroxy-C_{1-6}alkyl; amino-C_{1-6}alkyl; C_{1-6}alkylsulfonyl-C_{1-6}alkyl; C_{3-6}cycloalkyl optionally substituted with C_{1-6}alkyl; C_{3-6}cycloalkyl-C_{1-6}alkyl wherein the C_{3-6}cycloalkyl portion is optionally substituted with C_{1-6}alkyl; tetrahydrofuranyl; tetrahydrofuranyl-C_{1-6}alkyl; oxetanyl; or oxetan-C_{1-6}alkyl;

[0131] R^2 is: halo; C_{1-6}alkoxy; cyano; C_{2-6}alkynyl; C_{2-6}alkenyl; halo-C_{1-6}alkyl; halo-C_{1-6}alkoxy; C_{3-6}cycloalkyl wherein the C_{3-6}cycloalkyl portion is optionally substituted with C_{1-6}alkyl; C_{3-6}cycloalkyl-C_{1-6}alkyl wherein the C_{3-6}cycloalkyl portion is optionally substituted with C_{1-6}alkyl; tetrahydrofuranyl; tetrahydrofuranyl-C_{1-6}alkyl; oxetanyl; or oxetan-C_{1-6}alkyl;

[0132] R^3 is: —OR^4; halo; cyano; C_{3-6}cycloalkyl optionally substituted with C_{1-6}alkyl; C_{3-6}cycloalkyl-C_{1-6}alkyl wherein the C_{3-6}cycloalkyl portion is optionally substituted with C_{1-6}alkyl; tetrahydrofuranyl; tetrahydrofuranyl-C_{1-6}alkyl; oxetanyl; or oxetan-C_{1-6}alkyl;

[0133] R^4 is: C_{1-6}alkyl; halo-C_{1-6}alkyl; C_{1-6}alkoxy-C_{1-6}alkyl; C_{3-6}cycloalkyl optionally substituted with C_{1-6}alkyl; C_{3-6}cycloalkyl-C_{1-6}alkyl wherein the C_{3-6}cycloalkyl portion is optionally substituted with C_{1-6}alkyl; tetrahydrofuranyl; tetrahydrofuranyl-C_{1-6}alkyl; oxetanyl; or oxetan-C_{1-6}alkyl;

[0134] R^5 is: hydrogen; or C_{1-6}alkyl;

[0135] R^6 is: hydrogen; C_{1-6}alkyl; C_{1-6}alkoxy-C_{1-6}alkyl; amino-C_{1-6}alkyl; C_{3-6}cycloalkyl; C_{3-6}cycloalkyl-C_{1-6}alkyl; heterocyclyl; or heterocyclyl-C_{1-6}alkyl; wherein the C_{3-6}cycloalkyl, C_{3-6}cycloalkyl-C_{1-6}alkyl, heterocyclyl and heterocyclyl-C_{1-6}alkyl each may be optionally substituted with one, two or three groups independently selected from: C_{1-6}alkyl; halo-C_{1-6}alkyl; C_{1-6}alkoxy; halo-C_{1-6}alkoxy; hydroxy; hydroxy-C_{1-6}alkyl; halo; nitrile; C_{1-6}alkyl-carbonyl; C_{1-6}alkyl-sulfonyl; C_{3-6}cycloalkyl; C_{3-6}cycloalkyl-C_{1-6}alkyl; C_{3-6}cycloalkyl-carbonyl; amino; or heterocyclyl; or two of the groups together with the atoms to which they are attached may form a five or six-membered ring;

[0136] or R^5 and R^6 together with the nitrogen atom to which they are attached form a three- to seven-membered ring that optionally includes an additional heteroatom selected from O, N and $S(O)_n$, and which is optionally substituted with one, two or three groups independently selected from: C_{1-6}alkyl; halo-C_{1-6}alkyl; C_{1-6}alkoxy; halo-C_{1-6}alkoxy; hydroxy; hydroxy-C_{1-6}alkyl; halo, nitrile; C_{1-6}alkyl-carbonyl; C_{1-6}alkyl-sulfonyl; C_{3-6}cycloalkyl; C_{3-6}cycloalkyl-C_{1-6}alkyl; C_{3-6}cycloalkyl-carbonyl; amino; or heterocyclyl; or

two of the groups together with the atoms to which they are attached may form a five or six-membered ring; and

[0137] R^7 is: halo; C_{1-6}alkyl; C_{1-6}alkoxy; halo-C_{1-6}alkyl; or halo-C_{1-6}alkoxy.

[0138] In certain embodiments of formula I, when R^1 is C_{3-6}cycloalkyl or C_{3-6}cycloalkyl-C_{1-6}alkyl, then X is —O—.

[0139] In certain embodiments of formula I, when R^1 is cyclopropyl, cyclobutyl, cyclopropyl-C_{1-6}alkyl or cyclobutyl-C_{1-6}alkyl, then X is —O—.

[0140] In certain embodiments of formula I or formula II, m is from 0 to 2.

[0141] In certain embodiments of formula I or formula II, m is 0 or 1.

[0142] In certain embodiments of formula I or formula II, m is 0.

[0143] In certain embodiments of formula I or formula II, m is 1.

[0144] In certain embodiments of formula I or formula II, r is 0.

[0145] In certain embodiments of formula I or formula II, r is 2.

[0146] In certain embodiments of formula I or formula II, X is —NR^a— or —O—.

[0147] In certain embodiments of formula I or formula II, X is —NR^a.

[0148] In certain embodiments of formula I or formula II, X is —O—.

[0149] In certain embodiments of formula I or formula II, X is —$S(O)_n$—.

[0150] In certain embodiments of formula I or formula II, X is —NH— or —O—.

[0151] In certain embodiments of formula I or formula II, R^a is hydrogen.

[0152] In certain embodiments of formula I or formula II, R^a is C_{1-6}alkyl.

[0153] In certain embodiments of formula I or formula II, R^1 is: C_{1-6}alkyl; halo-C_{1-6}alkyl; C_{1-6}alkoxy-C_{1-6}alkyl; amino-C_{1-6}alkyl; C_{1-6}alkylsulfonyl-C_{1-6}alkyl; C_{3-6}cycloalkyl; or C_{3-6}cycloalkyl-C_{1-6}alkyl.

[0154] In certain embodiments of formula I or formula II, R^1 is: C_{1-6}alkyl; C_{3-6}cycloalkyl optionally substituted with C_{1-6}alkyl; or C_{3-6}cycloalkyl-C_{1-6}alkyl wherein the C_{3-6}cycloalkyl portion is optionally substituted with C_{1-6}alkyl.

[0155] In certain embodiments of formula I or formula II, R^1 is: C_{1-6}alkyl; halo-C_{1-6}alkyl; C_{1-6}alkoxy-C_{1-6}alkyl; amino-C_{1-6}alkyl; C_{1-6}alkylsulfonyl-C_{1-6}alkyl; tetrahydrofuranyl; tetrahydrofuranyl-C_{1-6}alkyl; oxetanyl; or oxetan-C_{1-6}alkyl.

[0156] In certain embodiments of formula I or formula II, R^1 is: C_{1-6}alkyl; halo-C_{1-6}alkyl; C_{1-6}alkoxy-C_{1-6}alkyl; amino-C_{1-6}alkyl; or C_{1-6}alkylsulfonyl-C_{1-6}alkyl.

[0157] In certain embodiments of formula I or formula II, R^1 is C_{1-6}alkyl.

[0158] In certain embodiments of formula I or formula II, R^1 is halo-C_{1-6}alkyl.

[0159] In certain embodiments of formula I or formula II, R^1 is C_{1-6}alkoxy-C_{1-6}alkyl.

[0160] In certain embodiments of formula I or formula II, R^1 is amino-C_{1-6}alkyl.

[0161] In certain embodiments of formula I or formula II, R^1 is C_{1-6}alkylsulfonyl-C_{1-6}alkyl optionally substituted with C_{1-6}alkyl.

[0162] In certain embodiments of formula I or formula II, R^1 is C_{3-6}cycloalkyl optionally substituted with C_{1-6}alkyl.

[0163] In certain embodiments of formula I or formula II, R^1 is C_{3-6}cycloalkyl-C_{1-6}alkyl wherein the C_{3-6}cycloalkyl portion is optionally substituted with C_{1-6}alkyl.

[0164] In certain embodiments of formula I or formula II, R^1 is tetrahydropyranyl.

[0165] In certain embodiments of formula I or formula II, R^1 is tetrahydrofuranyl.

[0166] In certain embodiments of formula I or formula II, R^1 is tetrahydrofuranyl-C_{1-6}alkyl; oxetanyl.

[0167] In certain embodiments of formula I or formula II, R^1 is or oxetan-C_{1-6}alkyl.

[0168] In certain embodiments of formula I or formula II, R^1 is: methyl; ethyl; n-propyl; isopropyl; isobutyl; 3,3-dimethylpropyl; cyclopropyl; cyclobutyl; cyclopentyl; cyclohexyl; cyclopropylmethyl; cyclobutylmethyl; cyclopentylmethyl; cyclopropylethyl; methoxyethyl; oxetanyl; or tetrahydrofuranylmethyl.

[0169] In certain embodiments of formula I or formula II, R^1 is: methyl; ethyl; n-propyl; isopropyl; isobutyl; 3,3-dimethylpropyl; cyclopentyl; cyclohexyl; cyclopropylmethyl; cyclobutylmethyl; cyclopentylmethyl; cyclopropylethyl; methoxyethyl; oxetanyl; or tetrahydrofuranylmethyl.

[0170] In certain embodiments of formula I or formula II, R^1 is: methyl; ethyl; n-propyl; isopropyl; isobutyl; 3,3-dimethylpropyl; cyclopentyl; cyclohexyl; cyclopentylmethyl; methoxyethyl; oxetanyl; or tetrahydrofuranylmethyl.

[0171] In certain embodiments of formula I or formula II, R^1 is: methyl; ethyl; n-propyl; isopropyl; or isobutyl.

[0172] In certain embodiments of formula I or formula II, R^1 is methyl or ethyl.

[0173] In certain embodiments of formula I or formula II, R^1 is methyl.

[0174] In certain embodiments of formula I or formula II, R^1 is ethyl.

[0175] In certain embodiments of formula I or formula II, R^1 is: cyclopropyl; cyclobutyl; cyclopentyl; cyclohexyl; cyclopropylmethyl; cyclobutylmethyl; cyclopentylmethyl; or cyclopropylethyl.

[0176] In certain embodiments of formula I or formula II, R^1 is: cyclopentyl; cyclohexyl; or cyclopentylmethyl.

[0177] In certain embodiments of formula I or formula II, R^2 is: halo; C_{1-6}alkoxy; halo-C_{1-6}alkyl; halo-C_{1-6}alkoxy; C_{3-6}cycloalkyl wherein the C_{3-6}cycloalkyl portion is optionally substituted with C_{1-6}alkyl; C_{3-6}cycloalkyl-C_{1-6}alkyl wherein the C_{3-6}cycloalkyl portion is optionally substituted with C_{1-6}alkyl; tetrahydrofuranyl; tetrahydrofuranyl-C_{1-6}alkyl; oxetanyl; or oxetan-C_{1-6}alkyl.

[0178] In certain embodiments of formula I or formula II, R^2 is: halo; C_{1-6}alkoxy; halo-C_{1-6}alkyl; cyano; C_{2-6}alkynyl; C_{2-6}alkenyl; C_{3-6}cycloalkyl; or C_{3-6}cycloalkyl-C_{1-6}alkyl.

[0179] In certain embodiments of formula I or formula II, R^2 is: halo; C_{1-6}alkoxy; halo-C_{1-6}alkyl; cyano; C_{3-6}cycloalkyl; or C_{3-6}cycloalkyl-C_{1-6}alkyl.

[0180] In certain embodiments of formula I or formula II, R^2 is: halo; C_{1-6}alkoxy; halo-C_{1-6}alkyl; C_{3-6}cycloalkyl; or C_{3-6}cycloalkyl-C_{1-6}alkyl.

[0181] In certain embodiments of formula I or formula II, R^2 is: halo; halo-C_{1-6}alkyl; or cyano.

[0182] In certain embodiments of formula I or formula II, R^2 is: halo; or halo-C_{1-6}alkyl.

[0183] In certain embodiments of formula I or formula II, R^2 is halo.

[0184] In certain embodiments of formula I or formula II, R^2 is C_{1-6}alkoxy.

[0185] In certain embodiments of formula I or formula II, R^2 is halo-C_{1-6}alkoxy.

[0186] In certain embodiments of formula I or formula II, R^2 is halo-C_{1-6}alkyl.

[0187] In certain embodiments of formula I or formula II, R^2 is C_{3-6}cycloalkyl.

[0188] In certain embodiments of formula I or formula II, R^2 is C_{3-6}cycloalkyl-C_{1-6}alkyl.

[0189] In certain embodiments of formula I or formula II, R^2 is tetrahydrofuranyl.

[0190] In certain embodiments of formula I or formula II, R^2 is tetrahydrofuranyl-C_{1-6}alkyl.

[0191] In certain embodiments of formula I or formula II, R^2 is oxetanyl.

[0192] In certain embodiments of formula I or formula II, R^2 is oxetan-C_{1-6}alkyl.

[0193] In certain embodiments of formula I or formula II, R^2 is halo, trifluoromethyl or cyano.

[0194] In certain embodiments of formula I or formula II, R^2 is chloro, trifluoromethyl or cyano.

[0195] In certain embodiments of formula I or formula II, R^2 is fluoro, chloro or bromo.

[0196] In certain embodiments of formula I or formula II, R^2 is chloro.

[0197] In certain embodiments of formula I or formula II, R^2 is fluoro.

[0198] In certain embodiments of formula I or formula II, R^2 is bromo.

[0199] In certain embodiments of formula I or formula II, R^2 is trifluoromethyl.

[0200] In certain embodiments of formula I or formula II, R^2 is methoxy.

[0201] In certain embodiments of formula I or formula II, R^2 is cyano.

[0202] In certain embodiments of formula I or formula II, R^2 is C_{2-6}alkynyl.

[0203] In certain embodiments of formula I or formula II, R^2 is C_{2-6}alkenyl.

[0204] In certain embodiments of formula I or formula II, R^3 is —OR^4.

[0205] In certain embodiments of formula I or formula II, R^3 is: C_{1-6}alkyl; or halo-C_{1-6}alkyl.

[0206] In certain embodiments of formula I or formula II, R^3 is: halo; or —OR^4.

[0207] In certain embodiments of formula I or formula II, R^3 is: halo; C_{1-6}alkoxy; halo-C_{1-6}alkoxy; C_{3-6}cycloalkyloxy; or C_{3-6}cycloalkyl-C_{1-6}alkyloxy.

[0208] In certain embodiments of formula I or formula II, R^3 is: C_{1-6}alkoxy; halo-C_{1-6}alkoxy; C_{3-6}cycloalkyloxy; or C_{3-6}cycloalkyl-C_{1-6}alkyloxy.

[0209] In certain embodiments of formula I or formula II, R^3 is: halo; C_{1-6}alkoxy; cyano; or halo-C_{1-6}alkoxy.

[0210] In certain embodiments of formula I or formula II, R^3 is: halo; C_{1-6}alkoxy; or halo-C_{1-6}alkoxy.

[0211] In certain embodiments of formula I or formula II, R^3 is: methoxy; halo; trifluoromethoxy; difluoromethoxy; 2-halo-ethoxy or 2,2,2-trihaloethoxy.

[0212] In certain embodiments of formula I or formula II, R^3 is: methoxy; or halo.

[0213] In certain embodiments of formula I or formula II, R^3 is: methoxy; chloro; or fluoro.

[0214] In certain embodiments of formula I or formula II, R^3 is methoxy.

[0215] In certain embodiments of formula I or formula II, R^3 is chloro.

[0216] In certain embodiments of formula I or formula II, R^3 is fluoro.

[0217] In certain embodiments of formula I or formula II, R^3 is: C_{1-6}alkoxy; cyano; or halo-C_{1-6}alkoxy.

[0218] In certain embodiments of formula I or formula II, R^3 is: C_{1-6}alkoxy; or halo-C_{1-6}alkoxy.

[0219] In certain embodiments of formula I or formula II, R^3 is C_{1-6}alkoxy.

[0220] In certain embodiments of formula I or formula II, R^3 is methoxy.

[0221] In certain embodiments of formula I or formula II, R^3 is cyano.

[0222] In certain embodiments of formula I or formula II, R^3 is C_{3-6}cycloalkyl.

[0223] In certain embodiments of formula I or formula II, R^3 is C_{3-6}cycloalkyl-C_{1-6}alkyl.

[0224] In certain embodiments of formula I or formula II, R^3 is tetrahydrofuranyl. In certain embodiments of formula I or formula II, R^3 is tetrahydrofuranyl-C_{1-6}alkyl.

[0225] In certain embodiments of formula I or formula II, R^3 is oxetanyl.

[0226] In certain embodiments of formula I or formula II, R^3 is oxetan-C_{1-6}alkyl.

[0227] In certain embodiments of formula I or formula II, R^4 is: C_{1-6}alkyl; halo-C_{1-6}alkyl; C_{1-6}alkoxy-C_{1-6}alkyl; C_{3-6}cycloalkyl optionally substituted with C_{1-6}alkyl; C_{3-6}cycloalkyl-C_{1-6}alkyl wherein the C_{3-6}cycloalkyl portion is optionally substituted with C_{1-6}alkyl; tetrahydrofuranyl; tetrahydrofuranyl-C_{1-6}alkyl; oxetanyl; or oxetan-C_{1-6}alkyl;

[0228] In certain embodiments of formula I or formula II, R^4 is: C_{1-6}alkyl; halo-C_{1-6}alkyl; C_{1-6}alkoxy-C_{1-6}alkyl; C_{3-6}cycloalkyl; or C_{3-6}cycloalkyl-C_{1-6}alkyl.

[0229] In certain embodiments of formula I or formula II, R^4 is: C_{1-6}alkyl; halo-C_{1-6}alkyl; or C_{3-6}cycloalkyl.

[0230] In certain embodiments of formula I or formula II, R^4 is C_{1-6}alkyl.

[0231] In certain embodiments of formula I or formula II, R^4 is halo-C_{1-6}alkyl.

[0232] In certain embodiments of formula I or formula II, R^4 is C_{1-6}alkoxy-C_{1-6}alkyl.

[0233] In certain embodiments of formula I or formula II, R^4 is C_{3-6}cycloalkyl.

[0234] In certain embodiments of formula I or formula II, R^4 is C_{3-6}cycloalkyl-C_{1-6}alkyl.

[0235] In certain embodiments of formula I or formula II, R^4 is tetrahydrofuranyl.

[0236] In certain embodiments of formula I or formula II, R^4 is tetrahydrofuranyl-C_{1-6}alkyl.

[0237] In certain embodiments of formula I or formula II, R^4 is oxetanyl.

[0238] In certain embodiments of formula I or formula II, R^4 is or oxetan-C_{1-6}alkyl.

[0239] In certain embodiments of formula I or formula II, R^4 is: methyl; ethyl; isopropyl; cyclopropyl; cyclobutyl; cyclopropylmethyl; cyclobutylmethyl; 2-haloethyl; or 2,2,2-trihaloethyl.

[0240] In certain embodiments of formula I or formula II, R^4 is methyl.

[0241] In certain embodiments of formula I or formula II, R^5 is hydrogen.

[0242] In certain embodiments of formula I or formula II, R^5 is C_{1-6}alkyl.

[0243] In certain embodiments of formula I or formula II, R^5 is methyl.

[0244] In certain embodiments of formula I or formula II, R^5 is ethyl.

[0245] In certain embodiments of formula I or formula II, R^6 is hydrogen.

[0246] In certain embodiments of formula I or formula II, R^6 is C_{1-6}alkyl.

[0247] In certain embodiments of formula I or formula II, R^6 is C_{1-6}alkoxy-C_{1-6}alkyl.

[0248] In certain embodiments of formula I or formula II, R^6 is hydroxy-C_{1-6}alkyl.

[0249] In certain embodiments of formula I or formula II, R^6 is amino-C_{1-6}alkyl.

[0250] In certain embodiments of formula I or formula II, R^6 is C_{3-6}cycloalkyl optionally substituted with one, two or three groups independently selected from: C_{1-6}alkyl; halo-C_{1-6}alkyl; C_{1-6}alkoxy; halo-C_{1-6}alkoxy; hydroxy; hydroxy-C_{1-6}alkyl; halo; nitrile; C_{1-6}alkyl-carbonyl; C_{1-6}alkyl-sulfonyl; C_{3-6}cycloalkyl; C_{3-6}cycloalkyl-C_{1-6}alkyl; C_{3-6}cycloalkyl-carbonyl; amino; or heterocyclyl; or two of the groups together with the atoms to which they are attached may form a five or six-membered ring.

[0251] In certain embodiments of formula I or formula II, R^6 is C_{3-6}cycloalkyl-C_{1-6}alkyl wherein the C_{3-6}cycloalkyl portion thereof is optionally substituted with one, two or three groups independently selected from: C_{1-6}alkyl; halo-C_{1-6}alkyl; C_{1-6}alkoxy; halo-C_{1-6}alkoxy; hydroxy; hydroxy-C_{1-6}alkyl; halo; nitrile; C_{1-6}alkyl-carbonyl; C_{1-6}alkyl-sulfonyl; C_{3-6}cycloalkyl; C_{3-6}cycloalkyl-C_{1-6}alkyl; C_{3-6}cycloalkyl-carbonyl; amino; or heterocyclyl; or two of the groups together with the atoms to which they are attached may form a five or six-membered ring.

[0252] In embodiments of formula I or formula II wherein R^6 is heterocyclyl, such heterocycle may be: azetidinyl; pyrrolidinyl; piperidinyl; piperazinyl; morpholinyl; thiomorpholinyl; 3-oxa-8-aza-bicyclo[3.2.1]oct-8-yl; 2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl; or 8-oxa-3-aza-bicyclo[3.2.1]oct-3-yl; each optionally substituted as defined herein.

[0253] In embodiments of formula I or formula II wherein R^6 is heterocyclyl, such heterocycle may be: azetidinyl; pyrrolidinyl; piperidinyl; piperazinyl; or morpholinyl; each optionally substituted as defined herein, i.e., such heterocycyl is optionally substituted with one, two or three groups independently selected from: C_{1-6}alkyl; halo-C_{1-6}alkyl; C_{1-6}alkoxy; halo-C_{1-6}alkoxy; hydroxy; hydroxy-C_{1-6}alkyl; halo; nitrile; C_{1-6}alkyl-carbonyl; C_{1-6}alkyl-sulfonyl; C_{3-6}cycloalkyl; C_{3-6}cycloalkyl-C_{1-6}alkyl; C_{3-6}cycloalkyl-carbonyl; amino; or heterocyclyl; or two of the groups together with the atoms to which they are attached may form a five or six-membered ring.

[0254] In certain embodiments of formula I or formula II, R^6 is heterocyclyl optionally substituted with one, two or three groups independently selected from: C_{1-6}alkyl; halo-C_{1-6}alkyl; C_{1-6}alkoxy; halo-C_{1-6}alkoxy; hydroxy; hydroxy-C_{1-6}alkyl; halo; nitrile; C_{1-6}alkyl-carbonyl; C_{1-6}alkyl-sulfonyl; C_{3-6}cycloalkyl; C_{3-6}cycloalkyl-C_{1-6}alkyl; C_{3-6}cycloalkyl-carbonyl; amino; or heterocyclyl; or two of the groups together with the atoms to which they are attached may form a five or six-membered ring.

[0255] In embodiments of formula I or formula II wherein R^6 is heterocyclyl-C_{1-6}alkyl, the heterocyclyl portion thereof may be: azetidinyl; pyrrolidinyl; piperidinyl; piperazinyl; morpholinyl; thiomorpholinyl; 3-oxa-8-aza-bicyclo[3.2.1]oct-8-yl; 2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl; or 8-oxa-3-aza-bicyclo[3.2.1]oct-3-yl; each optionally substituted as defined herein, i.e., such heterocycyl portion is optionally substituted with one, two or three groups independently selected from: C_{1-6}alkyl; halo-C_{1-6}alkyl; C_{1-6}alkoxy; halo-C_{1-6}alkoxy; hydroxy; hydroxy-C_{1-6}alkyl; halo; nitrile; C_{1-6}alkyl-carbonyl; C_{1-6}alkyl-sulfonyl; C_{3-6}cycloalkyl; C_{3-6}cycloalkyl-C_{1-6}alkyl; C_{3-6}cycloalkyl-carbonyl; amino; or heterocyclyl; or two of the groups together with the atoms to which they are attached may form a five or six-membered ring.

[0256] In embodiments of formula I or formula II wherein R^6 is heterocyclyl-C_{1-6}alkyl, the heterocyclyl portion thereof may be: azetidinyl; pyrrolidinyl; piperidinyl; piperazinyl; or morpholinyl; each optionally substituted as defined herein.

[0257] In certain embodiments of formula I or formula II, R^6 is heterocyclyl-C_{1-6}alkyl wherein the heterocyclyl portion thereof is optionally substituted with one, two or three groups independently selected from: C_{1-6}alkyl; halo-C_{1-6}alkyl; C_{1-6}alkoxy; halo-C_{1-6}alkoxy; hydroxy; hydroxy-C_{1-6}alkyl; halo; nitrile; C_{1-6}alkyl-carbonyl; C_{1-6}alkyl-sulfonyl; C_{3-6}cycloalkyl; C_{3-6}cycloalkyl-C_{1-6}alkyl; C_{3-6}cycloalkyl-carbonyl; amino; or heterocyclyl; or two of the groups together with the atoms to which they are attached may form a five or six-membered ring.

[0258] In certain embodiments of formula I or formula II, R^6 is: hydrogen; methyl; ethyl; isopropyl; or cyclopropyl.

[0259] In certain embodiments of formula I or formula II, R^6 is: hydrogen; methyl; ethyl; isopropyl;2-amino-propyl; oxetan-3-yl; 2-methoxy-ethyl; 2-hydroxy-ethyl; cyclopropyl; piperidin-4-yl; 1-methyl-piperidin-4-yl; tert-butl; 2-hydroxy-2-methyl-propyl; cyclobutyl; 1-methyl-cyclobutyl; 2-hydroxy-propyl; 1-cyano-cyclopropyl; 3,3-difluoro-cyclobutyl; cyclopropylmethyl; 3-fluoro-cyclobutyl; or 2,2-difluoroethyl;

[0260] In certain embodiments of formula I or formula II, R^6 is hydrogen.

[0261] In certain embodiments of formula I or formula II, R^6 is methyl.

[0262] In certain embodiments of formula I or formula II, R^6 is ethyl.

[0263] In certain embodiments of formula I or formula II, R^6 is isopropyl.

[0264] In certain embodiments of formula I or formula II, R^6 is 2-amino-propyl.

[0265] In certain embodiments of formula I or formula II, R^6 is oxetan-3-yl.

[0266] In certain embodiments of formula I or formula II, R^6 is 2-methoxy-ethyl.

[0267] In certain embodiments of formula I or formula II, R^6 is 2-hydroxy-ethyl.

[0268] In certain embodiments of formula I or formula II, R^6 is cyclopropyl.

[0269] In certain embodiments of formula I or formula II, R^6 is piperidin-4-yl.

[0270] In certain embodiments of formula I or formula II, R^6 is 1-methyl-piperidin-4-yl.

[0271] In certain embodiments of formula I or formula II, R^6 is tert-butl.

[0272] In certain embodiments of formula I or formula II, R^6 is 2-hydroxy-2-methyl-propyl.

[0273] In certain embodiments of formula I or formula II, R^6 is cyclobutyl.

[0274] In certain embodiments of formula I or formula II, R^6 is 1-methyl-cyclobutyl.

[0275] In certain embodiments of formula I or formula II, R^6 is 2-hydroxy-propyl.

[0276] In certain embodiments of formula I or formula II, R^6 is 1-cyano-cyclopropyl.

[0277] In certain embodiments of formula I or formula II, R^6 is 3,3-difluoro-cyclobutyl.

[0278] In certain embodiments of formula I or formula II, R^6 is cyclopropylmethyl.

[0279] In certain embodiments of formula I or formula II, R^6 is 3-fluoro-cyclobutyl.

[0280] In certain embodiments of formula I or formula II, R^6 is 2,2-difluoroethyl.

[0281] In certain embodiments of formula I or formula II, R^5 and R^6 together with the nitrogen atom to which they are attached form a three- to seven-membered ring that is optionally includes an additional heteroatom selected from O, N and $S(O)_n$, and which is optionally substituted with one, two or three groups independently selected from C_{1-6}alkyl, halo-C_{1-6}alkyl, C_{1-6}alkoxy, halo-C_{1-6}alkoxy, hydroxy, hydroxy-C_{1-6}alkyl, halo, nitrile, C_{1-6}alkyl-carbonyl, C_{1-6}alkyl-sulfonyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkyl-C_{1-6}alkyl, C_{3-6}cycloalkyl-carbonyl, or heterocyclyl, or two of the groups together with the atoms to which they are attached may form a five or six-membered ring.

[0282] In embodiments of formula I or formula II wherein R^5 and R^6 together with the nitrogen atom to which they are attached form a three- to seven-membered ring that is optionally includes an additional heteroatom selected from O, N and $S(O)_n$, such ring may be: azetidinyl; pyrrolidinyl; piperidinyl; piperazinyl; morpholinyl; thiomorpholinyl; azepinyl; 3-oxa-8-aza-bicyclo[3.2.1]oct-8-yl; 2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl; or 8-oxa-3-aza-bicyclo[3.2.1]oct-3-yl; each optionally substituted as defined herein.

[0283] In embodiments of formula I or formula II wherein R^5 and R^6 together with the nitrogen atom to which they are attached form a three- to seven-membered ring that is optionally includes an additional heteroatom selected from O, N and $S(O)_n$, such ring may be: azetidinyl; pyrrolidinyl; piperidinyl; piperazinyl; or morpholinyl; each optionally substituted as defined herein.

[0284] In certain embodiments of formula I or formula II, R^5 and R^6 together with the nitrogen atom to which they are attached form a morpholinyl group that is optionally substituted once or twice with groups independently selected from C_{1-6}alkyl, halo-C_{1-6}alkyl, C_{1-6}alkoxy, halo-C_{1-6}alkoxy, hydroxy, hydroxy-C_{1-6}alkyl, halo, nitrile, C_{1-6}alkyl-carbonyl, C_{1-6}alkyl-sulfonyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkyl-C_{1-6}alkyl, C_{3-6}cycloalkyl-carbonyl, amino, or heterocyclyl, or the two groups together with the atoms to which they are attached may form a five or six-membered ring.

[0285] In certain embodiments of formula I or formula II, R^5 and R^6 together with the nitrogen atom to which they are attached form a piperidinyl group that is optionally substituted once or twice with groups independently selected from C_{1-6}alkyl, halo-C_{1-6}alkyl, C_{1-6}alkoxy, halo-C_{1-6}alkoxy, hydroxy, hydroxy-C_{1-6}alkyl, halo, nitrile, C_{1-6}alkyl-carbonyl, C_{1-6}alkyl-sulfonyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkyl-C_{1-6}alkyl, C_{3-6}cycloalkyl-carbonyl, amino, or heterocyclyl, or the two groups together with the atoms to which they are attached may form a five or six-membered ring.

[0286] In certain embodiments of formula I or formula II, R^5 and R^6 together with the nitrogen atom to which they are attached form a piperazinyl group that is optionally substituted once or twice with groups independently selected from C_{1-6}alkyl, halo-C_{1-6}alkyl, C_{1-6}alkoxy, halo-C_{1-6}alkoxy, hydroxy, hydroxy-C_{1-6}alkyl, halo, nitrile, C_{1-6}alkyl-carbonyl, C_{1-6}alkyl-sulfonyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkyl-C_{1-6}alkyl, C_{3-6}cycloalkyl-carbonyl, amino, or heterocyclyl, or the two groups together with the atoms to which they are attached may form a five or six-membered ring.

[0287] In certain embodiments of formula I or formula II, R^5 and R^6 together with the nitrogen atom to which they are attached form a pyrrolidinyl group that is optionally substituted once or twice with groups independently selected from C_{1-6}alkyl, halo-C_{1-6}alkyl, C_{1-6}alkoxy, halo-C_{1-6}alkoxy, hydroxy, hydroxy-C_{1-6}alkyl, halo, nitrile, C_{1-6}alkyl-carbonyl, C_{1-6}alkyl-sulfonyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkyl-C_{1-6}alkyl, C_{3-6}cycloalkyl-carbonyl, amino, or heterocyclyl, or the two groups together with the atoms to which they are attached may form a five or six-membered ring.

[0288] In certain embodiments of formula I or formula II, R^a and R^6 together with the nitrogen atom to which they are attached form a group selected from: morpholin-4-yl; 4-hydroxy-piperidin-1-yl; octahydro-pyrido[1,2-a]pyrazin-2-yl; 2-hydroxy-piperidin-1-yl; 4,4-dimethyl-piperidin-1-yl; 3,5-dimethyl-piperidin-1-yl; 1-hydroxy-1-methyl-ethyl)-piperidin-1-yl; 3-hydroxy-pyrrolidin-1-yl; 4-methyl-piperidin-1-yl; piperidin-1-yl; azetidin-1-yl; 4,4-difluoro-piperidin-1-yl; 3-methyl-piperidin-1-yl; 4-methoxy-piperidin-1-yl; 3,3-difluoro-piperidin-1-yl; 4-cyano-piperidin-1-yl; 4-fluoro-piperidin-1-yl; 3-methoxy-piperidin-1-yl; 4-ethyl-piperazin-1-yl; 4-acetyl-piperazin-1-yl; 3-trifluoromethyl-piperidin-1-yl; 4-tert-butyl-piperidin-1-yl; 2-hydroxy-ethyl)-piperazin-1-yl; 2-methyl-pyrrolidin-1-yl; 4-hydroxymethyl-piperidin-1-yl; 2-methyl-piperidin-1-yl; pyrrolidin-1-yl; 4-methanesulfonyl-piperazin-1-yl; 3-trifluoromethyl-pyrrolidin-1-yl; 4-(2,2,2-trifluoro-ethyl)-piperazin-1-yl; 2-methyl-morpholin-4-yl; (2,6-dimethyl-morpholin-4-yl; 2,2-diethyl-morpholin-4-yl; 3-hydroxymethyl-morpholin-4-yl; 2-isobutyl-morpholin-4-yl; 2-hydroxymethyl-morpholin-4-yl; 3,3-dimethyl-morpholin-4-yl; 4-methyl-piperazin-1-yl; 4-isopropyl-piperazin-1-yl; piperazin-1-yl; 3-oxa-8-aza-bicyclo[3.2.1]oct-8-yl; (S)-3-methyl-morpholin-4-yl; 2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl; 8-oxa-3-aza-bicyclo[3.2.1]oct-3-yl; (R)-3-methyl-morpholin-4-yl; 4-cyclopropanecarbonyl-piperazin-1-yl; 4-(1-hydroxy-1-methyl-ethyl)-piperidin-1-yl; 4-cyclobutyl-piperazin-1-yl; (R)-3-hydroxy-pyrrolidin-1-yl; 4-oxetan-3-yl-piperazin-1-yl; 3-morpholin-4-yl-azetidin-1-yl; 4-(1-methyl-piperidin-4-yl)-piperazin-1-yl; 3,3-difluoro-azetidin-1-yl; 4-dimethylamino-piperidin-1-yl; 4-piperidin-4-yl-piperazin-1-yl; (4,4-difluoro-piperidin-1-yl; (3-morpholin-4-yl-azetidin-1-yl; 2-oxa-6-aza-spiro[3.3]hept-6-yl; 2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl); 4-methoxy-piperidin-1-yl); [1,4]oxazepan-4-yl; 2R,6-dimethyl-morpholin-4-yl; 3-hydroxy-azetidin-1-yl; 3-cyano-pyrrolidin-1-yl; 3,5-dimethyl-piperazin-1-yl; (3R,5S)-dimethyl-piperazin-1-yl; 3-Fluoro-pyrrolidin-1-yl; (S)-3-Fluoro-pyrrolidin-1-yl; piperazin-1-yl; 3,3-Difluoro-pyrrolidin-1-yl; 3,3-Difluoro-azetidin-1-yl; 2,2,6,6-tetrafluoro-morpholin-4-yl; 2-methoxymethyl-pyrrolidin-1-yl; (S)-2-methoxymethyl-pyrrolidin-1-yl; (1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl; (3S,4S)-3,4-difluoro-pyrrolidin-1-yl; 3,4-difluoropyrrolidin-1-yl; and 3-methoxypyrrolidin-1-yl.

[0289] In certain embodiments of formula I or formula II, R^5 and R^6 together with the nitrogen atom to which they are attached form a group selected from: morpholin-4-yl; 4-hy-

droxy-piperidin-1-yl; octahydro-pyrido[1,2-a]pyrazin-2-yl; 2-hydroxy-piperidin-1-yl; 4,4-dimethyl-piperidin-1-yl; 3,5-dimethyl-piperidin-1-yl; 1-hydroxy-1-methyl-ethyl)-piperidin-1-yl; 3-hydroxy-pyrrolidin-1-yl; 4-methyl-piperidin-1-yl; piperidin-1-yl; azetidin-1-yl; 4,4-difluoro-piperidin-1-yl; 3-methyl-piperidin-1-yl; 4-methoxy-piperidin-1-yl; 3,3-difluoro-piperidin-1-yl; 4-cyano-piperidin-1-yl; 4-fluoro-piperidin-1-yl; 3-methoxy-piperidin-1-yl; 4-ethyl-piperazin-1-yl; 4-acetyl-piperazin-1-yl; 3-trifluoromethyl-piperidin-1-yl; 4-tert-butyl-piperidin-1-yl; 2-hydroxy-ethyl)-piperazin-1-yl; 2-methyl-pyrrolidin-1-yl; 4-hydroxymethyl-piperidin-1-yl; 2-methyl-piperidin-1-yl; pyrrolidin-1-yl; 4-methanesulfonyl-piperazin-1-yl; 3-trifluoromethyl-pyrrolidin-1-yl; 4-(2,2,2-trifluoro-ethyl)-piperazin-1-yl; 2-methyl-morpholin-4-yl; (2,6-dimethyl-morpholin-4-yl; 2,2-diethyl-morpholin-4-yl; 3-hydroxymethyl-morpholin-4-yl; 2-isobutyl-morpholin-4-yl; 2-hydroxymethyl-morpholin-4-yl; 3,3-dimethyl-morpholin-4-yl; 4-methyl-piperazin-1-yl; 4-isopropyl-piperazin-1-yl; piperazin-1-yl; 3-oxa-8-aza-bicyclo[3.2. 1] oct-8-yl; (S)-3-methyl-morpholin-4-yl; 2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl; 8-oxa-3-aza-bicyclo[3.2.1]oct-3-yl; (R)-3-methyl-morpholin-4-yl; 4-cyclopropanecarbonyl-piperazin-1-yl; 4-(1-hydroxy-1-methyl-ethyl)-piperidin-1-yl; 4-cyclobutyl-piperazin-1-yl; (R)-3-hydroxy-pyrrolidin-1-yl; 4-oxetan-3-yl-piperazin-1-yl; 3-morphlin-4-yl-azetidin-1-yl; 4-(1-methyl-piperidin-4-yl)-piperazin-1-yl; 3,3-difluoro-azetidin-1-yl; 4-dimethylamino-piperidin-1-yl; and 4-piperidin-4-yl-piperazin-1-yl.

[0290] In certain embodiments of formula I or formula II, R^5 and R^6 together with the nitrogen atom to which they are attached form morpholin-4-yl.

[0291] In certain embodiments of formula I or formula II, R^5 and R^6 together with the nitrogen atom to which they are attached form 4-hydroxy-piperidin-1-yl.

[0292] In certain embodiments of formula I or formula II, R^5 and R^6 together with the nitrogen atom to which they are attached form octahydro-pyrido[1,2-a]pyrazin-2-yl.

[0293] In certain embodiments of formula I or formula II, R^5 and R^6 together with the nitrogen atom to which they are attached form 2-hydroxy-piperidin-1-yl.

[0294] In certain embodiments of formula I or formula II, R^5 and R^6 together with the nitrogen atom to which they are attached form 4,4-dimethyl-piperidin-1-yl.

[0295] In certain embodiments of formula I or formula II, R^5 and R^6 together with the nitrogen atom to which they are attached form 3,5-dimethyl-piperidin-1-yl.

[0296] In certain embodiments of formula I or formula II, R^5 and R^6 together with the nitrogen atom to which they are attached form 1-hydroxy-1-methyl-ethyl)-piperidin-1-yl.

[0297] In certain embodiments of formula I or formula II, R^5 and R^6 together with the nitrogen atom to which they are attached form 3-hydroxy-pyrrolidin-1-yl.

[0298] In certain embodiments of formula I or formula II, R^a and R^6 together with the nitrogen atom to which they are attached form 4-methyl-piperidin-1-yl.

[0299] In certain embodiments of formula I or formula II, R^a and R^6 together with the nitrogen atom to which they are attached form piperidin-1-yl.

[0300] In certain embodiments of formula I or formula II, R^a and R^6 together with the nitrogen atom to which they are attached form azetidin-1-yl.

[0301] In certain embodiments of formula I or formula II, R^a and R^6 together with the nitrogen atom to which they are attached form 4,4-difluoro-piperidin-1-yl.

[0302] In certain embodiments of formula I or formula II, R^a and R^6 together with the nitrogen atom to which they are attached form 3-methyl-piperidin-1-yl.

[0303] In certain embodiments of formula I or formula II, R^a and R^6 together with the nitrogen atom to which they are attached form 4-methoxy-piperidin-1-yl.

[0304] In certain embodiments of formula I or formula II, R^a and R^6 together with the nitrogen atom to which they are attached form 3,3-difluoro-piperidin-1-yl.

[0305] In certain embodiments of formula I or formula II, R^a and R^6 together with the nitrogen atom to which they are attached form 4-cyano-piperidin-1-yl.

[0306] In certain embodiments of formula I or formula II, R^a and R^6 together with the nitrogen atom to which they are attached form 4-fluoro-piperidin-1-yl.

[0307] In certain embodiments of formula I or formula II, R^a and R^6 together with the nitrogen atom to which they are attached form 3-methoxy-piperidin-1-yl.

[0308] In certain embodiments of formula I or formula II, R^a and R^6 together with the nitrogen atom to which they are attached form 4-ethyl-piperazin-1-yl.

[0309] In certain embodiments of formula I or formula II, R^a and R^6 together with the nitrogen atom to which they are attached form 4-acetyl-piperazin-1-yl.

[0310] In certain embodiments of formula I or formula II, R^a and R^6 together with the nitrogen atom to which they are attached form 3-trifluoromethyl-piperidin-1-yl.

[0311] In certain embodiments of formula I or formula II, R^a and R^6 together with the nitrogen atom to which they are attached form 4-tert-butyl-piperidin-1-yl.

[0312] In certain embodiments of formula I or formula II, R^a and R^6 together with the nitrogen atom to which they are attached form.

[0313] In certain embodiments of formula I or formula II, R^a and R^6 together with the nitrogen atom to which they are attached form 2-hydroxy-ethyl)-piperazin-1-yl.

[0314] In certain embodiments of formula I or formula II, R^a and R^6 together with the nitrogen atom to which they are attached form 2-methyl-pyrrolidin-1-yl.

[0315] In certain embodiments of formula I or formula II, R^a and R^6 together with the nitrogen atom to which they are attached form 4-hydroxymethyl-piperidin-1-yl.

[0316] In certain embodiments of formula I or formula II, R^a and R^6 together with the nitrogen atom to which they are attached form 2-methyl-piperidin-1-yl.

[0317] In certain embodiments of formula I or formula II, R^a and R^6 together with the nitrogen atom to which they are attached form pyrrolidin-1-yl.

[0318] In certain embodiments of formula I or formula II, R^a and R^6 together with the nitrogen atom to which they are attached form 4-methanesulfonyl-piperazin-1-yl.

[0319] In certain embodiments of formula I or formula II, R^a and R^6 together with the nitrogen atom to which they are attached form 3-trifluoromethyl-pyrrolidin-1-yl.

[0320] In certain embodiments of formula I or formula II, R^a and R^6 together with the nitrogen atom to which they are attached form 4-(2,2,2-trifluoro-ethyl)-piperazin-1-yl.

[0321] In certain embodiments of formula I or formula II, R^a and R^6 together with the nitrogen atom to which they are attached form 2-methyl-morpholin-4-yl.

[0322] In certain embodiments of formula I or formula II, R^a and R^6 together with the nitrogen atom to which they are attached form (2,6-dimethyl-morpholin-4-yl.

[0323] In certain embodiments of formula I or formula II, R^a and R^6 together with the nitrogen atom to which they are attached form 2,2-diethyl-morpholin-4-yl.

[0324] In certain embodiments of formula I or formula II, R^a and R^6 together with the nitrogen atom to which they are attached form 3-hydroxymethyl-morpholin-4-yl.

[0325] In certain embodiments of formula I or formula II, R^a and R^6 together with the nitrogen atom to which they are attached form 2-isobutyl-morpholin-4-yl.

[0326] In certain embodiments of formula I or formula II, R^a and R^6 together with the nitrogen atom to which they are attached form 2-hydroxymethyl-morpholin-4-yl.

[0327] In certain embodiments of formula I or formula II, R^a and R^6 together with the nitrogen atom to which they are attached form 3,3-dimethyl-morpholin-4-yl.

[0328] In certain embodiments of formula I or formula II, R^a and R^6 together with the nitrogen atom to which they are attached form 4-methyl-piperazin-1-yl.

[0329] In certain embodiments of formula I or formula II, R^a and R^6 together with the nitrogen atom to which they are attached form 4-isopropyl-piperazin-1-yl.

[0330] In certain embodiments of formula I or formula II, R^a and R^6 together with the nitrogen atom to which they are attached form piperazin-1-yl.

[0331] In certain embodiments of formula I or formula II, R^a and R^6 together with the nitrogen atom to which they are attached form 3-oxa-8-aza-bicyclo[3.2.1]oct-8-yl.

[0332] In certain embodiments of formula I or formula II, R^a and R^6 together with the nitrogen atom to which they are attached form (S)-3-methyl-morpholin-4-yl.

[0333] In certain embodiments of formula I or formula II, R^a and R^6 together with the nitrogen atom to which they are attached form 2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl.

[0334] In certain embodiments of formula I or formula II, R^5 and R^6 together with the nitrogen atom to which they are attached form 8-oxa-3-aza-bicyclo[3.2.1]oct-3-yl.

[0335] In certain embodiments of formula I or formula II, R^5 and R^6 together with the nitrogen atom to which they are attached form (R)-3-methyl-morpholin-4-yl.

[0336] In certain embodiments of formula I or formula II, R^5 and R^6 together with the nitrogen atom to which they are attached form 4-cyclopropanecarbonyl-piperazin-1-yl.

[0337] In certain embodiments of formula I or formula II, R^5 and R^6 together with the nitrogen atom to which they are attached form 4-(1-hydroxy-1-methyl-ethyl)-piperidin-1-yl.

[0338] In certain embodiments of formula I or formula II, R^5 and R^6 together with the nitrogen atom to which they are attached form 4-cyclobutyl-piperazin-1-yl.

[0339] In certain embodiments of formula I or formula II, R^5 and R^6 together with the nitrogen atom to which they are attached form (R)-3-hydroxy-pyrrolidin-1-yl.

[0340] In certain embodiments of formula I or formula II, R^5 and R^6 together with the nitrogen atom to which they are attached form 4-oxetan-3-yl-piperazin-1-yl.

[0341] In certain embodiments of formula I or formula II, R^5 and R^6 together with the nitrogen atom to which they are attached form 3-morpholin-4-yl-azetidin-1-yl.

[0342] In certain embodiments of formula I or formula II, R^5 and R^6 together with the nitrogen atom to which they are attached form 4-(1-methyl-piperidin-4-yl)-piperazin-1-yl.

[0343] In certain embodiments of formula I or formula II, R^5 and R^6 together with the nitrogen atom to which they are attached form 3,3-difluoro-azetidin-1-yl.

[0344] In certain embodiments of formula I or formula II, R^5 and R^6 together with the nitrogen atom to which they are attached form 4-dimethylamino-piperidin-1-yl.

[0345] In certain embodiments of formula I or formula II, R^5 and R^6 together with the nitrogen atom to which they are attached form 4-piperidin-4-yl-piperazin-1-yl.

[0346] In certain embodiments of formula I or formula II, R^5 and R^6 together with the nitrogen atom to which they are attached form (4,4-difluoro-piperidin-1-yl.

[0347] In certain embodiments of formula I or formula II, R^5 and R^6 together with the nitrogen atom to which they are attached form (3-morpholin-4-yl-azetidin-1-yl.

[0348] In certain embodiments of formula I or formula II, R^5 and R^6 together with the nitrogen atom to which they are attached form 2-oxa-6-aza-spiro[3.3]hept-6-yl.

[0349] In certain embodiments of formula I or formula II, R^5 and R^6 together with the nitrogen atom to which they are attached form 2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl). In certain embodiments of formula I or formula II, R^5 and R^6 together with the nitrogen atom to which they are attached form 4-methoxy-piperidin-1-yl).

[0350] In certain embodiments of formula I or formula II, R^5 and R^6 together with the nitrogen atom to which they are attached form [1,4]oxazepan-4-yl.

[0351] In certain embodiments of formula I or formula II, R^5 and R^6 together with the nitrogen atom to which they are attached form 2R,6S)-2,6-dimethyl-morpholin-4-yl.

[0352] In certain embodiments of formula I or formula II, R^5 and R^6 together with the nitrogen atom to which they are attached form 3-hydroxy-azetidin-1-yl.

[0353] In certain embodiments of formula I or formula II, R^5 and R^6 together with the nitrogen atom to which they are attached form 3-cyano-pyrrolidin-1-yl.

[0354] In certain embodiments of formula I or formula II, R^5 and R^6 together with the nitrogen atom to which they are attached form 3,5-dimethyl-piperazin-1-yl.

[0355] In certain embodiments of formula I or formula II, R^5 and R^6 together with the nitrogen atom to which they are attached form (3R,5S)-dimethyl-piperazin-1-yl.

[0356] In certain embodiments of formula I or formula II, R^5 and R^6 together with the nitrogen atom to which they are attached form 3-Fluoro-pyrrolidin-1-yl.

[0357] In certain embodiments of formula I or formula II, R^5 and R^6 together with the nitrogen atom to which they are attached form (S)-3-Fluoro-pyrrolidin-1-yl.

[0358] In certain embodiments of formula I or formula II, R^5 and R^6 together with the nitrogen atom to which they are attached form piperazin-1-yl.

[0359] In certain embodiments of formula I or formula II, R^5 and R^6 together with the nitrogen atom to which they are attached form 3,3-difluoro-pyrrolidin-1-yl.

[0360] In certain embodiments of formula I or formula II, R^5 and R^6 together with the nitrogen atom to which they are attached form 3,3-difluoro-azetidin-1-yl.

[0361] In certain embodiments of formula I or formula II, R^5 and R^6 together with the nitrogen atom to which they are attached form 2,2,6,6-tetrafluoro-morpholin-4-yl.

[0362] In certain embodiments of formula I or formula II, R^5 and R^6 together with the nitrogen atom to which they are attached form 2-methoxymethyl-pyrrolidin-1-yl. In certain embodiments of formula I or formula II, R^5 and R^6 together with the nitrogen atom to which they are attached form (S)-2-methoxymethyl-pyrrolidin-1-yl.

[0363] In certain embodiments of formula I or formula II, R^5 and R^6 together with the nitrogen atom to which they are attached form (1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl.

[0364] In certain embodiments of formula I or formula II, R^5 and R^6 together with the nitrogen atom to which they are attached form (3 S,4S)-3,4-difluoropyrrolidin-1-yl; 3,4-difluoropyrrolidin-1-yl; and 3-methoxypyrrolidin-1-yl.

[0365] In certain embodiments of formula I or formula II, R^7 is halo.

[0366] In certain embodiments of formula I or formula II, R^7 is C_{1-6}alkyl.

[0367] In certain embodiments of formula I or formula II, R^7 is C_{1-6}alkoxy.

[0368] In certain embodiments of formula I or formula II, R^7 is halo-C_{1-6}alkyl.

[0369] In certain embodiments of formula I or formula II, R^7 is halo-C_{1-6}alkoxy.

[0370] In certain embodiments of formula I or formula II, R^7 is halo or methoxy.

[0371] In certain embodiments of formula I or formula II, R^7 is fluoro, chloro or methoxy.

[0372] In certain embodiments of formula I or formula II, R^7 is fluoro or chloro.

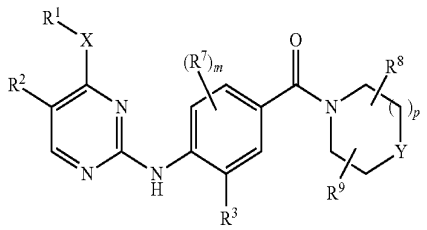
[0373] In certain embodiments of formula I or formula II, R^7 is methoxy.

[0374] In certain embodiments of formula I or formula II, R^7 is chloro.

[0375] In certain embodiments of formula I or formula II, R^7 is fluoro.

[0376] In embodiments of formula I or formula II wherein R^5 and R^6 together with the nitrogen atom to which they are attached form a three- to six-membered ring, the subject compounds may be represented by formula III:

III



wherein:

[0377] p is from 0 to 2;

[0378] Y is: —O—; —S(O)$_r$—; —NR^{10}; or —CR^{11}R^{12}— when p is 1 or 2; and Y is —CR^{11}R^{12}— when p is 0;

[0379] R^8 and R^9 each independently is: hydrogen; C_{1-6}alkyl; halo-C_{1-6}alkyl; C_{1-6}alkoxy; halo-C_{1-6}alkoxy; hydroxy; hydroxy-C_{1-6}alkyl; halo; nitrile; C_{1-6}alkyl-carbonyl; C_{1-6}alkyl-sulfonyl; C_{3-6}cycloalkyl; C_{3-6}cycloalkyl-C_{1-6}alkyl; C_{3-6}cycloalkyl-carbonyl; amino; or heterocyclyl;

[0380] or R^8 and R^9 together with the atoms to which they are attached form a five- or six-membered ring;

[0381] R^{10} is: hydrogen; C_{1-6}alkyl; hydroxy-C_{1-6}alkyl; halo-C_{1-6}alkyl; hydroxy-C_{1-6}alkyl; C_{1-6}alkyl-carbonyl; C_{1-6}alkyl-sulfonyl; C_{3-6}cycloalkyl; C_{3-6}cycloalkyl-C_{1-6}alkyl; C_{3-6}cycloalkyl-carbonyl; heterocyclyl; or heterocyclyl-C_{1-6}alkyl;

[0382] or one of R^8 and R^9 together with R^{10} and the atoms to which they are attached form a five- or six-membered ring;

[0383] R^{11} is: hydrogen; C_{1-6}alkyl; or halo;

[0384] R^{12} is: hydrogen; C_{1-6}alkyl; halo-C_{1-6}alkyl; C_{1-6}alkoxy; halo-C_{1-6}alkoxy; hydroxy; hydroxy-C_{1-6}alkyl; halo; nitrile; C_{1-6}alkyl-carbonyl; C_{1-6}alkyl-sulfonyl; C_{3-6}cycloalkyl; C_{3-6}cycloalkyl-C_{1-6}alkyl; C_{3-6}cycloalkyl-carbonyl; amino; heterocyclyl; or heterocyclyl-C_{1-6}alkyl;

[0385] or R^{11} and R^{12} together with the atom to which they are attached may form a 3- to six-membered ring that optionally includes a heteroatom selected from O, N and S;

[0386] or one of R^8 and R^9 together with R^{10} and the atoms to which they are attached form a five- or six-membered ring;

[0387] or one of R^8 and R^9 together with R^{12} and the atoms to which they are attached form a five- or six-membered ring; and

[0388] m, r, X, R^1, R^2, R^3 and R^7 are as defined herein.

[0389] In certain embodiments of formula III, p is 0 or 1.

[0390] In certain embodiments of formula III, p is 0.

[0391] In certain embodiments of formula III, p is 1.

[0392] In certain embodiments of formula III, p is 2.

[0393] In certain embodiments of formula III, Y is —O—; —NR^{10}; or —CR^{11}R^{12}—;

[0394] In certain embodiments of formula III, Y is —O—.

[0395] In certain embodiments of formula III, Y is —NR^{10}—.

[0396] In certain embodiments of formula III, Y is —S(O)$_r$—.

[0397] In certain embodiments of formula III, Y is —CR^{11}R^{12}—.

[0398] In certain embodiments of formula III, R^8 is hydrogen.

[0399] In certain embodiments of formula III, R^9 is hydrogen.

[0400] In certain embodiments of formula III, R^8 and R^9 are hydrogen.

[0401] In certain embodiments of formula III, R^8 and R^9 are hydrogen, C_{1-6}alkyl or halo.

[0402] In certain embodiments of formula III, R^8 and R^9 together with the atoms to which they are attached form a five- or six-membered ring.

[0403] In certain embodiments of formula III, one of R^8 and R^9 together with R^{10} and the atoms to which they are attached form a five- or six-membered ring.

[0404] In certain embodiments of formula III, one of R^8 and R^9 together with R^{12} and the atoms to which they are attached form a five- or six-membered ring.

[0405] In certain embodiments of formula III, R^{10} is hydrogen.

[0406] In certain embodiments of formula III, R^{10} is C_{1-6}alkyl.

[0407] In certain embodiments of formula III, R^{10} is hydroxy-C_{1-6}alkyl.

[0408] In certain embodiments of formula III, R^{10} is halo-C_{1-6}alkyl

[0409] In certain embodiments of formula III, R^{10} is hydroxy-C_{1-6}alkyl.

[0410] In certain embodiments of formula III, R^{10} is C_{1-6}alkyl-carbonyl.

[0411] In certain embodiments of formula III, R^{10} is C_{1-6}alkyl-sulfonyl.

[0412] In certain embodiments of formula III, R^{10} is C_{3-6}cycloalkyl

[0413] In certain embodiments of formula III, R^{10} is C_{3-6}cycloalkyl-C_{1-6}alkyl.

[0414] In certain embodiments of formula III, R^{10} is C_{3-6}cycloalkyl-carbonyl.

[0415] In certain embodiments of formula III, R^{10} is heterocyclyl.

[0416] In certain embodiments of formula III, R^{10} is heterocyclyl-C_{1-6}alkyl.

[0417] In certain embodiments of formula III, R^{11} is hydrogen or C_{1-6}alkyl.

[0418] In certain embodiments of formula III, R^{11} and R^{12} are hydrogen.

[0419] In certain embodiments of formula III, R^{11} is hydrogen.

[0420] In certain embodiments of formula III, R^{11} is C_{1-6}alkyl.

[0421] In certain embodiments of formula III, R^{11} is halo.

[0422] In certain embodiments of formula III, R^{12} is hydrogen.

[0423] In certain embodiments of formula III, R^{12} is C_{1-6}alkyl.

[0424] In certain embodiments of formula III, R^{12} is halo-C_{1-6}alkyl.

[0425] In certain embodiments of formula III, R^{12} is C_{1-6}alkoxy.

[0426] In certain embodiments of formula III, R^{12} is halo-C_{1-6}alkoxy.

[0427] In certain embodiments of formula III, R^{12} is hydroxy.

[0428] In certain embodiments of formula III, R^{12} is hydroxy-C_{1-6}alkyl.

[0429] In certain embodiments of formula III, R^{12} is halo.

[0430] In certain embodiments of formula III, R^{12} is nitrile.

[0431] In certain embodiments of formula III, R^{12} is C_{1-6}alkyl-carbonyl.

[0432] In certain embodiments of formula III, R^{12} is C_{1-6}alkyl-sulfonyl.

[0433] In certain embodiments of formula III, R^{12} is C_{3-6}cycloalkyl.

[0434] In certain embodiments of formula III, R^{12} is C_{3-6}cycloalkyl-C_{1-6}alkyl.

[0435] In certain embodiments of formula III, R^{12} is C_{3-6}cycloalkyl-carbonyl.

[0436] In certain embodiments of formula III, R^{12} is amino.

[0437] In certain embodiments of formula III, R^{12} is dimethylamino.

[0438] In certain embodiments of formula III, R^{12} is heterocyclyl.

[0439] In embodiments of formula III wherein R^{10} is heterocyclyl, such heterocyclyl may be: azetidinyl; pyrrolidinyl; piperidinyl; piperazinyl; morpholinyl; thiomorpholinyl; 3-oxa-8-aza-bicyclo[3.2.1]oct-8-yl; 2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl; or 8-oxa-3-aza-bicyclo[3.2.1]oct-3-yl; each optionally substituted with one, two or three groups independently selected from: C_{1-6}alkyl; halo-C_{1-6}alkyl; C_{1-6}alkoxy; halo-C_{1-6}alkoxy; hydroxy; hydroxy-C_{1-6}alkyl; halo; nitrile; C_{1-6}alkyl-carbonyl; C_{1-6}alkyl-sulfonyl; C_{3-6}cycloalkyl; C_{3-6}cycloalkyl-C_{1-6}alkyl; C_{3-6}cycloalkyl-carbonyl; amino; or heterocyclyl; or two of the groups together with the atoms to which they are attached may form a five or six-membered ring.

[0440] In embodiments of formula III wherein R^{10} is heterocyclyl, such heterocyclyl may be: azetidinyl; pyrrolidinyl; piperidinyl; piperazinyl; or morpholinyl; each optionally substituted as defined herein.

[0441] In embodiments of formula III wherein R^{10} is heterocyclyl-C_{1-6}alkyl, the heterocyclyl portion thereof may be: azetidinyl; pyrrolidinyl; piperidinyl; piperazinyl; morpholinyl; thiomorpholinyl; 3-oxa-8-aza-bicyclo[3.2.1]oct-8-yl; 2-oxa-5-aza-bicyclo[2.2. 1]hept-5-yl; or 8-oxa-3-aza-bicyclo[3.2.1]oct-3-yl; each optionally substituted as defined herein.

[0442] In embodiments of formula III wherein R^{10} is heterocyclyl-C_{1-6}alkyl, the heterocyclyl portion thereof may be: azetidinyl; pyrrolidinyl; piperidinyl; piperazinyl; or morpholinyl; each optionally substituted with one, two or three groups independently selected from: C_{1-6}alkyl; halo-C_{1-6}alkyl; C_{1-6}alkoxy; halo-C_{1-6}alkoxy; hydroxy; hydroxy-C_{1-6}alkyl; halo; nitrile; C_{1-6}alkyl-carbonyl; C_{1-6}alkyl-sulfonyl; C_{3-6}cycloalkyl; C_{3-6}cycloalkyl-C_{1-6}alkyl; C_{3-6}cycloalkyl-carbonyl; amino; or heterocyclyl; or two of the groups together with the atoms to which they are attached may form a five or six-membered ring.

[0443] In embodiments of formula III wherein R^{12} is heterocyclyl, such heterocyclyl may be: azetidinyl; pyrrolidinyl; piperidinyl; piperazinyl; morpholinyl; thiomorpholinyl; 3-oxa-8-aza-bicyclo[3.2.1]oct-8-yl; 2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl; or 8-oxa-3-aza-bicyclo[3.2.1]oct-3-yl; each optionally substituted as defined herein.

[0444] In embodiments of formula III wherein R^{12} is heterocyclyl, such heterocyclyl may be: azetidinyl; pyrrolidinyl; piperidinyl; piperazinyl; or morpholinyl; each optionally substituted with one, two or three groups independently selected from: C_{1-6}alkyl; halo-C_{1-6}alkyl; C_{1-6}alkoxy; halo-C_{1-6}alkoxy; hydroxy; hydroxy-C_{1-6}alkyl; halo; nitrile; C_{1-6}alkyl-carbonyl; C_{1-6}alkyl-sulfonyl; C_{3-6}cycloalkyl; C_{3-6}cycloalkyl-C_{1-6}alkyl; C_{3-6}cycloalkyl-carbonyl; amino; or heterocyclyl; or two of the groups together with the atoms to which they are attached may form a five or six-membered ring.

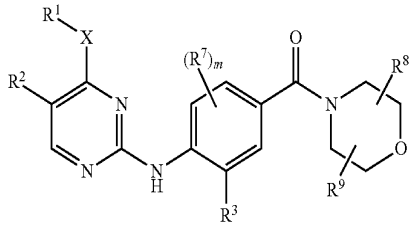
[0445] In embodiments of formula III wherein R^{12} is heterocyclyl-C_{1-6}alkyl, the heterocyclyl portion thereof may be: azetidinyl; pyrrolidinyl; piperidinyl; piperazinyl; morpholinyl; thiomorpholinyl; 3-oxa-8-aza-bicyclo[3.2.1]oct-8-yl; 2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl; or 8-oxa-3-aza-bicyclo [3.2.1]oct-3-yl; wherein the heterocyclyl portion each is optionally substituted with one, two or three groups independently selected from: C_{1-6}alkyl; halo-C_{1-6}alkyl; C_{1-6}alkoxy; halo-C_{1-6}alkoxy; hydroxy; hydroxy-C_{1-6}alkyl; halo; nitrile; C_{1-6}alkyl-carbonyl; C_{1-6}alkyl-sulfonyl; C_{3-6}cycloalkyl; C_{3-6}cycloalkyl-C_{1-6}alkyl; C_{3-6}cycloalkyl-carbonyl; amino; or heterocyclyl; or two of the groups together with the atoms to which they are attached may form a five or six-membered ring.

[0446] In embodiments of formula III wherein R^{12} is heterocyclyl-C_{1-6}alkyl, the heterocyclyl portion thereof may be: azetidinyl; pyrrolidinyl; piperidinyl; piperazinyl; or morpholinyl; each optionally substituted as defined herein.

[0447] In certain embodiments of formula III, R^{11} and R^{12} together with the atom to which they are attached form a 3- to six-membered ring that optionally includes a heteroatom selected from O, N and S.

[0448] In certain embodiments, the subject compounds may be represented more particularly by formula IV:

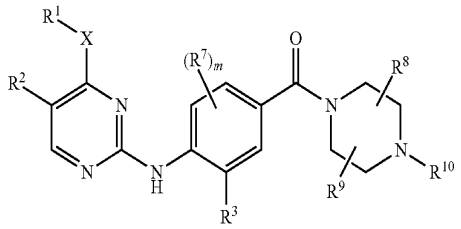
IV



wherein m, X, R^1, R^2, R^3, R^7, R^8 and R^9 are as defined herein.

[0449] In certain embodiments, the subject compounds may be represented more particularly by formula V:

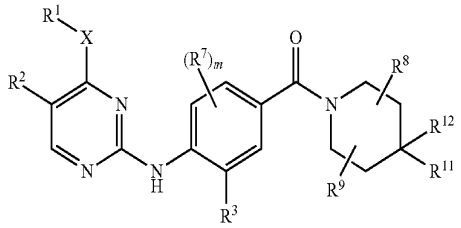
V



wherein m, X, R^1, R^2, R^3, R^7, R^8, R^9 and R^{10} are as defined herein.

[0450] In certain embodiments, the subject compounds may be represented more particularly by formula VI:

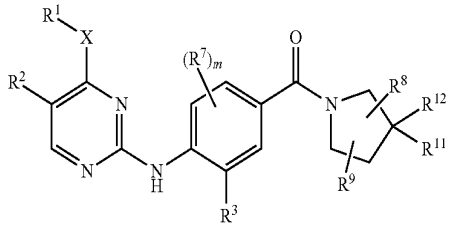
VI



wherein m, X, R^1, R^2, R^3, R^7, R^8, R^9, R^{11} and R^{12} are as defined herein.

[0451] In certain embodiments, the subject compounds may be represented more particularly by formula VII:

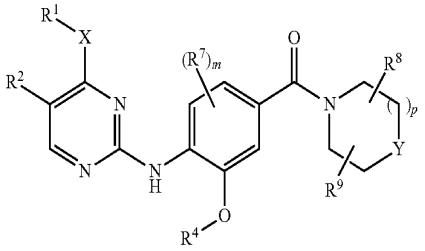
VII



wherein m, X, R^1, R^2, R^3, R^7, R^8, R^9, R^{11} and R^{12} are as defined herein.

[0452] In certain embodiments, the subject compounds may be represented more particularly by formula VIII:

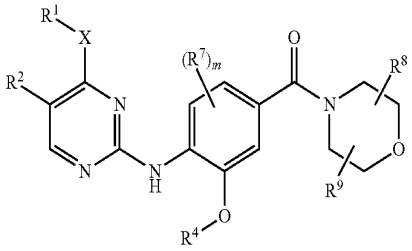
VIII



wherein m, p, X, Y, R^1, R^2, R^4, R^7, R^8 and R^9 are as defined herein.

[0453] In certain embodiments, the subject compounds may be represented more particularly by formula IX:

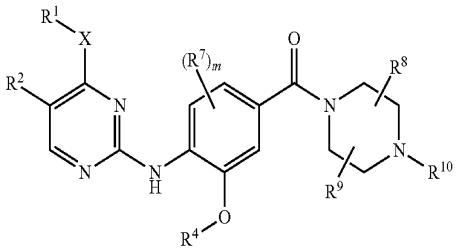
IX



wherein m, X, R^1, R^2, R^4, R^7, R^8 and R^9 are are as defined herein.

[0454] In certain embodiments, the subject compounds may be represented more particularly by formula X:

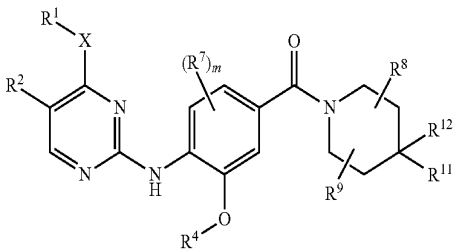
X



wherein m, X, R^1, R^2, R^4, R^7, R^8, R^9 and R^{10} are as defined herein.

[0455] In certain embodiments, the subject compounds may be represented more particularly by formula XI:

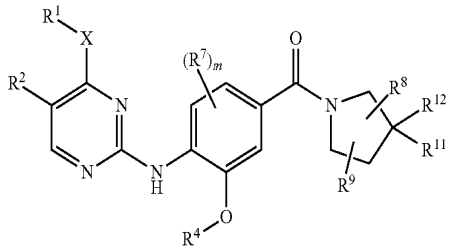
XI



wherein m, X, R^1, R^2, R^4, R^7, R^8, R^9, R^{11} and R^{12} are as defined herein.

[0456] In certain embodiments, the subject compounds may be represented more particularly by formula XII:

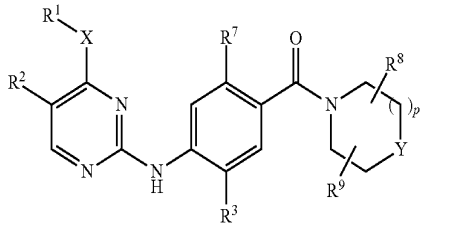
XII



wherein m, X, R^1, R^2, R^4, R^7, R^8, R^9, R^{11} and R^{12} are as defined herein.

[0457] In embodiments the subject compounds may be represented by formula XIII:

XIII



wherein p, X, Y, R^1, R^2, R^3, R^7, R^8 and R^9 are as defined herein.

[0458] Where any of R^1, R^2, R' R^4, R^5, R^6, R^7, R^8, R^9, R^{11} and $R^{12}$is alkyl or contains an alkyl moiety, such alkyl is preferably lower alkyl, i.e. C_1-C_6alkyl, and in many embodiments may be C_1-C_4alkyl.

[0459] The invention also provides a method for treating a disease or condition mediated by or otherwise associated with the LRRK2 receptor, the method comprising administering to a subject in need thereof an effective amount of a compound of the invention.

[0460] The disease may be a neurodegenerative disease such as Parkinson's disease, Huntington's disease or Lewie body dementia.

[0461] The disease may be a CNS disorder such as Alzheimer's disease and L-Dopa induced dyskinesia.

[0462] The disease may be a cancer or proliferative disorder such as kidney, breast, prostate, blood, papillary or lung cancer, acute myelogenous leukemia, or multiple myeloma.

[0463] The disease may be an inflammatory disease such as leprosy, Crohn's disease, amyotrophic lateral sclerosis, rheumatoid arthritis, and ankylosing spondylytis.

[0464] The invention also provides a method for enhancing cognitive memory, the method comprising administering to a subject in need thereof an effective amount of a compound of the invention.

[0465] Representative compounds in accordance with the methods of the invention are shown in the experimental examples below.

Synthesis

[0466] Compounds of the present invention can be made by a variety of methods depicted in the illustrative synthetic reaction schemes shown and described below.

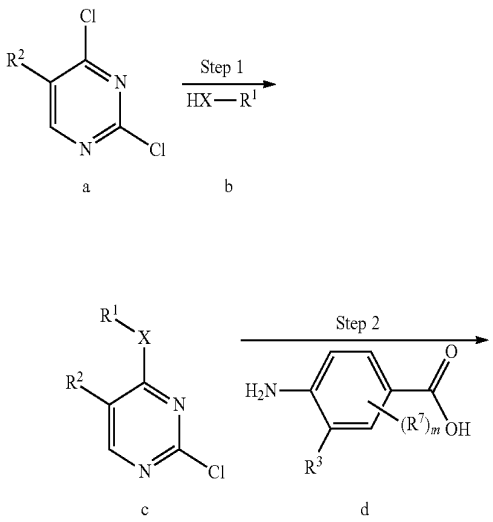
[0467] The starting materials and reagents used in preparing these compounds generally are either available from commercial suppliers, such as Aldrich Chemical Co., or are prepared by methods known to those skilled in the art following procedures set forth in references such as *Fieser and Fieser's Reagents for Organic Synthesis;* Wiley & Sons: New York, 1991, Volumes 1-15; *Rodd's Chemistry of Carbon Compounds,* Elsevier Science Publishers, 1989, Volumes 1-5 and Supplementals; and *Organic Reactions,* Wiley & Sons: New York, 1991, Volumes 1-40. The following synthetic reaction schemes are merely illustrative of some methods by which the compounds of the present invention can be synthesized, and various modifications to these synthetic reaction schemes can be made and will be suggested to one skilled in the art having referred to the disclosure contained in this Application.

[0468] The starting materials and the intermediates of the synthetic reaction schemes can be isolated and purified if desired using conventional techniques, including but not limited to, filtration, distillation, crystallization, chromatography, and the like. Such materials can be characterized using conventional means, including physical constants and spectral data.

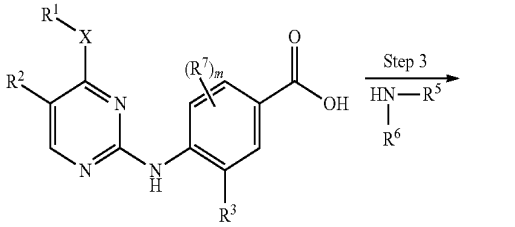
[0469] Unless specified to the contrary, the reactions described herein may be conducted under an inert atmosphere at atmospheric pressure at a reaction temperature range of from about −78 ° C. to about 150 ° C., for example, from about 0 ° C. to about 125 ° C., or conveniently at about room (or ambient) temperature, e.g., about 20 ° C.

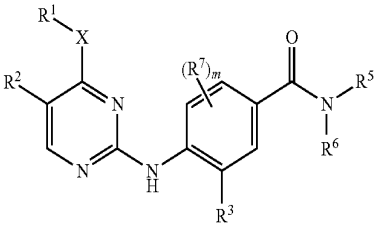
[0470] Scheme A below illustrates one synthetic procedure usable to prepare specific compounds of formula I or formula II, wherein X, m, R^1, R^2, R^3, R^5, R^6 and R^7 are as defined herein.

SCHEME A



-continued





I

[0471] In step 1 of Scheme A, dichloropyrimidine compound a is reacted with reagent b to afford pyrimidine compound c. The reaction of step 1 may take place under polar solvent conditions. In embodiments of the invention where X is —O— (reagent b is an alcohol), the reaction of step 1 may be carried out in the presence of base.

[0472] In step 2, pyrimidine compound c undergoes reaction with aminobenzoic acid compound d to provide aminopyridine compound e. The reaction of step 2 may take place in polar protic solvent and in the presence of acid such as HCl.

[0473] An amide coupling reaction is carried out in step 3 wherein compound e is reacted with amine f to yield a compound of formula I or formula II in accordance with the invention. The amide coupling reaction of step 3 may utilize various well known amide coupling reagents such as carbodiimides (such as DCC, DIC, EDC and the like), aminium salts (such as HATU, HBTU, TBTU and the like), or phosphonium salts (such as BOP, PyBOP and the like), with or without the presence of benzotriazole derivatives such as HOBt, HOAt, DhbtOH, and the like. In other embodiments amide formation may be achieved using an acid chloride or anhydride intermediate (not shown).

[0474] Many variations on the procedure of Scheme A are possible and will suggest themselves to those skilled in the art. Specific details for producing compounds of the invention are described in the Examples below.

Administration and Pharmaceutical Composition

[0475] The invention includes pharmaceutical compositions comprising at least one compound of the present invention, or an individual isomer, racemic or non-racemic mixture of isomers or a pharmaceutically acceptable salt or solvate thereof, together with at least one pharmaceutically acceptable carrier, and optionally other therapeutic and/or prophylactic ingredients.

[0476] In general, the compounds of the invention will be administered in a therapeutically effective amount by any of the accepted modes of administration for agents that serve similar utilities. Suitable dosage ranges are typically 1-500 mg daily, for example 1-100 mg daily, and most preferably 1-30 mg daily, depending upon numerous factors such as the severity of the disease to be treated, the age and relative health of the subject, the potency of the compound used, the route and form of administration, the indication towards which the administration is directed, and the preferences and experience of the medical practitioner involved. One of ordinary skill in the art of treating such diseases will be able, without undue experimentation and in reliance upon personal knowledge and the disclosure of this Application, to ascertain a therapeutically effective amount of the compounds of the present invention for a given disease.

[0477] Compounds of the invention may be administered as pharmaceutical formulations including those suitable for oral (including buccal and sub-lingual), rectal, nasal, topical, pulmonary, vaginal, or parenteral (including intramuscular, intraarterial, intrathecal, subcutaneous and intravenous) administration or in a form suitable for administration by inhalation or insufflation. A particular manner of administration is generally oral using a convenient daily dosage regimen which can be adjusted according to the degree of affliction.

[0478] A compound or compounds of the invention, together with one or more conventional adjuvants, carriers, or diluents, may be placed into the form of pharmaceutical compositions and unit dosages. The pharmaceutical compositions and unit dosage forms may be comprised of conventional ingredients in conventional proportions, with or without additional active compounds or principles, and the unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed. The pharmaceutical compositions may be employed as solids, such as tablets or filled capsules, semisolids, powders, sustained release formulations, or liquids such as solutions, suspensions, emulsions, elixirs, or filled capsules for oral use; or in the form of suppositories for rectal or vaginal administration; or in the form of sterile injectable solutions for parenteral use. Formulations containing about one (1) milligram of active ingredient or, more broadly, about 0.01 to about one hundred (100) milligrams, per tablet, are accordingly suitable representative unit dosage forms.

[0479] The compounds of the invention may be formulated in a wide variety of oral administration dosage forms. The pharmaceutical compositions and dosage forms may comprise a compound or compounds of the present invention or pharmaceutically acceptable salts thereof as the active component. The pharmaceutically acceptable carriers may be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier may be one or more substances which may also act as diluents, flavouring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material. In powders, the carrier generally is a finely divided solid which is a mixture with the finely divided active component. In tablets, the active component generally is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted in the shape and size desired. The powders and tablets may contain from about one (1) to about seventy (70) percent of the active compound. Suitable carriers include but are not limited to magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatine, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating mate-

rial as carrier, providing a capsule in which the active component, with or without carriers, is surrounded by a carrier, which is in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges may be as solid forms suitable for oral administration.

[0480] Other forms suitable for oral administration include liquid form preparations including emulsions, syrups, elixirs, aqueous solutions, aqueous suspensions, or solid form preparations which are intended to be converted shortly before use to liquid form preparations. Emulsions may be prepared in solutions, for example, in aqueous propylene glycol solutions or may contain emulsifying agents, for example, such as lecithin, sorbitan monooleate, or acacia. Aqueous solutions can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizers, and thickening agents. Aqueous suspensions can be prepared by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well known suspending agents. Solid form preparations include solutions, suspensions, and emulsions, and may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

[0481] The compounds of the invention may be formulated for parenteral administration (e.g., by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, for example solutions in aqueous polyethylene glycol. Examples of oily or nonaqueous carriers, diluents, solvents or vehicles include propylene glycol, polyethylene glycol, vegetable oils (e.g., olive oil), and injectable organic esters (e.g., ethyl oleate), and may contain formulatory agents such as preserving, wetting, emulsifying or suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilization from solution for constitution before use with a suitable vehicle, e.g., sterile, pyrogen-free water.

[0482] The compounds of the invention may be formulated for topical administration to the epidermis as ointments, creams or lotions, or as a transdermal patch. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also containing one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, or coloring agents. Formulations suitable for topical administration in the mouth include lozenges comprising active agents in a flavored base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatine and glycerine or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

[0483] The compounds of the invention may be formulated for administration as suppositories. A low melting wax, such as a mixture of fatty acid glycerides or cocoa butter is first melted and the active component is dispersed homogeneously, for example, by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and to solidify.

[0484] The compounds of the invention may be formulated for vaginal administration. Pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

[0485] The subject compounds may be formulated for nasal administration. The solutions or suspensions are applied directly to the nasal cavity by conventional means, for example, with a dropper, pipette or spray. The formulations may be provided in a single or multidose form. In the latter case of a dropper or pipette, this may be achieved by the patient administering an appropriate, predetermined volume of the solution or suspension. In the case of a spray, this may be achieved for example by means of a metering atomizing spray pump.

[0486] The compounds of the invention may be formulated for aerosol administration, particularly to the respiratory tract and including intranasal administration. The compound will generally have a small particle size for example of the order of five (5) microns or less. Such a particle size may be obtained by means known in the art, for example by micronization. The active ingredient is provided in a pressurized pack with a suitable propellant such as a chlorofluorocarbon (CFC), for example, dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane, or carbon dioxide or other suitable gas. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by a metered valve. Alternatively the active ingredients may be provided in a form of a dry powder, for example a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidine (PVP). The powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form for example in capsules or cartridges of e.g., gelatine or blister packs from which the powder may be administered by means of an inhaler.

[0487] When desired, formulations can be prepared with enteric coatings adapted for sustained or controlled release administration of the active ingredient. For example, the compounds of the present invention can be formulated in transdermal or subcutaneous drug delivery devices. These delivery systems are advantageous when sustained release of the compound is necessary and when patient compliance with a treatment regimen is crucial. Compounds in transdermal delivery systems are frequently attached to an skin-adhesive solid support. The compound of interest can also be combined with a penetration enhancer, e.g., Azone (1-dodecylazacycloheptan-2-one). Sustained release delivery systems are inserted subcutaneously into the subdermal layer by surgery or injection. The subdermal implants encapsulate the compound in a lipid soluble membrane, e.g., silicone rubber, or a biodegradable polymer, e.g., polylactic acid.

[0488] The pharmaceutical preparations may be in unit dosage forms. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

[0489] Other suitable pharmaceutical carriers and their formulations are described in *Remington: The Science and Practice of Pharmacy* 1995, edited by E. W. Martin, Mack Pub-

lishing Company, 19th edition, Easton, Pa. Representative pharmaceutical formulations containing a compound of the present invention are described below. Utility

[0490] The compounds of the invention are useful for treatment of LRRK2-mediated diseases or conditions, including neurodegenerative diseases such as Parkinson's disease, Lewy body dementia and Huntington's disease, and for enhancemenent of cognitive memory generally in subjects in need thereof.

EXAMPLES

[0491] The following preparations and examples are given to enable those skilled in the art to more clearly understand and to practice the present invention. They should not be considered as limiting the scope of the invention, but merely as being illustrative and representative thereof.

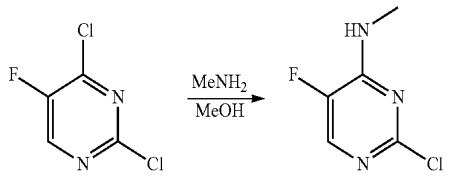
[0492] Unless otherwise stated, all temperatures including melting points (i.e., MP) are in degrees celsius (° C.). It should be appreciated that the reaction which produces the indicated and/or the desired product may not necessarily result directly from the combination of two reagents which were initially added, i.e., there may be one or more intermediates which are produced in the mixture which ultimately leads to the formation of the indicated and/or the desired product. The following abbreviations may be used in the Preparations and Examples.

LIST OF ABBREVIATIONS

[0493] AcOH Acetic acid
[0494] AIBN 2,2'-Azobis(2-methylpropionitrile)
[0495] Atm. Atmosphere
[0496] $(BOC)_2O$ di-tent-Butyl dicarbonate
[0497] DCM Dichloromethane/Methylene chloride
[0498] DIAD Diisopropyl azodicarboxylate
[0499] DIPEA Diisopropylethylamine
[0500] DMAP 4-Dimethylaminopyridine
[0501] DME 1,2-Dimethoxyethane
[0502] DMF N,N-Dimethylformamide
[0503] DMSO Dimethyl sulfoxide
[0504] DPPF 1,1'-Bis(diphenylphosphino)ferrocene
[0505] Et_2O Diethyl ether
[0506] EtOH Ethanol/Ethyl alcohol
[0507] EtOAc Ethyl acetate
[0508] HATU 2-(1H-7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate Methanaminium
[0509] HBTU O-Benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate
[0510] HOBT 1-Hydroxybenzotriazole
[0511] HPLC High pressure liquid chromatography
[0512] RP HPLC Reverse phase high pressure liquid chromatography
[0513] i-PrOH Isopropanol/isopropyl alcohol
[0514] LCMS Liquid Chromatograph/Mass Spectroscopy
[0515] MeOH Methanol/Methyl alcohol
[0516] MW Microwaves
[0517] NBS N-Bromosuccinimide
[0518] NMP 1-Methyl-2-pyrrolidinone
[0519] PSI Pound per square inch
[0520] RT Room temperature
[0521] TBDMS tert-Butyldimethylsilyl
[0522] TFA Trifluoroacetic acid
[0523] THF Tetrahydrofuran
[0524] TLC Thin layer chromatography

Preparation 1: 2-chloro-5-fluoro-N-methylpyrimidin-4-amine

[0525]



[0526] To a 250 mL round bottom flask equipped with a stir bar was added 9.0 g 5-fluoro-2,4-dichloro-pyrimidine, 40 mL methanol and 15 mL of 8M methylamine in ethanol. The reaction heated up (mild exo-therm) and was allowed to stir at room temperature for ~30 minutes. A check by TLC (1:1 EtOAc: heptane) and LCMS showed complete reaction. The reaction was concentrated down to give 9.77 g crude material which was purified on a silica column running a gradient of 1% to 10% MeOH in DCM over 35 minutes to give 6.77 g pure 2-chloro-5-fluoro-N-methylpyrimidin-4-amine

[0527] The same method was used to make the compounds shown in Table 1 below, using the appropriate commercially available substituted 2,4-dichloro-pyrimidines and amines

TABLE 1

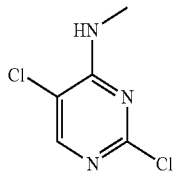
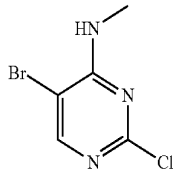
1	2-chloro-5-chloro-N-methylpyrimidin-4-amine	
2	2-chloro-5-bromo-N-methylpyrimidin-4-amine	

TABLE 1-continued

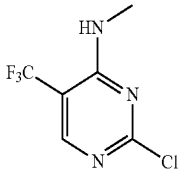
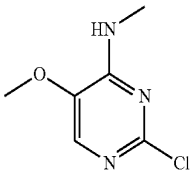
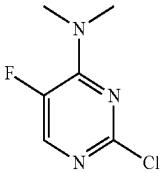
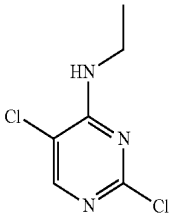
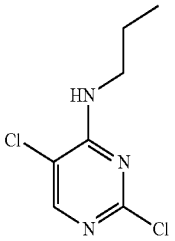
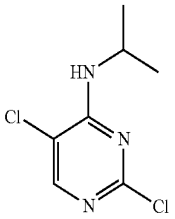
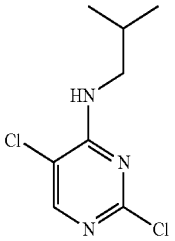
3	2-chloro-5-trifluoromethyl-N-methylpyrimidin-4-amine	
6	2-chloro-5-methoxy-N-methylpyrimidin-4-amine	
8	2-chloro-5-fluoro-N,N-dimethypyrimidin-4-amine	
9	2-chloro-5-chloro-N-ethylpyrimidin-4-amine	
10	2-chloro-5-chloro-N-propylpyrimidin-4-amine	
11	2-chloro-5-chloro-N-isopropylpyrimidin-4-amine	
12	2-chloro-5-chloro-N-isobutylpyrimidin-4-amine	

TABLE 1-continued

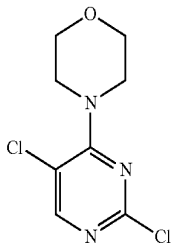
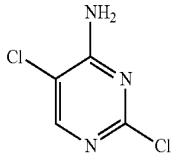
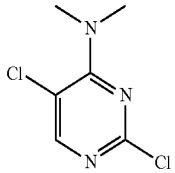
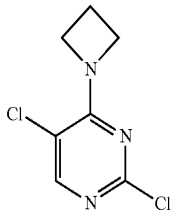
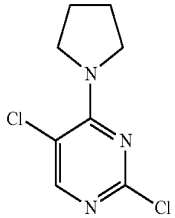
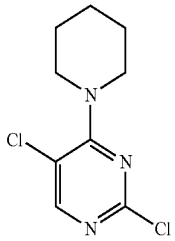
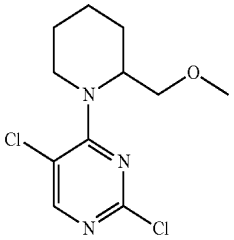
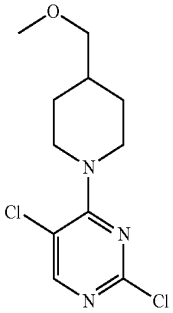
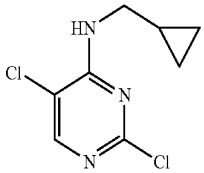
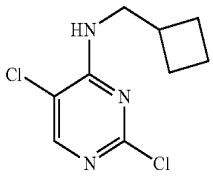
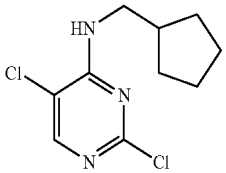
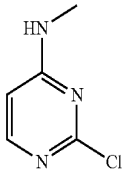
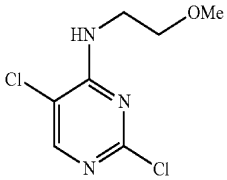
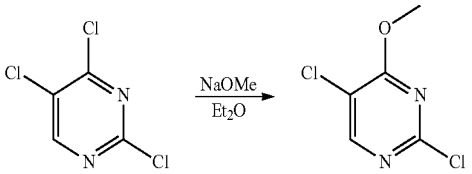
13 4-(2,5-dichloropyrimidin-4-yl)morpholine	
14 2,5-dichloropyrimidin-4-amine	
15 2,5-dichloro-N,N-dimethylpyrimidin-4-amine	
16 4-(azetidin-1-yl)-2,5-dichloropyrimidine	
17 2,5-dichloro-4-(pyrrolidin-1-yl)pyrimidine	
18 2,5-dichloro-4-(piperidin-1-yl)pyrimidine	
19 2,5-dichloro-4-(2-(methoxymethyl)piperidin-1-yl)pyrimidine	

TABLE 1-continued

20 2,5-dichloro-4-(4-(methoxymethyl)piperidin-1-yl)pyrimidine	
21 2,5-dichloro-N-(cyclopropylmethyl)pyrimidin-4-amine	
22 2,5-dichloro-N-(cyclobutylmethyl)pyrimidin-4-amine	
23 2,5-dichloro-N-(cyclopentylmethyl)pyrimidin-4-amine	
24 2-chloro-N-methylpyrimidin-4-amine	
25 2,5-dichloro-N-(2-methoxyethyl)pyrimidin-4-amine	

Preparation 2: 2,5-dichloro-4-methoxypyrimidine

[0528]



[0529] To a 250 mL round bottom flask equipped with a stir bar was added 1 g 5-chloro-2,4-dichloro-pyrimidine, and 15 mL of diethyl ether. The mixture was cooled to 0° C. in an ice bath and then 1 equivalent of sodium methoxide in methanol (prepared from reacting 120 mg of sodium with 4 mL of methanol at room temperature) was slowly added. The reaction was stirred over night at room temperature and checked by LCMS. The white precipitate was filtered and the solid washed with cold methanol. After drying, 0.98 g of pure 2,5-dichloro-4-methoxypyrimidine was obtained and this material was used without further purification.

[0530] The same method was used to make the compounds shown in Table 2 below, using the appropriate commercially available alcohols and the appropriately substituted 2,4-dichloro-pyrimidines.

TABLE 2

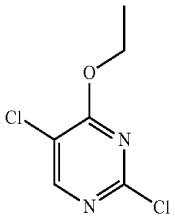
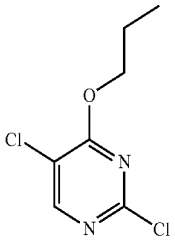
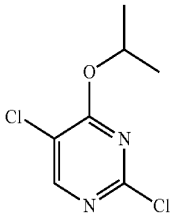
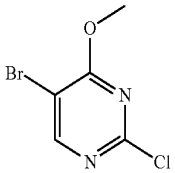
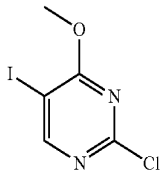
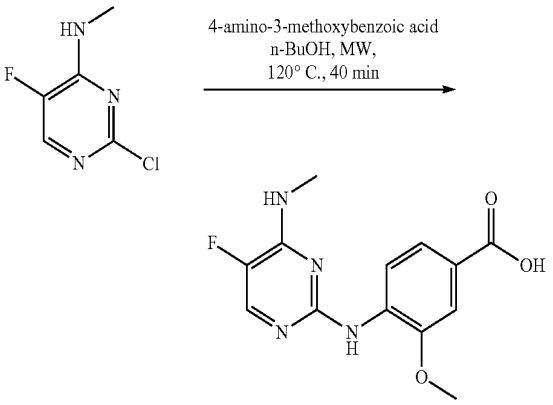
1	2,5-dichloro-4-ethoxypyrimidine	
2	2,5-dichloro-4-propoxypyrimidine	
3	2,5-dichloro-4-isoprpoxypyrimidine	
6	5-bromo-2-chloro-4-methoxypyrimidine	

TABLE 2-continued

7	2-chloro-5-iodo-4-methoxypyrimidine	

Preparation 3: 4-(5-fluoro-4-(methylamino)pyrimidin-2-ylamino)-3-methoxybenzoic acid

[0531]



[0532] A mixture of 50 mg 2-chloro-5-fluoro-N-methylpyrimidin-4-amine, 57 mg 4-Amino-3-methoxybenzoic acid, 0.1 mL 4N HCl in 1,4-dioxane and 1 mL N-butanol was placed in a 10 mL snap-top microwave vial (CEM Corp.) and heated to 120° C. microwave for 40 min. The reaction was monitored by LC/MS. The precipitated solid was filtered to yield 80 mg of 4-(5-fluoro-4-(methylamino)pyrimidin-2-ylamino)-3-methoxybenzoic acid.

[0533] The same method was used to make the compounds shown in Table 3 below, using the appropriate amines and the appropriately substituted 2-chloropyrimidines.

TABLE 3

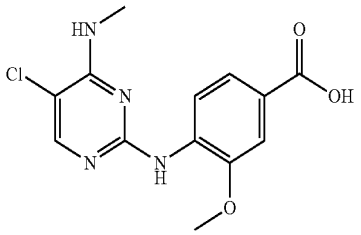
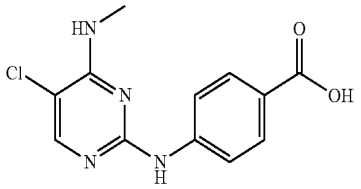
1	4-(5-chloro-4-(methylamino)pyrimidin-2-ylamino)-3-methoxybenzoic acid	
2	4-(5-chloro-4-(methylamino)pyrimidin-2-ylamino)benzoic acid	

TABLE 3-continued

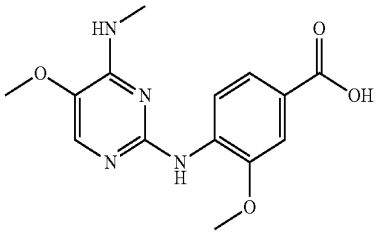
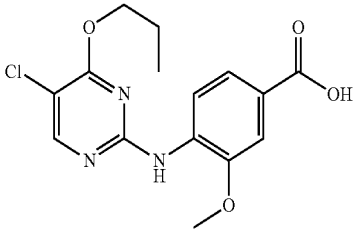
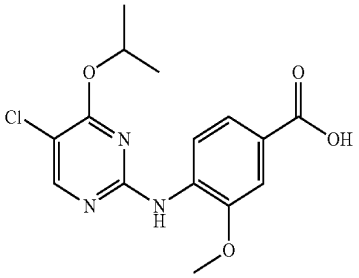
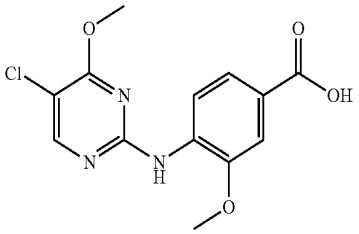
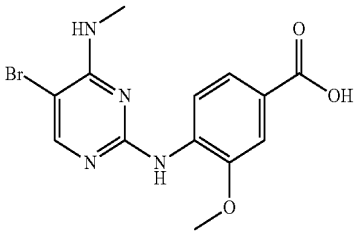
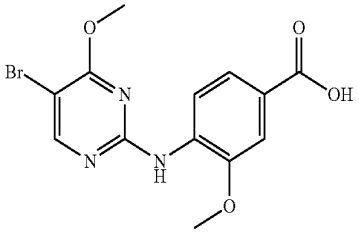
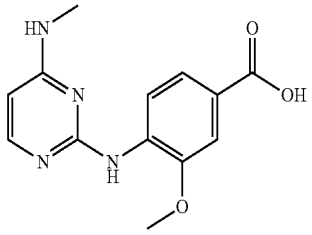
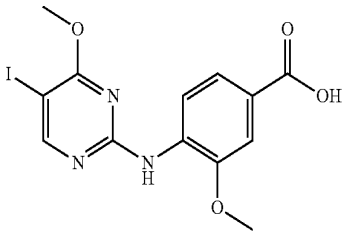
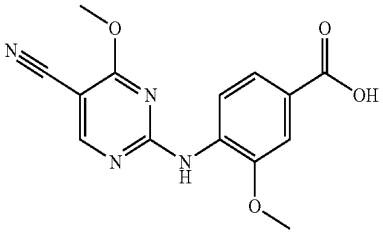
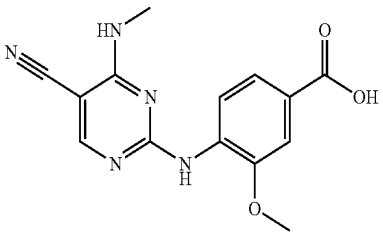
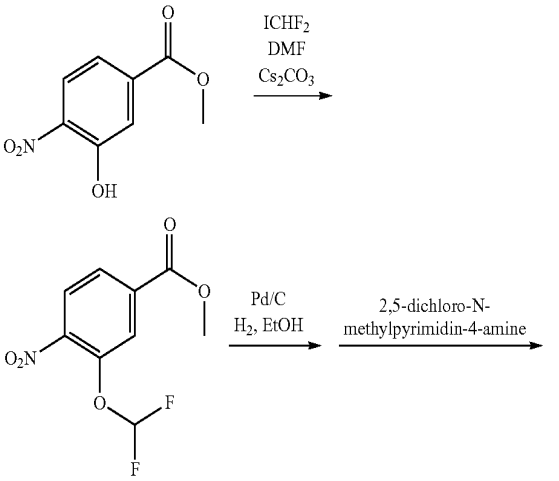
3	3-methoxy-4-(5-methoxy-4-(methylamino)pyrimidin-2-ylamino)benzoic acid	
5	4-(5-chloro-4-propoxypyrimidin-2-ylamino)-3-methoxybenzoic acid	
7	4-(5-chloro-4-isopropoxypyrimidin-2-ylamino)-3-methoxybenzoic acid	
8	4-(5-chloro-4-methoxypyrimidin-2-ylamino)-3-methoxybenzoic acid	
10	4-(5-bromo-4-(methylamino)pyrimidin-2-ylamino)-3-methoxybenzoic acid	
11	4-(5-bromo-4-methoxypyrimidin-2-ylamino)-3-methoxybenzoic acid	

TABLE 3-continued

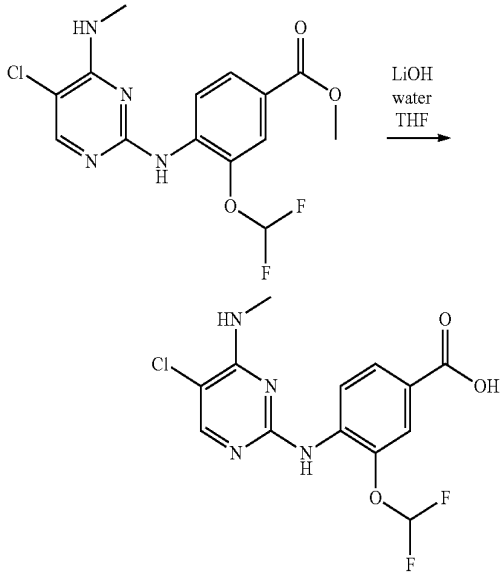
12	3-methoxy-4-(4-(methylamino)pyrimidin-2-ylamino)benzoic acid	
13	4-(5-iodo-4-methoxypyrimidin-2-ylamino)-3-methoxybenzoic acid	
14	4-(5-cyano-4-methoxypyrimidin-2-ylamino)-3-methoxybenzoic acid	
15	4-(5-cyano-4-methoxypyrimidin-2-ylamino)-3-methoxybenzoic acid	

Preparation 4: 4-(5-chloro-4-(methylamino)pyrimidin-2-ylamino)-3-(difluoromethoxy)benzoic acid

[0534]



-continued



[0535] To a cooled solution of 1 g of methyl-3-hydroxy-4-nitrobenzoate, 3.31 g of cesium carbonate in 20 mL of DMF, was carefully added 1.5 equivalents of difluoroiodomethane. The reaction was allowed to warm to room temperature and followed by TLC. Upon completion of the reaction, the mixture was concentrated and purified by silica get chromatography to give 1.2 g of methyl 3-(difluoromethoxy)-4-nitrobenzoate.

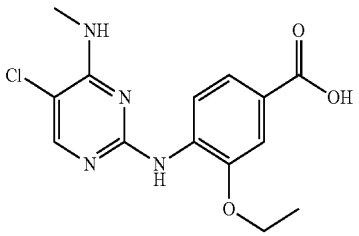
[0536] Methyl 3-(difluoromethoxy)-4-nitrobenzoate (0.9 g) was placed in a 250 mL round bottom flask and dissolved in 30 mL of ethanol. Pd/C (0.15 g, 10% Pd) was carefully added and a balloon of hydrogen was attached to the flask. The reaction was vigorously stirred over night. After checking by TLC, the reaction was filtered through a pad of celite and concentrated to give 0.6 g of methyl 4-amino-3-(difluoromethoxy)benzoate which was used without further purification.

[0537] Methyl 4-amino-3-(difluoromethoxy)benzoate (70 mg), 2,5-dichloro-N-methylpyrimidin-4-amine, 0.1 mL of 4N HCl/dioxane and 1 mL of n-butanol were placed in a microwave vial. The reaction was heated for 30 minutes at 150° C. and monitored by LCMS. The mixture was concentrated and purified by silica gel chromatography to give 100 mg of pure methyl 4-(5-chloro-4-(methylamino)pyrimidin-2-ylamino)-3-(difluoromethoxy)benzoate.

[0538] Methyl 4-(5-chloro-4-(methylamino)pyrimidin-2-ylamino)-3-(difluoromethoxy)benzoate (500 mg) was dissolved in 5 mL of THF and 5 mL of water. After dissolution, 234 mg of lithium hydroxide was added and the reaction was stirred at room temperature over night. The mixture was checked by LCMS and then carefully acidified with 1N HCl and partitioned with ethyl acetate. The organic layer was concentrated and purified by silica gel chromatography to give 250 mg of 4-(5-chloro-4-(methylamino)pyrimidin-2-ylamino)-3-(difluoromethoxy)benzoic acid.

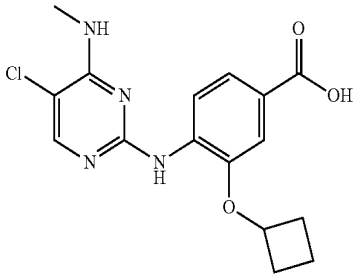
[0539] Similarly made were:

1



4-(5-chloro-4-(methylamino)pyrimidin-2-ylamino)-3-ethoxybenzoic acid

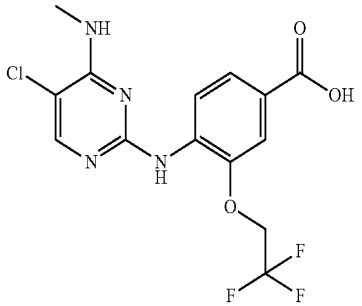
2



4-(5-chloro-4-(methylamino)pyrimidin-2-ylamino)-3-cyclobutoxybenzoic acid

-continued

3

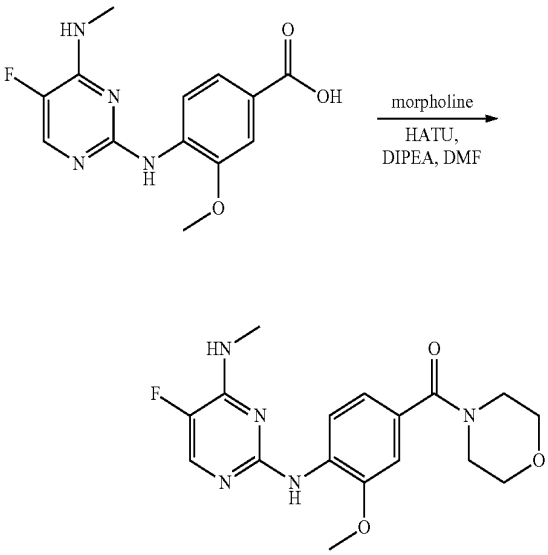


4-(5-chloro-4-(methylamino)pyrimidin-2-ylamino)-3-(2,2,2-trifluoroethoxy)benzoic acid

Example 1

(4-(5-fluoro-4-(methylamino)pyrimidin-2-ylamino)-3-methoxyphenyl)(morpholino)methanone

[0540]



[0541] A mixture of 100 mg 4-(5-fluoro-4-(methylamino)pyrimidin-2-ylamino)-3-methoxybenzoic acid, 47 μL morpholine, 205 mg HATU, 188 mL diisopropylethylamine in 1 mL of dimethylformamide was stirred at room temperature overnight. The reaction was checked by LCMS and found to be complete. The reaction was diluted with EtOAc, and the organic layer washed with saturated $NaHCO_3$ and brine. The organic layer was concentrated and purified by preparative reverse phase HPLC to yield 12 mg of (4-(5-fluoro-4-(methylamino)pyrimidin-2-ylamino)-3-methoxyphenyl)(morpholino)methanone.

[0542] Compounds made using the above procedure are shown in Table 4 below, together with proton NMR, and LRRK2 K_i (micromolar) data for selected compounds determined from the assay described below.

TABLE 4

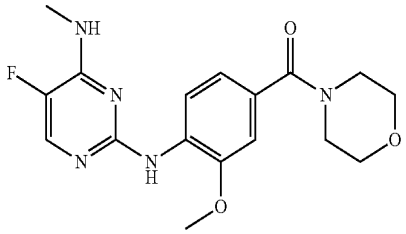
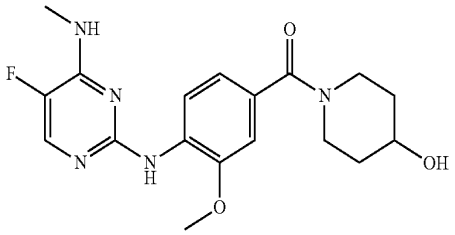
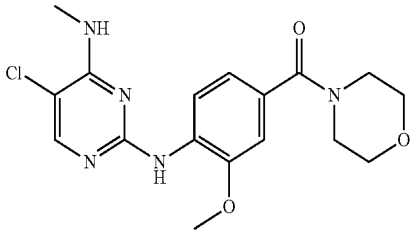
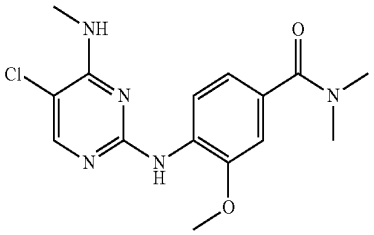
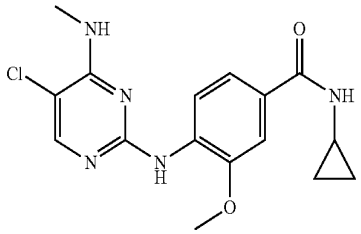
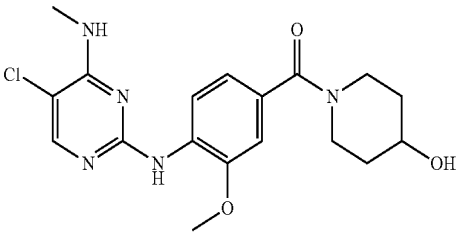
	Name	Structure	^{1}H NMR	K_I
1	[4-(5-Fluoro-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-morpholin-4-yl-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.46(d, 1H), 7.89(d, 1H), 7.56(d, 2H), 7.04(s, 1H), 7.00(d, 1H), 3.90(s, 3H), 3.58(d, 4H), 3.52(s, 3H), 2.90(t, 3H)	
2	[4-(5-Fluoro-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-(4-hydroxy-piperidin-1-yl)-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.43(d, 1H), 7.89(d, 1H), 7.55(d, 2H), 7.00(s, 1H), 6.96(d, 1H), 4.77(d, 1H), 3.90(s, 3H), 3.73(dd, 2H), 3.23-3.12 (m, 2H), 2.89(d, 3H), 1.74 (s, 2H), 1.36(d, 2H).	0.0446
3	[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-morpholin-4-yl-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.41(d, 1H), 7.96(s, 1H), 7.68(s, 1H), 7.32(d, 1H), 7.05(s, 1H), 7.01(d, 1H), 3.90(s, 3H), 3.56(d, 8H), 2.90(t, 3H).	
4	4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-N,N-dimethyl-benzamide		^{1}H NMR(400 MHz, DMSO) δ 8.39(d, 1H), 7.96(s, 1H), 7.67(s, 1H), 7.31(d, 1H), 7.05(s, 1H), 7.00(d, 1H), 3.87(d, 3H), 2.97(s, 6H), 2.91(d, 3H).	0.0061
5	4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-N-cyclopropyl-3-methoxy-benzamide		^{1}H NMR(400 MHz, DMSO) δ 8.43(d, 1H), 8.28(s, 1H), 7.97(s, 1H), 7.70(s, 1H), 7.46(d, 2H), 7.35(d ,1H), 3.93(s, 3H), 2.91(d, 3H), 2.82(d, 1H), 0.75-0.62(m, 2H), 0.56 (d, 2H).	0.0024
6	[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-(4-hydroxy-piperidin-1-yl)-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.38(d, 1H), 7.96(s, 1H), 7.67(s, 1H), 7.31(d, 1H), 7.01(s, 1H), 6.96(d, 1H), 4.77(d, 1H), 3.88(d, 3H), 3.73(d, 2H), 3.18(t, 2H), 2.91(d, 3H), 1.74(s, 2H), 1.36(d, 2H).	

TABLE 4-continued

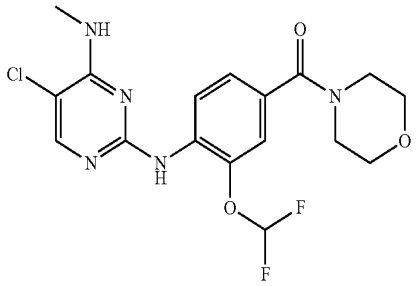
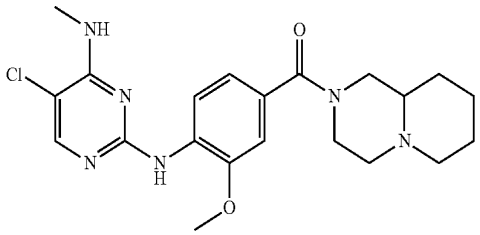
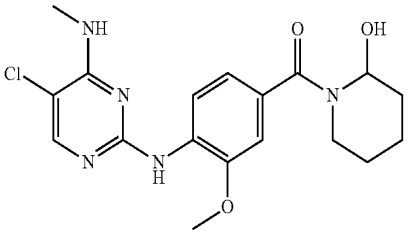
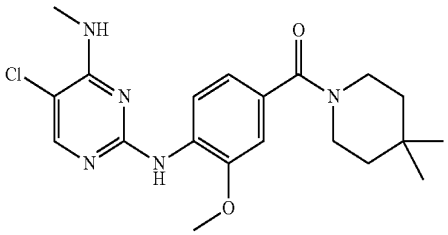
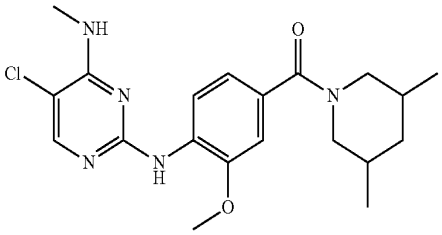
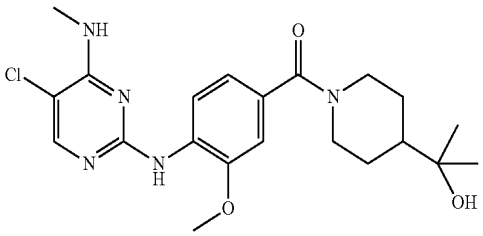
	Name	Structure	^{1}H NMR	K_I
7	[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-difluoromethoxy-phenyl]-morpholin-4-yl-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.34(d, 1H), 8.07(s, 1H), 7.95(s, 1H), 7.29(ddd, 3H), 3.56(d, 8H), 2.98-2.83(m, 3H).	00049
8	[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-(octahydro-pyrido[1,2-a]pyrazin-2-yl)-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.40(d, 1H), 7.96(s, 1H), 7.67(s, 1H), 7.32(d, 1H), 7.02(d, 1H), 6.97(dd, 1H), 3.91(d, 3H), 2.91(d, 3H), 2.81-2.61 (m, 3H), 2.12-1.89(m, 2H), 1.81(t, 1H), 1.76-1.36(m, 4H), 1.34-0.97 (m, 2H).	0.0035
9	[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-(2-hydroxy-piperidin-1-yl)-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.38(d, 1H), 7.96(s, 1H), 7.67(s, 1H), 7.31(d, 1H), 7.04(s, 1H), 6.98(d, 1H), 4.91(s, 1H), 3.91(d, 3H), 3.51(s, 2H), 3.11(s, 1H), 2.91(d, 3H), 1.86(s, 1H), 1.70(s, 1H), 1.41(s, 2H).	
10	[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-(4,4-dimethyl-piperidin-1-yl)-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.38(d, 1H), 7.96(s, 1H), 7.67(s, 1H), 7.31(d, 1H), 6.98(d, 1H), 6.94(d, 1H), 3.89(s, 3H), 3.39(d, 1H), 3.24(d, 2H), 2.91(d, 3H), 1.54(s, 2H), 1.44-1.33(m, 2H), 0.87 (s, 6H).	
11	[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-(3,5-dimethyl-piperidin-1-yl)-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.38(d, 1H), 7.96(s, 1H), 7.67(s, 1H), 7.31(d, 1H), 7.00(d, 1H), 6.99-6.91(m, 1H), 3.91 (d, 3H), 2.90(d, 3H), 1.95-1.71(m, 2H), 1.67-1.49 (m, 2H), 1.43(t, 1H), 1.00-0.68(m, 7H).	0.0062
12	[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-[4-(1-hydroxy-1-methyl-ethyl)-piperidin-1-yl]-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.38(d, 1H), 7.96(s, 1H), 7.67(s, 1H), 7.31(d, 1H), 7.01(d, 1H), 6.96(dd, 1H), 4.14(s, 1H), 3.90(s, 3H), 2.91(d, 3H), 1.71(s, 2H), 1.44(t, 1H), 1.24-1.08(m 2H), 1.04 (s, 6H).	

TABLE 4-continued

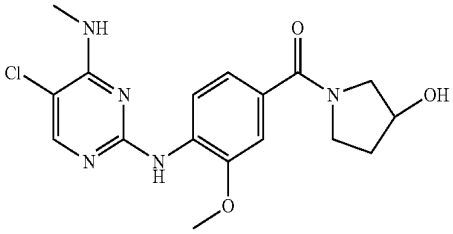
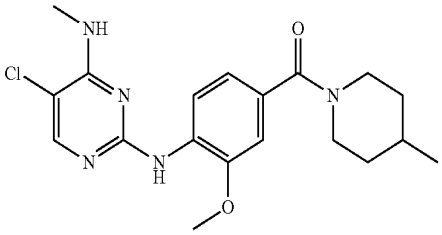
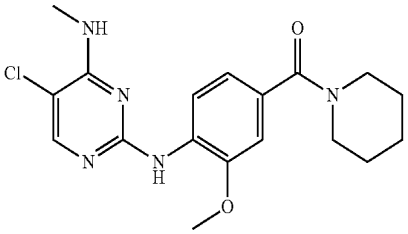
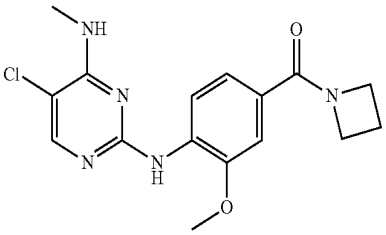
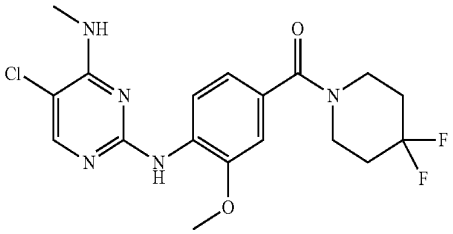
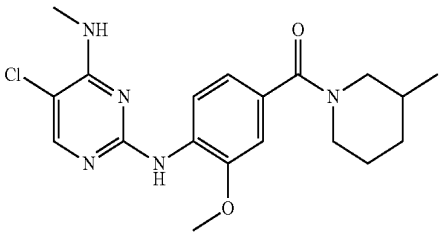
	Name	Structure	^{1}H NMR	K_I
13	[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-(3-hydroxy-pyrrolidin-1-yl)-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.40(d, 1H), 7.97(s, 1H), 7.68(s, 1H), 7.32(d, 1H), 7.14(d, 2H), 4.97(s, 1H), 4.28(d, 1H), 3.92(d, 3H), 3.72-3.39 (m, 3H), 2.90(t, 3H), 1.89 (dd, 2H).	
14	[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-(4-methyl-piperidin-1-yl)-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.38(d, 1H), 7.95(s, 1H), 7.66(s, 1H), 7.31(d, 1H), 7.00(d, 1H), 6.95(dd, 1H), 3.91(d, 3H), 2.91(d, 4H), 1.62(d, 3H), 1.08(q, 2H), 0.94(t, 3H).	
15	[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-piperidin-1-yl-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.38(d, 1H), 7.96(s, 1H), 7.66(s, 1H), 7.31(d, 1H), 7.00(d, 1H), 6.95(dd, 1H), 3.89(s, 3H), 3.41(d, 4H), 2.91(d, 3H), 1.62(d, 2H), 1.51(s, 4H).	0.0025
16	Azetidin-1-yl-[4-(5-chloro-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.44(d, 1H), 7.97(s, 1H), 7.70(s, 1H), 7.34(d, 1H), 7.26-7.20 (m, 2H), 4.35(s, 2H), 4.03 (s, 2H), 3.91(s, 3H), 2.91 (d, 3H), 2.30-2.20(m, 2H).	0.0052
17	[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-(4,4-difluoro-piperidin-1-yl)-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.41(d, 1H), 7.96(s, 1H), 7.68(s, 1H), 7.33(d, 1H), 7.09(d, 1H), 7.04(dd, 1H), 3.91(s, 3H), 3.60(s, 4H), 2.91(d, 3H), 2.11-1.97(m, 4H).	0.0030
18	[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-(3-methyl-piperidin-1-yl)-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.38(d, 1H), 7.96(s, 1H), 7.67(s, 1H), 7.31(d, 1H), 7.00(d, 1H), 6.95(dd, 1H), 3.89(s, 3H), 2.90(d, 3H), 1.78(d, 1H), 1.70-1.50(m, 2H), 1.42 (d, 1H), 1.22-1.08(m, 1H), 0.84(s, 3H).	

TABLE 4-continued

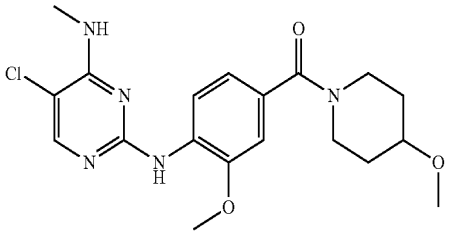
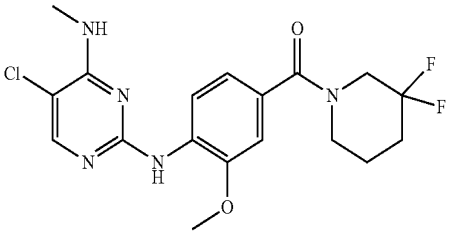
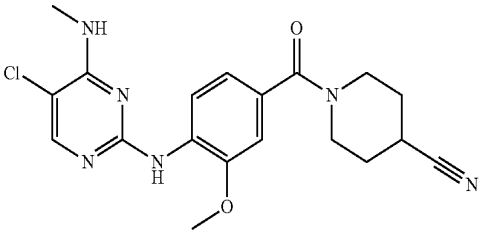
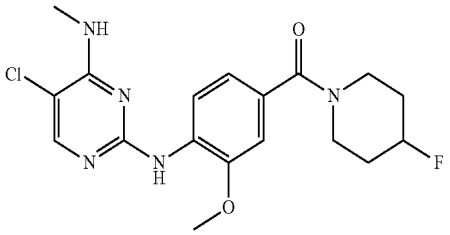
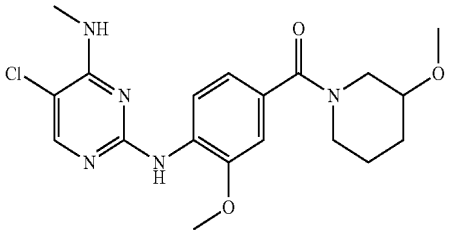
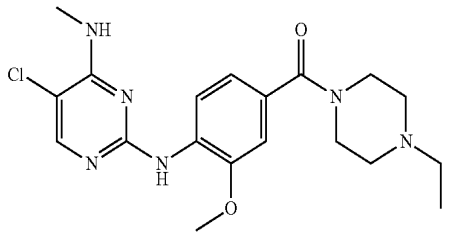
	Name	Structure	^{1}H NMR	K_I
19	[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-(4-methoxy-piperidin-1-yl)-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.39(d, 1H), 7.96(s, 1H), 7.67(s, 1H), 7.31(d, 1H), 7.02(d, 1H), 6.97(dd, 1H), 3.90(s, 3H), 3.49-3.39(m, 2H), 3.26 (s, H), 3.22(d, 2H), 2.91 (d, 3H), 1.84(s, 2H), 1.44 (d, 2H).	
20	[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-(3,3-difluoro-piperidin-1-yl)-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.43(d, 1H), 7.97(s, 1H), 7.70(s, 1H), 7.33(d, 1H), 7.04-6.96 (m, 2H), 3.90(s, 3H), 3.84 (s, 2H), 3.53(s, 2H), 2.91 (d, 3H), 2.18-2.01(m, 2H), 1.70(s, 2H).	
21	1-[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-benzoyl]-piperidine-4-carbonitrile		^{1}H NMR(400 MHz, DMSO) δ 8.40(d, 1H), 7.96(s, 1H), 7.67(s, 1H), 7.32(d, 1H), 7.05(d, 1H), 6.99(dd, 1H), 3.89(d, 3H), 3.72(s, 2H), 3.20-3.09 (m, 1H), 2.91(d, 3H), 1.90 (s, 2H), 1.81-1.67(m, 2H).	
22	[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-(4-fluoro-piperidin-1-yl)-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.40(d, 1H), 7.96(s, 1H), 7.67(s, 1H), 7.32(d, 1H), 7.05(d, 1H), 7.00(dd, 1H), 5.02-4.81 (m, 1H), 3.90(s, 3H), 3.68-3.37(m, 4H), 2.91(d, 3H), 2.00-1.80(m, 2H), 1.73(s, 2H).	
23	[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-(3-methoxy-piperidin-1-yl)-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.38(d, 1H), 7.96(s, 1H), 7.67(s, 1H), 7.31(d, 1H), 7.03(s, 1H), 6.97(d, 1H), 3.90(s, 3H), 3.41(d, 2H), 2.90(d, 3H), 1.86(s, 1H), 1.63(d, 2H), 1.42(s, 1H).	
24	[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-(4-ethyl-piperazin-1-yl)-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.40(d, 1H), 7.96(s, 1H), 7.67(s, 1H), 7.32(d, 1H), 7.02(d, 1H), 6.97(dd, 1H), 3.90(s, 3H), 3.50(s, 4H), 2.91(d, 3H), 2.35(dd, 6H), 1.00(t, 3H).	

TABLE 4-continued

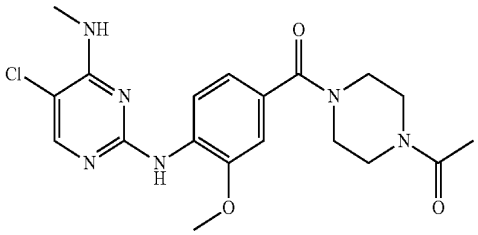
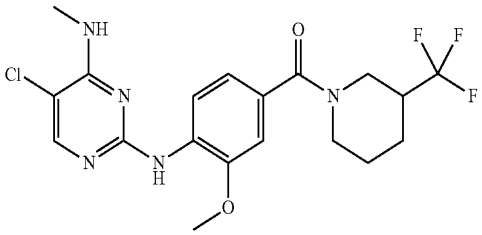
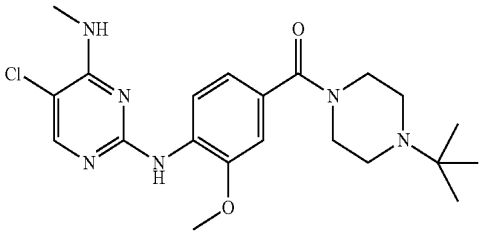
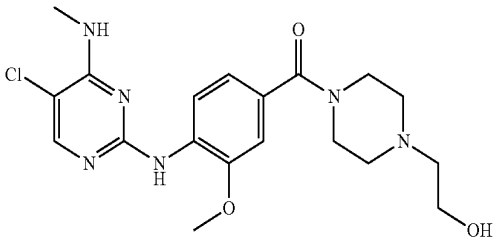
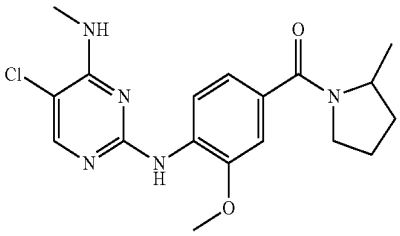
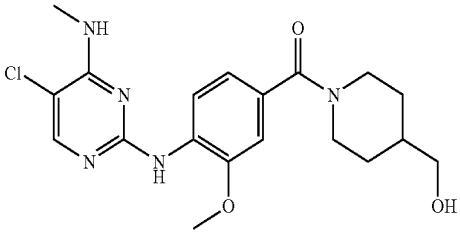
	Name	Structure	^{1}H NMR	K_I
25	1-{4-[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-benzoyl]-piperazin-1-yl}-ethanone		^{1}H NMR(400 MHz, DMSO) δ 8.42(d, 1H), 7.96(s, 1H), 7.68(s, 1H), 7.33(d, 1H), 7.07(d, 1H), 7.02(dd, 1H), 3.91(s, 3H), 3.51(d, 8H), 2.91(d, 3H), 2.02(s, 3H).	0.0034
26	[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-(3-trifluoromethyl-piperidin-1-yl)-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.40(d, 1H), 7.96(s, 1H), 7.69(s, 1H), 7.32(d, 1H), 7.05(d, 1H), 7.03-6.97(m, 1H), 3.90 (s, 3H), 2.97(d, 2H), 2.89 (t, 3H), 2.67(s, 1H), 1.99 (d, 1H), 1.72(s, 1H), 1.65-1.44(m, 2H).	0.0028
27	(4-tert-Butyl-piperidin-1-yl)-[4-(5-chloro-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.38(d, 1H), 7.96(s, 1H), 7.67(s, 1H), 7.31(d, 1H), 7.01(d, 1H), 6.96(dd, 1H), 3.89(s, 3H), 2.92(t, 3H), 1.67(s, 2H), 1.33-1.03(m, 3H), 0.85 (s, 9H).	
28	[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.40(d, 1H), 7.96(s, 1H), 7.67(s, 1H), 7.32(d, 1H), 7.02(d, 1H), 6.97(dd, 1H), 4.42(t, 1H), 3.90(s, 3H), 3.50(dd, 6H), 2.91(d, 3H), 2.41(t, 6H).	
29	[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-(2-methyl-pyrrolidin-1-yl)-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.39(d, 1H), 7.96(s, 1H), 7.67(s, 1H), 7.32(d, 1H), 7.11(s, 2H), 4.17-4.05(m, 1H), 3.90 (s, 3H), 3.54(s, 1H), 3.48-3.36(m ,1H), 2.90(t, 3H), 2.07(td, 1H), 1.87(s, 1H), 1.70(s, 1H), 1.59-1.46(m, 1H), 1.24(s, 2H).	0.0038
30	[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-(4-hydroxymethyl-piperidin-1-yl)-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.38(d, 1H), 7.96(s, 1H), 7.66(s, 1H), 7.31(d, 1H), 7.00(d, 1H), 6.95(dd, 1H), 4.49(t, 1H), 3.89(s, 3H), 3.28(t, 2H), 2.91(d, 4H), 1.66(s, 3H), 1.09(q, 2H).	

TABLE 4-continued

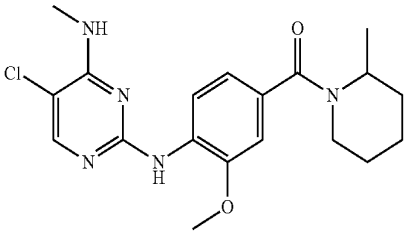
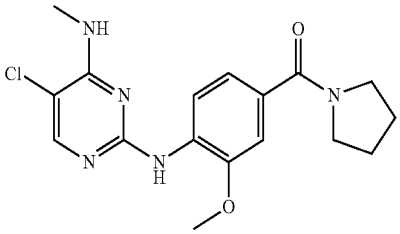
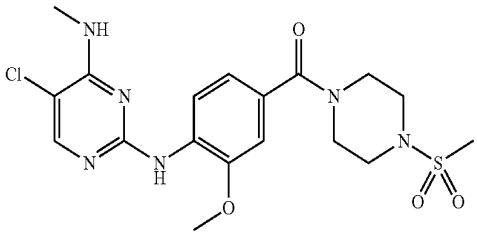
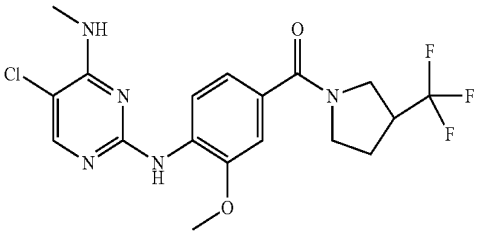
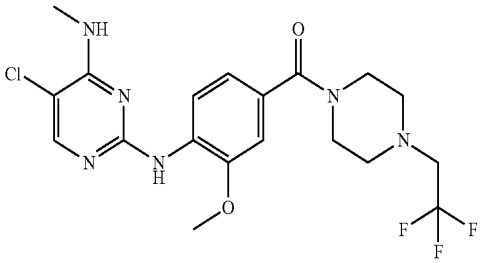
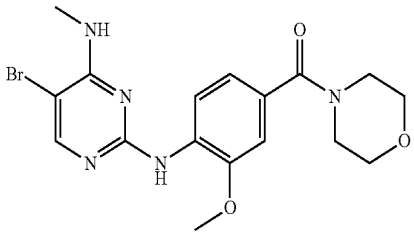
	Name	Structure	^{1}H NMR	K_I
31	[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-(2-methyl-piperidin-1-yl)-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.37(d, 1H), 7.95(s, 1H), 7.66(s, 1H), 7.30(d, 1H), 6.98(d, 1H), 6.93(dd, 1H), 4.39(s, 1H), 3.89(s, 4H), 2.97(t, 1H), 2.90(d, 3H), 1.73-1.28 (m, 6H), 1.20(d, 3H).	
32	[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-pyrrolidin-1-yl-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.40(d, 1H), 7.96(s, 1H), 7.67(s, 1H), 7.32(d, 1H), 7.18-7.11 (m, 2H), 3.90(s, 3H), 3.47 (d, 4H), 2.91(d, 3H), 1.83 (s, 4H).	0.0047
33	[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-(4-methanesulfonyl-piperazin-1-yl)-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.43(d, 1H), 7.97(s, 1H), 7.69(s, 1H), 7.33(d, 1H), 7.09-6.99 (m, 2H), 3.91(s, 3H), 3.62 (s, 4H), 3.17(s, 4H), 2.91 (d, 6H).	0.0036
34	[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-(3-trifluoromethyl-pyrrolidin-1-yl)-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.46-8.39(m, 1H), 7.95(d, 1H), 7.69(s, 1H), 7.33(d, 1H), 7.16(dd, 2H), 3.91(s, 3H), 3.76(dt, 1H), 3.60(dd, 3H), 2.91(d, 3H), 2.17(s, 1H), 2.05-1.95(m, 1H).	
35	[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-[4-(2,2,2-trifluoro-ethyl)-piperazin-1-yl]-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.40(d, 1H), 7.95(d, 1H), 7.67(s, 1H), 7.32(d, 1H), 7.03(d, 1H), 6.98(dd, 1H), 3.89(d, 3H), 3.52(s, 4H), 3.28-3.13 (m, 2H), 2.90(t, 3H), 2.64 (s, 4H).	
36	[4-(5-Bromo-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-morpholin-4-yl-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.40(d, 1H), 8.04(s, 1H), 7.68(s, 1H), 7.14(d, 1H), 7.05(d, 1H), 7.01(dd, 1H), 3.90(s, 3H), 3.56(d, 8H), 2.90(d, 3H).	

TABLE 4-continued

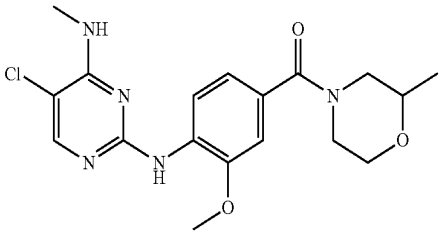
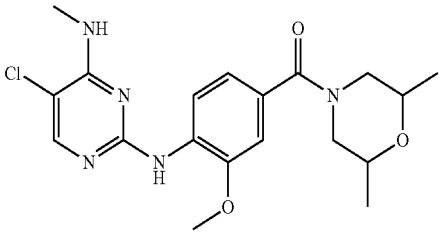
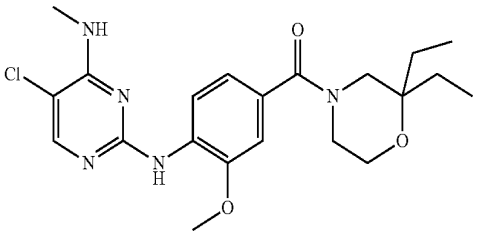
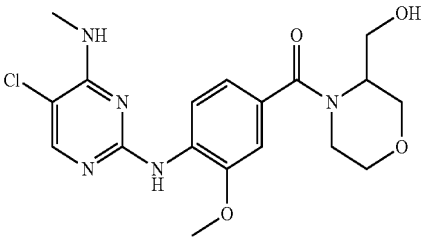
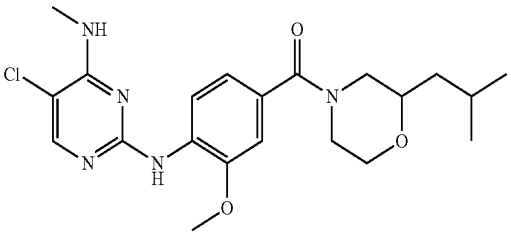
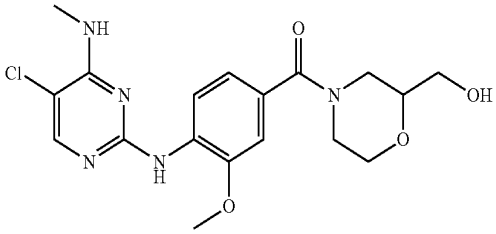
	Name	Structure	^{1}H NMR	K_I
37	[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-(2-methyl-morpholin-4-yl)-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.41(d, 1H), 7.96(s, 1H), 7.68(s, 1H), 7.32(d, 1H), 7.05(d, 1H), 7.00(dd, 1H), 3.90(s, 3H), 3.79(s, 1H), 3.48(ddd, 2H), 2.91(d, 3H), 1.08(s, 3H).	
38	[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-(2,6-dimethyl-morpholin-4-yl)-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.41(d, 1H), 7.96(s, 1H), 7.68(s, 1H), 7.32(d, 1H), 7.04(d, 1H), 7.00(dd, 1H), 3.90(s, 3H), 3.54(ddd, 2H), 2.89(t, 3H), 1.07(s, 6H).	
39	[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-(2,2-diethyl-morpholin-4-yl)-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.41(d, 1H), 7.96(s, 1H), 7.68(s, 1H), 7.32(d, 1H), 7.01(dd, 2H), 3.90(s, 3H), 3.69-3.36 (m, 6H), 2.91(d, 3H), 1.47 (d, 4H), 0.75(s, 6H).	0.0055
40	[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-(3-hydroxymethyl-morpholin-4-yl)-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.39(d, 1H), 7.96(s, 1H), 7.67(s, 1H), 7.32(d, 1H), 7.08(s, 1H), 7.02(d, 1H), 4.92(s, 1H), 3.90(s, 3H), 3.88-3.44 (m, 6H), 2.91(d, 3H).	0.0044
41	[4-(-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-(2-isobutyl-morpholin-4-yl)-methanone		^{1}H NMR(400 Mhz, DMSO) δ 8.41(d, 1H), 7.96(s, 1H), 7.68(s, 1H), 7.32(d, 1H), 7.06(d, 1H), 7.00(dd, 1H), 3.90(s, 3H), 3.76(d, 1H), 3.44(dd, 3H), 2.91(d, 3H), 1.69(s, 1H), 1.36(s, 1H), 1.18(s, 1H), 0.86(s, 6H).	0.0042
42	[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-(2-hydroxymethyl-morpholin-4-yl)-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.41(d, 1H), 7.96(s, 1H), 7.68(s, 1H), 7.32(d, 1H), 7.06(d, 1H), 7.01(dd, 1H), 4.78(s, 1H), 3.90(s, 3H), 3.85(d, 1H), 3.42(ddd, 4H), 2.91(d, 3H).	

TABLE 4-continued

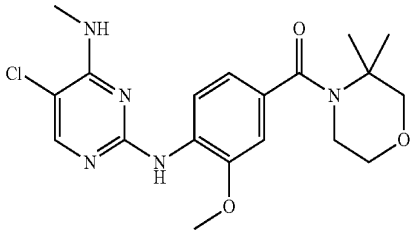
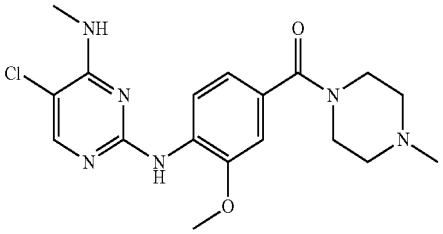
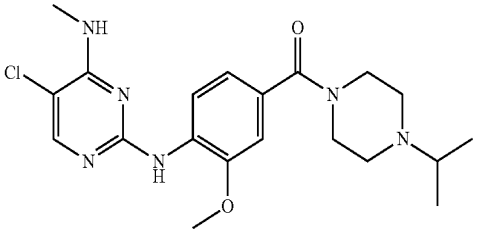
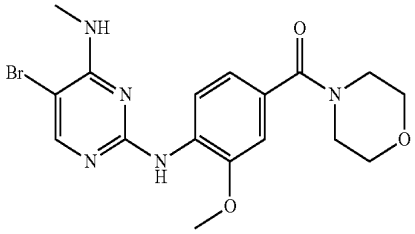
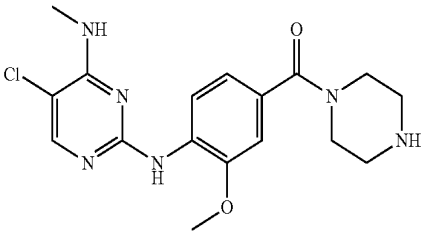
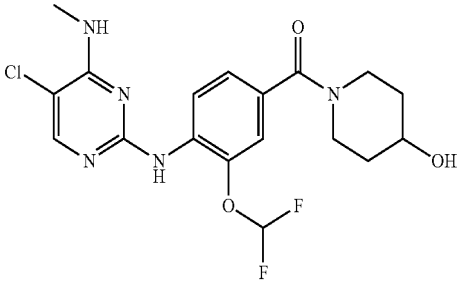
	Name	Structure	^{1}H NMR	K_I
43	[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-(3,3-dimethyl-morpholin-4-yl)-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.44-8.37(m, 1H), 7.96(s, 1H), 7.68(s, 1H), 7.33(d, 1H), 7.04(dd, 2H), 3.91(s, 3H), 3.73-3.63(m, 2H), 3.39(d, 2H), 2.91(d, 3H), 1.41(d, 6H).	
44	[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-(4-methyl-piperazin-1-yl)-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.40(d, 1H), 7.96(s, 1H), 7.67(s, 1H), 7.32(d, 1H), 7.02(d, 1H), 6.97(dd, 1H), 3.90(s, 3H), 3.50(s, 4H), 2.89(t, 3H), 2.31(s, 4H), 2.21(d, 3H).	
45	[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-(4-isopropyl-piperazin-1-yl)-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.39(d, 1H), 7.96(s, 1H), 7.67(s, 1H), 7.32(d, 1H), 7.02(s, 1H), 6.97(d, 1H), 3.90(s, 3H), 3.44(d, 4H), 2.91(d, 3H), 2.74-2.60(m, 1H), 2.44 (s, 4H), 0.97(d, 6H).	
46	[4-(5-Bromo-4-methoxy-pyrimidin-2-ylamino)-3-methoxy-phenyl]-morpholin-4-yl-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.38(s, 1H), 8.31(s, 1H), 8.15(d, 1H), 7.08(d, 1H), 7.02(dd, 1H), 3.98(s, 3H), 3.89(s, 3H), 3.56(d, 8H).	
47	[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-piperazin-1-yl-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.42(d, 1H), 7.96(s, 1H), 7.69(s, 1H), 7.33(d, 1H), 7.06(d, 1H), 7.05-7.00(m, 1H), 3.91 (s, 3H), 3.59(s, 4H), 2.97 (s, 4H), 2.90(t, 3H).	0.0028
48	[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-difluoromethoxy-phenyl]-(4-hydroxy-piperidin-1-yl)-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.30(d, 1H), 8.06(s, 1H), 7.95(s, 1H), 7.37-7.14(m, 3H), 3.74 (s, 2H), 2.88(dd, 3H), 1.75 (s, 2H), 1.37(s, 2H).	

TABLE 4-continued

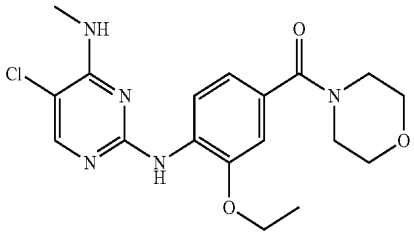
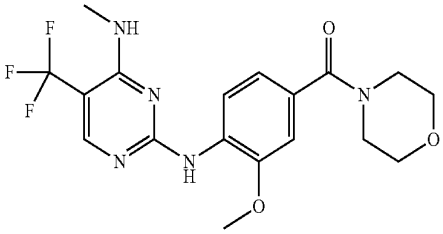
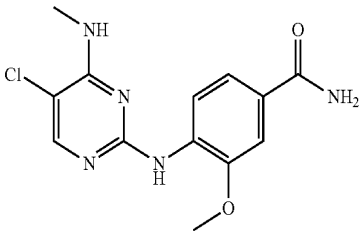
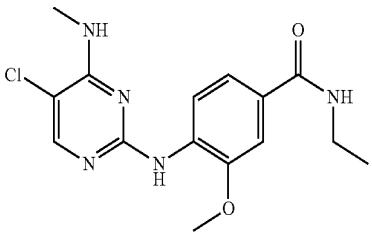
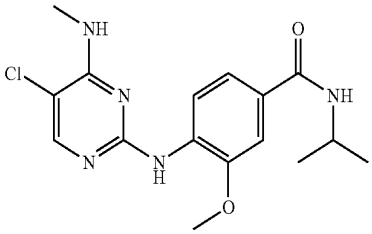
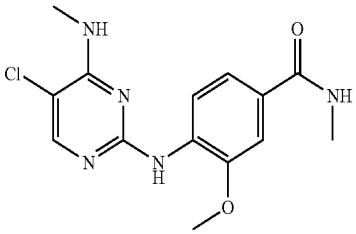
	Name	Structure	^{1}H NMR	K_I
49	[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-ethoxy-phenyl]-morpholin-4-yl-methanone		1H NMR(400 MHz, DMSO) · 8.44(d, J = 8.3 Hz, 1H), 7.96(s, 1H), 7.65 (s, 1H), 7.33(d, J = 4.5 Hz, 1H), 7.04(d, J = 1.4 Hz, 1H), 7.00(d, J = 8.3 Hz, 1H), 4.16(q, J = 6.9 Hz, 2H), 3.55(d, J = 35.7 Hz, 8H), 2.92(d, J = 4.6 Hz, 3H), 1.45-1.33(m, 3H).	0.0043
50	[3-Methoxy-4-(4-methylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-phenyl]-morpholin-4-yl-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.31(d, 1H), 8.19(s, 1H), 8.07(s, 1H), 7.21(d, 1H), 7.07(s, 1H), 7.02(d, 1H), 3.90(s, 3H), 3.56(d, 9H), 2.92(d, 3H).	0.0027
51	4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-benzamide		^{1}H NMR(400 MHz, DMSO) δ 8.47-8.39(m, 1H), 7.97(s, 1H), 7.83(s, 1H), 7.69(s, 1H), 7.51(d, 2H), 7.32(d, 1H), 7.16(s, 1H), 3.93(s, 3H), 2.92(d, 3H).	0.0051
52	4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-N-ethyl-3-methoxy-benzamide		^{1}H NMR(400 MHz, DMSO) δ 8.46-8.41(m, 1H), 8.30(t, 1H), 7.96(d, 1H), 7.69(s, 1H), 7.48(t, 2H), 7.32(d, 1H), 3.91(d, 3H), 2.92(d, 3H), 1.12(t, 3H).	
53	4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-N-isopropyl-3-methoxy-benzamide		^{1}H NMR(400 MHz, DMSO) δ 8.44(d, 1H), 8.03(d, 1H), 7.97(s, 1H), 7.69(s, 1H), 7.53-7.45 (m, 2H), 7.32(d, 1H), 4.10 (dq, 1H), 3.94(s, 3H), 2.92 (d, 3H), 1.17(d, 6H).	0.0020
54	4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-N-methyl-benzamide		^{1}H NMR(400 MHz, DMSO) δ 8.43(d, J = 8.2 Hz, 1H), 8.27(d, J = 4.2 Hz, 1H), 7.97(s, 1H), 7.69(s, 1H), 7.46(d, J = 8.2 Hz, 2H), 7.32(d, J = 4.2 Hz, 1H), 6.48(s, 1H), 3.93(s, 3H), 2.92(d, J = 4.5 Hz, 3H), 2.78(d, J = 4.4 Hz, 3H).	

TABLE 4-continued

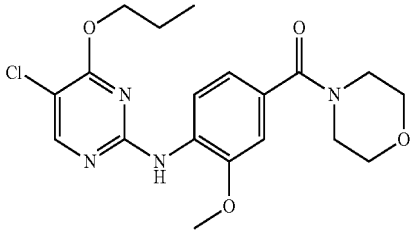
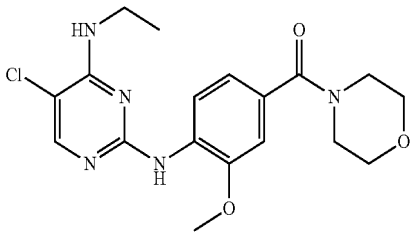
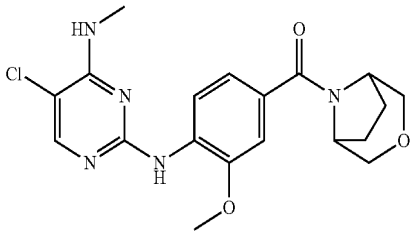
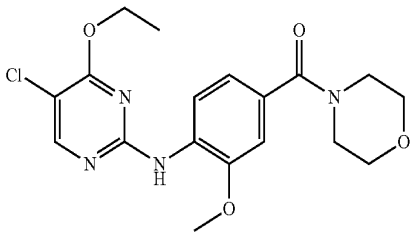
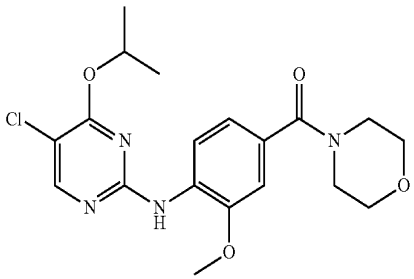
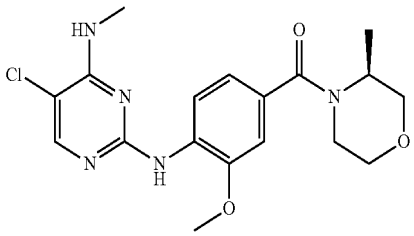
	Name	Structure	^{1}H NMR	K_I
55	[4-(5-Chloro-4-propoxy-pyrimidin-2-ylamino)-3-methoxy-phenyl]-morpholin-4-yl-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.31(s, 1H), 8.26(s, 1H), 8.13(d, 1H), 7.07(s, 1H), 7.02(d, 1H), 4.35(t, 2H), 3.88(s, 3H), 3.56(d, 8H), 1.76(d, 2H), 0.97(t, 3H).	
56	[4-(5-Chloro-4-ethylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-morpholin-4-yl-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.37(d, 1H), 7.96(s, 1H), 7.66(s, 1H), 7.29(t, 1H), 7.05(s, 1H), 7.02-6.97(m, 1H), 3.90 (s, 3H), 3.64-3.48(m, 7H), 3.48-3.40(m, 2H), 1.17(t, 3H).	
57	[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-(3-oxa-8-aza-bicyclo[3.2.1]oct-8-yl)-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.43(d, 1H), 7.96(s, 1H), 7.68(s, 1H), 7.31(d, 1H), 7.11(d, 2H), 3.92(s, 3H), 3.67(d, 2H), 3.59(s, 2H), 2.91(d, 3H), 1.87(s, 4H).	0.0025
58	[4-(5-Chloro-4-ethoxy-pyrimidin-2-ylamino)-3-methoxy-phenyl]-morpholin-4-yl-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.31(s, 1H), 8.25(s, 1H), 8.14(d, 1H), 7.08(s, 1H), 7.02(d, 1H), 4.45(q, 2H), 3.89(s, 3H), 3.56(d, 8H), 1.36(t, 3H).	
59	[4-(5-Chloro-4-isopropoxy-pyrimidin-2-ylamino)-3-methoxy-phenyl]-morpholin-4-yl-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.30(s, 1H), 8.25 (s, 1H), 8.11(d, J = 8.2 Hz, 1H), 7.43-7.32(m, 1H), 7.08(d, J = 1.4 Hz, 1H), 7.02(d, J = 8.2 Hz, 1H), 5.34(dt, J = 12.3, 6.2 Hz, 1H), 3.88(s, 3H), 3.56(d, J = 38.0 Hz, 8H), 1.35(d, J = 6.2 Hz, 6H).	0.0130
60	[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-((S)-3-methyl-morpholin-4-yl)-methanone		^{1}H NMR(500 MHz, DMSO) δ 8.40(d, 1H), 7.95(s, 1H), 7.66(s, 1H), 7.29(s, 1H), 7.02(s, 1H), 6.98(d, 1H), 3.91(s, 3H), 3.83-3.78(m, 3H), 3.63-3.59(m, 1H), 3.57-3.53 (m, 1H), 3.42-3.34(m, 2H), 2.91(d, 3H), 1.26(d, 3H);	

TABLE 4-continued

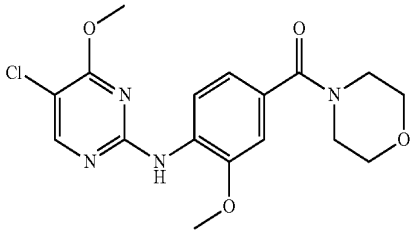
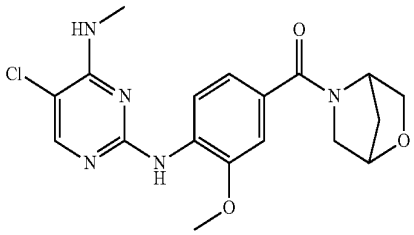
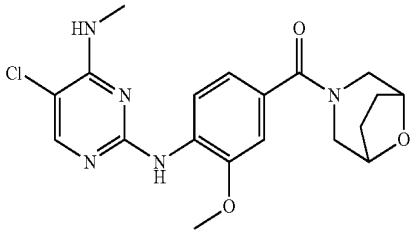
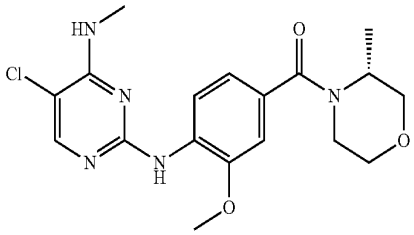
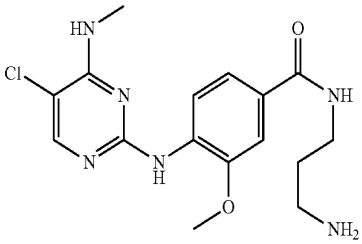
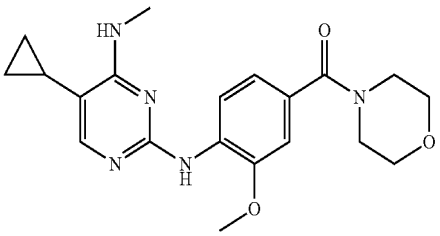
	Name	Structure	^{1}H NMR	K_I
61	[4-(5-Chloro-4-methoxy-pyrimidin-2-ylamino)-3-methoxy-phenyl]-morpholin-4-yl)-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.32(s, 2H), 8.15(d, 1H), 7.08(d, 1H), 7.02(dd, 1H), 3.99(s, 3H), 3.89(s, 3H), 3.56(d, 8H).	0.0104
62	[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-(2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl)-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.44(d, 1H), 7.97(s, 1H), 7.70(s, 1H), 7.36(d, 1H), 7.24-7.05 (m, 2H), 4.63(dd, 3H), 3.93(d, 3H), 3.67(ddd, 3H), 2.91(d, 2H), 1.83(t, 2H).	0.0045
63	[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-(8-oxa-3-aza-bicyclo[3.2.1]oct-3-yl)-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.40(d, 1H), 7.96(s, 1H), 7.68(s, 1H), 7.34(d, 1H), 7.03(d, 1H), 6.98(dd, 1H), 4.28(s, 3H), 3.90(s, 3H), 2.91(d, 3H), 1.72(d, 5H).	0.0020
64	[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-((R)-3-methyl-morpholin-4-yl)-methanone		^{1}H NMR(500 MHz, DMSO) δ 8.40(d, 1H), 7.96(s, 1H), 7.67(s, 1H), 7.33(d, 1H), 7.02(d, 1H), 6.97(d, 1H), 3.90(s, 3H), 3.84-3.73(m, 3H), 3.61 (d, 1H), 3.54(d, 1H), 3.42-3.35(m, 2H), 2.90(d, 3H), 1.25(d, 3H)	
65	N-(3-Amino-propyl)-4-(5-chloro-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-benzamide			0.0023
66	[4-(5-Cyclopropyl-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-morpholin-4-yl-methanone		1H NMR(400 MHz, DMSO) 8.39(d, J = 8.2, 1H), 7.93(s, 1H), 7.82(s, 1H), 7.07(s, 1H), 7.02(d, 1H), 3.97(s, 3H), 3.91(s, 3H), 3.56(m, 8H), 1.80-1.71(m, 1H), 0.86-0.78 (m, 2H), 0.69-0.61(m, 2H)	0.0359

TABLE 4-continued

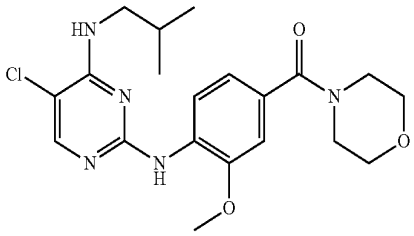
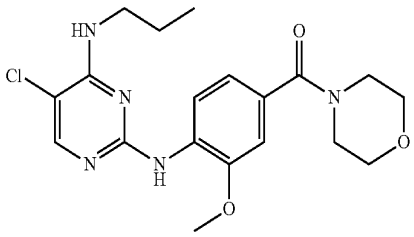
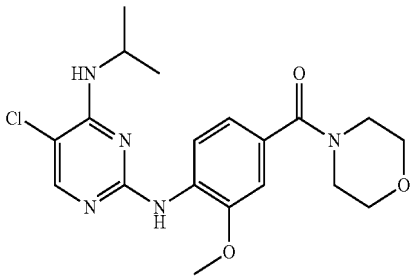
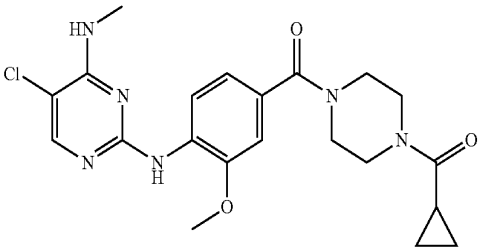
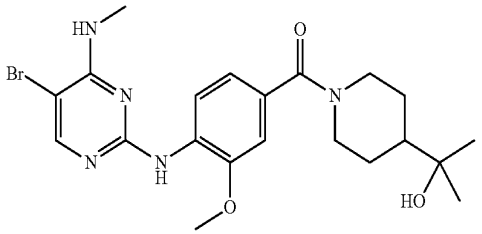
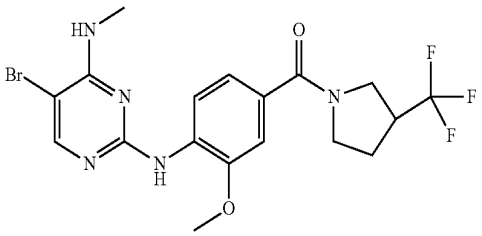
	Name	Structure	^{1}H NMR	K_I
67	[4-(5-Chloro-4-isobutylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-morpholin-4-yl-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.36(d, 1H), 7.96(s, 1H), 7.68(s, 1H), 7.39(s, 1H), 7.05(s, 1H), 6.98(d, 1H), 3.90(s, 3H), 3.68-3.42(m, 8H), 3.21 (t, 3H), 1.98(dt, 1H), 0.90 (d, 6H).	0.0040
68	[4-(5-Chloro-4-propylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-morpholin-4-yl-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.36(d, 1H), 7.96(s, 1H), 7.67(s, 1H), 7.35(dd, 1H), 7.05(s, 1H), 6.99(d, 1H), 3.90(s, 3H), 3.56(d, 8H), 1.68-1.51 (m, 2H), 0.90(t, 3H).	
69	[4-(5-Chloro-4-isopropylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-morpholin-4-yl-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.34(d, 1H), 7.97(s, 1H), 7.67(s, 1H), 7.05(s, 1H), 7.00(d, 1H), 6.89(d, 1H), 4.38-4.21 (m ,1H), 3.90(s, 3H), 3.56 (d, 8H), 1.22(d, 6H).	
70	[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-(4-cyclopropanecarbonyl-piperazin-1-yl)-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.42(d, 1H), 7.97(s, 1H), 7.69(s, 1H), 7.33(d, 1H), 7.08(d, 1H), 7.03(dd, 1H), 3.88(d, 3H), 3.63(d, 8H), 2.91(d, 3H), 1.97(s, 1H), 0.81-0.66 (m, 4H).	0.0022
71	[4-(5-Bromo-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-[4-(1-hydroxy-1-methyl-ethyl)-piperidin-1-yl]-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.38(s, 1H), 8.29 (s, 1H), 8.12(d, 1H), 7.04 (s, 1H), 6.98(d, 1H), 4.13 (s, 1H), 3.98(s, 3H), 3.88(s, 3H), 1.42(m, 2H) ,1.18(m, 2H), 1.05(s, 6H)	0.0024
72	[4-(5-Bromo-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-(3-trifluoromethyl-pyrrolidin-1-yl)-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.39(s, 1H), 8.31 (s, 1H), 8.18(d, 1H), 7.17 (m, 2H), 3.99(s, 3H), 3.90 (s, 3H), 3.77(m, 1H), 3.62 (m, 3H)	0.0064

TABLE 4-continued

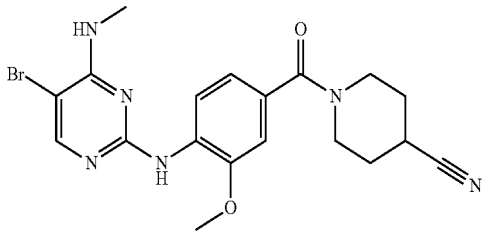
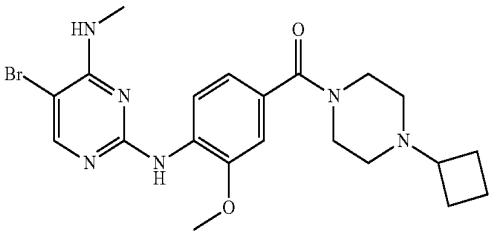
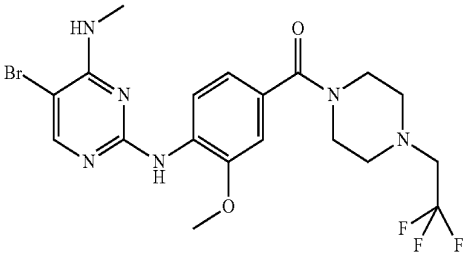
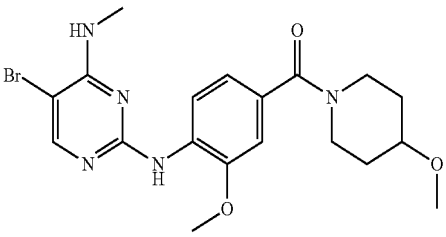
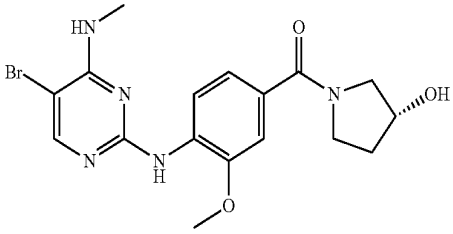
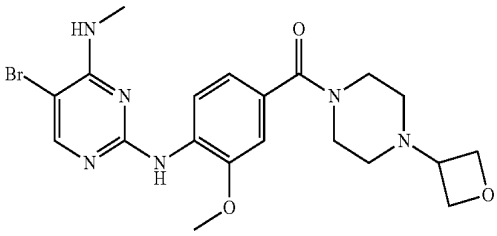
	Name	Structure	^{1}H NMR	K_I
73	1-[4-(5-Bromo-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-benzoyl]-piperidine-4-carbonitrile		^{1}H NMR(400 MHz, DMSO) δ 8.38(s, 1H), 8.30 (s, 1H), 8.15(d, 1H), 7.08 (s, 1H), 7.01(d, 1H), 3.98 (s, 3H), 3.89(s, 3H), 3.15 (m, 2H), 1.90(m, 2H), 1.75 (m, 2H)	0.0041
74	[4-(5-Bromo-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-(4-cyclobutyl-piperazin-1-yl)-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.4(s, 1H), 8.35 (s, 1H), 8.2(d, 1H), 7.1(s, 1H), 6.99(d, 1H), 3.9(s, 3H), 3.8(s, 3H), 3.5(m, 4H), 2.69(m, 1H), 2.25(s, 4H), 1.98(m, 2H), 1.75(m, 2H), 1.62(m, 2H)	0.0023
75	[4-(5-Bromo-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-[4-(2,2,2-trifluoro-ethyl)-piperaizn-1-yl]-methanone			0.0038
76	[4-(5-Bromo-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-(4-methoxy-piperidin-1-yl)-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.38(s, 1H), 8.29 (s, 1H), 8.13(d, J = 8.2, 1H), 7.05(s, 1H), 6.99(d, J = 8.2, 1H), 3.98(s, 3H), 3.88(s, 3H), 3.50-3.38(m, 1H), 3.26(m, 4H), 1.85(m, 2H), 1.45(m, 2H).	0.0024
77	4-(5-Bromo-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-((R)-3-hydroxy-pyrrolidin-1-yl)-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.38(s, 1H), 8.29 (d, J = 7.7, 1H), 8.14(d, J = 8.2, 1H), 7.06(s, 1H), 7.00 (d, J = 8.3, 1H), 4.54(m, 2H), 4.44(m, 2H), 3.98(s, 2H), 3.88(s, 2H).	0.0051
78	[4-(5-Bromo-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-(4-oxetan-3-yl-piperazin-1-yl)-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.38(s, 1H), 8.29 (d, J = 7.7, 1H), 8.14(d, J = 8.2, 1H), 7.06(s, 1H), 7.00 (d, J = 8.3, 1H), 4.54(t, J = 6.5, 2H), 4.44(t, J = 6.1, 2H), 3.98(s, 2H), 3.88(s, 2H).	0.0080

TABLE 4-continued

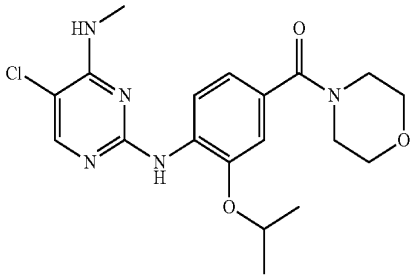
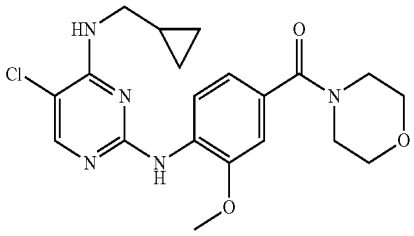
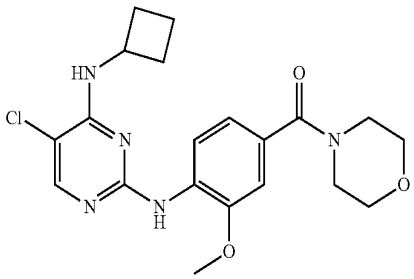
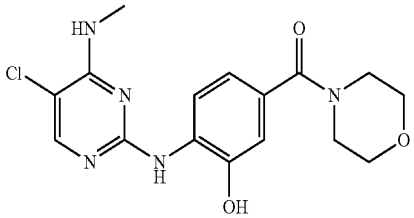
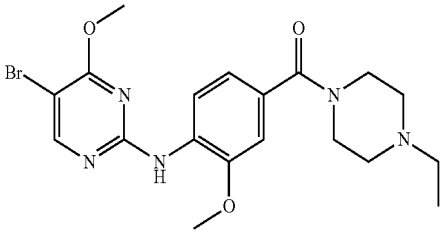
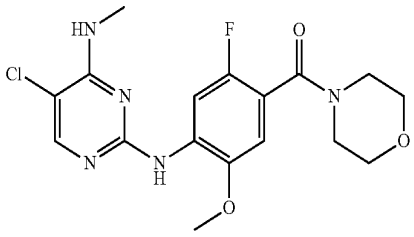
	Name	Structure	^{1}H NMR	K_I
79	[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-isopropoxy-phenyl]-morpholin-4-yl-methanone		1H NMR(400 MHz, DMSO) · 8.47(d, J = 8.3 Hz, 1H), 7.96(s, 1H), 7.61 (s, 1H), 7.33(d, J = 4.5 Hz, 1H), 7.06(s, 1H), 6.99(d, J = 8.3 Hz, 1H), 4.73(dt, J = 12.0, 6.0 Hz, 1H), 3.55(d, J = 36.7 Hz, 8H), 2.93(d, J = 4.6 Hz, 3H), 1.33(d, J = 6.0 Hz, 6H).	0.0156
80	{4-[5-Chloro-4-(cyclopropylmethyl-amino)-pyrimidin-2-ylamino]-3-methoxy-phenyl}-morpholin-4-yl-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.34(d, J = 8.3 Hz, 1H), 7.97(s, 1H), 7.68 (s, 1H), 7.38(s, 1H), 7.05(s, 1H), 6.99(d, J = 8.2 Hz, 1H), 3.90(s, 2H), 3.56(d, J = 33.7 Hz, 8H), 1.15(s, 1H), 0.46-0.37(m, 2H), 0.26(d, J = 4.6 Hz, 2H).	0.0027
81	[4-(5-Chloro-4-cyclobutylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-morpholin-4-yl-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.35(d, J = 8.2 Hz, 1H), 7.98(s, 1H), 7.68 (s, 1H), 7.35(d, J = 7.1 Hz, 1H), 7.04(dd, J = 11.1, 4.9 Hz, 2H), 4.52(dd, J = 16.1, 7.9 Hz, 1H), 3.90(s, 3H), 3.56(d, J = 35.5 Hz, 8H), 2.26(d, J = 2.9 Hz, 2H), 2.21-2.07(m, 2H), 1.75-1.60(m, 2H).	0.0015
82	[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-hydroxy-phenyl]-morpholin-4-yl-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.18(d, J = 8.3 Hz, 1H), 7.95(s, 1H), 7.86 (s, 1H), 7.32(d, J = 4.6 Hz, 1H), 6.92-6.80(m, 2H), 3.54(d, J = 36.7 Hz, 8H), 2.91(d, J = 4.6 Hz, 3H).	0.0289
83	[4-(5-Bromo-4-methoxy-pyrimidin-2-ylamino)-3-methoxy-phenyl]-(4-ethyl-piperazin-1-yl)-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.38(s, 1H), 8.29 (s, 1H), 8.14(d, J = 8.2, 1H), 7.05(d, J = 1.4, 1H), 6.99(d, J = 8.2, 1H), 3.98 (s, 3H), 3.88(s, 3H), 3.50(s, 4H), 2.35(m, 6H), 1.00(t, J = 7.1, 3H).	0.0025
84	[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-2-fluoro-5-methoxy-phenyl]-morpholin-4-yl-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.37(d, J = 12.4 Hz, 1H), 8.01(s, 1H), 7.74 (s, 1H), 7.42(d, J = 4.3 Hz, 1H), 6.99(d, J = 6.2 Hz, 1H), 3.89(s, 3H), 3.64(m, 4H), 3.55(m, 4H), 2.92(d, J = 4.5 Hz, 3H).	

TABLE 4-continued

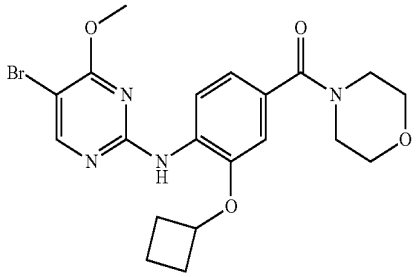
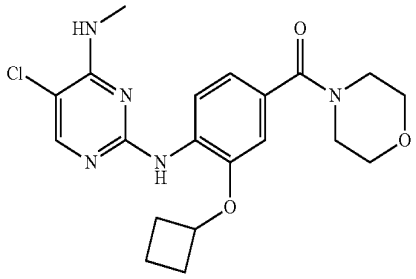
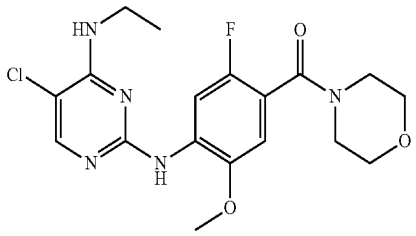
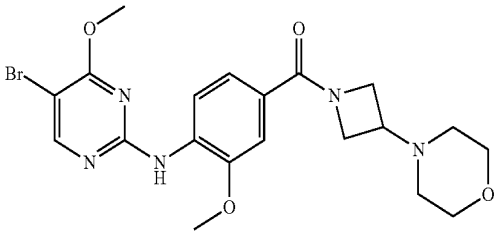
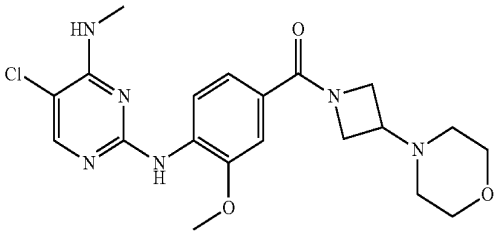
	Name	Structure	^{1}H NMR	K_I
85	[4-(5-Bromo-4-methoxy-pyrimidin-2-ylamino)-3-cyclobutoxy-phenyl]-morpholin-4-yl-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.39(s, 1H), 8.24 (s, 1H), 8.19(d, J = 8.3 Hz, 1H), 7.01(d, J = 8.2 Hz, 1H), 6.88(s, 1H), 4.90-4.75(m, 1H), 4.00(s, 3H), 3.55(m, 8H), 2.43(m, 2H), 2.21-2.04(m, 2H), 1.80 (m, 1H), 1.72-1.55(m, 1H).	0.0028
86	[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-cyclobutoxy-phenyl]-morpholin-4-yl-methanone		^{1}H NMR(400 Mhz, DMSO) δ 8.44(d, J = 8.3 Hz, 1H), 7.96(s, 1H), 7.64 (s, 1H), 7.33(d, J = 4.5 Hz, 1H), 7.00(d, J = 8.3 Hz, 1H), 6.86(s, 1H), 4.90-4.69(m, 1H), 3.55(m, 8H), 2.92(d, J = 4.6 Hz, 3H), 2.50-2.36(m, 2H), 2.14 (m, 2H), 1.82(m, 1H), 1.68 (m, 1H).	
87	[4-(5-Chloro-4-ethylamino-pyrimidin-2-ylamino)-2-fluoro-5-methoxy-phenyl]-morpholin-4-yl-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.34(d, J = 12.5 Hz, 1H), 8.01(s, 1H), 7.73 (s, 1H), 7.43(t, 1H), 6.99(d, J = 6.2 Hz, 1H), 3.89(s, 3H), 3.59(m, 8H), 3.49-3.39(m, 2H), 1.18(t, 3H).	0.0025
88	[4-(5-Bromo-4-methoxy-pyrimidin-2-ylamino)-3-methoxy-phenyl]-(3-morpholin-4-yl-azetidin-1-yl)-methanone		1H NMR(400 MHz, DMSO) δ 8.41(s, 1H), 8.30 (s, 1H), 8.22(d, J = 8.9, 1H), 7.27(d, J = 6.8, 2H), 4.36(s, 2H), 4.17(s, 1H), 4.05(s, 1H), 3.99(s, 3H), 3.91(s, 3H), 3.88(s, 1H), 3.59(t, J = 4.4, 4H), 3.19-3.09(m, 2H), 2.33(s, 5H).	0.0050
89	[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-(3-morpholin-4-yl-azetidin-1-yl)-methanone		1H NMR(400 MHz, DMSO) δ 8.45(d, J = 8.2, 1H), 7.98(s, 1H), 7.71(s, 1H), 7.34(dd, J = 8.2, 4.1, 1H), 7.25(d, J = 9.3, 2H), 4.45-4.31(m, 1H), 4.23-4.11(m, 1H), 4.02(dd, J = 14.9, 9.3, 1H), 3.92(s, 3H), 3.86(dd, J = 9.8, 7.5, 1H), 3.59(t, J = 4.3, 3H), 3.17-3.08(m, 1H), 2.92(d, J = 4.6, 3H), 2.32(s, 4H).	0.0027

TABLE 4-continued

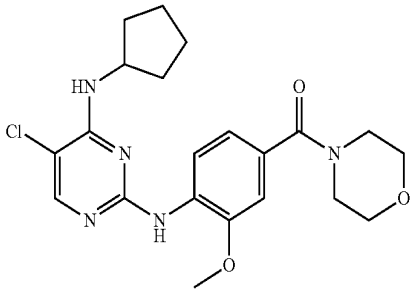
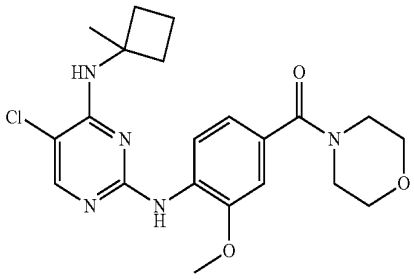
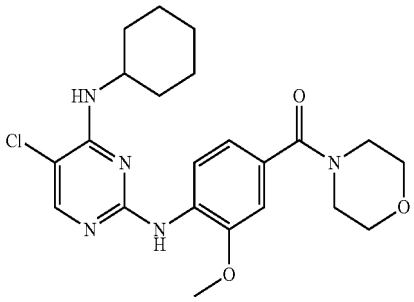
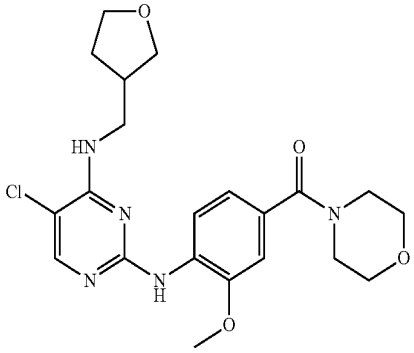
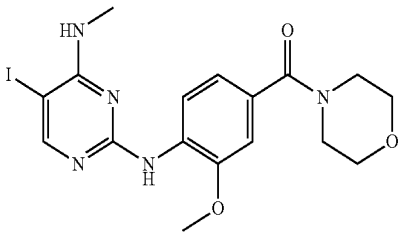
	Name	Structure	^{1}H NMR	K_I
90	[4-(5-Chloro-4-cyclopentylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-morpholin-4-yl-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.36(d, J = 8.3 Hz, 1H), 7.96(s, 1H), 7.68 (s, 1H), 7.05(d, J = 1.5 Hz, 1H), 7.00(d, J = 8.3 Hz, 1H), 6.93(d, J = 7.2 Hz, 1H), 4.36(dd, J = 14.2, 7.1 Hz, 1H), 3.90(s, 3H), 3.56 (d, J = 33.8 Hz, 8H), 1.97 (d, J = 11.7 Hz, 2H), 1.72(s, 2H), 1.59(m, J = 11.5, 7.5 Hz, 4H).	
91	{4-[5-Chloro-4-(1-methyl-cyclobutylamino)-pyrimidin-2-ylamino]-3-methoxy-phenyl}-morpholin-4-yl-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.21(d, J = 8.2 Hz, 1H), 7.95(s, 1H), 7.65 (s, 1H), 7.09-6.88(m, 3H), 3.88(s, 3H), 3.56(d, J = 37.1 Hz, 8H), 2.32(d, J = 11.8 Hz, 2H), 2.07(s, 2H), 1.78(d, J = 6.7 Hz, 2H), 1.52(s, 3H).	0.0024
92	[4-(5-Chloro-4-cyclohexylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-morpholin-4-yl-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.33(d, J = 8.3 Hz, 1H), 7.96(s, 1H), 7.70 (s, 1H), 7.05(d, J = 1.4 Hz, 1H), 6.98(d, J = 8.3 Hz, 1H), 6.86(d, J = 7.8 Hz, 1H), 3.90(s, 3H), 3.56(d, J = 34.3 Hz, 8H), 1.83(dd, J = 48.5, 11.4 Hz, 4H), 1.65 (d, J = 12.7 Hz, 1H), 1.48-1.22(m, 4H), 1.14(d, J = 12.6 Hz, 1H).	
93	(4-{5-Chloro-4-[(tetrahydro-furan-3-ylmethyl)-amino]-pyrimidin-2-ylamino}-3-methoxy-phenyl)-morpholin-4-yl-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.33(d, J = 8.3 Hz, 1H), 7.97(s, 1H), 7.71 (s, 1H), 7.49(s, 1H), 7.05(s, 1H), 6.99(d, J = 8.3 Hz, 1H), 3.90(s, 3H), 3.75(dd, J = 13.8, 7.9 Hz, 1H), 3.67-3.44(m, 8H), 3.38(t, J = 6.6 Hz, 2H), 2.63(s, 2H), 1.93 (dd, J = 12.4, 5.8 Hz, 2H), 1.63(dd, J = 12.3, 5.4 Hz, 2H).	0.0141
94	[4-(5-Iodo-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-morpholin-4-yl-methanone		1H NMR(400 MHz, DMSO) δ 8.46(s, 1H), 8.23(s, 1H), 8.18(d, 1H), 7.08(s, 1H), 7.02(d, 1H), 3.95(s, 3H), 3.89(s, 3H), 3.56(m, 8H)	

TABLE 4-continued

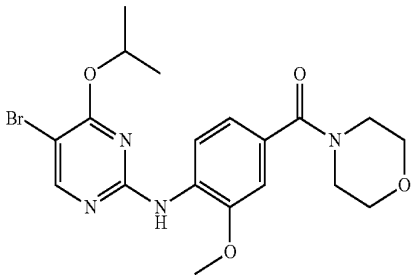
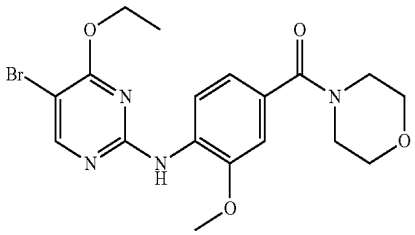
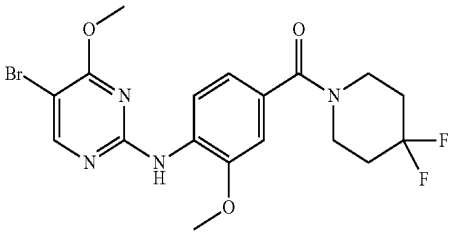
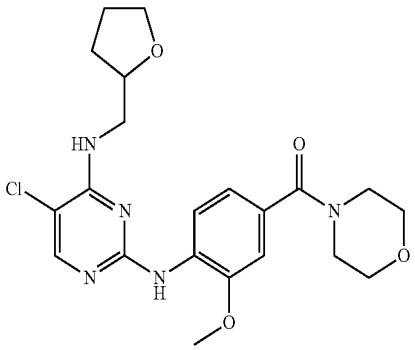
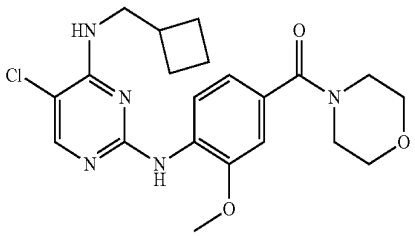
	Name	Structure	^{1}H NMR	K_I
95	[4-(5-Bromo-4-isopropoxy-pyrimidin-2-ylamino)-3-methoxy-phenyl]-morpholin-4-yl-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.36(s, 1H), 8.26(s, 1H), 8.10(d, 1H), 7.08(d, 1H), 7.02(dd, 1H), 5.32(sept, 1H), 3.88(s, 3H), 3.66-3.44(m, 8H), 1.34(d, 6H)	
96	[4-(5-Bromo-4-ethoxy-pyrimidin-2-ylamino)-3-methoxy-phenyl]-morpholin-4-yl-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.38(s, 1H), 8.26(s, 1H), 8.13(d, 1H), 7.08(d, 1H), 7.02(dd, 1H), 4.44(q, 2H), 3.88(s, 3H), 3.70-3.43(m, 8H), 1.36 (t, 3H)	
98	[4-(5-Bromo-4-methoxy-pyrimidin-2-ylamino)-3-methoxy-phenyl]-(4,4-difluoro-piperidin-1-yl)-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.39(s, 1H), 8.30(s, 1H), 8.16(d, 1H), 7.12(s, 1H), 7.06(d, 1H), 3.98(s, 3H), 3.89(s, 3H), 3.61(s, 4H), 2.14-1.94 (m, 4H)	
99	(4-{5-Chloro-4-[(tetrahydro-furan-2-ylmethyl)-amino]-pyrimidin-2-ylamino}-3-methoxy-phenyl)-morpholin-4-yl-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.32(d, J = 8.3 Hz, 1H), 7.98(s, 1H), 7.71 (s, 1H), 7.23(t, J = 5.8 Hz, 1H), 7.05(d, J = 1.4 Hz, 1H), 6.98(d, J = 8.3 Hz, 1H), 4.13-4.05(m, 1H), 3.90(s, 3H), 3.78(dd, J = 13.9, 7.0 Hz, 1H), 3.65-3.47(m, 8H), 3.47-3.41 (m, 2H), 1.96-1.74(m, 3H), 1.70-1.53(m, 1H).	
100	{4-[5-Chloro-4-(cyclobutylmethyl-amino)-pyrimidin-2-ylamino]-3-methoxy-phenyl}-morpholin-4-yl-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.36(d, J = 8.3 Hz, 1H), 7.95(s, 1H), 7.67 (s, 1H), 7.32(s, 1H), 7.05 (d, J = 1.5 Hz, 1H), 6.98(d, J = 8.3 Hz, 1H), 3.90(s, 3H), 3.56(d, J = 34.2 Hz, 8H), 3.47-3.41(m, 2H), 2.72-2.59(m, 1H), 1.98(d, J = 8.3 Hz, 2H), 1.82(dd, J = 13.9, 6.2 Hz, 2H), 1.74 (dd, J = 18.4, 7.4 Hz, 2H).	

TABLE 4-continued

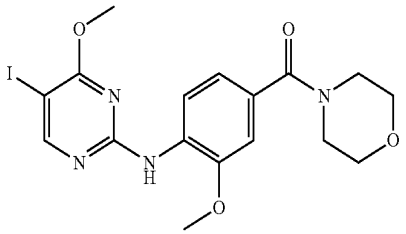
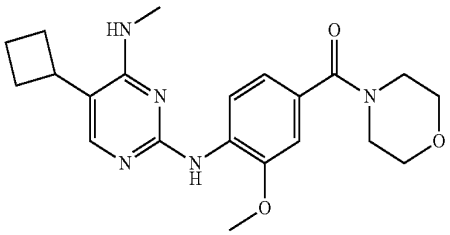
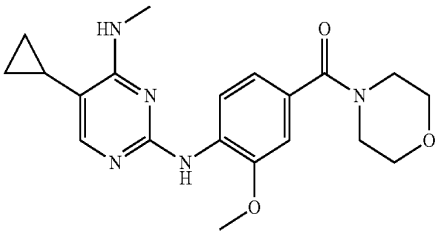
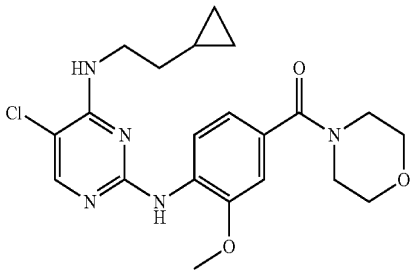
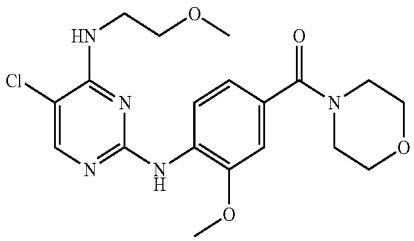
	Name	Structure	^{1}H NMR	K_I
101	[4-(5-Iodo-4-methoxy-pyrimidin-2-ylamino)-3-methoxy-phenyl]-morpholin-4-yl-methanone			0.0021
102	[4-(5-Cyclobutyl-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-morpholin-4-yl-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.39(d, 1H), 7.93(s, 1H), 7.82(s, 1H), 7.07(s, 1H), 7.02(d, 1H), 3.97(s, 3H), 3.91(s, 3H), 3.56(m, 8H), 1.80-1.71 (m, 1H), 0.86-0.78(m, 2H), 0.69-0.61(m, 2H)	
103	[4-(5-Cyclopropyl-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-morpholin-4-yl-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.60(d, 1H), 7.74(s, 1H), 7.41(s, 1H), 7.03(s, 1H), 7.00(d, 1H), 6.50(d, J = 4.7, 1H), 3.91 (s, 3H), 3.56(m, 8H), 2.87 (d, 3H), 2.35-2.27(m, 2H), 2.02-1.91(m, 3H), 1.24(s, 2H)	0.0895
104	{4-[5-Chloro-4-(2-cyclopropyl-ethylamino)-pyrimidin-2-ylamino]-3-methoxy-phenyl}-morpholin-4-yl-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.36(d, J = 8.3 Hz, 1H), 7.95(s, 1H), 7.67 (s, 1H), 7.31(s, 1H), 7.05 (d, J = 1.4 Hz, 1H), 6.99(d, J = 8.2 Hz, 1H), 3.90(s, 3H), 3.65-3.43(m, 8H), 1.49(dd, J = 14.6, 7.1 Hz, 2H), 0.71(s, 1H), 0.47-0.34(m, 2H), 0.06(d, J = 3.8 Hz, 2H).	0.0018
105	{4-[5-Chloro-4-(2-methoxy-ethylamino)-pyrimidin-2-ylamino]-3-methoxy-phenyl}-morpholin-4-yl-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.32(d, J = 8.3 Hz, 1H), 7.98(s, 1H), 7.71 (s, 1H), 7.24(d, J = 5.5 Hz, 1H), 7.05(s, 1H), 6.98(d, J = 8.2 Hz, 1H), 3.90(s, 3H), 3.66-3.45(m, 12H), 3.26 (d, J = 9.4 Hz, 3H).	0.0094

TABLE 4-continued

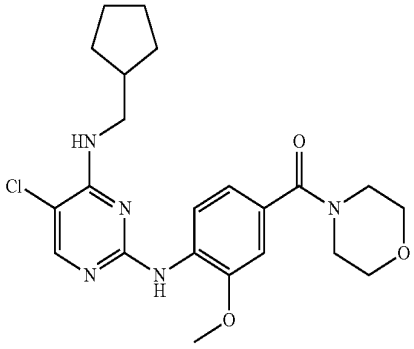
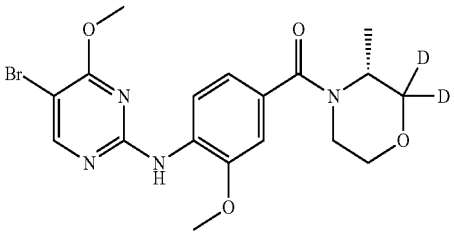
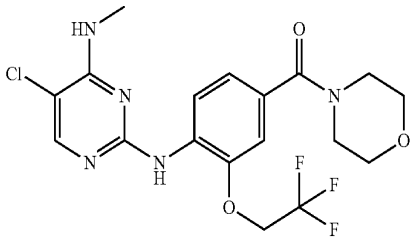
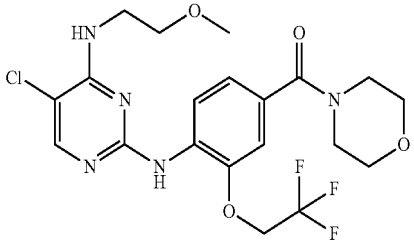
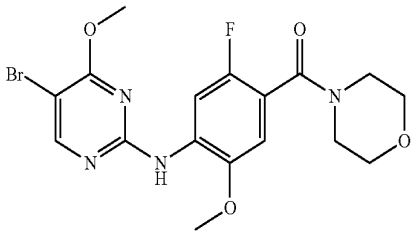
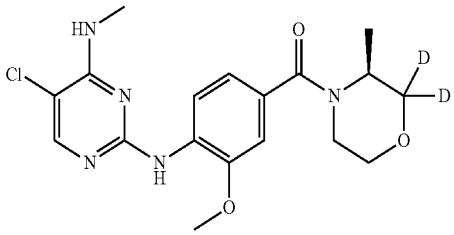
	Name	Structure	^{1}H NMR	K_I
106	{4-[5-Chloro-4-(cyclopentylmethyl-amino)-pyrimidin-2-ylamino]-3-methoxy-phenyl}-morpholin-4-yl-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.37(d, J = 8.3 Hz, 1H), 7.95(s, 1H), 7.67 (s, 1H), 7.38(t, J = 5.4 Hz, 1H), 7.05(s, 1H), 6.97(d, J = 8.3 Hz, 1H), 3.90(s, 3H), 3.56(d, J = 34.6 Hz, 8H), 2.35-2.24(m, 1H), 1.73-1.44(m, 6H), 1.29(dd, J = 11.7, 7.1 Hz, 2H).	
107	[4-(5-Bromo-4-methoxy-pyrimidin-2-ylamino)-3-methoxy-phenyl]-((R)-2,2-di-deutero-3-methyl-morpholin-4-yl)-methanone			0.002
108	[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-(2,2,2-trifluoro-ethoxy)-phenyl]-morpholin-4-yl-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.40(d, J = 8.3 Hz, 1H), 7.96(s, 1H), 7.65 (s, 1H), 7.34(d, J = 4.7 Hz, 1H), 7.23(s, 1H), 7.12(d, J = 8.4 Hz, 1H), 4.92(q, J = 8.8 Hz, 2H), 3.56(m, 8H), 2.91(d, J = 4.5 Hz, 3H).	
109	[4-[5-Chloro-4-(2-methoxy-ethylamino)-pyrimidin-2-ylamino]-3-(2,2,2-trifluoro-ethoxy)-phenyl]-morpholin-4-yl-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.31(d, J = 8.3 Hz, 1H), 7.98(s, 1H), 7.70 (s, 1H), 7.27(m, 1H), 7.22 (s, 1H), 7.09(d, J = 8.3 Hz, 1H), 4.92(m, 2H), 3.52(m, 12H), 3.26(s, 3H).	0.0096
110	[4-(5-Bromo-4-methoxy-pyrimidin-2-ylamino)-2-fluoro-5-methoxy-phenyl]-morpholin-4-yl-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.46(s, 1H), 8.34 (s, 1H), 8.16(d, J = 12.0 Hz, 1H), 7.04(d, J = 6.1 Hz, 1H), 4.01(s, 3H), 3.89(s, 3H), 3.60(m, 8H).	
111	[4-(5-Bromo-4-methoxy-pyrimidin-2-ylamino)-3-methoxy-phenyl]-((S)-2,2-di-deutero-3-methyl-morpholin-4-yl)-methanone			

TABLE 4-continued

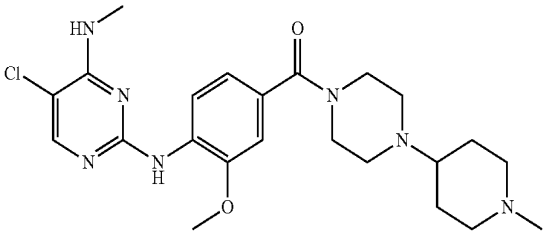
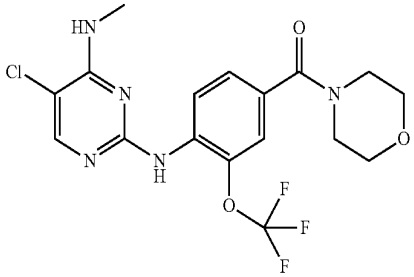
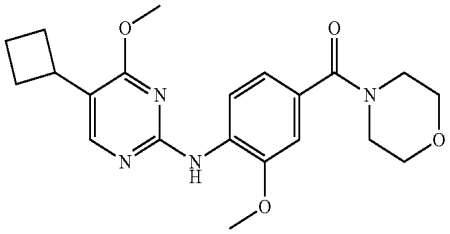
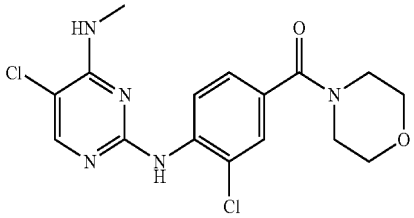
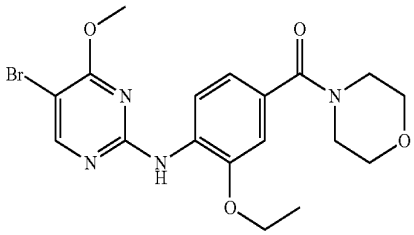
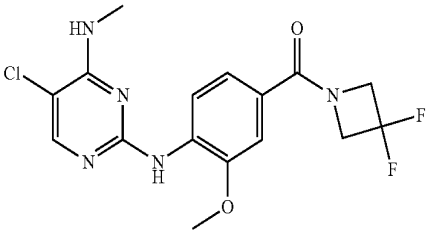
	Name	Structure	^{1}H NMR	K_I
112	[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-[4-(1-methyl-piperidin-4-yl)-piperazin-1-yl]-methanone			
113	[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-trifluoromethoxy-phenyl]-morpholin-4-yl-methanone			
114	[4-(5-Cyclobutyl-4-methoxy-pyrimidin-2-ylamino)-3-methoxy-phenyl]-morpholin-4-yl-methanone			
115	[3-Chloro-4-(5-chloro-4-methylamino-pyrimidin-2-ylamino)-phenyl]-morpholin-4-yl-methanone			0.006
116	[4-(5-Bromo-4-methoxy-pyrimidin-2-ylamino)-3-ethoxy-phenyl]-morpholin-4-yl-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.39(s, 1H), 8.27-8.14(m, 2H), 7.11-6.94 (m, 2H), 4.15(q, J = 7.0 Hz, 2H), 3.99(s, 3H), 3.55(d, J = 37.7 Hz, 8H), 1.37(t, J = 6.9 Hz, 3H).	
117	[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-(3,3-difluoro-azetidin-1-yl)-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.64(d, J = 6.7 Hz, 1H), 8.47(d, J = 8.5 Hz, 1H), 7.98(s, 1H), 7.73(s, 1H), 7.55-7.42(m, 2H), 7.35(d, J = 4.5 Hz, 1H), 4.38-4.15(m, 1H), 3.94(s, 3H), 3.00-2.92(m, 1H), 2.93(d, J = 5.0 Hz, 3H), 2.85-2.59(m, 2H).	

TABLE 4-continued

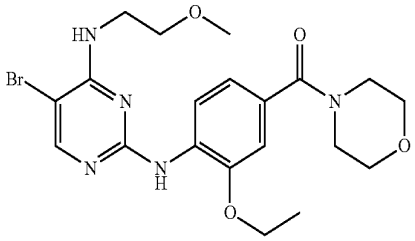
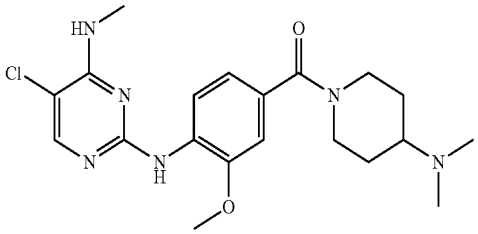
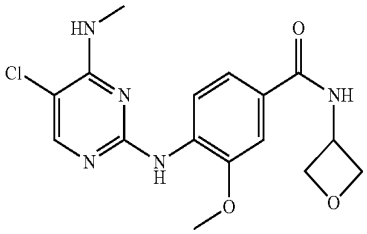
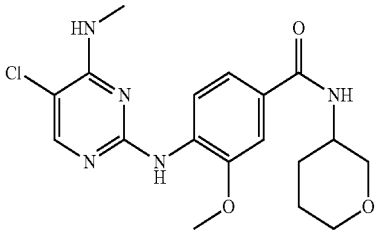
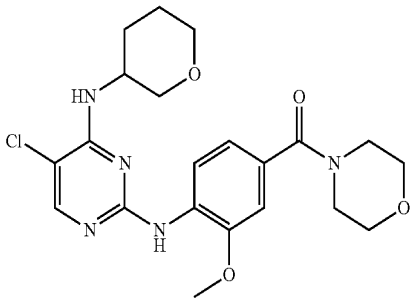
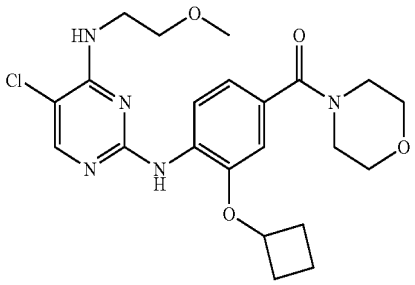
	Name	Structure	^{1}H NMR	K_I
118	{4-[5-Bromo-4-(2-methoxy-ethylamino)-pyrimidin-2-ylamino]-3-ethoxy-phenyl}-morpholin-4-yl-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.33(d, J = 8.3 Hz, 1H), 8.06(s, 1H), 7.68 (s, 1H), 7.07-6.93(m, 3H), 4.16(q, J = 6.9 Hz, 2H), 3.69-3.38(m, 12H), 3.28 (s, 3H), 1.39(t, J = 6.9 Hz, 3H).	
119	[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-(4-dimethylamino-piperidin-1-yl)-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.39(d, 1H), 7.96(s, 1H), 7.67(s, 1H), 7.31(d, 1H), 7.05(s, 1H), 7.00(d, 1H), 3.87(d, 3H), 2.97(s, 6H), 2.91(d, 3H).	
120	4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-N-oxetan-3-yl-benzamide		^{1}H NMR(400 MHz, DMSO) δ 8.93(d, J = 6.4 Hz, 1H), 8.47(d, J = 8.4 Hz, 1H), 7.98(s, 1H), 7.73(s, 1H), 7.54(d, J = 8.7 Hz, 1H), 7.51(s, 1H), 7.35(d, J = 4.6 Hz, 1H), 5.00(dt, J = 13.9, 7.0 Hz, 1H), 4.78(t, J = 6.9 Hz, 2H), 4.60(t, J = 6.4 Hz, 2H), 3.95(s, 3H), 2.92(d, J = 4.5 Hz, 3H).	
121	4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-N-(tetrahydro-pyran-3-yl)-benzamide		^{1}H NMR(400 MHz, DMSO) δ 8.45(d, J = 8.5 Hz, 2H), 8.04(d, J = 7.6 Hz, 1H), 7.98(s, 1H), 7.71(s, 1H), 7.50(d, J = 8.7 Hz, 1H), 7.47(s, 1H), 7.35(d, J = 4.2 Hz, 1H), 3.94(s, 3H), 3.79(t, 2H), 3.15(t, 2H), 2.92(d, J = 4.5 Hz, 3H), 1.91(m, 1H), 1.70(m, 2H), 1.63-1.58(m, 2H).	
122	{4-[5-Chloro-4-(tetrahydro-pyran-3-ylamino)-pyrimidin-2-ylamino]-3-methoxy-phenyl}-morpholin-4-yl-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.29(s, 1H), 8.27 (s, 1H), 8.00(s, 1H), 7.76(s, 1H), 7.05(s, 1H), 6.98(d, J = 8.3 Hz, 1H), 6.82(d, J = 8.0 Hz, 2H), 4.09(m ,2H), 3.90(s, 3H), 3.86-3.74(m, 3H), 3.56(m, 8H), 3.46-3.11(m, 64H), 1.93(s, 1H), 1.77-1.52(m, 3H).	
123	{4-[5-Chloro-4-(2-methoxy-ethylamino)-pyrimidin-2-ylamino]-3-cyclobutoxy-phenyl}-morpholin-4-yl-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.35(d, J = 8.3 Hz, 1H), 7.98(s, 1H), 7.67 (s, 1H), 7.25(t, J = 5.2 Hz, 1H), 6.97(d, J = 8.3 Hz, 1H), 6.86(s, 1H), 4.87-4.72(m, 1H), 3.68-3.35 (m, 12H), 3.28(s, 3H), 2.48-2.36(m, 2H), 2.13(m, 2H), 1.81(m, 1H), 1.74-1.56(m, 1H).	

TABLE 4-continued

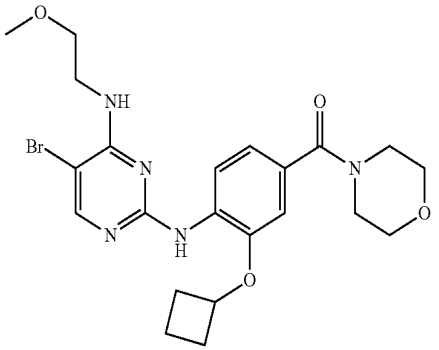
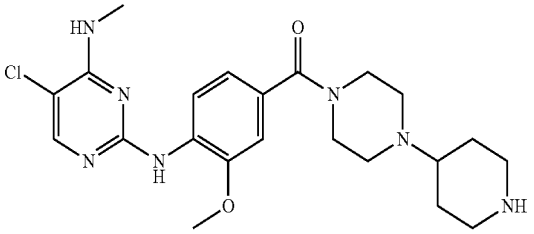
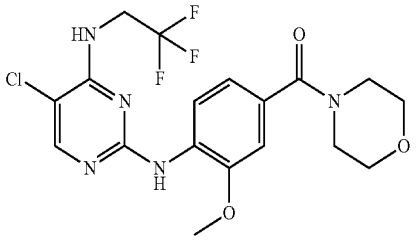
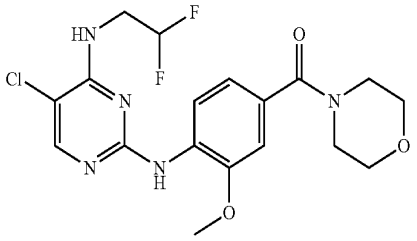
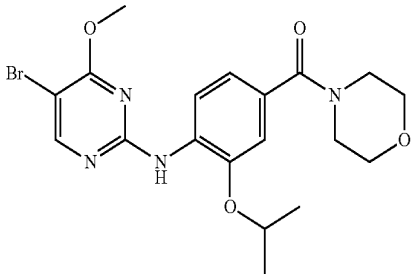
Name	Structure	^{1}H NMR	K_I
124 {4-[5-Bromo-4-(2-methoxy-ethylamino)-pyrimidin-2-ylamino]-3-cyclobutoxy-phenyl}-morpholin-4-yl-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.34(d, J = 8.3 Hz, 1H), 8.06(s, 1H), 7.68 (s, 1H), 7.02(t, J = 5.5 Hz, 1H), 6.97(d, J = 8.4 Hz, 1H), 6.86(s, 1H), 4.90-4.67(m, 1H), 3.67-3.41 (m, 12H), 3.27(s, 3H), 2.41 (m, 2H), 2.26-2.04(m, 2H), 1.81(m, 1H), 1.68(m, 1H).	
125 [4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-(4-piperidin-4-yl-piperazin-1-yl)-methanone			
126 {4-[5-Chloro-4-(2,2,2-trifluoro-ethylamino)-pyrimidin-2-ylamino]-3-methoxy-phenyl}-morpholin-4-yl-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.20(d, J = 8.3 Hz, 1H), 8.10(s, 1H), 7.92 (s, 1H), 7.80(t, J = 6.4 Hz, 1H), 7.06(s, 1H), 6.97(d, J = 8.2 Hz, 1H), 4.28-4.12 (m, 2H), 3.89(s, 3H), 3.56 (d, J = 36.1 Hz, 8H).	
127 {4-[5-Chloro-4-(2,2-difluoro-ethylamino)-pyrimidin-2-ylamino]-3-methoxy-phenyl}-morpholin-4-yl-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.22(d, J = 8.3 Hz, 1H), 8.05(s, 1H), 7.91 (s, 1H), 7.58(s, 1H), 7.06(s, 1H), 6.97(d, J = 8.3 Hz, 1H), 6.39-6.03(m, 1H), 3.86(d, J = 19.1 Hz, 3H), 3.87-3.69(m, 2H), 3.56(d, J = 35.6 Hz, 8H).	
128 [4-(5-Bromo-4-methoxy-pyrimidin-2-ylamino)-3-isopropoxy-phenyl]-morpholin-4-yl-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.40(s, 1H), 8.23 (d, J = 8.3 Hz, 1H), 8.13(s, 1H), 7.08(s, 1H), 7.00(d, J = 8.3 Hz, 1H), 6.73(s, 1H), 4.81-4.61(m, 1H), 4.00(s, 3H), 3.55(d, J = 39.2 Hz, 8H), 1.32(d, J = 6.0 Hz, 6H).	

TABLE 4-continued

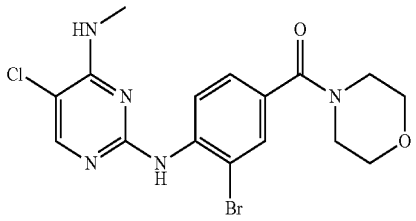
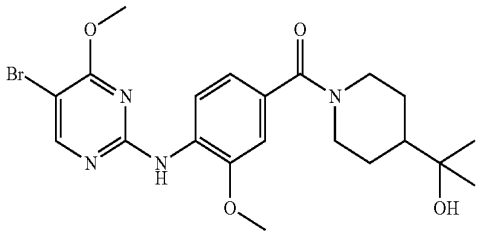
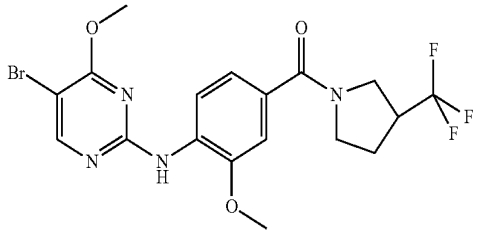
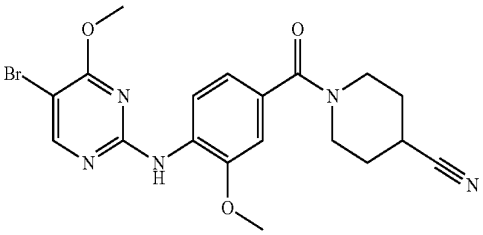
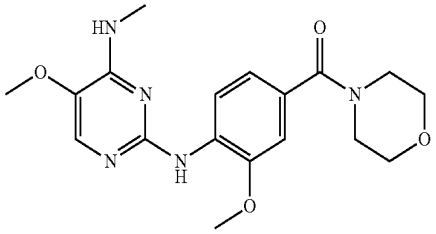
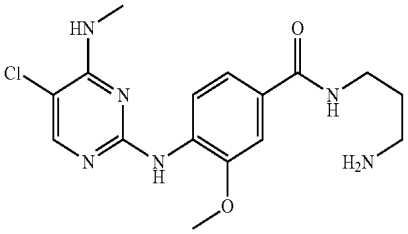
	Name	Structure	^{1}H NMR	K_I
129	[3-Bromo-4-(5-chloro-4-methylamino-pyrimidin-2-ylamino)-phenyl]-morpholin-4-yl-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.21(d, J = 8.5 Hz, 1H), 8.06(s, 1H), 7.94 (s, 1H), 7.67(d, J = 1.6 Hz, 1H), 7.44-7.39(m, 1H), 7.35-7.29(m, 1H), 3.67-3.38(m, 8H), 2.87(d, J = 4.6 Hz, 3H).	
130	[4-(5-Bromo-4-methoxy-pyrimidin-2-ylamino)-3-methoxy-phenyl]-[4-(1-hydroxy-1-methyl-ethyl)-piperidin-1-yl]-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.38(s, 1H), 8.29(s, 1H), 8.12(d, 1H), 7.04(s, 1H), 6.98(d, 1H), 4.13(s, 1H), 3.98(s, 3H), 3.88(s, 3H), 1.51-1.32(m, 2H), 1.17(d, 2H), 1.05(s, 6H).	
131	(4-(5-bromo-4-methoxypyrimidin-2-ylamino)-3-methoxyphenyl)(3-(trifluoromethyl)pyrro-lidin-1-yl)methanone		^{1}H NMR(400 MHz, DMSO) δ 8.39(s, 1H), 8.31(s, 1H), 8.18(d, 1H), 7.17(d, 2H), 3.99(s, 3H), 3.90(s, 3H), 3.77(dd, 1H), 3.60(d, 3H).	
132	1-(4-(5-bromo-4-methoxypyrimidin-2-ylamino)-3-methoxybenzoyl)pipe-ridine-4-carbonitrile		^{1}H NMR(400 MHz, DMSO) δ 8.38(s, 1H), 8.30(s, 1H), 8.14(d, 1H), 7.08(s, 1H), 7.01(d, 1H), 3.98(s, 3H), 3.89(s, 3H), 3.15(s, 2H), 1.90(s, 2H), 1.80-1.67(m, 2H).	
133	(3-methoxy-4-(5-methoxy-4-(methylamino)pyrimi din-2-ylamino)phenyl) (morpholino)methanone		^{1}H NMR(400 MHz, DMSO) δ 8.56(d, 1H), 7.58(s, 1H), 7.32(s, 1H), 7.06-6.95(m, 3H), 3.92 (d, 3H), 3.75(d, 3H), 3.65-3.46(m, 8H), 2.86(d, 3H).	0.259
134	N-(3-aminopropyl)-4-(5-chloro-4-(methylamino)pyrimi din-2-ylamino)-3-methoxybenzamide			

TABLE 4-continued

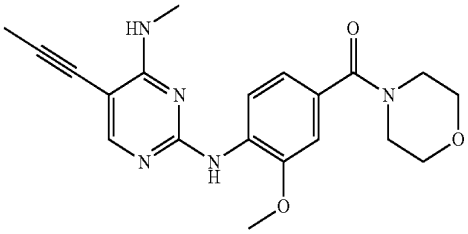
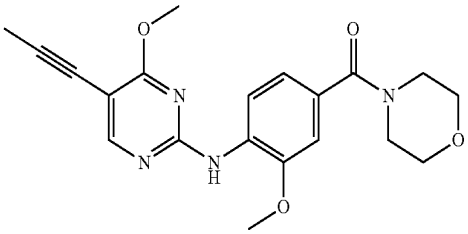
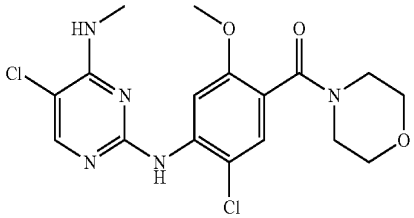
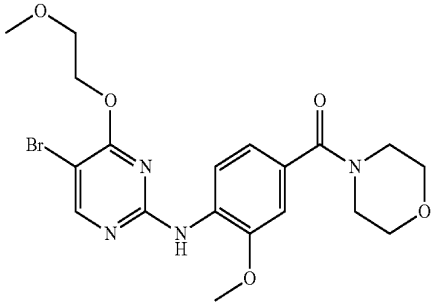
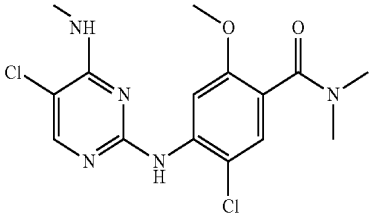
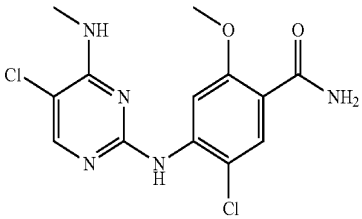
	Name	Structure	^{1}H NMR	K_I
135	[3-Methoxy-4-(4-methylamino-5-prop-1-ynyl-pyrimidin-2-ylamino)-phenyl]-morpholin-4-yl-methanone		1H NMR(400 MHz, DMSO) δ 8.46(d, J = 8.3, 1H), 7.93(s, 1H), 7.66(s, 1H), 7.05(s, 1H), 7.00(d, J = 7.9, 2H), 3.90(s, 3H), 3.60(s, 4H), 3.52(s, 4H), 2.91(d, J = 4.6, 3H), 2.08(s, 3H).	
136	[3-Methoxy-4-(4-methoxy-5-prop-1-ynyl-pyrimidin-2-ylamino)-phenyl]-morpholin-4-yl-methanone		1H NMR(400 MHz, DMSO) δ 8.28(s, 2H), 8.20 (d, J = 8.2, 2H), 7.08(s, 1H), 7.02(d, J = 8.0, 2H), 3.95(s, 3H), 3.89(s, 3H), 3.61(s, 4H), 3.52(s, 4H), 2.05(s, 3H).	
137	[5-Chloro-4-(5-chloro-4-methylamino-pyrimidin-2-ylamino)-2-methoxy-phenyl]-morpholin-4-yl-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.11(s, 1H), 7.99 (s, 1H), 7.97(s, 1H), 7.38 (m, 1H), 7.29(s, 1H), 3.82 (s, 3H), 3.60(s, 4H), 3.52(t, J = 4.3, 2H), 3.17(s, 2H), 2.92(d, J = 4.6, 3H).	
139	{4-[5-Bromo-4-(2-methoxy-ethoxy)-pyrimidin-2-ylamino]-3-methoxy-phenyl}-morpholin-4-yl-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.39(s, 1H), 8.31 (s, 1H), 8.10(d, J = 8.2 Hz, 1H), 7.08(s, 1H), 7.02(d, J = 8.2 Hz, 1H), 4.53-4.49 (m, 2H), 3.88(s, 3H), 3.72-3.67(m, 2H), 3.64-3.46 (m, 8H).	0.0057
140	5-Chloro-4-(5-chloro-4-methylamino-pyrimidin-2-ylamino)-2-methoxy-N,N-dimethyl-benzamide		^{1}H NMR(400 MHz, DMSO): δ 8.09(s, 1H), 8.03(s, 1H), 7.98(s, 1H), 7.40(d, J = 5.3 Hz, 1H), 7.25(s, 1H), 3.81(s, 3H), 2.95(s, 3H), 2.92(d, J = 4.5 Hz, 3H), 2.79(s, 3H).	0.0118
141	5-Chloro-4-(5-chloro-4-methylamino-pyrimidin-2-ylamino)-2-methoxy-benzamide		^{1}H NMR(400 MHz, DMSO): δ 8.27(s, 1H), 8.02(s, 2H), 7.87(s, 1H), 7.59(d, J = 13.4 Hz, 2H), 7.47(d, J = 5.4 Hz, 1H), 3.93(s, 3H), 2.94(t, J = 2.2 Hz, 3H).	0.0093

TABLE 4-continued

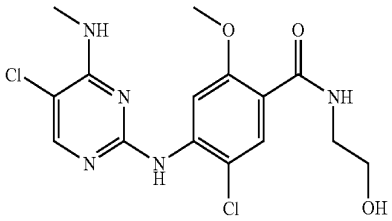
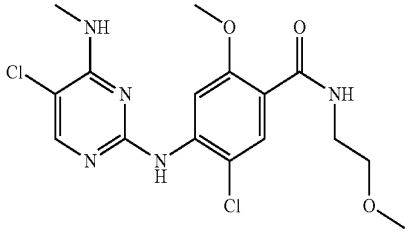
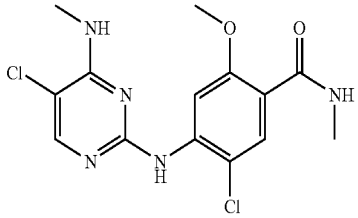
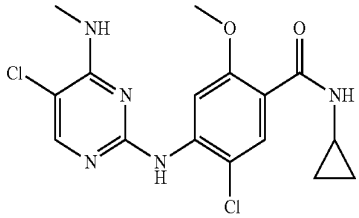
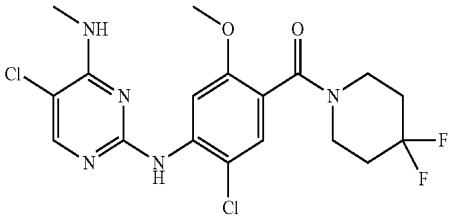
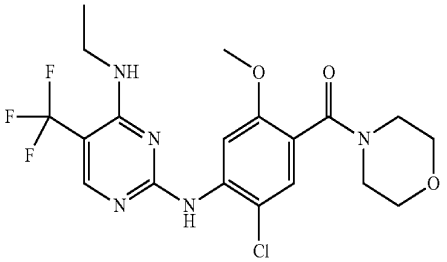
	Name	Structure	^{1}H NMR	K_I
142	5-Chloro-4-(5-chloro-4-methylamino-pyrimidin-2-ylamino)-N-(2-hydroxy-ethyl)-2-methoxy-benzamide		^{1}H NMR(400 MHz, DMSO): δ 8.27(s, 1H), 8.20(t, J = 5.5 Hz, 1H), 8.02(d, J = 6.9 Hz, 2H), 7.88(s, 1H), 7.47(d, J = 5.3 Hz, 1H), 4.81(s, 1H), 3.94 (s, 3H), 3.51(t, J = 5.9 Hz, 2H), 3.40-3.35(m, 2H), 2.95-2.88(m, 3H).	0.0110
143	5-Chloro-4-(5-chloro-4-methylamino-pyrimidin-2-ylamino)-2-methoxy-N-(2-methoxy-ethyl)-benzamide		^{1}H NMR(400 MHz, DMSO): δ 8.28(s, 1H), 8.20(s, 1H), 8.02(d, J = 6.8 Hz, 2H), 7.87(s, 1H), 7.47 (d, J = 5.1 Hz, 1H), 3.94(s, 3H), 3.47-3.43(m, 5H), 2.96-2.88(m, 5H).	
144	5-Chloro-4-(5-chloro-4-methylamino-pyrimidin-2-ylamino)-2-methoxy-N-methyl-benzamide		^{1}H NMR(400 MHz, DMSO): δ 8.24(s, 1H), 8.11(d, J = 5.5 Hz, 1H), 8.03(d, J = 10.5 Hz, 2H), 7.84(s, 1H), 7.48(d, J = 5.5 Hz, 1H), 3.92(s, 3H), 2.94 (d, J = 2.3 Hz, 3H), 2.81(d, J = 4.6 Hz, 3H).	0.0113
145	5-Chloro-4-(5-chloro-4-methylamino-pyrimidin-2-ylamino)-N-cyclopropyl-2-methoxy-benzamide		^{1}H NMR(400 MHz, DMSO): δ 8.21(s, 1H), 8.02(d, J = 8.4 Hz, 3H), 7.75(s, 1H), 7.45(d, J = 5.3 Hz, 1H), 3.89(s, 3H), 2.92 (t, J = 4.5 Hz, 3H), 2.82(tq, J = 7.4, 3.7 Hz, 1H), 0.73-0.66(m, 2H), 0.59-0.53(m, 2H).	
146	[5-Chloro-4-(5-chloro-4-methylamino-pyrimidin-2-ylamino)-2-methoxy-phenyl]-(4,4-difluoro-piperidin-1-yl)-methanone		^{1}H NMR(400 MHz, CDCl3): δ 8.47(s, 1H), 7.96(s, 1H), 7.52(s, 1H), 7.28(s, 1H), 5.40(d, J = 5.8 Hz, 1H), 3.99(s, 1H), 3.87 (s, 3H), 3.79(s, 1H), 3.47 (s, 1H), 3.38(s, 1H), 3.12 (d, J = 4.9 Hz, 3H), 2.06(d, J = 17.3 Hz, 2H), 1.94(s, 2H).	0.0078
147	[5-Chloro-4-(4-ethylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-2-methoxy-phenyl]-morpholin-4-yl-methanone		^{1}H NMR(400 MHz, CDCl3): δ 8.38(s, 1H), 8.22(d, J = 1.1 Hz, 1H), 7.64(s, 1H), 7.31(s, 1H), 5.19(s, 1H), 3.87(s, 3H), 3.78(d, J = 11.5 Hz, 4H), 3.66-3.56(m, 4H), 3.32(s, 2H0, 1.30(t, J = 7.3 Hz, 3H).	0.0034

TABLE 4-continued

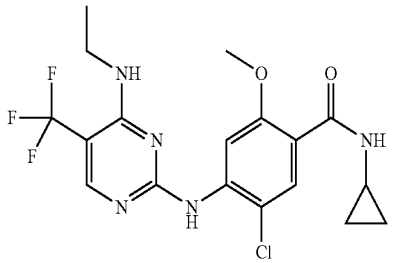
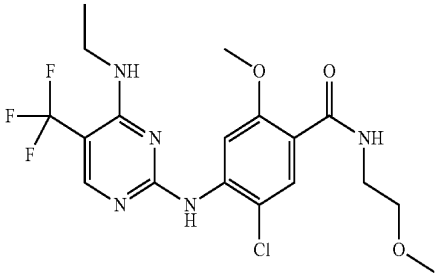
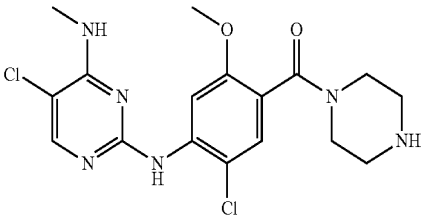
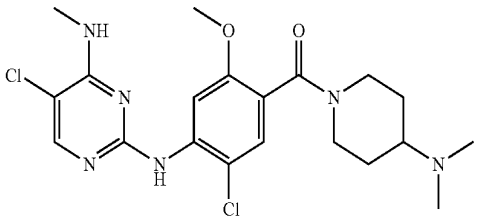
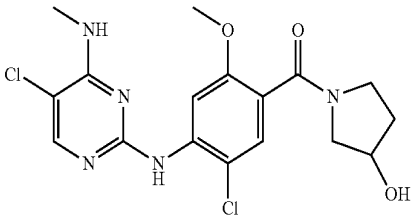
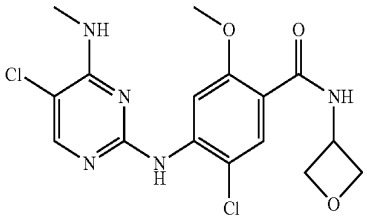
	Name	Structure	^{1}H NMR	K_I
148	5-Chloro-N-cyclopropyl-4-(4-ethylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-2-methoxy-benzamide		^{1}H NMR(400 MHz, CDCl3): δ 8.48(s, 1H), 8.25-8.22(m, 2H), 7.81(s, 1H), 7.75(s, 1H), 5.19(s, 1H), 3.98(s, 3H), 3.61(qd, J = 7.3, 5.2 Hz, 2H), 2.92 (tq, J = 7.1, 3.7 Hz, 1H), 1.30(t, J = 7.3 Hz, 3H), 0.89-0.83(m, 2H), 0.60-0.55(m, 2H).	0.0035
149	5-Chloro-4-(4-ethylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-2-methoxy-N-(2-methoxy-ethyl)-benzamide		^{1}H NMR(400 MHz, CDCl3): δ 8.49(s, 1H), 8.24(s, 2H), 8.12(s, 1H), 7.75(s, 1H), 5.19(s, 1H), 4.00(s, 3H), 3.69-3.55(m, 6H), 3.41(s, 3H), 1.30(t, J = 7.3 Hz, 3H).	0.0093
150	[5-Chloro-4-(5-chloro-4-methylamino-pyrimidin-2-ylamino)-2-methoxy-phenyl]-piperazin-1-yl-methanone		^{1}H NMR(400 MHz, DMSO): δ 8.08(s, 1H), 8.03(s, 1H), 7.97(s, 1H), 7.40(d, J = 5.3 Hz, 1H), 7.26(s, 1H), 3.81(s, 3H), 3.51(d, J = 17.9 Hz, 2H), 3.08(s, 2H), 2.92(d, J = 4.5 Hz, 3H), 2.70(t, J = 5.2 Hz, 2H), 2.60(s, 3H).	0.0089
151	[5-Chloro-4-(5-chloro-4-methylamino-pyrimidin-2-ylamino)-2-methoxy-phenyl]-(4-dimethylamino-piperidin-1-yl)-methanone		^{1}H NMR(400 MHz, DMSO): δ 8.08(s, 1H), 8.03(s, 1H), 7.97(s, 1H), 7.40(d, J = 5.2 Hz, 1H), 7.30(s, 0.5H), 7.23(s, 0.5H), 4.43(s, 1H), 3.80(s, 3H), 2.92(d, J = 4.5 Hz, 3H), 2.80-2.66(m, 1H), 2.35(d, J = 12.5 Hz, 3H), 2.19(s, 6H), 1.81(s, 1H), 1.67(s, 1H), 1.32(s, 2H).	0.0028
152	[5-Chloro-4-(5-chloro-4-methylamino-pyrimidin-2-ylamino)-2-methoxy-phenyl]-(3-hydroxy-pyrrolidin-1-yl)-methanone		^{1}H NMR(400 MHz, DMSO): δ 8.10(d, J = 4.1, Hz, 1H), 8.05-7.97(m, 2H), 7.40(d, J = 5.2 Hz, 1H), 7.26(s, 1H), 4.98(s, 1H), 4.32(s, 1H), 4.21(s, 1H), 3.81(s, 3H), 3.49(dd, J = 9.9, 5.4 Hz, 2H), 3.00(d, J = 11.2 Hz, 1H), 2.93-2.86 (m, 3H), 1.98-1.80(m, 1H), 1.78-1.71(m, 1H).	0.0086
153	5-Chloro-4-(5-chloro-4-methylamino-pyrimidin-2-ylamino)-2-methoxy-N-oxetan-3-yl-benzamide		^{1}H NMR(400 MHz, DMSO): δ 8.67(d, J = 6.3 Hz, 1H), 8.29(s, 1H), 8.06 (d, J = 9.2 Hz, 2H), 7.79(s, 1H), 7.50(d, J = 5.3 Hz, 1H), 5.04-4.96(m, 1H), 4.86-4.76(m, 2H), 4.64-4.57(m, 2H), 3.97(s, 3H), 2.97(d, J = 4.6 Hz, 3H).	0.0274

TABLE 4-continued

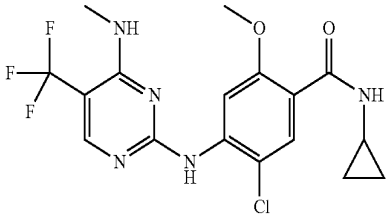
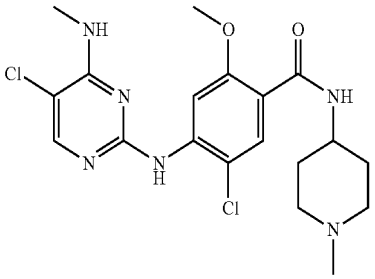
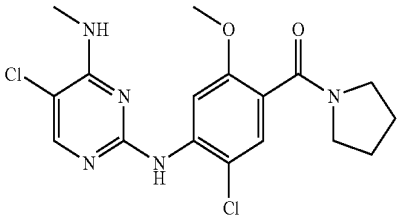
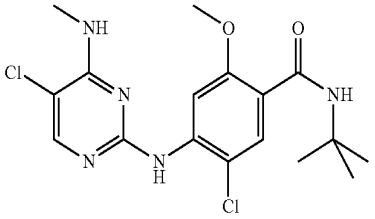
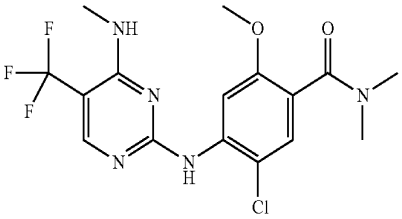
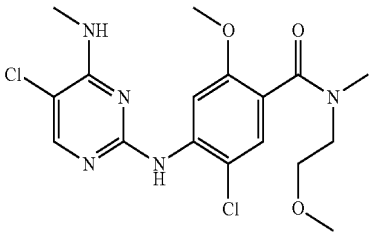
	Name	Structure	^{1}H NMR	K_I
154	5-Chloro-N-cyclopropyl-2-methoxy-4-(4-methylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-benzamide		^{1}H NMR(400 MHz, CDCl3): δ 8.54(s, 1H), 8.26(d, J = 6.2 Hz, 2H), 7.82(d, J = 14.2 Hz, 2H), 5.32(s, 1H), 4.00(s, 3H), 3.15(d, J = 4.7 Hz, 3H), 2.97-2.91(m, 1H), 0.91-0.84(m, 2H), 0.64-0.58(m, 2H).	0.0052
155	5-Chloro-4-(5-chloro-4-methylamino-pyrimidin-2-ylamino)-2-methoxy-N-(1-methyl-piperidin-4-yl)-benzamide		^{1}H NMR(400 MHz, CDCl3): δ 8.54(s, 1H), 8.20(s, 1H), 7.97(s, 1H), 7.75(d, J = 8.0 Hz, 1H), 7.62(s, 1H), 5.40(d, J = 5.7 Hz, 1H), 4.07-3.94(m, 4H), 3.12(d, J = 4.9 Hz, 3H), 2.76(s, 2H), 2.31(s, 3H), 2.32-2.11(m, 2H), 2.04(d, J = 12.5 Hz, 2H), 1.68(s, 2H).	0.0045
156	[5-Chloro-4-(5-chloro-4-methylamino-pyrimidin-2-ylamino)-2-methoxy-phenyl]-pyrrolidin-1-yl-methanone		^{1}H NMR(400 MHz, CDCl3): δ 8.44(s, 1H), 7.96(s, 1H), 7.54-7.48(m, 1H), 7.30(s, 1H), 5.37(s, 1H), 3.87(s, 3H), 3.62(t, J = 7.0 Hz, 2H), 3.29(t, J = 6.7 Hz, 2H), 3.12(d, J = 4.9 Hz, 3H), 1.98-1.81(m, 4H).	0.0074
157	N-tert-Butyl-5-chloro-4-(5-chloro-4-methylamino-pyrimidin-2-ylamino)-2-methoxy-benzamide		^{1}H NMR(400 MHz, CDCl3): δ 8.51(s, 1H), 8.20(s, 1H), 7.97(s, 1H), 7.76(s, 1H), 7.60(s, 1H), 5.38(s, 1H), 3.98(s, 3H), 3.12(d, J = 4.9 Hz, 3H), 1.45(s, 9H)	0.0282
158	5-Chloro-2-methoxy-N,N-dimethyl-4-(4-methylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-benzamide		^{1}H NMR(400 MHz, CDCl3): δ 8.41(s, 1H), 8.22(s, 1H), 7.66(s, 1H), 7.29(s, 1H), 5.30(s, 1H), 3.87(s, 3H), 3.15-3.06(m, 6H), 2.93-2.85(m, 3H).	0.0068
159	5-Chloro-4-(5-chloro-4-methylamino-pyrimidin-2-ylamino)-2-methoxy-N-(2-methoxy-ethyl)-N-methyl-benzamide		^{1}H NMR(400 MHz, DMSO): δ 8.15-8.02(m, 2H), 8.01(s, 1H), 7.42(s, 1H), 7.26(d, J = 2.2 Hz, 1H), 3.83(d, J = 4.7 Hz, 3H), 3.59-3.56(m, 2H), 3.33(s, 2H), 3.19(S, 2H), 2.99(s, 3H), 2.94(s, 2H). 2.86(s, 1H)	

TABLE 4-continued

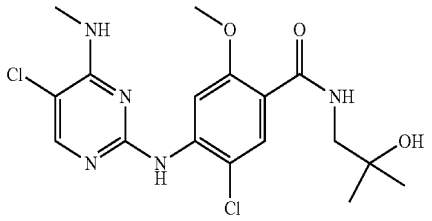
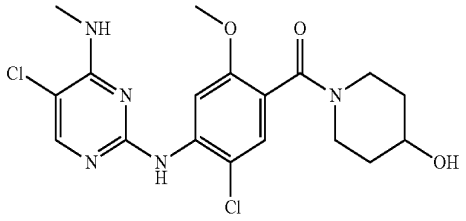
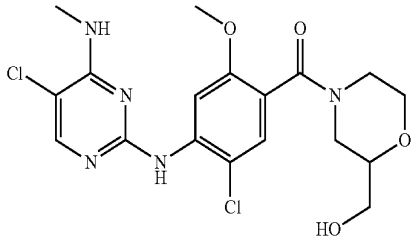
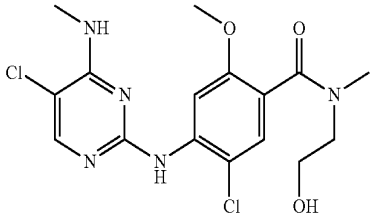
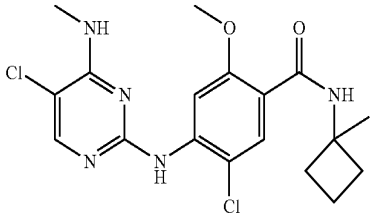
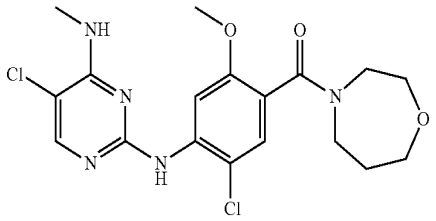
	Name	Structure	^{1}H NMR	K_I
160	5-Chloro-4-(5-chloro-4-methylamino-pyrimidin-2-ylamino)-N-(2-hydroxy-2-methyl-propyl)-2-methoxy-benzamide		^{1}H NMR(400 MHz, DMSO): δ 8.30(s, 1H), 8.16(t, J = 5.6 Hz, 1H), 8.04(d, J = 10.5 Hz, 2H), 7.90(s, 1H), 7.47(d, J = 5.1 Hz, 1H), 4.68(s, 1H), 3.96 (s, 3H), 3.29(d, J = 5.6 Hz 2H), 2.95(d, J = 3.8 Hz, 3H), 1.13(s, 6H).	
161	[5-Chloro-4-(5-chloro-4-methylamino-pyrimidin-2-ylamino)-2-methoxy-phenyl]-(4-hydroxy-piperidin-1-yl)-methanone		^{1}H NMR(400 MHz, DMSO): δ 8.08(s, 1H), 8.03(s, 1H), 7.98(s, 1H), 7.40(d, J = 5.0 Hz, 1H), 7.26(s, 1H), 4.77(d, J = 4.0 Hz, 1H), 4.01(s, 1H), 3.81 (s, 3H), 3.72(d, J = 7.5 Hz, 1H), 3.01(s, 2H), 2.93(d, J = 4.5 Hz, 3H), 1.77(s, 1H), 1.67(s, 1H), 1.36(d, J = 11.6 Hz, 2H), 1.33-1.20(m, 1H).	0.0036
162	[5-Chloro-4-(5-chloro-4-methylamino-pyrimidin-2-ylamino)-2-methoxy-phenyl]-(2-hydroxymethyl-morpholin-4-yl)-methanone		^{1}H NMR(400 MHz, DMSO): δ 8.14(d, J = 3.1 Hz, 1H), 8.09-7.98(m, 2H), 7.43(s, 1H), 7.34(d, J = 15.4 Hz, 1H), 4.86(t, J = 5.6 Hz, 1H), 4.74(s, 1H), 4.46(d, J = 13.2 Hz, 1H), 4.33(d, J = 12.8 Hz, 1H), 4.00-3.90(m, 1H), 3.85(s, 3H), 3.39-3.49(m, 3H), 3.19-3.30(m, 2H), 2.96-2.83(m, 3H).	0.0069
163	5-Chloro-4-(5-chloro-4-methylamino-pyrimidin-2-ylamino)-N-(2-hydroxy-ethyl)-2-methoxy-N-methyl-benzamide		^{1}H NMR(400 MHz, DMSO): δ 8.15-8.03(m, 2H), 8.00(s, 1H), 7.42(d, J = 5.3 Hz, 1H), 7.28(d, J = 7.7 Hz, 1H), 4.76(dt, J = 16.0, 5.4 Hz, 1H), 3.83(d, J = 5.5 Hz, 3H), 3.61(d, J = 6.2 Hz, 1H), 3.42-3.51(m, 1H), 3.15(s, 1H), 3.03-2.82 (m, 7H)	0.0078
164	5-Chloro-4-(5-chloro-4-methylamino-pyrimidin-2-ylamino)-2-methoxy-N-(1-methyl-cyclobutyl)-benzamide		^{1}H NMR(400 MHz, DMSO): δ 8.27(s, 1H), 8.06-8.03(m, 3H), 7.81(s, 1H), 7.49(d, J = 5.1 Hz, 1H), 3.96(s, 3H), 2.97(d, J = 4.5 Hz, 3H), 2.41-2.29 (m, 2H), 2.06-1.98(m, 2H), 1.89-1.79(m, 2H), 1.50(s, 3H).	
165	[5-Chloro-4-(5-chloro-4-methylamino-pyrimidin-2-ylamino)-2-methoxy-phenyl]-[1,4]oxazepan-4-yl-methanone		^{1}H NMR(400 MHz, DMSO): δ 8.12(s, 1H), 8.06(d, J = 5.2 Hz, 1H), 8.01(s, 1H), 7.42(d, J = 5.4 Hz, 1H), 7.31(s, 1H), 3.93-3.71(m, 4H), 3.79-3.58(m 5H), 3.59(s, 2H), 2.95(d, J = 4.5 Hz, 3H), 1.89(s, 1H), 1.72(s, 1H).	0.0057

TABLE 4-continued

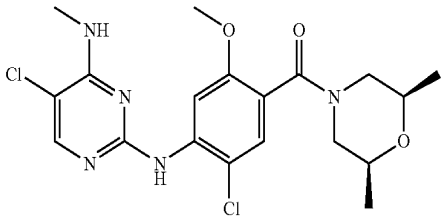
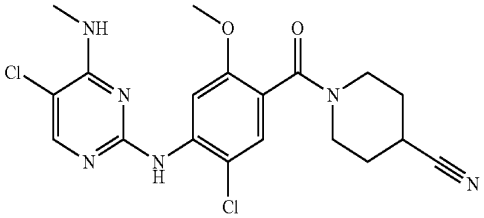
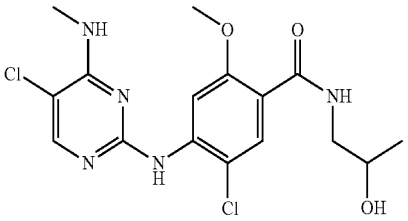
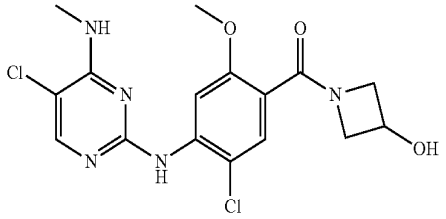
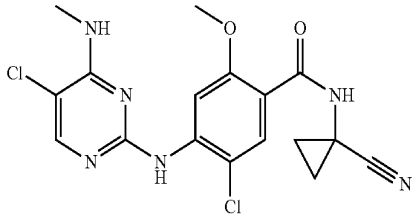
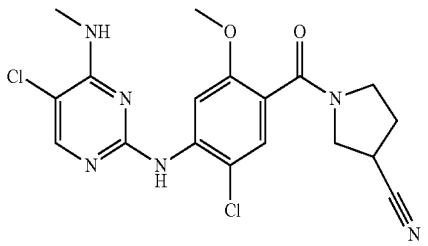
	Name	Structure	^{1}H NMR	K_I
166	[5-Chloro-4-(5-chloro-4-methylamino-pyrimidin-2-ylamino)-2-methoxy-phenyl]-((2R,6S)-2,6-dimethyl-morpholin-4-yl)-methanone		^{1}H NMR(400 MHz, DMSO): δ 8.16(s, 1H), 8.03(d, J = 13.9 Hz, 2H), 7.44(d, J = 5.1 Hz, 1H), 7.32(d, J = 12.3 Hz, 1H), 4.40(d, J = 13.0 Hz, 1H), 3.84(s, 3H), 3.55(m, 1H), 3.21(m, 1H), 2.88-2.74(m, 4H), 2.73(d, J = 15.3 Hz, 1H), 2.44(m, 1H), 1.19-1.09 (m, 3H), 1.03(s, 3H).	
167	1-[5-Chloro-4-(5-chloro-4-methylamino-pyrimidin-2-ylamino)-2-methoxy-benzoyl]-piperidine-4-carbonitrile		^{1}H NMR(400 MHz, DMSO): δ 8.04(s, 1H), 7.96(s, 1H), 7.91(s, 1H), 7.31(t, J = 10.1 Hz, 1H), 7.22(s, 1H), 3.88(m, 1H), 3.75(d, J = 9.5 Hz, 3H), 3.22(m, 1H), 3.07(s, 2H), 2.86(d, J = 4.5 Hz, 3H), 1.86-1.61(m, 5H).	0.0033
168	5-Chloro-4-(5-chloro-4-methylamino-pyrimidin-2-ylamino)-N-(2-hydroxy-propyl)-2-methoxy-benzamide		^{1}H NMR(400 MHz, DMSO): δ 8.21(s, 1H), 8.12(t, J = 5.6 Hz, 1H), 7.96(d, J = 8.5 Hz, 2H), 7.81(s, 1H), 7.40(d, J = 5.2 Hz, 1H), 4.79(s, 1H), 3.87 (s, 3H), 3.75-3.67(m, 1H), 3.13-3.04(m, 1H), 2.87(d, J = 4.0 Hz, 3H), 1.01(d, J = 6.2 Hz, 3H).	
169	[5-Chloro-4-(5-chloro-4-methylamino-pyrimidin-2-ylamino)-2-methoxy-phenyl]-(3-hydroxy-azetidin-1-yl)-methanone		^{1}H NMR(400 MHz, DMSO): δ 8.17(s, 1H), 8.03(d, J = 7.5 Hz, 2H), 7.45(d, J = 5.4 Hz, 1H), 7.38(s, 1H), 5.77(s, 1H), 4.49(d, J = 6.4 Hz, 1H), 4.21(t, J = 8.5 Hz, 1H), 4.09(t, J = 8.1 Hz, 1H), 3.87(s, 3H), 3.74(t, J = 6.6 Hz, 2H), 2.98-2.92(m, 3H).	0.0054
170	5-Chloro-4-(5-chloro-4-methylamino-pyrimidin-2-ylamino)-N-(1-cyano-cyclopropyl)-2-methoxy-benzamide		^{1}H NMR(400 MHz, DMSO): δ 8.83(s, 1H), 8.30(s, 1H), 8.07(d, J = 13.6 Hz, 2H), 7.83(s, 1H), 7.51(d, J = 5.2 Hz, 1H), 3.94(s, 3H), 2.97(d, J = 4.5 Hz, 3H), 1.61-1.55(m, 2H), 1.35-1.35(m, 2H).	0.0139
171	1-[5-Chloro-4-(5-chloro-4-methylamino-pyrimidin-2-ylamino)-2-methoxy-benzoyl]-pyrrolidine-3-carbonitrile		^{1}H NMR(400 MHz, DMSO): δ 8.05(d, J = 6.3 Hz, 2H), 7.93(d, J = 2.0 Hz, 1H), 7.42(s, 1H), 7.26-7.22(m, 1H), 3.78-3.64(m, 4H), 3.55-3.19(m, 4H), 2.88-2.81(m, 3H), 2.28-2.00(m, 2H).	0.0045

TABLE 4-continued

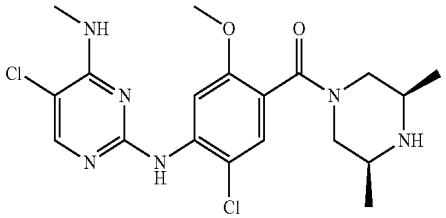
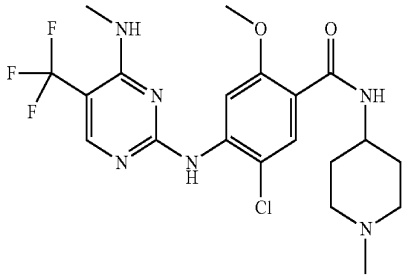
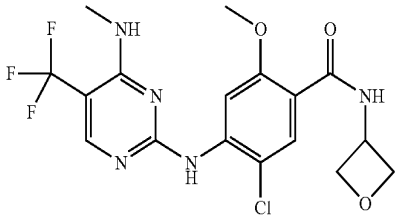
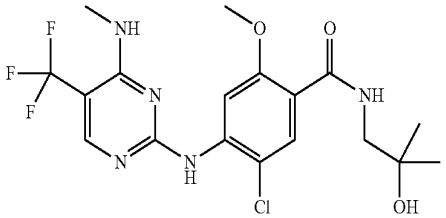
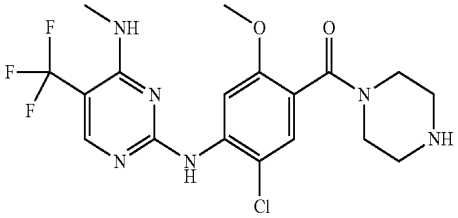
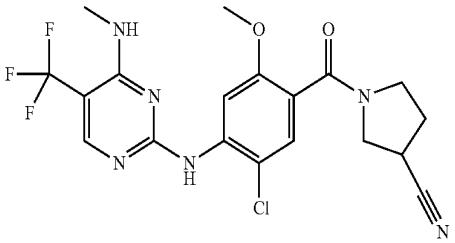
	Name	Structure	^{1}H NMR	K_I
172	[5-Chloro-4-(5-chloro-4-methylamino-pyrimidin-2-ylamino)-2-methoxy-phenyl]-((3R,5S)-dimethyl-piperazin-1-yl)-methanone		^{1}H NMR(400 MHz, DMSO): δ 8.14(s, 1H), 8.02(t, J = 13.3 Hz, 2H), 7.43(d, J = 5.2 Hz, 1H), 7.30(s, 1H), 4.42(d, J = 12.5 Hz, 1H), 3.83(s, 3H), 3.22(m, 2H), 2.83-2.53(m, 7H), 1.08(d, J = 6.2 Hz, 2H), 1.02(s, 2H), 0.92(s, 2H).	0.0333
173	5-Chloro-2-methoxy-4-(4-methylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-N-(1-methyl-piperidin-4-yl)-benzamide		^{1}H NMR(400 MHz, DMSO): δ 8.63(s, 1H), 8.25(s, 1H), 8.06-7.96(m, 2H), 7.78(s, 1H), 7.36(d, J = 5.2 Hz, 1H), 3.94(s, 3H), 3.79(m, 1H), 2.95(d, J = 4.3 Hz, 3H), 2.74(s, 2H), 2.24(s, 3H), 2.16-2.09(m, 2H), 1.84(d, J = 12.2 Hz, 2H), 1.66-1.54(m, 2H0.	0.0015
174	5-Chloro-2-methoxy-4-(4-methylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-N-oxetan-3-yl-benzamide		^{1}H NMR(400 MHz, DMSO): δ 8.73(d, J = 6.4 Hz, 1H), 8.64(s, 1H), 8.26 (s, 1H), 8.06(s, 1H), 7.78 (s, 1H), 7.37(d, J = 5.1 Hz, 1H), 5.06-4.96(m, 1H), 4.79(t, J = 6.9 Hz, 2H), 4.60(t, J = 6.4 Hz, 2H), 3.95(s, 3H), 2.96(d, J = 4.3 Hz, 3H).	0.0041
175	5-Chloro-N-(2-hydroxy-2-methyl-propyl)-2-methoxy-4-(4-methylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-benzamide		^{1}H NMR(400 MHz, DMSO): δ 8.63(s, 1H), 8.28(s, 1H), 8.16(m, 1H), 8.10(s, 1H), 7.92(s, 1H), 7.37(s, 1H), 4.68(s, 1H), 3.97(s, 3H), 3.29(d, J = 5.8 Hz), 2H, 2.95(s, 3H), 1.16 (s, 6H).	0.0079
176	[5-Chloro-2-methoxy-4-(4-methylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-phenyl]-piperazin-1-yl-methanone		^{1}H NMR(400 MHz, CDCl3): δ 8.43(s, 1H), 8.24(d, J = 1.1 Hz, 1H), 7.69(s, 1H), 7.30(d, J = 11.0 Hz, 1H), 5.32(s, 1H), 3.89(s, 3H), 3.84-3.69(m, 2H), 3.30(d, J = 15.4 Hz, 3H), 3.14(d, J = 4.7 Hz, 3H), 2.95(s, 2H), 2.82(s, 2H).	0.0041
177	1-[5-Chloro-2-methoxy-4-(4-methylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-benzoyl]-pyrrolidine-3-carbonitrile		^{1}H NMR(400 MHz, DMSO): δ 8.66(s, 1H), 8.24(s, 1H), 7.94(d, J = 6.7 Hz, 1H), 7.36(s, 1H), 7.31 (s, 1H), 3.88-3.75(m, 4H), 3.63-3.49(m, 4H), 2.94(t, J = 3.9 Hz, 3H), 2.37-2.10 (m, 2H).	0.0029

TABLE 4-continued

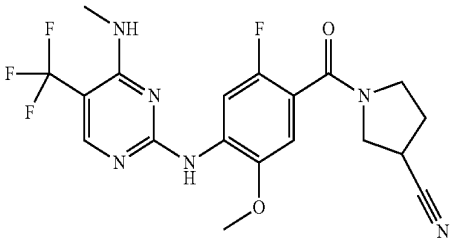
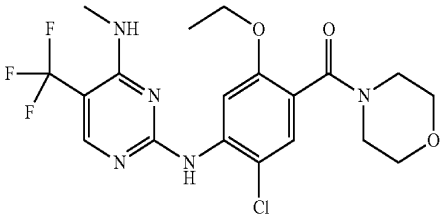
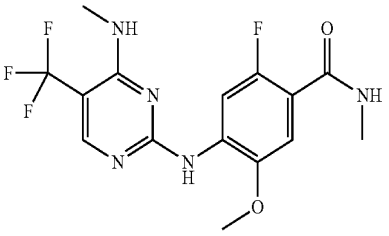
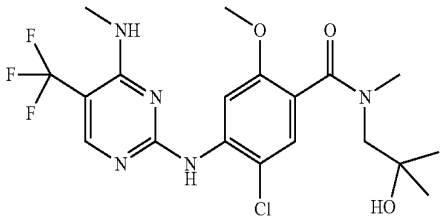
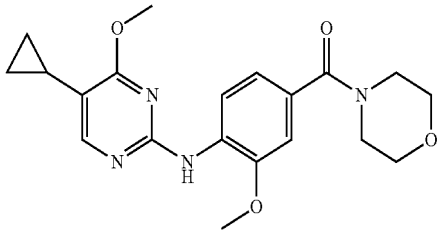
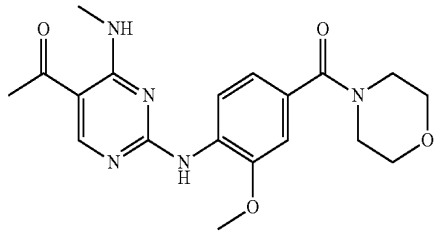
	Name	Structure	^{1}H NMR	K_I
178	1-[2-Fluoro-5-methoxy-4-(4-methylamino-5-trilfuoromethyl-pyrimidin-2-ylamino)-benozyl]-pyrrolidine-3-carbonitrile		^{1}H NMR(400 MHz, DMSO): δ 8.38(dd, J = 12.4, 3.9 Hz, 1H), 8.29(s, 1H), 8.17(s, 1H), 7.41(s, 1H), 7.08(d, J = 6.2 Hz, 1H), 3.93(d, J = 1.6 Hz, 3H), 3.67(d, J = 23.8 Hz, 2H), 3.58(t, J = 8.9 Hz, 2H), 3.50-3.43(m, 1H), 2.98(dd, J = 4.3, 2.3 Hz, 3H), 2.39-2.13(m, 2H).	0.0018
179	[5-Chloro-2-ethoxy-4-(4-methylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-phenyl]-morpholin-4-yl-methanone		^{1}H NMR(400 MHz, CDCl3): δ 8.39(s, 1H), 8.22(d, J = 1.1 Hz, 1H), 7.65(s, 1H), 7.32(s, 1H), 5.29(s, 1H), 4.10(s, 2H), 3.76(s, 4H), 3.67(s, 1H), 3.61(s, 1H), 3.37(s, 1H), 3.29(s, 1H), 3.11(d, J = 4.7 Hz, 3H), 1.43(t, J = 7.0 Hz, 3H).	
180	2-Fluoro-5-methoxy-N-methyl-4-(4-methylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-benzamide		^{1}H NMR(400 MHz, DMSO): δ 8.37(d, J = 13.4 Hz, 1H), 8.30(s, 1H), 8.18 (s, 1H), 8.07(s, 1H), 7.42 (d, J = 5.1 Hz, 1H), 7.30(d, J = 6.7 Hz, 1H), 3.94(s, 3H), 2.98(d, J = 4.2 Hz, 3H), 2.82(d, J = 4.5 Hz, 3H).	0.0047
181	5-Chloro-N-(2-hydroxy-2-methyl-propyl)-2-methoxy-N-methyl-4-(4-methylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-benzamide		^{1}H NMR(400 MHz, CDCl3) δ 8.44(s, 1H), 8.22(s, 1H), 7.68(s, 1H), 7.32(s, 1H), 5.31(s, 1H), 4.08(s, 1H), 3.95(s, 3H), 3.58(s, 2H), 3.13(d, J = 4.6 Hz, 3H), 3.01(s, 3H), 1.32 (s, 6H).	0.0063
182	(4-(5-cyclopropyl-4-methoxypyrimidin-2-ylamino)-3-methoxyphenyl)(morpholino)methanone		1H NMR(400 MHz, DMSO) δ 8.60(d, 1H), 7.74 (s, 1H), 7.41(s, 1H), 7.03(s, 1H), 7.00(d, 1H), 6.50(d, J = 4.7, 1H), 3.91(s, 3H), 3.56(m, 8H), 2.87(d, 3H), 2.35-2.27(m, 2H), 2.02-1.91(m, 3H), 1.24(s, 2H)	0.0895
183	1-{2-[2-Methoxy-4-(morpholine-4-carbonyl)-phenylamino]-4-methylamino-pyrimidin-5-yl}-ethanone		1H NMR(400 MHz, DMSO) δ 9.21-9.05(m, 1H), 8.71(s, 1H), 8.35(d, J = 8.2, 1H), 8.25(s, 1H), 7.09(s, 1H), 7.03(d, J = 8.3, 1H), 3.90(s, 3H), 3.56(s, 8H), 2.99(d, J = 4.8, 3H), 2.45(s, 3H).	0.0682

TABLE 4-continued

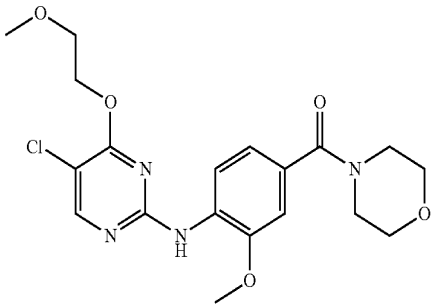
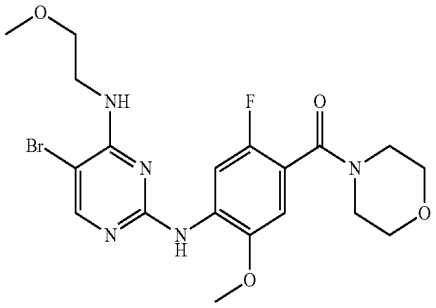
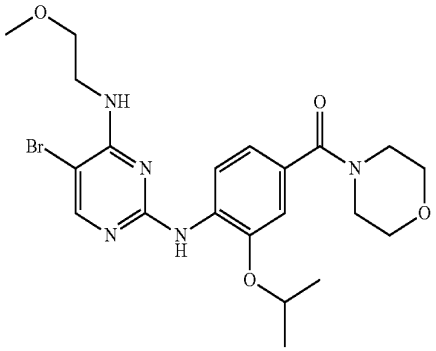
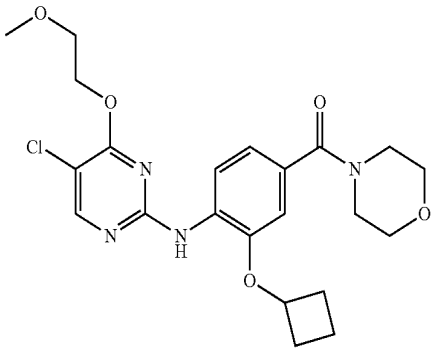
	Name	Structure	^{1}H NMR	K_I
184	{4-[5-Chloro-4-(2-methoxy-ethoxy)-pyrimidin-2-ylamino]-3-methoxy-phenyl}-morpholin-4-yl-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.32(m, 2H), 8.11(d, J = 8.2 Hz, 1H), 7.08(s, 1H), 7.02(d, J = 8.2 Hz, 1H), 4.60-4.41(m, 2H), 3.88(s, 3H), 3.74-3.65(m, 2H), 3.56(m, 8H).	
185	{4-[5-Bromo-4-(2-methoxy-ethylamino)-pyrimidin-2-ylamino]-2-fluoro-5-methoxy-phenyl}-morpholin-4-yl-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.27(d, J = 12.3 Hz, 1H), 8.11(s, 1H), 7.78 (s, 1H), 7.12(t, J = 5.5 Hz, 1H0, 7.01(t, J = 10.3 Hz, 1H), 3.89(s, 3H), 3.57(m, 12H), 3.27(s, 3H).	0.0069
186	{4-[5-Bromo-4-(2-methoxy-ethylmaino)-pyrimidin-2-ylamino]-3-isopropoxy-phenyl}-morpholin-4-yl-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.37(d, J = 8.3 Hz, 1H), 8.06(s, 1H), 7.64 (s, 1H), 7.15-7.00(m, 2H), 6.96(d, J = 8.3 Hz, 1H), 4.72(dt, J = 12.0, 6.0 Hz, 1H0, 3.71-3.40(m, 12H), 3.28(s, 3H), 1.33(d, 6H).	0.0135
187	{4-[5-Chloro-4-(2-methoxy-ethoxy)-pyrimidin-2-ylamino]-3-cyclobutoxy-phenyl}-morpholin-4-yl-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.34(s, 1H), 8.24 (s, 1H), 8.13(d, J = 8.2 Hz, 1H), 7.01(d, J = 8.3 Hz, 1H), 6.88(s, 1H), 4.93-4.73(m, 1H), 4.59-4.47 (m, 2H), 3.78-3.66(m, 2H), 3.55(m, 8H), 2.43(m, 2H), 2.25-2.00(m, 2H), 1.80(m, 1H), 1.74-1.47 (m, 1H).	0.0143

TABLE 4-continued

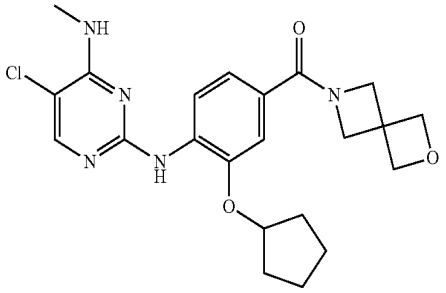
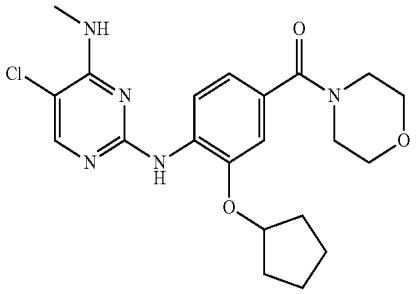
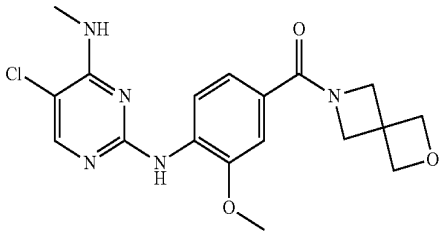
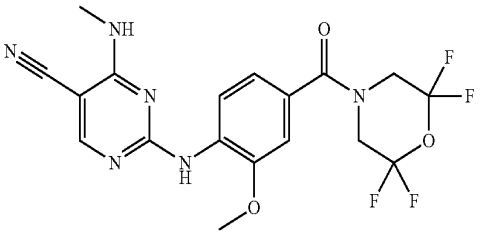
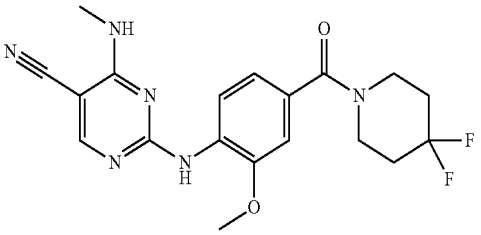
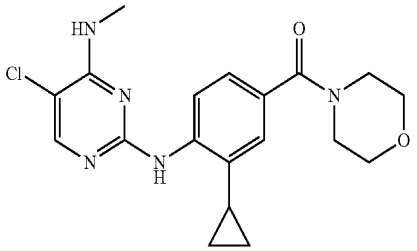
	Name	Structure	^{1}H NMR	K_I
188	[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-cyclopentyloxy-phenyl]-(2-oxa-6-aza-spiro[3.3]hept-6-yl)-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.43(d, J = 8.3 Hz, 1H), 7.95(s, 1H), 7.59 (s, 1H), 7.33(d, J = 4.3 Hz, 1H), 7.03(s, 1H), 6.99(d, J = 8.3 Hz, 1H), 4.96(m, 1H), 3.56(dm, 8H), 2.92(d, J = 4.5 Hz, 3H), 2.00-1.85(m, 2H), 1.73(m, 6H).	0.0063
189	[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-cyclopentyloxy-phenyl]-morpholin-4-yl-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.43(d, J = 8.3 Hz, 1H), 7.95(s, 1H), 7.59 (s, 1H), 7.33(d, J = 4.3 Hz, 1H), 7.03(s, 1H), 6.99(d, J = 8.3 Hz, 1H), 4.96(sm, 1H), 3.56(dm, 8H), 2.92(d, J = 4.5 Hz, 3H), 2.02-1.85 (m, 2H), 1.73(tm, 6H).	
190	[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-(2-oxa-6-aza-spiro[3.3]hept-6-yl)-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.45(d, J = 8.9 Hz, 1H), 7.98(s, 1H), 7.71 (s, 1H), 7.34(d, J = 4.4 Hz, 1H), 7.23(d, 2H), 4.69(s, 4H), 4.53(s, 2H), 4.19(s, 2H), 3.92(s, 3H), 2.92(d, J = 4.5 Hz, 3H).	0.0063
191	2-(2-methoxy-4-(2,2,6,6-tetrafluoromorpholine-4-carbonyl)phenylamino)-4-(methylamino)pyrimidine-5-carbonitrile		^{1}H NMR(400 MHz, DMSO) δ 8.37(s, 1H), 8.33 (d, J = 8.1 Hz, 1H), 7.13-7.07(m, 2H), 4.32(t, J = 8.6 Hz, 4H), 3.91(s, 3H), 2.90 (s, 3H)	0.0208
192	2-(4-(4,4-difluoropiperidine-1-carbonyl)-2-methoxyphenylamino)-4-(methyalmino)pyrimidine-5-carbonitrile		^{1}H NMR(400 MHz, DMSO) δ 8.36(s, 1H), 8.35 (s, 1H), 8.18(d, J = 8.2 Hz, 1H), 7.79(d, J = 4.3 Hz, 1H), 7.12(s, 1H), 7.05(d, J = 9.1 Hz, 1H), 3.88(s, 3H), 3.59(br s, 4H), 2.88(d, J = 4.4 Hz, 3H), 2.12-1.96(m, 4H)	
193	[4-(5-Choro-4-methylamino-pyrimidin-2-ylamino)-3-cyclopropyl-phenyl]-morpholin-4-yl-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.19(s, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.91(s, 1H), 7.26-7.18(m, 2H), 7.07-7.03(m, 1H), 3.66-3.41(m, 8H), 2.88(d, J = 4.6 Hz, 3H), 2.06-2.97(m, 1H), 0.99-0.91(m, 2H), 0.63-0.57(m, 2H).	0.0239

TABLE 4-continued

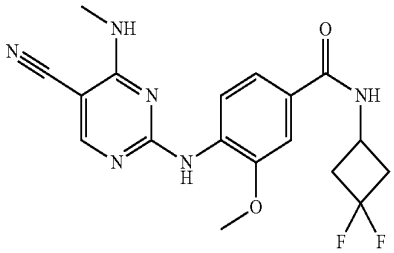
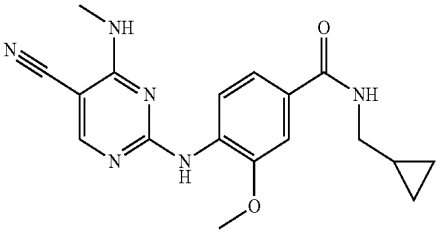
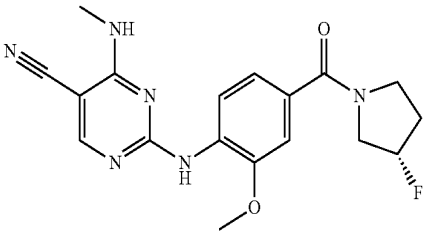
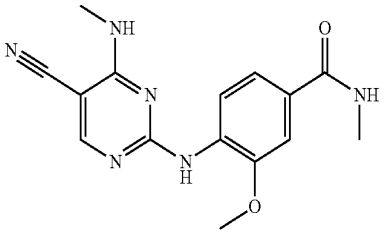
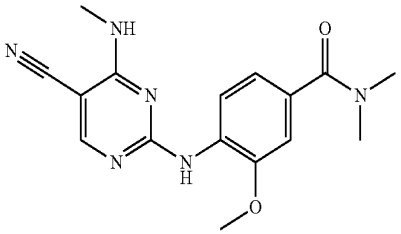
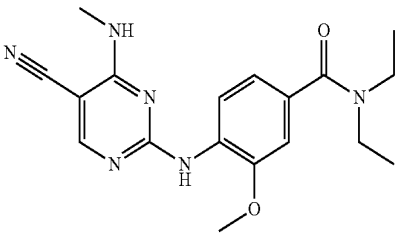
	Name	Structure	^{1}H NMR	K_I
194	4-(5-Cyano-4-methylamino-pyrimidin-2-ylamino)-N-(3,3-difluoro-cyclobutyl)-3-methoxy-benzamide		^{1}H NMR(400 MHz, DMSO): δ 8.69(d, J = 6.6 Hz, 1H), 8.36(s, 1H), 8.33 (s, 1H), 8.29(d, J = 8.3 Hz, 1H), 7.80(m, 1H), 7.41(m, 2H), 4.37-4.19(m, 1H), 3.92 (s, 3H), 3.06-2.84(m, 5H), 2.84-2.63(m, 2H).	0.0065
195	4-(5-Cyano-4-methylamino-pyrimidin-2-ylamino)-N-cyclopropylmethyl-3-methoxy-benzamide		^{1}H NMR(400 MHz, DMSO): δ 8.46(t, J = 5.6 Hz, 1H), 8.35(s, 1H), 8.33-8.17(m, 2H), 7.78(s, 1H), 7.51(d, J = 7.1 Hz, 2H), 3.92(s, 3H), 3.15(app t, J = 6.2 Hz, 2H), 2.90(d, J = 2.0 Hz, 3H), 1.21-0.90, m, 1H), 0.64-0.35(m, 2H), 0.30-0.12(m, 2H).	0.0042
196	2-[4-((S)-3-Fluoro-pyrrolidine-1-carbonyl)-2-methoxy-phenylamino]-4-methylamino-pyrimidine-5-carbonitrile		^{1}H NMR(400 MHz, DMSO): δ 8.35(s, 1H), 8.31(s, 1H), 8.21(d, J = 8.2 Hz), 1H), 7.75(m, 1H), 7.22-7.14(m, 2H), 3.89(s, 3H), 3.84-3.54(m, 5H), 2.89 (d, J = 4.5 Hz, 3H), 2.27-2.00(m, 2H).	0.0060
197	4-(5-Cyano-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-N-methyl-benzamide		^{1}H NMR(400 MHz, DMSO): δ 8.43-8.27(m, 3H), 8.24(d, J = 8.4 Hz, 1H), 7.77(m, 1H), 7.51-7.45 (m, 2H), 3.91(s, 3H), 2.89 (d, J = 4.5 Hz, 3H), 2.78(d, J = 4.5 Hz, 3H).	0.0066
198	4-(5-Cyano-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-N,N-dimethyl-benzamide		^{1}H NMR(400 MHz, DMSO): δ 8.33(s, 1H), 8.31(s, 1H), 8.15(d, J = 8.2 Hz, 1H), 7.73(m, 1H), 7.07 (d, J = 1.4 Hz, 1H), 7.00 (dd, J = 8.2, 1.5 Hz, 1H), 3.87(s, 3H), 2.97(s, 6H), 2.85(d, J = 3.6 Hz, 3H).	
199	4-(5-Cyano-4-methylamino-pyrimidin-2-ylamino)-N,N-diethyl-3-methoxy-benzamide		^{1}H NMR(400 MHz, DMSO): δ 8.32(s, 1H), 8.30(s, 1H), 8.13(d, J = 8.2 Hz, 1H), 7.71(m, 1H), 7.00 (d, J = 1.3 Hz, 1H), 6.93 (dd, J = 8.2, 1.5 Hz, 1H), 3.87(s, 3H), 3.42-3.30(m, 4H), 2.87(s, 3H), 1.11(t, J = 6.8 Hz, 6H).	0.0068

TABLE 4-continued

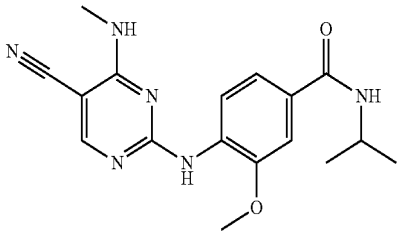
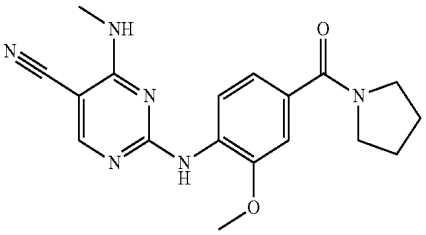
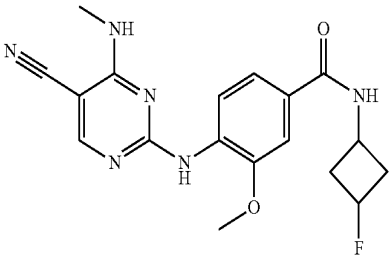
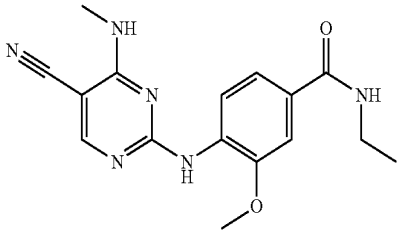
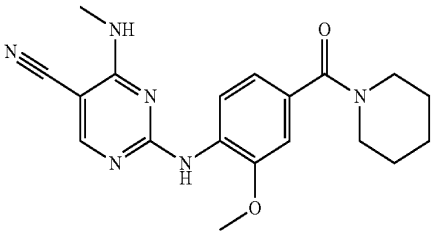
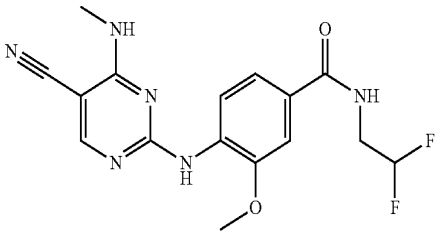
	Name	Structure	^{1}H NMR	K_I
200	4-(5-Cyano-4-methylamino-pyrimidin-2-ylamino)-N-isopropyl-3-methoxy-benzamide		^{1}H NMR(400 MHz, DMSO): δ 8.35(s, 1H), 8.30(s, 1H), 8.25(d, J = 8.6 Hz, 1H), 8.09(d, J = 7.7 Hz, 1H), 7.76(m, 1H), 7.51(s, 1H), 7.49(s, 1H), 4.10(dq, J = 13.5, 6.7 Hz, 1H), 3.92(s, 3H), 2.90(d, J = 4.1 Hz, 3H), 1.17(d, J = 6.6 Hz, 6H).	0.0044
201	2-[2-Methoxy-4-(pyrrolidine-1-carbonyl)-phenylamino]-4-methylamino-pyrimidine-5-carbonitrile		^{1}H NMR(400 MHz, DMSO): δ 8.34(s, 1H), 8.30(s, 1H), 8.18(d, J = 8.2 Hz, 1H), 7.74(m, 1H), 7.17 (d, J = 1.3 Hz, 1H), 7.13 (dd, J = 8.3, 1.5 Hz, 1H), 3.88(s, 3H), 3.46(t, J = 6.6 Hz, 4H), 2.89(d, J = 3.3 Hz, 3H), 1.92-1.78(m, 4H).	
202	2-[4-(3-Fluoro-azetidine-1-carbonyl)-2-methoxy-phenylamino]-4-methylamino-pyrimidine-5-carbonitrile		^{1}H NMR(400 MHz, DMSO): δ 8.36(s, 1H), 8.31 (s, 1H), 8.27(d, J = 8.5 Hz, 1H), 7.79(m, 1H), 7.27(dd, J = 4.2, 2.6 Hz, 2H), 4.75-4.00(m, 5H), 3.91(s, 3H), 3.29(m, 2H), 2.90(d, J = 2.0 Hz, 3H).	
203	4-(5-Cyano-4-methylamino-pyrimidin-2-ylamino)-N-ethyl-3-methoxy-benzamide		^{1}H NMR(400 MHz, DMSO): δ 8.40-8.33(m, 2H), 8.30(s, 1H), 8.20(d, J = 8.2 Hz, 1H), 7.78(m, 1H), 7.50(s, 1H), 7.48(s, 1H), 3.89(s, 3H), 3.30(m, 2H), 2.93(s, 3H), 1.13(t, J = 7.2 Hz, 3H).	0.0096
204	2-[2-Methoxy-4-(piperidine-1-carbonyl)-phenylamino]-4-methylamino-pyrimidine-5-carbonitrile		^{1}H NMR(400 MHz, DMSO): δ 8.32(s, 1H), 8.31(s, 1H), 8.15(d, J = 8.2 Hz, 1H), 7.72(m, 1H), 7.03 (d, J = 1.4 Hz, 1H), 6.96 (dd, J = 8.2, 1.4 Hz, 1H), 3.87(s, 3H), 3.45(br s, 4H), 2.88(d, J = 4.5 Hz, 3H), 1.68-1.45(m, 6H).	0.0033
205	4-(5-Cyano-4-methylamino-pyrimidin-2-ylamino)-N-(2,2-difluoro-ethyl)-3-methoxy-benzamide		^{1}H NMR(400 MHz, DMSO): δ 8.76(t, J = 5.8 Hz, 1H), 8.36(s, 1H), 8.33 (s, 1H), 8.29(d, J = 8.8 Hz, 1H), 7.80(m, 1H), 7.55(s, 1H), 7.53(d, J = 1.6 Hz, 1H), 6.25-5.97(m, 1H), 3.92 (s, 3H), 3.82-3.56(m, 2H), 2.90(s, 3H).	0.0121

TABLE 4-continued

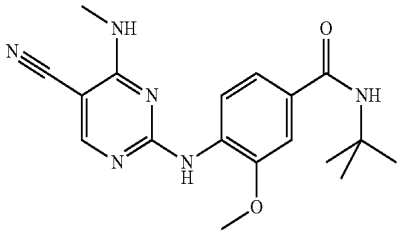
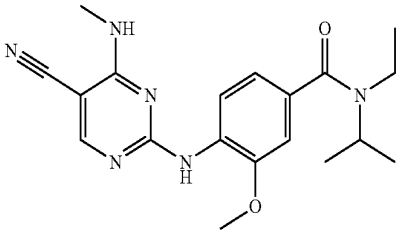
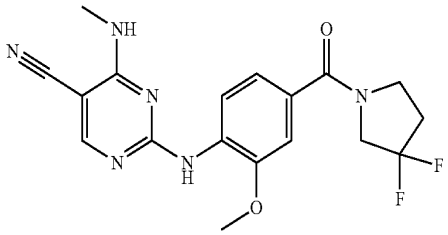
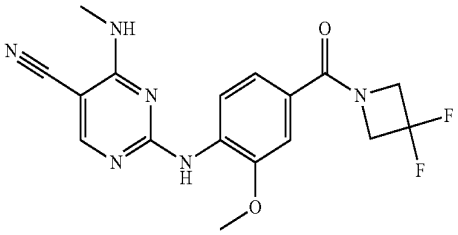
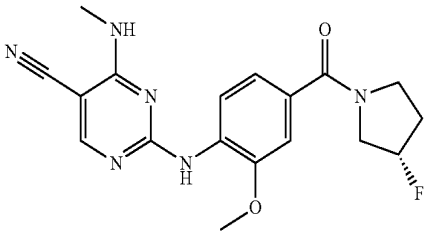
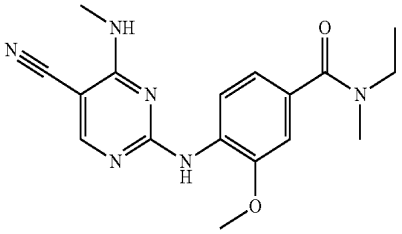
	Name	Structure	^{1}H NMR	K_I
206	N-tert-Butyl-4-(5-cyano-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-benzamide		^{1}H NMR(400 MHz, DMSO): δ 8.35(s, 1H), 8.29 (s, 1H), 8.22(d, J = 8.3 Hz, 1H), 7.78(m, 1H), 7.63(s, 1H), 7.51-7.44(m, 2H), 3.93 (s, 3H), 2.90(s, 3H), 1.39(s, 9H).	0.0046
207	4-(5-Cyano-4-methylamino-pyrimidin-2-ylamino)-N-ethyl-N-isopropyl-3-methoxy-benzamide		^{1}H NMR(400 MHz, DMSO): δ 8.32(s, 1H), 8.31(s, 1H), 8.12(d, J = 8.2 Hz, 1H), 7.71(m, 1H), 6.97 (d, J = 1.2 Hz, 1H), 6.90(d, J = 8.2 Hz, 1H), 4.10-3.88 (m, 3H), 3.87(s, 3H), 2.87 (d, J = 4.5 Hz, 3H), 1.15(m 9H).	0.0054
208	2-[4-(3,3-Difluoro-pyrrolidine-1-carobnyl)-2-methoxy-phenylamino]-4-methylamino-pyrimidine-5-carbonitrile		^{1}H NMR(400 MHz, DMSO): δ 8.35(s, 1H), 8.31(s, 1H), 8.24(d, J = 8.2 Hz, 1H), 7.77(m, 1H), 7.23-7.14(m, 2H), 3.91(s, 3H), 4.00-3.84(m, 2H), 3.74(t, J = 7.1 Hz, 2H), 89(d, J = 4.2 Hz, 3H), 2.534-2.37(m, 2H).	0.0081
209	2-[4-(3,3-Difluoro-azetidine-1-carobnyl)-2-methoxy-phenylamino]-4-methylamino-pyrimidine-5-carbonitrile		^{1}H NMR(400 MHz, DMSO): δ 8.37(s, 1H), 8.33 (s, 1H), 8.30(d, J = 8.3 Hz, 1H), 7.80(m, 1H), 7.38-7.27 (m, 2H), 4.90-4.40(m, 4H), 3.92(s, 3H), 2.90(d, J = 4.5 Hz, 3H).	
210	2-[4-((R)-3-Fluoro-pyrrolidine-1-carbonyl)-2-methoxy-phenylamino]-4-methylamino-pyrimidine-5-carbonitrile		^{1}H NMR(400 MHz, DMSO): δ 8.35(s, 1H), 8.31 (s, 1H), 8.21(d, J = 8.2 Hz, 1H), 7.75(m, 1H), 7.23-7.12 (m, 2H), 3.89(s, 3H), 3.85-3.49(m, 5H), 2.89(d, J = 4.5 Hz, 3H), 2.22-1.95(m, 2H).	0.0093
211	4-(5-Cyano-4-methylamino-pyrimidin-2-ylamino)-N-ethyl-3-methoxy-N-methyl-benzamide		^{1}H NMR(400 MHz, DMSO): δ 8.33(s, 1H), 8.31 (s, 1H), 8.14(d, J = 8.2 Hz, 1H), 7.72(m, 1H), 7.03(s, 1H), 6.97(d, J = 8.2 Hz, 1H), 3.87(s, 3H), 3.50-3.20 (m, 2H), 2.93(s, 3H), 2.88 (d, J = 4.4 Hz, 3H), 1.11(t, J = 6.9 Hz, 3H).	

TABLE 4-continued

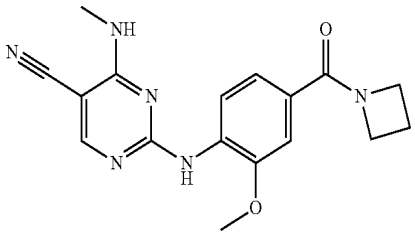
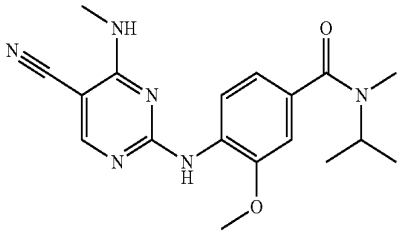
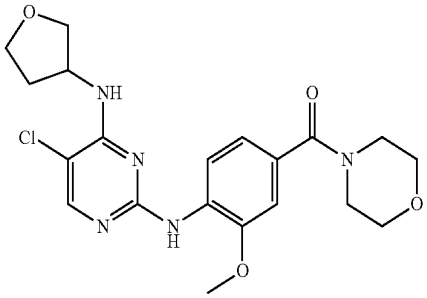
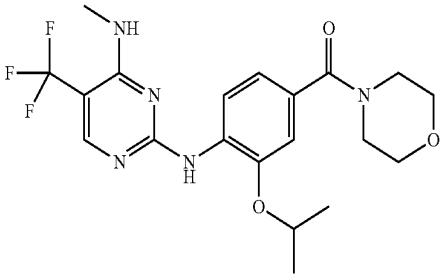
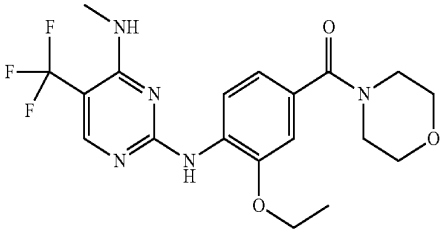
	Name	Structure	^{1}H NMR	K_I
212	2-[4-(Azetidine-1-carbonyl)-2-methoxy-phenylamino]-4-methylamino-pyrimidine-5-carbonitrile		^{1}H NMR(400 MHz, DMSO): δ 8.35(s, 1H), 8.30 (s, 1H), 8.23(d, J = 8.3 Hz, 1H), 7.77(m, 1H), 7.26-7.20 (m, 2H), 4.34(br s, 2H), 4.04(br s, 2H), 3.90(s, 3H), 2.89(d, J = 4.5 Hz, 3H), 2.36-2.18(m, 2H).	0.0264
213	4-(5-Cyano-4-methylamino-pyrimidin-2-ylamino)-N-isopropyl-3-methoxy-N-methyl-benzamide		^{1}H NMR(400 MHz, DMSO) δ 8.32(d, J = 4.6 Hz, 1H), 8.31(s, 1H), 8.14 (d, J = 8.2 Hz, 1H), 7.72(m, 1H), 7.02(s, 1H), 6.95(d, J = 8.1 Hz, 1H), 4.10-3.88(m, 1H), 3.87(s, 3H), 2.88(d, J = 4.5 Hz, 3H), 2.79(s, 3H), 1.13(d, J = 6.7 Hz, 6H).	0.0068
214	{4-[5-Chloro-4-(tetrahydro-furan-3-ylamino)-pyrimidin-2-ylamino]-3-methoxy-phenyl}-morpholin-4-yl-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.29(d, J = 8.3 Hz, 1H), 8.00(s, 1H), 7.76 (s, 1H), 7.16(d, J = 6.3 Hz, 1H), 7.03(dd, J = 15.4, 4.8 Hz, 2H), 3.96-3.78(m, 5H), 3.73(d, J = 6.2 Hz, 1H), 3.58(t, J = 21.4 Hz, 8H), 2.20(dd, J = 12.8, 6.7 Hz, 2H), 2.11-1.90(m, 2H).	0.0184
215	[3-Isopropoxy-4-(4-methylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-phenyl]-morpholin-4-yl-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.40(d, J = 8.3 Hz, 1H), 8.19(s, 1H), 7.95 (s, 1H), 7.26(d, J = 4.2 Hz, 1H), 7.08(s, 1H), 7.00(d, J = 8.3 Hz, 1H), 4.73(dt, J = 12.1, 6.1 Hz, 1H), 3.55(d, J = 38.1 Hz, 8H), 2.94(d, J = 4.3 Hz, 3H), 1.33(d, J = 6.0 Hz, 6H).	0.0094
216	[3-Ethoxy-4-(4-methylamino-5-trilfuoromethyl-pyrimidin-2-ylamino)-phenyl]-morpholin-4-yl-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.35(s, 1H), 8.19 (s, 1H), 8.02(s, 1H), 7.24(s, 1H), 7.06(s, 1H), 7.01(d, J = 8.2 Hz, 1H), 4.16(q, J = 7.0 Hz, 1H), 3.55(d, J = 38.1 Hz, 8H), 2.93(d, J = 4.3 Hz, 2H), 1.39(t, J = 6.9 Hz, 3H).	0.0042

TABLE 4-continued

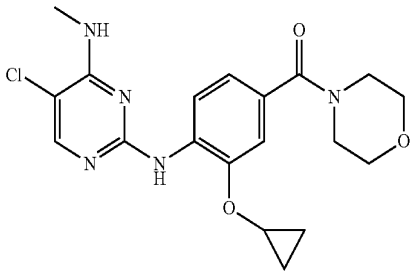
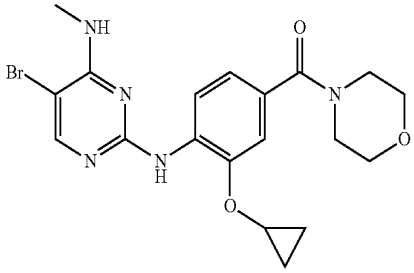
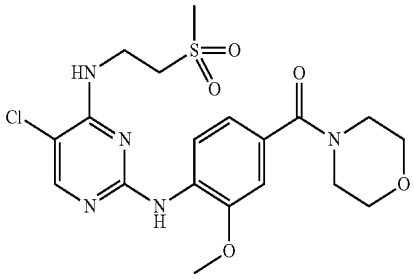
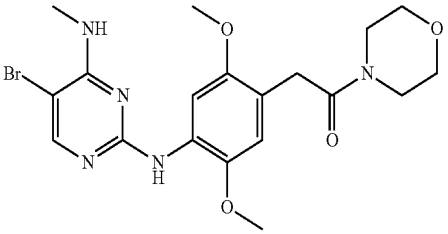
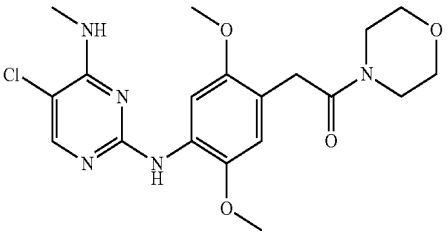
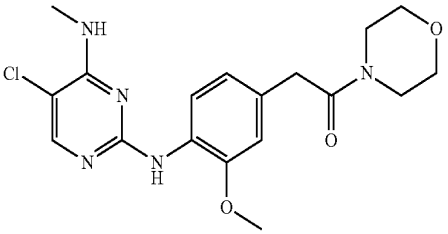
	Name	Structure	^{1}H NMR	K_I
217	[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-cyclopropoxy-phenyl]-morpholin-4-yl-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.39(d, J = 8.3 Hz, 1H), 7.94(s, 1H), 7.56 (s, 1H), 7.32(s, 2H), 7.03 (d, J = 8.3 Hz, 1H), 3.98(s, 1H), 3.57(d, J = 33.3 Hz, 8H), 2.91(d, J = 4.5 Hz, 3H), 0.88-0.69(m, 4H).	0.0020
218	[4-(5-Bromo-4-methoxy-pyrimidin-2-ylamino)-3-cyclopropoxy-phenyl]-morpholin-4-yl-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.37(s, 1H), 8.22 (s, 1H), 8.13(d, J = 8.2 Hz, 1H), 7.35(s, 1H), 7.05(d, J = 8.3 Hz, 1H), 3.98(s, 3H), 3.57(d, J = 36.5 Hz, 8H), 0.87-0.70(m, 4H).	0.0025
219	{4-[5-Chloro-4-(2-methanesulfonyl-ethylamino)-pyrimidin-2-ylamino]-3-methoxy-phenyl}-morpholin-4-yl-methanone		^{1}H NMR(400 MHz, DMSO) δ 8.30(d, J = 8.3 Hz, 1H), 8.02(s, 1H), 7.83 (s, 1H), 7.47(s, 1H), 7.06(s, 1H), 7.01(d, J = 8.2 Hz, 1H), 3.90(s, 3H), 3.82(d, J = 6.8 Hz, 2H), 3.56(d, J = 34.4 Hz, 8H), 3.44(t, J = 7.1 Hz, 2H), 3.03(s, 3H).	0.0264
220	2-[4-(5-Bromo-4-methylamino-pyrimidin-2-ylamino)-2,5-dimethoxy-phenyl]-1-morpholin-4-yl-ethanone		^{1}H NMR(400 MHz, DMSO) δ 8.14(s, 1H), 8.00 (s, 1H), 7.56(s, 1H), 7.11 (d, J = 4.5 Hz, 1H), 6.79(s, 1H), 3.79(s, 3H), 3.73(s, 3H), 3.56(s, 2H), 3.49(dd, J = 24.0, 5.0 Hz, 8H), 2.94 (d, J = 4.5 Hz, 3H).	0.0034
221	2-[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-2,5-dimethoxy-phenyl]-1-morpholin-4-yl-ethanone		^{1}H NMR(400 MHz, DMSO) δ 8.15(s, 1H), 7.93 (s, 1H), 7.55(s, 1H), 7.29 (d, J = 4.4 Hz, 1H), 6.79(s, 1H), 3.79(s, 3H), 3.73(s, 3H), 3.56(s, 2H), 3.49(dd, J = 24.0, 5.2 Hz, 8H), 2.94 (d, J = 4.6 Hz, 3H).	0.0087
222	2-[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-1-morpholin-4-yl-ethanone		^{1}H NMR(400 MHz, DMSO) δ 8.18(d, J = 8.2 Hz, 1H), 7.90(s, 1H), 7.54 (s, 1H), 7.22(s, 1H), 6.88(s, 1H), 6.77(d, J = 8.5 Hz, 1H), 3.83(s, 3H), 3.66(s, 2H), 3.51(d, J = 19.1 Hz, 8H), 2.88(d, J = 4.5 Hz, 3H).	0.0090

TABLE 4-continued

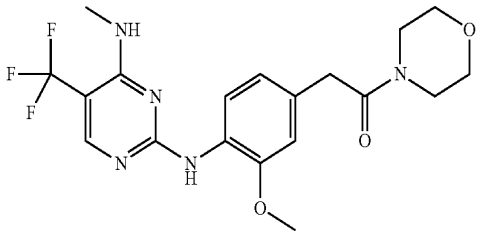
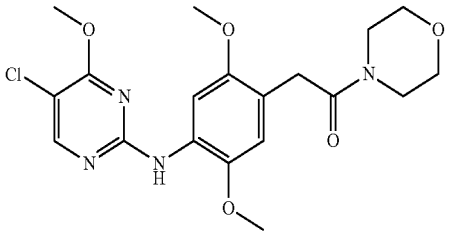
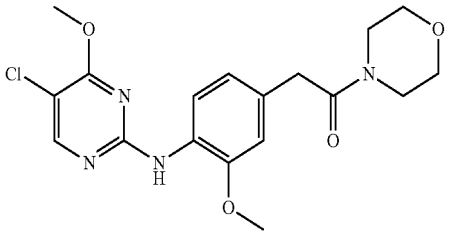
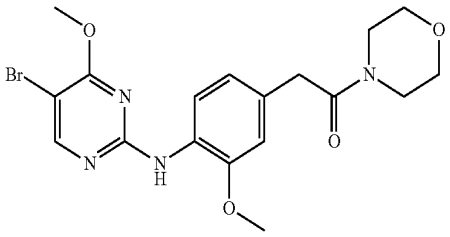
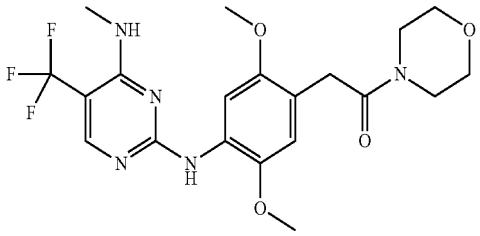
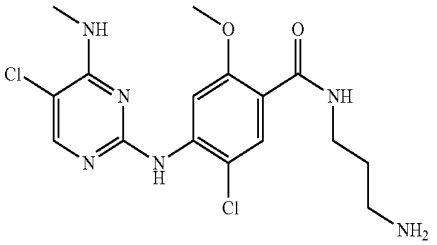
	Name	Structure	^{1}H NMR	K_I
223	2-[3-Methoxy-4-(4-methylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-phenyl]-1-morpholin-4-yl-ethanone		^{1}H NMR(400 MHz, DMSO) δ 8.13(s, 1H), 8.05 (d, J = 8.2 Hz, 1H), 7.99(s, 1H), 7.12(s, 1H), 6.90(s, 1H), 6.79(d, J = 8.7 Hz, 1H), 6.65(s, 1H), 3.82(s, 3H), 3.68(s, 2H), 3.51(d, J = 17.5 Hz, 8H), 2.88(d, J = 4.2 Hz, 3H).	0.0052
224	2-[4-(5-Chloro-4-methoxy-pyrimidin-2-ylamino)-2,5-dimethoxy-phenyl]-1-morpholin-4-yl-ethanone		^{1}H NMR(400 MHz, DMSO) δ 8.29(s, 1H), 8.18 (s, 1H), 7.81(s, 1H), 6.83(s, 1H), 4.01(s, 3H), 3.78(s, 3H), 3.73(s, 3H), 3.58(s, 2H), 3.49(d, J = 28.3 Hz, 8H).	
225	2-[4-(5-Chloro-4-methoxy-pyrimidin-2-ylamino)-3-methoxy-phenyl]-1-morpholin-4-yl-ethanone		^{1}H NMR(400 MHz, DMSO) δ 8.22(d, J = 16.9 Hz, 2H), 7.88(d, J = 8.2 Hz, 1H), 6.91(s, 1H), 6.80(d, J = 8.2 Hz, 1H), 3.95(s, 3H), 3.81(s, 3H), 3.69(s, 2H), 3.51(d, J = 17.2 Hz, 8H).	
226	2-[4-(5-Bromo-4-methoxy-pyrimidin-2-ylamino)-3-methoxy-phenyl]-1-morpholin-4-yl-ethanone		^{1}H NMR(400 MHz, DMSO) δ 8.31(s, 1H), 8.22 (s, 1H), 7.87(d, J = 8.1 Hz, 1H), 6.91(s, 1H), 6.80(d, J = 7.9 Hz, 1H), 3.94(s, 3H), 3.81(s, 3H), 3.69(s, 2H), 3.50(t, J = 12.7 Hz, 8H).	0.0056
227	2-[2,5-Dimethoxy-4-(4-methylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-phenyl]-1-morpholin-4-yl-ethanone		^{1}H NMR(400 MHz, DMSO) δ 8.16(s, 1H), 8.04 (s, 1H), 7.94(s, 1H), 7.20(s, 1H), 6.82(s, 1H), 3.79(s, 3H), 3.73(s, 3H), 3.58(s, 2H), 3.49(d, J = 24.9 Hz, 8H), 2.96(s, 3H).	0.0037
228	N-(3-Amino-propyl)-5-chloro-4-(5-chloro-4-methyalmino-pyrimidin-2-ylamino)-2-methoxy-benzamide			0.0038

TABLE 4-continued

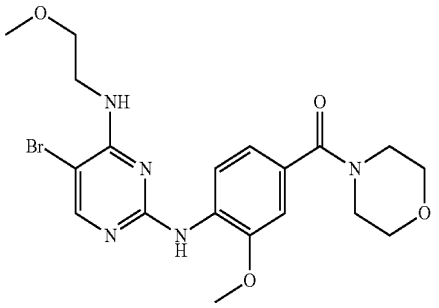
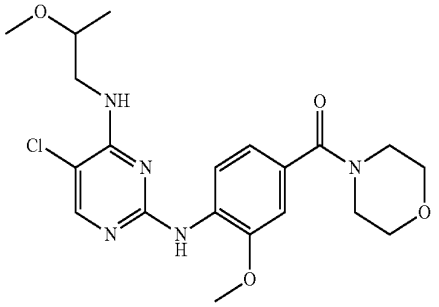
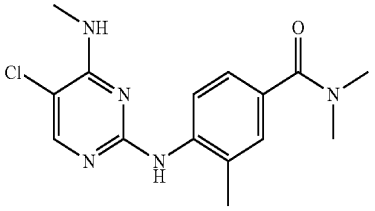
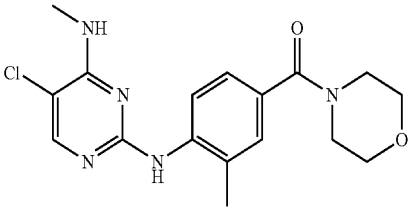
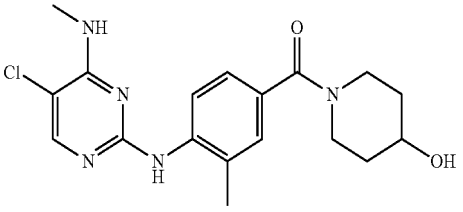
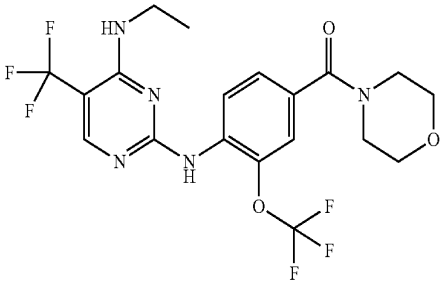
	Name	Structure	^{1}H NMR	K_I
229	{4-[5-Bromo-4-(2-methoxy-ethylamino)-pyrimidin-2-ylamino]-3-methoxy-phenyl}-morpholin-4-yl-methanone			0.0041
230	{4-[5-Chloro-4-(2-methoxy-propylamino)-pyrimidin-2-ylamino]-3-methoxy-phenyl}-morpholin-4-yl-methanone			0.0096
231	4-(5-chloro-4-(methylamino)pyrimidin-2-ylamino)-N,N,3-trimethylbenzamide			
232	(4-(5-chloro-4-(methyalmino)pyrimidin-2-ylamino)-3-methylphenyl)(morpholino)methanone			0.0074
233	(4-(5-chloro-4-(methylamino)pyrimidin-2-ylamino)-3-methylphenyl)(4-hydroxypiperidin-1-yl)methanone			0.0061
234	(4-(4-(ethylamino)-5-(trifluoromethyl)pyrimidin-2-ylamino)-3-(trifluoromethoxy)phenyl)(morpholino)methanone			0.0032

TABLE 4-continued

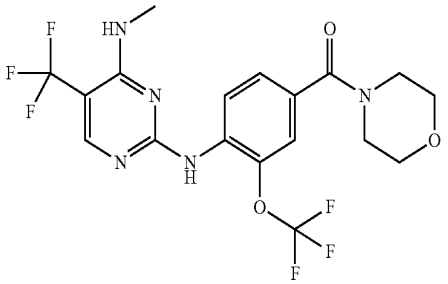
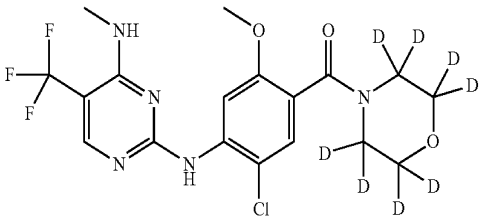
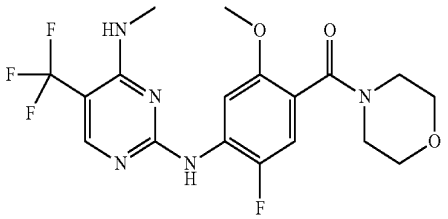
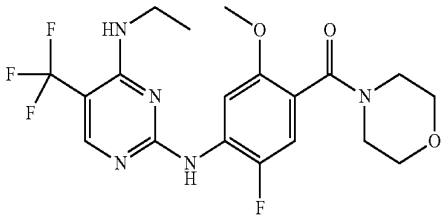
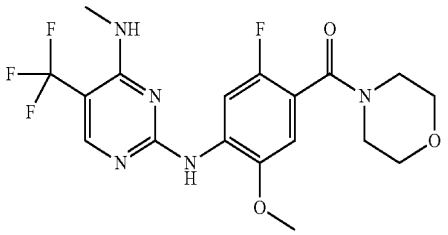
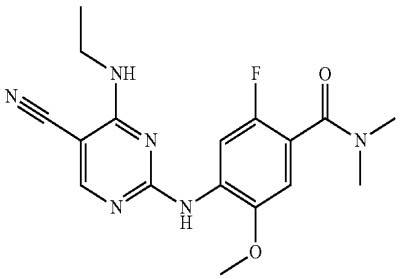
	Name	Structure	^{1}H NMR	K_I
235	(4-(4-(methylamino)-5-(trifluoromethyl)pyrimidin-2-ylamino)-3-(trifluoromethoxy)phenyl)(morpholino)methanone			0.0112
236	(5-chloro-2-methoxy-4-(4-(methylamino)-5-(trifluoromethyl)pyrimidin-2-ylamino)phenyl)(perdeuteromorpholino)methanone			0.0042
237	(5-fluoro-2-methoxy-4-(4-(methylamino)-5-(trifluoromethyl)pyrimidin-2-ylamino)phenyl)(morpholino)methanone			0.0048
238	(4-(4-(ethylamino)-5-(trifluoromethyl)pyrimidin-2-ylamino)-5-fluoro-2-methoxyphenyl)(morpholino)methanone			0.0014
239	[2-Fluoro-5-methoxy-4-(4-methylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-phenyl]-morpholin-4-yl-methanone			0.0029
240	4-(5-Cyano-4-ethylamino-pyrimidin-2-ylamino)-2-fluoro-5-methoxy-N,N-dimethyl-benzamide			0.0098

TABLE 4-continued

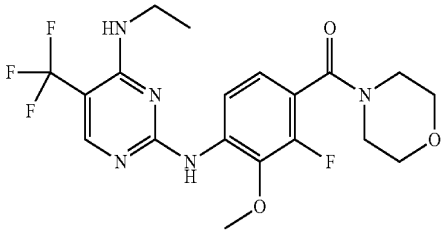
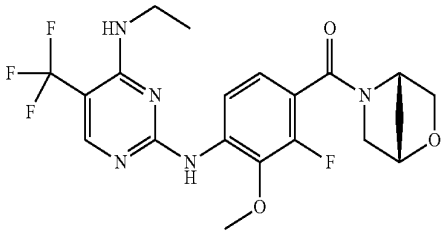
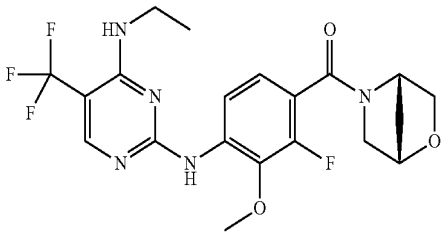
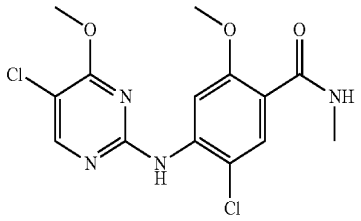
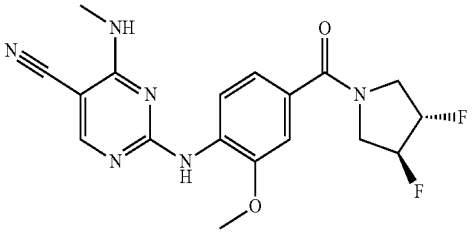
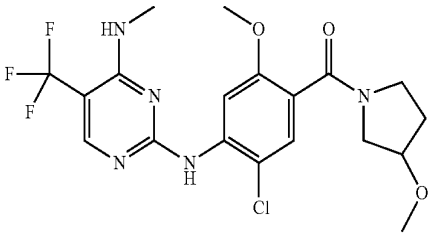
	Name	Structure	^{1}H NMR	K_I
241	(4-(4-(ethylamino)-5-(trifluoromethyl)pyrimidin-2-ylamino)-2-fluoro-3-methoxyphenyl)(morpholino)methanone			0.0018
242	(1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl(4-(4-(ethylamino)-5-(trifluoromethyl)pyrimidin-2-ylamino)-2-fluoro-3-methoxyphenyl)methanone			0.0028
243	(1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl(2-fluoro-3-methoxy-4-(4-(methylamino)-5-(trifluoromethyl)pyrimidin-2-ylamino)phenyl)methanone			
244	5-chloro-4-(5-chloro-4-methoxypyrimidin-2-ylamino)-2-methoxy-N-methylbenzamide			
245	2-(4-((3S,4S)-3,4-difluoropyrrolidine-1-carbonyl)-2-methoxyphenylamino)-4-(methyalmino)pyrimidine-5-carbonitrile			0.0135
246	(5-chloro-2-methoxy-4-(4-(methylamino)-5-(trifluoromethyl(pyrimidin-2-ylamino)phenyl)(3-methoxypyrrolidin-1-yl)methanone			0.0050

TABLE 4-continued

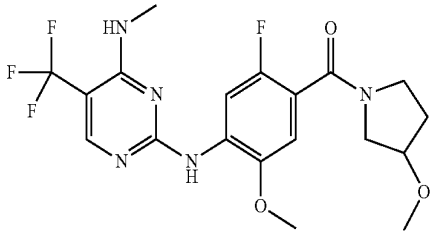
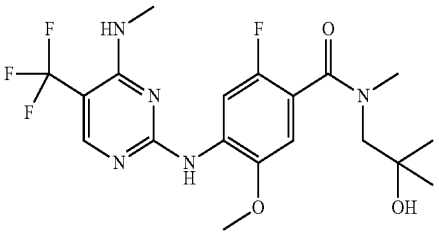
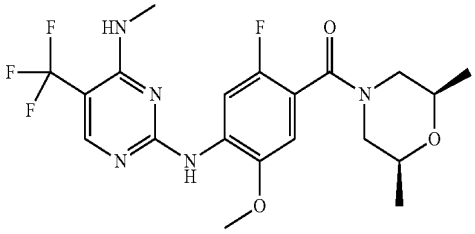
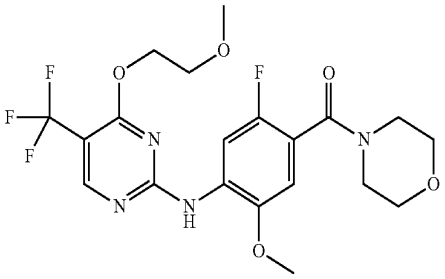
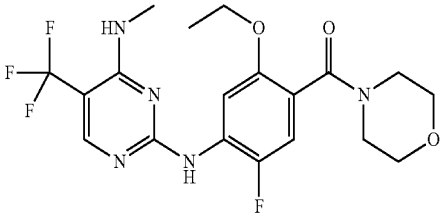
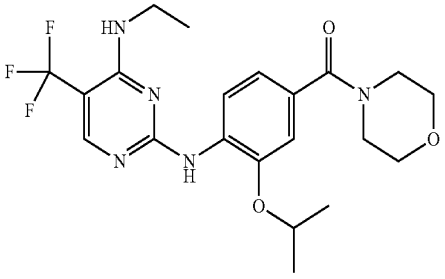
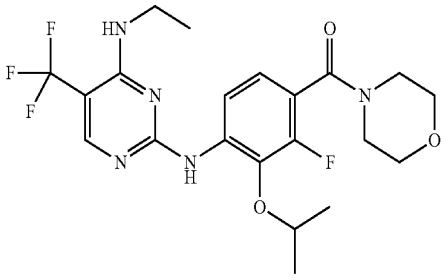
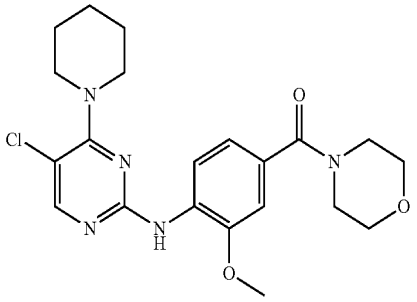
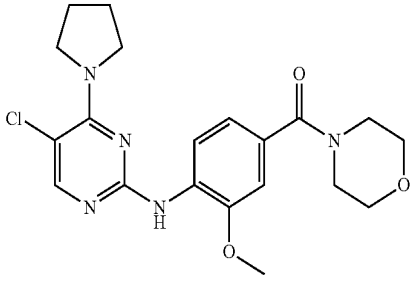
	Name	Structure	^{1}H NMR	K_I
247	(2-fluoro-5-methoxy-4-(4-(methylamino)-5-(trifluoromethyl)pyrimidin-2-ylamino)phenyl)(3-methoxypyrrolidin-1-yl)methanone			0.0027
248	2-fluoro-N-(2-hydroxy-2-methylpropyl)-5-methoxy-N-methyl-4-(4-(methylamino)-5-(trifluoromethyl)pyrimidin-2-ylamino)benzamide			0.0092
249	((2S,6R)-2,6-dimethylmorpholino)(2-fluoro-5-methoxy-4-(4-(methylamino)-5-(trifluoromethyl)pyrimidin-2-ylamino)phenyl)methanone			0.0080
250	(2-fluoro-5-methoxy-4-(4-(2-methoxyethoxy)-5-(trifluoromethyl)pyrimidin-2-ylamino)phenyl)(morpholino)methanone			
251	(2-ethoxy-5-fluoro-4-(4-(methylamino)-5-(trifluoromethyl)pyrimidin-2-ylamino)phenyl)(morpholin)methanone			
252	(4-(4-(ethylamino)-5-(trifluoromethyl)pyrimidin-2-ylamino)-3-isopropoxyphenyl)(morpholino)methanone			0.0045

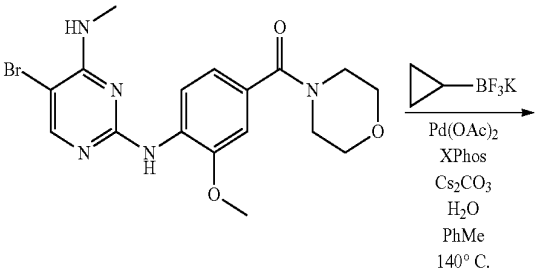
TABLE 4-continued

	Name	Structure	^{1}H NMR	K_I
253	(4-(4-(ethylamino)-5-(trifluoromethyl)pyrimidin-2-ylamino)-2-fluoro-3-isopropoxyphenyl)(morpholino)methanone			
254	(4-(5-chloro-4-(piperidin-1-yl)pyrimidin-2-ylamino)-3-methoxyphenyl)(morpholino)methanone			0.0121
255	(4-(5-chloro-4-(pyrrolidin-1-yl)pyrimidin-2-ylamino)-3-methoxyphenyl)(morpholino)methanone			0.0179

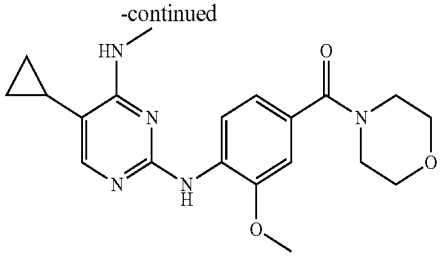
Example 2

[4-(5-Cyclopropyl-4-methylamino-pyrimidin-2-ylamino)-3-methoxy-phenyl]-morpholin-4-yl-methanone

[0543]



-continued



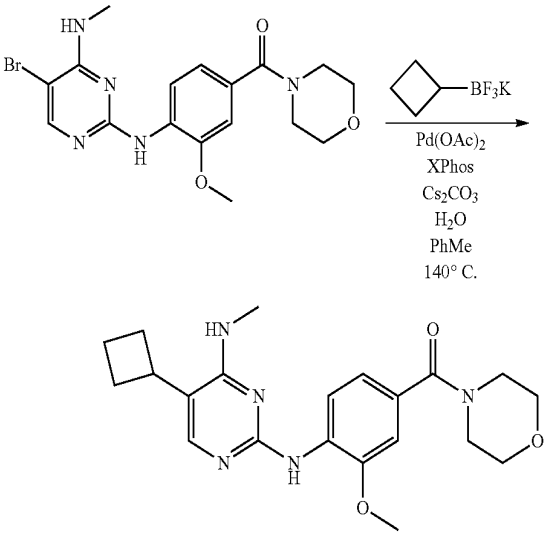
[0544] To a microwave tube was added (4-(5-bromo-4-(methylamino)pyrimidin-2-ylamino)-3-methoxyphenyl)(morpholino)methanone (56 mg, 0.13 mmol), potassium cyclopropyltrifluoroborate (39 mg, 0 27 mmol), cesium carbonate (0.13 g, 0.40 mmol), toluene (1.8 mL) and water (0.2 mL). The mixture was degassed by nitrogen bubbling for 15 mintues. XPhos (6.4 mg, 0 013 mmol) and palladium acetate (2 mg, 0.01 mmol) was then added. The reaction was heated in a Biotage microwave at 140° C. for 20 minutes. The reaction mixture was filtered and concentrated. The crude product was purified by RP-HPLC to give the desire product (12.6 mg, 25%).

[0545] Additional compounds made using the above procedure are shown in Table 4 above.

Example 3

(4-(5-cyclobutyl-4-(methylamino)pyrimidin-2-ylamino)-3-methoxyphenyl)(morpholino)methanone

[0546]



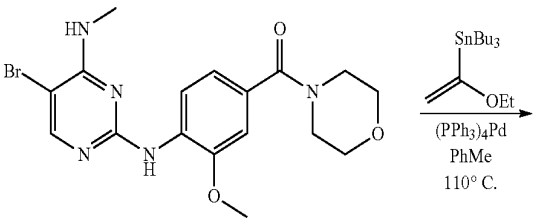
[0547] To a microwave tube was added (4-(5-bromo-4-(methylamino)pyrimidin-2-ylamino)-3-methoxyphenyl)(morpholino)methanone (100 mg, 0.24 mmol), potassium cyclobutyltrifluoroborate (177 mg, 1.1 mmol), cesium carbonate (0.23 g, 0.71 mmol), toluene (2.9 mL) and water (0.3 mL). The mixture was degassed by nitrogen bubbling for 15 mintues. di-(1-admantyl)-n-butylphosphine (19 mg, 0.053 mmol) and palladium acetate (2.6 mg, 0.026 mmol) was then added. The reaction was sealed and heated at 11° C. for 2 hours. The reaction mixture was filtered and concentrated. The crude product was purified by RP-HPLC to give the desire product (8.1 mg, 8.6%).

[0548] Additional compounds made using the above procedure are shown in Table 4 above.

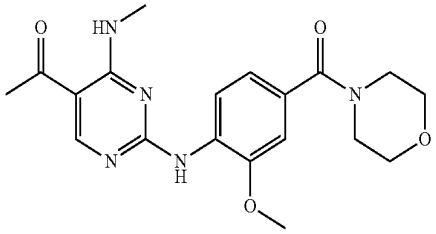
Example 4

1-{2-[2-Methoxy-4-(morpholine-4-carbonyl)-phenylamino]-4-methylamino-pyrimidin-5-yl}-ethanone

[0549]



-continued

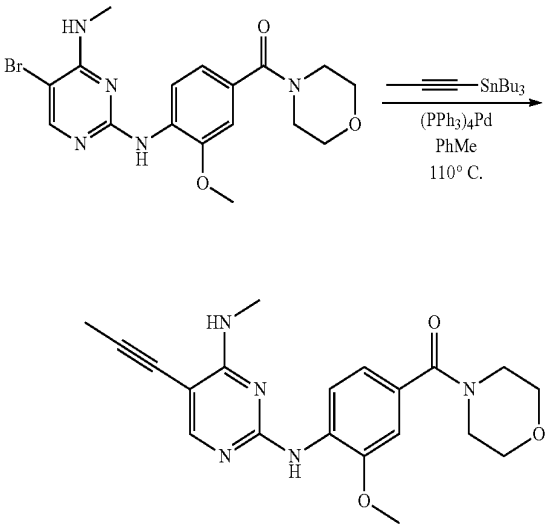


[0550] A mixture of (4-(5-bromo-4-(methylamino)pyrimidin-2-ylamino)-3-methoxyphenyl)(morpholino)methanone (100 mg, 0 24 mmol), $Pd(PPh_3)_4$ (36 mg, 0 03 mmol) and tributylethoxyvinyltin (0.16 mL, 0.47 mmol) in toluene was stirred in a sealed tube at 110° C. for 1 hour. The reaction mix was filtered and concentrated. The reaction mixture was filtered through a pad of silica gel (eluted with 0-100% EtOAc in heptane) to give the crude product. Purification of the crude product was achieved by reverse phase HPLC (9 mg, 10%). Additional compounds made using the above procedure are shown in Table 4 above.

Example 5

[3-Methoxy-4-(4-methylamino-5-prop-1-ynyl-pyrimidin-2-ylamino)-phenyl]-morpholin-4-yl-methanone

[0551]

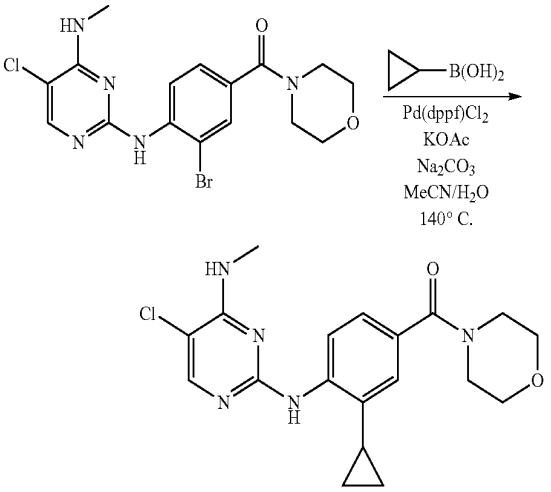


[0552] A mixture of (4-(5-bromo-4-(methylamino)pyrimidin-2-ylamino)-3-methoxyphenyl)(morpholino)methanone (140 mg, 0.233 mmol), $Pd(PPh_3)_4$ (50 mg, 0 04 mmol)and tributyl(prop-1-ynyl)stannane (0.20 mL, 0.66 mmol) in toluene (5 mL) was stirred in a sealed tube at 110° C. for 1 hour. The reaction mixture was filtered and concentrated. Purification of the crude product was achieved by reverse phase HPLC (9 mg, 10%). Additional compounds made using the above procedure are shown in Table 4 above.

Example 6

[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-cyclopropyl-phenyl]-morpholin-4-yl-methanone

[0553]

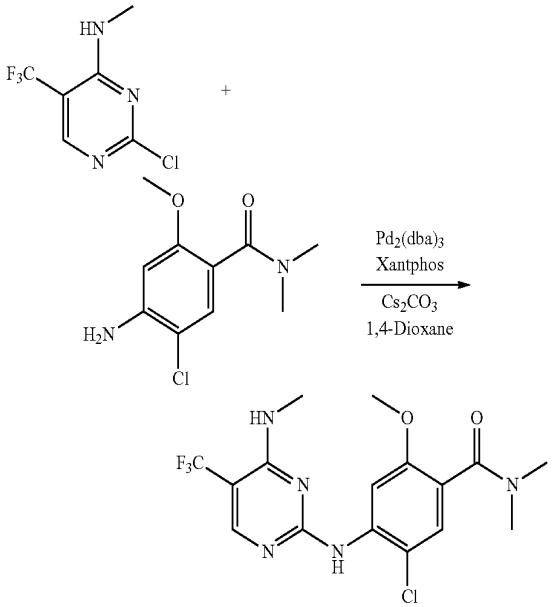


[0554] A mixture of [3-Bromo-4-(5-chloro-4-methylamino-pyrimidin-2-ylamino)-phenyl]-morpholin-4-yl-methanone (0.0500 g, 0.117 mmol), potassium acetate (0.0172 g, 0.176 mmol), sodium carbonate (0.0186 g, 0.176 mmol) and 1,1'-bis(diphenylphosphino)ferrocenepalladium (II) chloride (0.00478 g, 0.00585 mmol) were weighed into a microwave vial equipped with a stir bar. Acetonitrile (0.94 mL, 18 mmol) and degassed Water (0.3 mL, 20 mmol) were then added and the reaction mixture was degassed with nitrogen for 4 mins and then heated to 140° C. under microwave irradiation for 80 min. The mixture was then filtered through celite, eluting with ethyl acetate and concentrated in vacuo. Purification of the crude product was achieved by reverse phase HPLC.

Example 7

5-Chloro-2-methoxy-4-N,N-dimethyl-(4-methylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-benzamide

[0555]



[0556] A mixture of 4-amino-5-chloro-2-methoxy-N,N-dimethylbenzamide (110 mg, 0.48 mmol), 2-chloro-4-(methylamino)-5-trifluoromethylpyrimidine (50 mg, 0.23 mmol), tris(dibenzylideneacetone)dipalladium (11 mg, 0.012 mmol), xantphos (14 mg, 0.024 mmole) and cesium carbonate (235 mg, 0 72 mmol) in 1,4-dioxane was degassed with nitrogen for 5 minutes before heating to 100° C. for 2 hours. The cooled mixture was diluted with DCM (10 ml), washed with water, dried ($MgSO_4$) and concentrated in dryness in vacuum. The residue was triturated in diethyl ether to afford the title compound as a pale yellow solid, 45 mg, 47%.

[0557] Additional compounds made using the above procedure are shown in Table 5 below.

TABLE 5

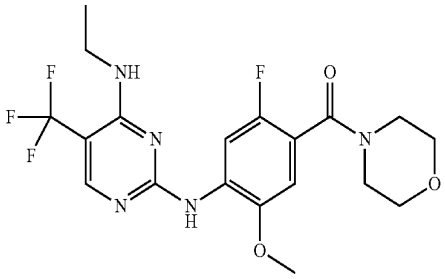
Name	Structure	^{1}H NMR	K_1
256 [4-(4-Ethylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-2-fluoro-5-methoxy-phenyl]-morpholin-4-yl-methanone		^{1}H NMR (400 MHz, CDCl3): δ 8.44 (d, J = 12.3 Hz, 1 H), 8.20 (s, 1 H), 7.84 (s, 1 H), 6.91 (d, J = 5.9 Hz, 1 H), 5.21 (s, 1 H), 3.92 (s, 3 H), 3.80 (d, J = 9.1 Hz, 4 H), 3.71-3.54 (m, 4 H), 3.44 (s, 2 H), 1.33 (t, J = 7.2 Hz, 3 H).	0.002

TABLE 5-continued

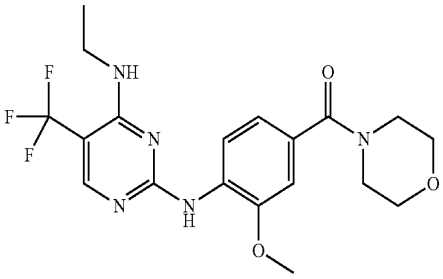
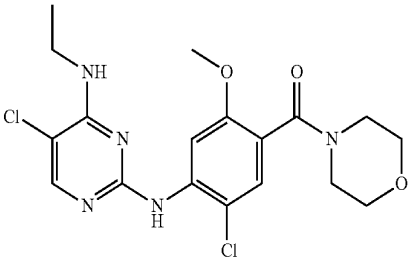
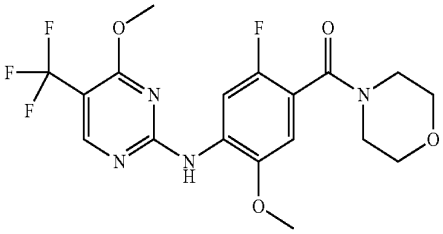
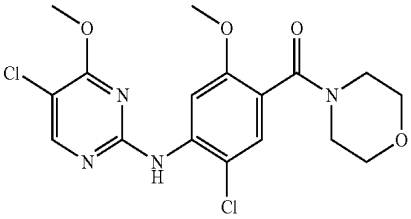
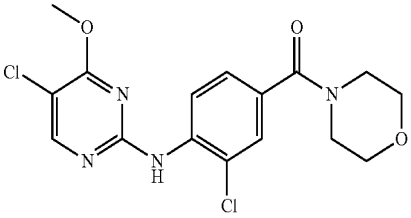
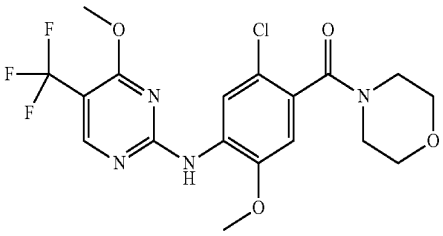
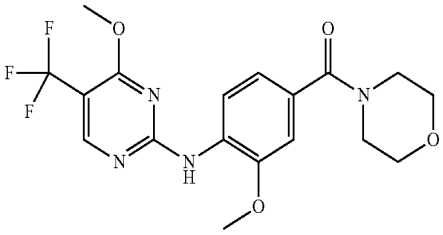
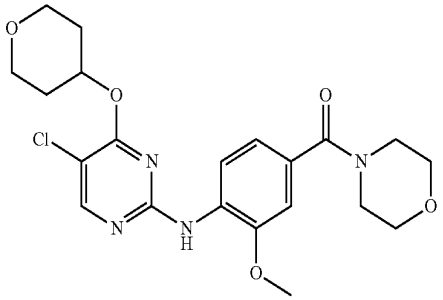
	Name	Structure	^{1}H NMR	K_1
257	4-(4-Ethylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-3-methoxy-phenyl]-morpholin-4-yl-methanone		^{1}H NMR (400 MHz, CDCl3): δ 8.54 (d, J = 8.2 Hz, 1 H), 8.19 (s, 1 H), 7.81 (s, 1 H), 7.04-7.00 (m, 2 H), 5.15 (s, 1 H), 3.94 (s, 3 H), 3.70 (s, 7 H), 3.65-3.55 (m, 3 H), 1.31 (t, J = 7.2 Hz, 3 H).	0.002
258	[5-Chloro-4-(5-chloro-4-ethylamino-pyrimidin-2-ylamino)-2-methoxy-phenyl]-morpholin-4-yl-methanone		^{1}H NMR (400 MHz, CDCl3): δ 8.41 (s, 1 H), 7.96 (s, 1 H), 7.49 (s, 1 H), 7.30 (s, 1 H), 5.35-5.25 (m, 1 H), 3.87 (s, 3 H), 3.77 (d, J = 11.6 Hz, 4 H), 3.59 (dt, J = 13.4, 7.2 Hz, 4 H), 3.32 (d, J = 18.3 Hz, 2 H), 1.31 (t, J = 7.3 Hz, 3 H).	0.005
259	[4-(5-Chloro-4-methoxy-pyrimidin-2-ylamino)-2-fluoro-5-methoxy-phenyl]-morpholin-4-yl-methanone		^{1}H NMR (400 MHz, CDCl3): δ 8.37 (d, J = 12.2 Hz, 1 H), 8.20 (s, 1 H), 7.81 (s, 1 H), 6.93 (d, J = 5.9 Hz, 1 H), 4.10 (s, 3 H), 3.94 (s, 3 H), 3.80 (d, J = 8.5 Hz, 4 H), 3.68 (s, 2 H), 3.44 (s, 2 H).	0.0192
260	[5-Chloro-4-(5-chloro-4-methoxy-pyrimidin-2-ylamino)-2-methoxy-phenyl]-morpholin-4-yl-methanone		^{1}H NMR (400 MHz, DMSO): δ 8.88 (s, 1 H), 8.31 (s, 1 H), 7.70 (s, 1 H), 7.32 (s, 1 H), 398 (s, 1 H), 3.80 (s, 3 H), 3.61 (m, 4 H), 3.53 (m, 2 H), 3.17 (m, 2 H).	0.047
261	[3-Chloro-4-(5-chloro-4-methoxy-pyrimidin-2-ylamino)-phenyl]-morpholin-4-yl-methanone		^{1}H NMR (400 MHz, DMSO): δ 9.03 (s, 1 H), 8.28 (s, 1 H), 7.92 (d, J = 8.3, 1 H), 7.55 (s, 1 H), 7.39 (d, J = 9.8, 1 H), 3.95 (m, 3 H), 3.56 (m, 8 H).	0.047
262	[2-Chloro-5-methoxy-4-(4-methoxy-5-trifluoromethyl-pyrimidin-2-ylamino)-phenyl]-morpholin-4-yl-methanone		1H NMR (400 MHz, DMSO) δ 8.98 (s, 1 H), 8.56 (s, 1 H), 8.15 (s, 1 H), 7.10 (s, 1 H), 4.01 (s, 3 H), 3.87 (s, 3 H), 3.73-3.48 (m, 6 H), 3.23-3.15 (m, 3 H).	0.024

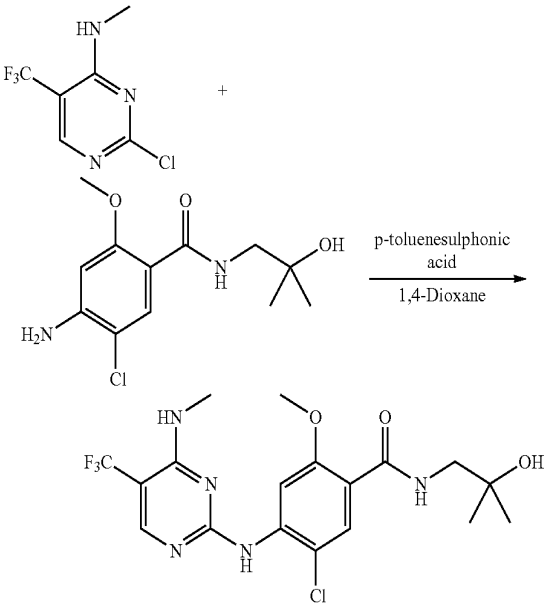
TABLE 5-continued

	Name	Structure	^{1}H NMR	K_1
263	[3-Methoxy-4-(4-methoxy-5-trifluoromethyl-pyrimidin-2-ylamino)-phenyl]-morpholin-4-yl-methanone			0.020
264	{4-[5-Chloro-4-(tetrahydro-pyran-4-yloxy)-pyrimidin-2-ylamino]-3-methoxy-phenyl}-morpholin-4-yl-methanone		^{1}H NMR (400 MHz, DMSO): δ 8.32 (m, 2 H), 8.06 (d, J = 8.2, 1 H), 7.08 (s, 1 H), 7.02 (d, J = 8.2, 1 H), 5.26 (m, 1 H), 3.86 (m, 5 H), 3.61 (m, 4 H), 3.50 (m, 6 H), 2.05 (m, 2 H), 1.68 (m, 2 H).	0.033

Example 8

5-Chloro-N-(2-hydroxy-2-methyl-propyl)-2-methoxy-4-(4-methylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-benzamide

[0558]



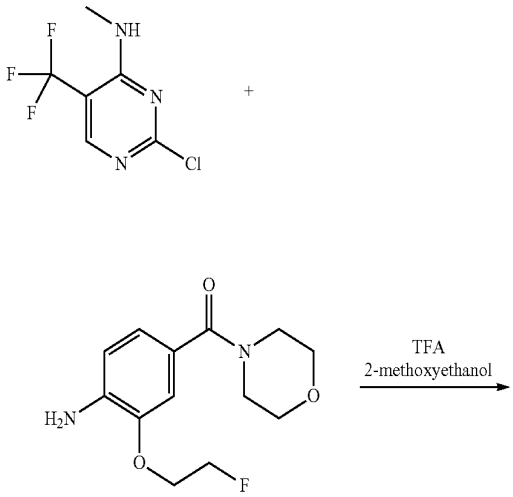
[0559] A mixture 4-amino-5-chloro-2-methoxy-N-(2-methyl-propan-2-o1)-benzamide (95 mg, 0.35 mmol), 2-chloro-4-(methylamino)-5-trifluoromethylpyrimidine (50 mg, 0 23 mmol) and p-toluenesulphonic acid monohydrate (49 mg, 0 26 mmol) in 1,4-dioxane (5 ml) was stirred at 100° C. for 18 hrs. The solvent was removed by evaporation in vacuum and the residue partitioned between DCM and aq K_2CO_3 solution. The organic phase was separated, concentrated to dryness in vacuum and the crude material purified by RP-HPLC which afforded the title compound as a cream solid, 57 mg, 55%.

[0560] Additional compounds made using the above procedure are shown in Table 6 below.

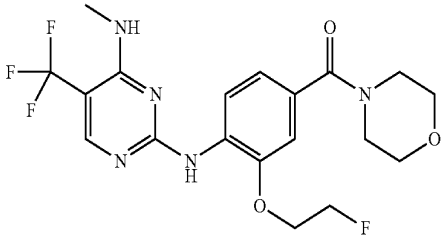
Example 9

(3-(2-fluoroethoxy)-4-(4-(methylamino)-5-(trifluoromethyl)pyrimidin-2-ylamino)phenyl)(morpholino)methanone

[0561]



-continued

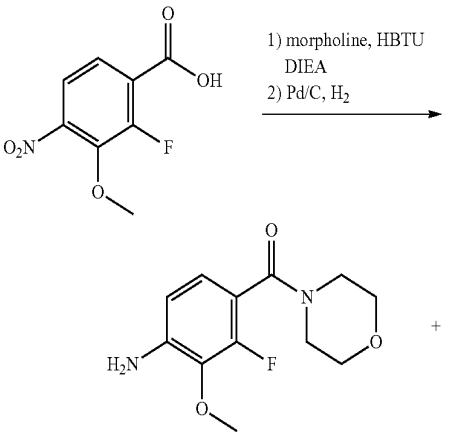


[0562] A mixture of 2-chloro-N-methyl-5-(trifluoromethyl)pyrimidin-4-amine (0.10 g, 0.47 mmol), (4-amino-3-(2-fluoroethoxy)phenyl)(morpholino)methanone (0.13 g, 0.47 mmol), trifluoroacetic acid (0.07 mL, 0.9 mmol) in 2-methoxyethanol (2.5 mL) was stirred at 95° C. for 6 hours. The reaction was the concentrated. The crude product was purified by reverse phase HPLC to give the title compound (61 mg, 29%). Additional compounds made using the above procedure are shown in Table 6 below.

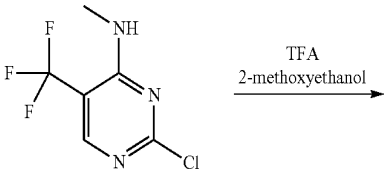
Example 10

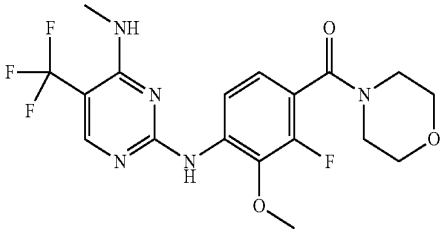
(2-fluoro-3-methoxy-4-(4-(methylamino)-5-(trifluoromethyl)pyrimidin-2-ylamino)phenyl)(morpholino) methanone

[0563]



-continued





[0564] To a suspension of 2-fluoro-3-methoxy-4-nitrobenzoic acid (180 mg, 0.97 mmol) in DCM (8 mL) was added morpholine (0.17 mL. 1.9 mmol), DIEA (0.25 mL) and HBTU (0.4 g, 1.05 mmol). The reaction was stirred at room temperature for 18 hours. The reaction was then diluted with water and extracted with DCM (3×). The combined extracts were washed with water, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography to give (2-fluoro-3-methoxy-4-nitrophenyl)(morpholino)methanone (0.20 g, 83%).

[0565] A suspenion of (2-fluoro-3-methoxy-4-nitrophenyl)(morpholino)methanone (0.20 g) and palladium on carbon (0.1 g, 10 wt %) in ethanol was stirred under hydrogen for 18 hours. The reaction then filtered through celite and concentrated to give (4-amino-2-fluoro-3-methoxyphenyl)(morpholino)methanone.

[0566] A mixture of (4-amino-2-fluoro-3-methoxyphenyl)(morpholino)methanone (0.18 g, 0.72 mmol) and 2-chloro-N-methyl-5-(trifluoromethyl)pyrimidin-4-amine (0.10 g, 0.47 mmol) in a solution of 2-methoxyethanol (2 mL) and TFA (0.055 mL) was stirred at 95° C. for 2 hours. The reaction was concentrated and purified by reverse phase HPLC to give the title compound. Additional compounds made using the above procedure are shown in Table 6 below.

TABLE 6

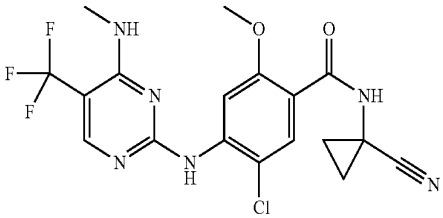
	Name	Structure	^{1}H NMR	K_1
265	5-Chloro-N-(1-cyano-cyclopropyl)-2-methoxy-4-(4-methylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-benzamide		^{1}H NMR (400 MHz, DMSO): δ 8.88 (s, 1 H), 8.64 (s, 1 H), 8.27 (s, 1 H), 8.08 (s, 1 H), 7.82 (s, 1 H), 7.39 (d, J = 5.1 Hz, 1 H), 3.93 (s, 3 H), 2.95 (t, J = 4.3 Hz, 3 H) 1.61-1.55 (m, 2 H), 1.35-1.29 (m, 2 H).	0.0042

TABLE 6-continued

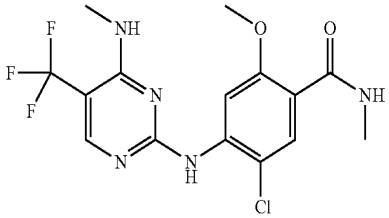
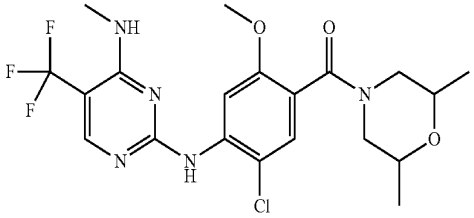
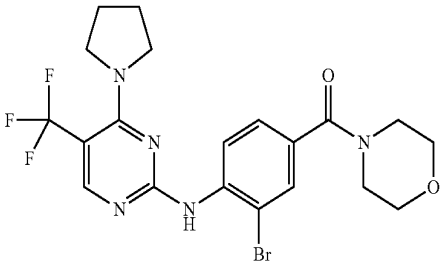
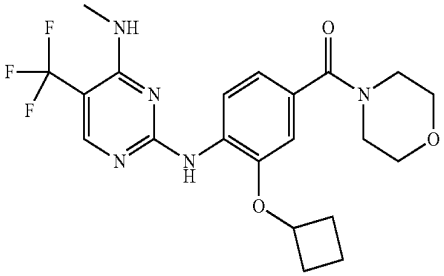
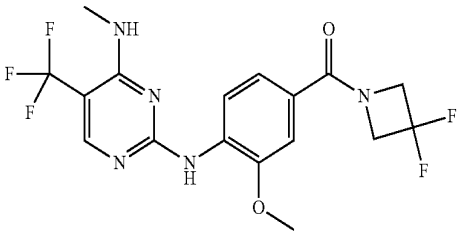
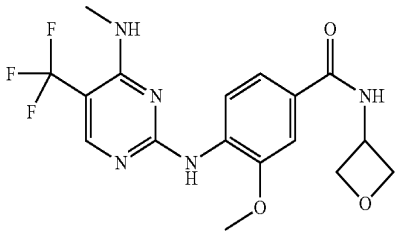
	Name	Structure	^{1}H NMR	K_1
266	5-Chloro-N-(1-cyano-cyclopropyl)-2-methoxy-4-(4-methylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-benzamide		^{1}H NMR (400 MHz, DMSO): δ 8.62 (s, 1 H), 8.26 (s, 1 H), 8.18 (d, J = 5.2 Hz, 1 H), 8.05 (s, 1 H), 7.87 (s, 1 H), 7.36 (d, J = 5.1 Hz, 1 H), 3.94 (s, 3 H), 2.95 (d, J = 4.4 Hz, 3 H), 2.84 (d, J = 4.6 Hz, 3 H).	0.0046
267	[5-Chloro-2-methoxy-4-(4-methylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-phenyl]-(2,6-dimethyl-morpholin-4-yl)-methanone		^{1}H NMR (400 MHz, DMSO): δ 8.64 (s, 1 H), 8.24 (s, 1 H), 7.92 (s, 1 H), 7.37 (s, 1 H), 7.31 (t, J = 5.5 Hz, 1 H), 4.40 (d, J =13.1 Hz, 1 H), 3.84 (s, 3 H), 3.55 (s, 2 H), 3.21 (m, 1 H), 2.93 (d, J = 4.4 Hz, 3 H), 2.82-2.70 (m, 1 H), 2.45 (m, 1 H), 1.17 (d, J = 6.1 Hz, 3 H), 1.03 (d, J = 6.3 Hz, 3 H).	0.0080
268	[3-Methoxy-4-(4-pyrrolidin-1-yl-5-trifluoromethyl-pyrimidin-2-ylamino)-phenyl]-morpholin-4-yl-methanone		^{1}H NMR (400 MHz, DMSO): δ 8.34 (s, 1 H), 8.27 (d, J = 8.2, 1 H), 8.06 (s, 1 H), 7.08 (s, 1 H), 7.03 (d, J = 8.2, 1 H), 3.90 (s, 3 H), 3.56 (m, 12 H), 1.93 (m, 4 H).	0.0019
269	[3-Cyclobutoxy-4-(4-methylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-phenyl]-morpholin-4-yl-methanone		^{1}H NMR (400 MHz, DMSO) δ 8.36 (d, J = 8.3 Hz, 1 H), 8.19 (s, 1 H), 8.02 (s, 1 H), 7.25 (s, 1 H), 7.01 (d, J = 8.3 Hz, 1 H), 6.88 (s, 1 H), 4.81 (dd, J = 14.2, 7.0 Hz, 1 H), 3.55 (dm, 8 H), 2.93 (d, J = 4.3 Hz, 3 H), 2.45 (m, 2 H), 2.24-2.02 (m, 2 H), 1.81 (m, 1 H), 1.66 (m, 1 H).	0.0025
270	N-(3,3-Difluoro-cyclobutyl)-3-methoxy-4-(4-methylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-benzamide		^{1}H NMR (400 MHz, DMSO) δ 8.69 (d, J = 6.4 Hz, 1 H), 8.41 (d, J = 8.3 Hz, 1 H), 8.21 (s, 1 H), 8.11 (s, 1 H), 7.57-7.46 (m, 2 H), 7.28 (s, 1 H), 4.28 (br, 1 H), 3.94 (s, 3 H), 2.93 (m, 4 H), 2.77 (br, 2 H).	0.0015
271	3-Methoxy-4-(4-methylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-N-oxetan-3-yl-benzamide		^{1}H NMR (400 MHz, DMSO) δ 8.98 (d, J = 6.3 Hz, 1 H), 8.41 (d, J = 8.4 Hz, 1 H), 8.21 (s, 1 H), 8.11 (s, 1 H), 7.59-7.47 (m, 2 H), 7.27 (s, 1 H), 5.01 (dd, 1 H), 4.78 (t, J = 6.8 Hz, 2 H), 4.60 (t, J = 6.4 Hz, 2 H), 3.94 (s, 3 H), 2.93 (d, J = 4.2 Hz, 3 H)	0.0037

TABLE 6-continued

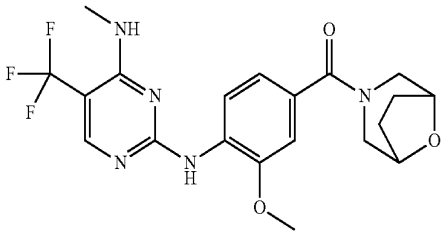
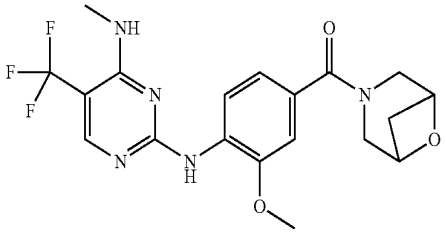
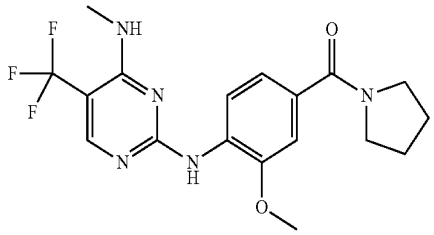
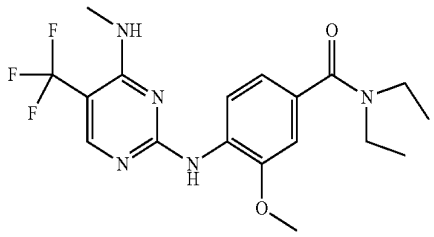
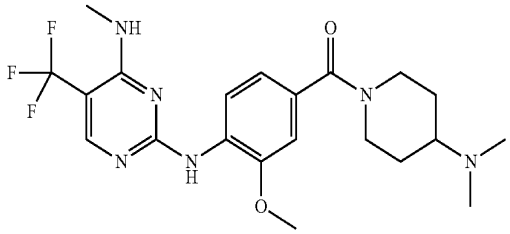
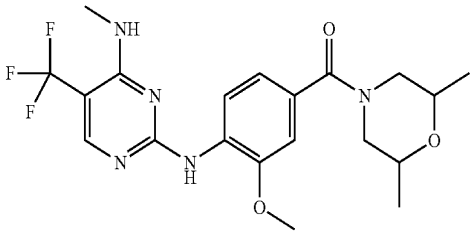
	Name	Structure	^{1}H NMR	K_1
272	[3-Methoxy-4-(4-methylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-phenyl]-(8-oxa-3-aza-bicyclo[3.2.1]oct-3-yl)-methanone		^{1}H NMR (400 MHz, DMSO) δ 8.31 (d, J = 8.3 Hz, 1 H), 8.19 (s, 1 H), 8.07 (s, 1 H), 7.23 (s, 1 H), 7.05 (s, 1 H), 6.99 (d, J = 8.3 Hz, 1 H), 4.30 (m, 6 H), 3.90 (s, 3 H), 2.92 (d, 7 = 4.3 Hz, 3 H), 1.73 (m, 4 H).	0.0017
273	[3-Methoxy-4-(4-methylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-phenyl]-(2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl)-methanone		^{1}H NMR (400 MHz, DMSO) δ 8.34 (d, J = 8.3 Hz, 1 H), 8.20 (s, 1 H), 8.08 (s, 1 H), 7.17 (m, 3 H), 4.63 (m, 2 H), 3.91 (s, 3 H), 3.88-3.41 (m, 4 H), 2.92 (d, J = 4.2 Hz, 3 H), 1.97-1.65 (m, 2 H).	0.0033
274	[3-Methoxy-4-(4-methylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-phenyl]-pyrrolidin-1-yl-methanone		n	0.0041
275	N,N-Diethyl-3-methoxy-4-(4-methylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-benzamide		^{1}H NMR (400 MHz, DMSO) δ 8.26 (d, J = 8.1 Hz, 1 H), 8.18 (s, 1 H), 8.07 (s, 1 H), 7.20 (s, 1 H), 7.00 (s, 1 H), 6.94 (d, J = 8.3 Hz, 1 H), 3.89 (s, 3 H), 2.91 (d, J = 4.2 Hz, 3 H), 1.12 (s, 6 H).	0.0033
276	(4-Dimethylamino-piperidin-1-yl)-[3-methoxy-4-(4-methylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-phenyl]-methanone		^{1}H NMR (400 MHz, DMSO) δ 8.28 (d, J = 8.2 Hz, 1 H), 8.19 (s, 1 H), 8.07 (s, 1 H), 7.22 (s, 1 H), 7.04 (s, 1 H), 6.98 (d, J = 8.3 Hz, 1 H), 3.89 (s, 3 H), 2.92 (m, 7 H), 2.32 (s, 1 H), 2.18 (s, 6 H), 1.76 (s, 2 H), 1.34 (m, 2 H).	0.0008
277	(2,6-Dimethyl-morpholin-4-yl)-[3-methoxy-4-(4-methylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-phenyl]-methanone		^{1}H NMR (400 MHz, DMSO) δ 8.31 (d, J = 8.4 Hz, 1 H), 8.19 (s, 1 H), 8.08 (s, 1 H), 7.23 (s, 1 H), 7.07 (s, 1 H), 7.01 (d, J = 8.3 Hz, 1 H), 3.89 (s, 3 H), 3.55 (s, 2 H), 2.92 (d, J = 4.1 Hz, 3 H), 1.08 (s, 6 H).	0.0049

TABLE 6-continued

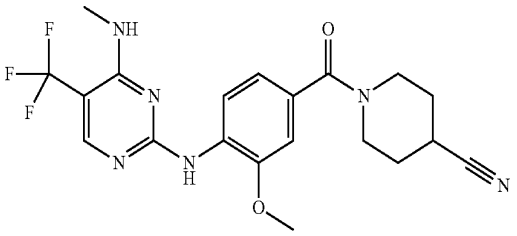
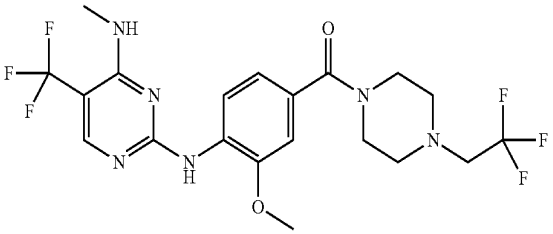
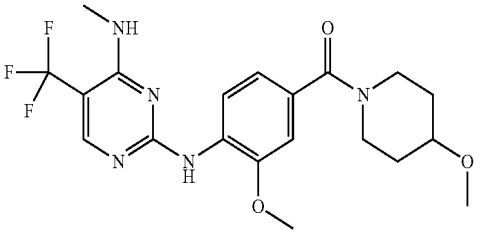
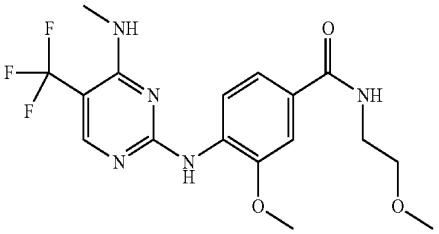
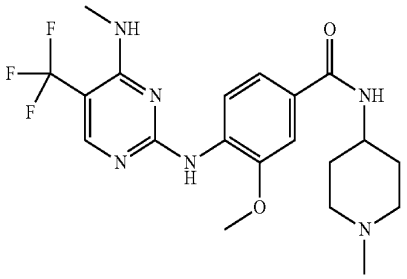
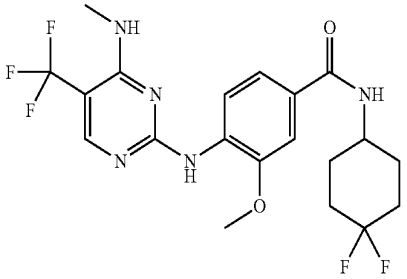
	Name	Structure	^{1}H NMR	K_1
278	1-[3-Methoxy-4-(4-methylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-benzoyl]-piperidine-4-carbonitrile		^{1}H NMR (400 MHz, DMSO) δ 8.30 (d, J = 8.2 Hz, 1 H), 8.19 (s, 1 H), 8.08 (s, 1 H), 7.22 (s, 1 H), 7.07 (s, 1 H), 7.01 (d, J = 7.9 Hz, 1 H), 3.90 (s, 3 H), 3.72 (s, 2 H), 3.36 (s, 2 H), 3.15 (s, 1 H), 2.92 (d, J = 4.2 Hz, 3 H), 1.90 (s, 2 H), 1.75 (m, 2 H).	0.0017
279	[3-Methoxy-4-(4-methylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-phenyl]-[4-(2,2,2-trifluoro-ethyl)-piperazin-1-yl]-methanone		^{1}H NMR (400 MHz, DMSO) δ 8.31 (d, J = 8.3 Hz, 1 H), 8.19 (s, 1 H), 8.08 (s, 1 H), 7.23 (s, 2 H), 7.05 (s, 1 H), 6.99 (d, J = 8.2 Hz, 1 H), 3.89 (s, 3 H), 3.52 (s, 4 H), 3.23 (m, 2 H), 2.92 (d, 3 H), 2.65 (s, 4 H).	0.0020
280	[3-Methoxy-4-(4-methylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-phenyl]-(4-methoxy-piperidin-1-yl)-methanone		^{1}H NMR (400 MHz, DMSO) δ 8.28 (d, J = 8.3 Hz, 1 H), 8.19 (s, 1 H), 8.07 (s, 1 H), 7.22 (s, 1 H), 7.05 (s, 1 H), 6.98 (d, J = 8.0 Hz, 1 H), 3.89 (s, 3 H), 3.75 (m, 4 H), 3.44 (s, 1 H), 3.26 (s, 3 H), 2.91 (d, J = 4.1 Hz, 3 H), 1.84 (s, 2 H), 1.46 (s, 2 H).	0.0016
281	3-Methoxy-N-(2-methoxy-ethyl)-4-(4-methylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-benzamide		^{1}H NMR (400 MHz, DMSO) δ 8.56-8.30 (m, 2 H), 8.21 (s, 1 H), 8.09 (s, 1 H), 7.51 (m, 2 H), 7.26 (s, 1 H), 3.93 (s, 3 H), 3.44 (m, 2 H), 3.27 (m, 5 H), 2.93 (d, J = 4.2 Hz, 3 H).	0.0023
282	3-Methoxy-4-(4-methylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-N-(1-methyl-piperidin-4-yl)-benzamide		^{1}H NMR (400 MHz, DMSO) δ 8.37 (d, J = 8.4 Hz, 1 H), 8.20 (s, 1 H), 8.16-8.01 (m, 2 H), 7.51 (m, 2 H), 7.27 (s, 1 H), 3.93 (s, 3 H), 3.74 (s, 1 H), 2.93 (d, J = 4.2 Hz, 3 H), 2.78 (d, 2 H), 2.17 (s, 3 H), 1.94 (t, 2 H), 1.76 (m, 2 H), 1.60 (m, 2 H).	0.0006
283	N-(4,4-Difluoro-cyclohexyl)-3-methoxy-4-(4-methylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-benzamide		^{1}H NMR (400 MHz, DMSO) δ 8.38 (d, J = 8.4 Hz, 1 H), 8.29-8.11 (m, 2 H), 8.09 (s, 1 H), 7.63-7.39 (m, 2 H), 7.27 (s, 1 H), 3.99 (m, 1 H), 3.93 (s, 3 H), 2.93 (d, J = 4.1 Hz, 3 H), 2.06 (s, 4 H), 1.88 (m, 2 H), 1.65 (m, 2 H).	0.0011

TABLE 6-continued

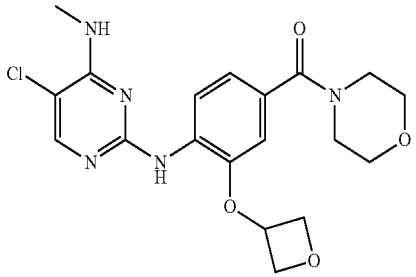
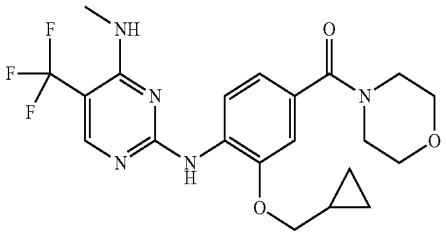
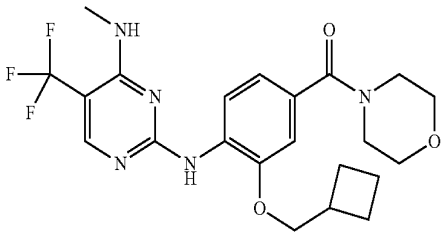
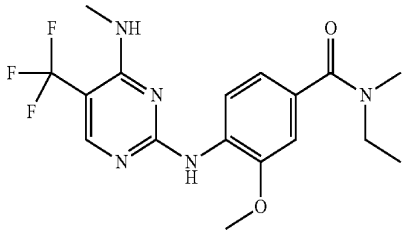
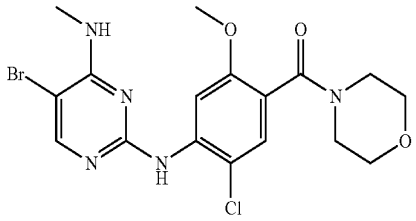
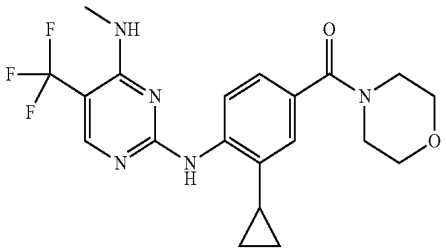
	Name	Structure	^{1}H NMR	K_1
284	[4-(5-Chloro-4-methylamino-pyrimidin-2-ylamino)-3-(oxetan-3-yloxy)-phenyl]-morpholin-4-yl-methanone			0.0128
285	[3-Cyclopropyl-methoxy-4-(4-methylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-phenyl]-morpholin-4-yl-methanone		^{1}H NMR (400 MHz, DMSO) δ 8.37 (d, J = 8.2 Hz, 1 H), 8.20 (s, 1 H), 8.03 (s, 1 H), 7.30 (d, J = 4.4 Hz, 1 H), 7.05 (s, 1 H), 7.04-6.98 (m, 1 H), 3.95 (d, J = 7.0 Hz, 2 H), 3.55 (dm, 8 H), 2.93 (d, J = 4.4 Hz, 3 H), 1.37-1.20 (m, 1 H), 0.66-0.55 (m, 2H), 0.37 (q, J = 4.5 Hz, 2 H).	0.0065
286	[3-Cyclobutylmethoxy-4-(4-methylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-phenyl]-morpholin-4-yl-methanone		^{1}H NMR (400 MHz, DMSO) δ 8.31 (d, J = 8.2 Hz, 1 H), 8.19 (s, 1 H), 8.01 (s, 1 H), 7.27 (d, J = 4.3 Hz, 1 H), 7.08 (d, J = 1.4 Hz, 1 H), 7.02 (d, J = 8.2 Hz, 1 H), 4.07 (d, J = 6.5 Hz, 2 H), 3.56 (dbr, 8 H), 2.91 (d, J = 4.3 Hz, 3 H), 2.78 (dd, 1 H), 2.18-1.99 (m, 2 H), 1.89 (m, 4 H).	0.0052
287	N-Ethyl-3-methoxy-N-methyl-4-(4-methylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-benzamide			
288	[4-(5-Bromo-4-methylamino-pyrimidin-2-ylamino)-5-chloro-2-methoxy-phenyl]-morpholin-4-yl-methanone		^{1}H NMR (400 MHz, DMSO): δ 8.10 (s, 1 H), 8.05 (s, 1 H), 7.99 (s, 1 H), 7.29 (s, 1 H), 7.18 (s, 1 H), 3.81 (m, 3 H), 3.56 (m, 6 H), 3.18 (m, 2 H), 2.92 (m, 3 H).	0.0026
289	[3-Cyclopropyl-4-(4-methylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-phenyl]-morpholin-4-yl-methanone		^{1}H NMR (400 MHz, DMSO): δ 8.71 (s, 1 H), 8.14 (s, 1 H), 7.86 (d, J = 7.8, 1 H), 7.22 (d, J = 8.0, 1 H), 7.02 (s, 2 H), 6.65 (s, 1 H), 3.59 (m, 4 H), 3.48 (m, 4 H), 2.86 (m, 3 H), 2.04 (m, 1 H), 0.93 (m, 2 H), 0.61 (m, 2 H).	0.0200

TABLE 6-continued

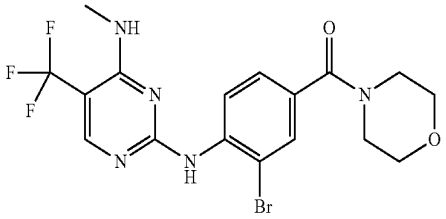
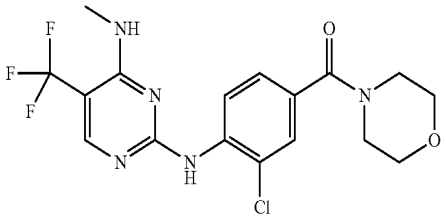
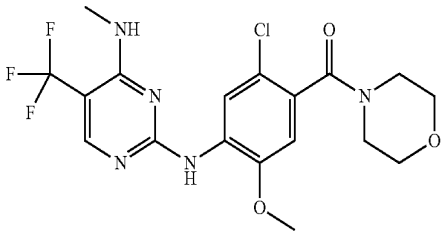
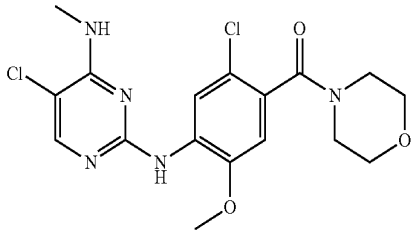
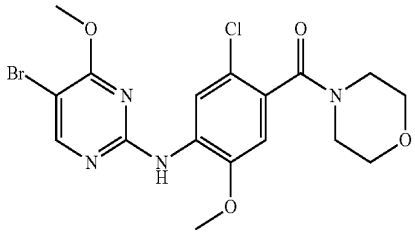
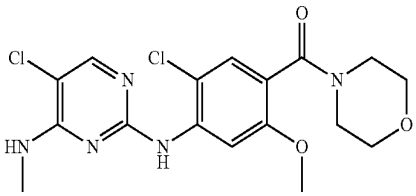
	Name	Structure	^{1}H NMR	K_1
290	[3-Bromo-4-(4-methylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-phenyl]-morpholin-4-yl-methanone		^{1}H NMR (400 MHz, DMSO): δ 8.64 (s, 1 H), 8.16 (s, 1 H), 8.00 (d, J = 8.3, 1 H), 7.69 (s, 1 H), 7.42 (d, J = 8.3, 1 H), 7.15 (d, J = 3.4, 1 H), 3.55 (m, 8 H), 2.86 (d, J = 4.2, 3 H).	0.0075
291	[3-Chloro-4-(4-methylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-phenyl]-morpholin-4-yl-methanone		^{1}H NMR (400 MHz, DMSO): δ 8.83 (s, 1 H), 8.17 (s, 1 H), 8.02 (d, J = 8.4, 1 H), 7.55 (s, 1 H), 7.39 (d, J = 7.6, 1 H), 7.22 (s, 1 H), 3.60 (s, 4 H), 2.86 (d, J = 4.2, 3 H).	0.017
292	[2-Chloro-5-methoxy-4-(4-methylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-phenyl]-morpholin-4-yl-methanone		1H NMR (400 MHz, DMSO) δ 8.51 (s, 1 H), 8.24 (s, 1 H), 8.12 (s, 1 H), 7.32 (d, J = 4.0, 1 H), 7.06 (s, 1 H), 3.89 (s, 3 H), 3.71-3.49 (m, 6 H), 3.24-3.15 (m, 2 H), 2.94 (d, J = 4.3, 3 H).	0.0020
293	[2-Chloro-4-(5-chloro-4-methylamino-pyrimidin-2-ylamino)-5-methoxy-phenyl]-morpholin-4-yl-methanone		1H NMR (400 MHz, DMSO) δ 8.58 (s, 1 H), 8.00 (s, 1 H), 7.71 (s, 1 H), 7.40 (m, 1 H), 7.02 (s, 1 H), 3.90 (s, 3 H), 3.70-3.60 (m, 4 H), 3.60-3.48 (m, 2 H), 3.23-3.15 (m, 3 H), 2.92 (d, J = 4.5, 3 H).	0.0027
294	[4-(5-Bromo-4-methoxy-pyrimidin-2-ylamino)-2-chloro-5-methoxy-phenyl]-morpholin-4-yl-methanone		1H NMR (400 MHz, DMSO) δ 8.44 (s, 1 H), 8.36 (s, 1 H), 8.30 (s, 1 H), 7.06 (s, 1 H), 4.00 (s, 3 H), 3.88 (s, 3 H), 3.72-3.59 (m, 4 H), 3.56 (d, J = 3.9, 2 H), 3.23-3.14 (m, 2 H).	0.0094
295	(5-chloro-4-(5-chloro-4-(methylamino) pyrimidin-2-ylamino)-2-methoxyphenyl) (morpholino) methanone		1H NMR (400 MHz, DMSO) δ 8.11 (s, 1 H), 7.99 (s, 1 H), 7.97 (s, 1 H), 7.38 (dd, J = 9.2, 4.6, 1 H), 7.29 (s, 1 H), 3.82 (s, 3 H), 3.60 (s, 4 H), 3.52 (t, J = 4.3, 2 H), 3.17 (s, 2 H), 2.92 (d, J = 4.6, 3 H).	0.0060

TABLE 6-continued

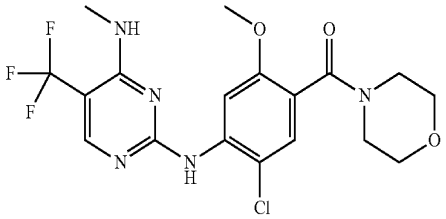
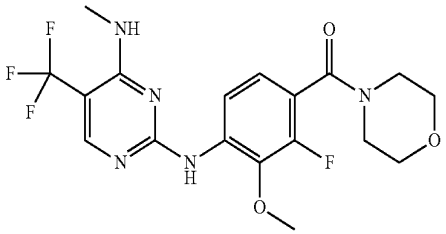
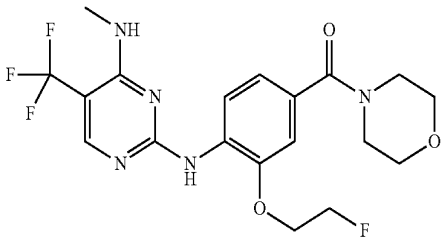
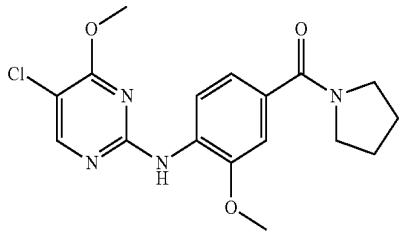
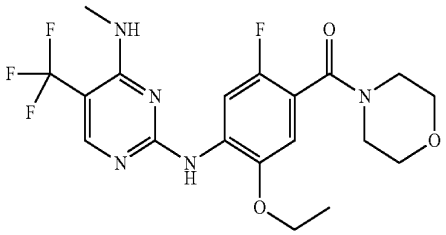
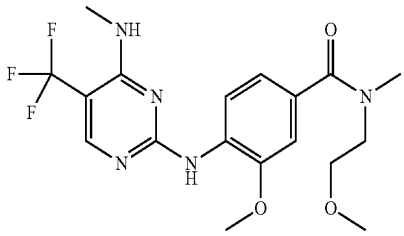
	Name	Structure	^{1}H NMR	K_1
296	[5-Chloro-2-methoxy-4-(4-methylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-phenyl]-morpholin-4-yl-methanone		1H NMR (400 MHz, DMSO) δ 8.59 (s, 1 H), 8.20 (s, 1 H), 7.88 (s, 1 H), 7.32 (s, 1 H), 7.25 (dd, J = 12.0, 7.5, 1 H), 3.81 (s, 3 H), 3.60 (s, 4 H), 3.53 (t, J = 4.4, 2 H), 3.17 (s, 2 H), 2.90 (d, J = 4.3, 3 H).	0.0020
297	[2-Fluoro-3-methoxy-4-(4-methylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-phenyl]-morpholin-4-yl-methanone		1H NMR (400 MHz, DMSO) δ 8.49 (s, 1 H), 8.20 (s, 1 H), 8.11 (d, J = 8.5, 1 H), 7.25 (d, J = 3.6, 1 H), 7.08 (t, J = 7.8, 1 H), 3.91 (s, 3 H), 3.59 (m, 6 H), 2.91 (d, J = 4.2, 3 H).	0.0145
298	[3-(2-Fluoro-ethoxy)-4-(4-methylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-phenyl]-morpholin-4-yl-methanone		1H NMR (400 MHz, DMSO) δ 8.38 (d, J = 8.3, 1 H), 8.19 (s, 1 H), 8.07 (s, 1 H), 7.24 (d, J = 4.3, 1 H), 7.13 (s, 1 H), 7.05 (d, J = 8.3, 1 H), 4.91-4.83 (m, 1 H), 4.80-4.72 (m, 1 H), 4.47-4.39 (m, 1 H), 4.39-4.29 (m, 1 H), 3.56 (d, J = 37.5, 8 H), 2.93 (d, J = 4.4, 3 H).	0.0024
299	(4-(5-chloro-4-methoxypyrimidin-2-ylamino)-3-methoxyphenyl)(pyrrolidin-1-yl)methanone		1H NMR (400 MHz, DMSO) δ 8.32 (s, 1 H), 8.26 (s, 1 H), 8.16 (d, J = 8.2 Hz, 1 H), 7.18 (s, 1 H), 7.15 (d, J = 8.3 Hz, 1 H), 4.00 (s, 3 H), 3.89 (s, 3 H), 3.46 (t, J = 6.6 Hz, 4 H), 1.83 (s, 4 H)	0.006
300	[5-Ethoxy-2-fluoro-4-(4-methylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-phenyl]-morpholin-4-yl-methanone		^{1}H NMR (400 MHz, DMSO) δ 8.34 (d, J = 12.2 Hz, 1 H), 8.24 (s, 1 H), 8.04 (s, 1 H), 7.35 (d, J = 4.3 Hz, 1 H), 7.02 (d, J = 6.2 Hz, 1 H), 4.15 (q, J = 6.9 Hz, 2 H), 3.59 (m, 6 H), 2.95 (d, J = 4.4 Hz, 3 H), 1.39 (t, J = 6.9 Hz, 3 H).	0.009
301	3-Methoxy-N-(2-methoxy-ethyl)-N-methyl-4-(4-methylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-benzamide		^{1}H NMR (400 MHz, DMSO) δ 8.27 (d, J = 8.2 Hz, 1 H), 8.18 (s, 1 H), 8.06 (s, 1 H), 7.19 (d, J = 4.3 Hz, 1 H), 7.07 (s, 1 H), 7.03-6.95 (m, 1 H), 3.88 (s, 3 H), 3.51 (s, 4 H), 3.26 (s, 3 H), 2.98 (s, 3 H), 2.91 (d, J = 4.4 Hz, 3 H).	0.0051

TABLE 6-continued

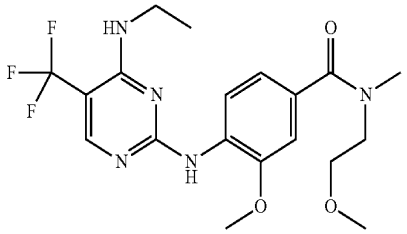
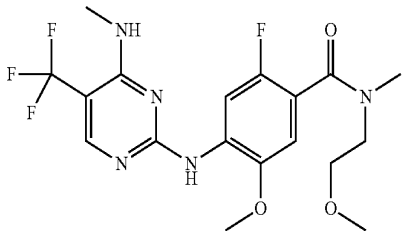
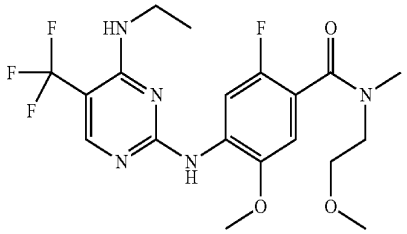
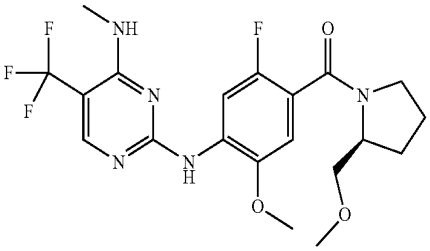
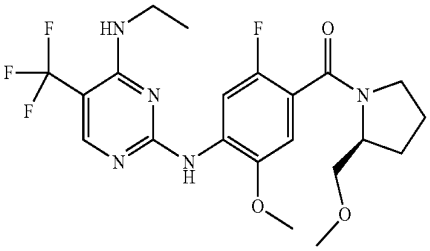
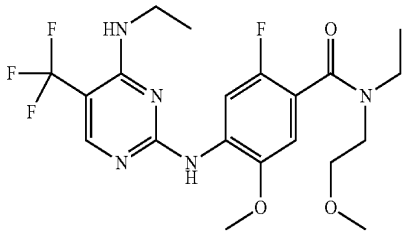
	Name	Structure	^{1}H NMR	K_1
302	4-(4-Ethylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-3-methoxy-N-(2-methoxy-ethyl)-N-methyl-benzamide		^{1}H NMR (400 MHz, DMSO) δ 8.21 (d, J = 8.2 Hz, 1 H), 8.18 (s, 1 H), 8.06 (s, 1 H), 7.19 (t, J = 5.4 Hz, 1 H), 7.07 (s, 1 H), 6.98 (dd, J = 8.2, 1.5 Hz, 1 H), 3.88 (s, 3 H), 3.62-3.40 (m, 6 H), 3.25 (s, 3 H), 2.98 (s, 3 H), 1.14 (t, J = 7.1 Hz, 3 H).	0.0023
303	2-Fluoro-5-methoxy-N-(2-methoxy-ethyl)-N-methyl-4-(4-methylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-benzamide		^{1}H NMR (400 MHz, DMSO) δ 8.34-8.25 (m, 1 H), 8.24 (s, 1 H), 8.09 (s, 1 H), 7.31 (s, 1 H), 6.98 (t, J = 6.3Hz, 1 H), 3.88 (d, J = 6.9 Hz, 3 H), 3.65-3.52 (m, 2 H), 3.44-3.33 (m, 2 H), 3.21-3.15 (m, 2 H), 3.02-2.89 (m, 6 H).	0.0059
304	4-(4-Ethylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-2-fluoro-5-methoxy-N-(2-methoxy-ethyl)-N-methyl-benzamide		^{1}H NMR (400 MHz, DMSO) δ 8.28-8.19 (m, 2 H), 8.09 (s, 1 H), 7.33 (d, J = 4.9 Hz, 1 H), 6.98 (t, J = 6.3 Hz, 1 H), 3.88 (d, J = 7.0 Hz, 3 H), 3.65-3.33 (m, 6 H), 3.29-3.15 (m, 3 H), 2.96 (d, J = 29.9 Hz, 3 H), 1.17 (t, J = 7.0 Hz, 3 H).	0.0016
305	[2-Fluoro-5-methoxy-4-(4-methylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-phenyl]-((S)-2-methoxymethyl-pyrrolidin-1-yl)-methanone		^{1}H NMR (400 MHz, DMSO) δ 8.34-8.26 (m, 1 H), 8.24 (s, 1 H), 8.09 (s, 1 H), 7.31 (s, 1 H), 7.07-6.96 (m, 1 H), 4.22 (s, 1 H), 3.63-3.53 (m, 1 H), 3.44-3.35 (m, 1 H), 3.30 (s, 2 H), 3.22 (s, 1 H), 3.09-3.00 (m, 2 H), 2.94 (d, J = 4.3Hz, 3 H), 2.06-1.65 (m, 5 H).	0.0030
306	[4-(4-Ethylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-2-fluoro-5-methoxy-phenyl]-((S)-2-methoxymethyl-pyrrolidin-1-yl)-methanone		^{1}H NMR (400 MHz, DMSO) δ 8.29-8.20 (m, 2 H), 8.12-8.06 (m, 1 H), 7.38-7.30 (m, 1 H), 7.07-6.96 (m, 1 H), 4.27-4.17 (m, 1 H), 3.63-3.34 (m, 4 H), 3.30 (s, 2 H), 3.27-3.20 (m, 1 H), 3.13-2.99 (m, 2 H), 2.04-1.64 (m, 5 H), 1.17 (t, J = 7.0 Hz, 3 H).	0.0006
307	N-Ethyl-4-(4-ethylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-2-fluoro-5-methoxy-N-(2-methoxy-ethyl)-benzamide		^{1}HNMR (400 MHz, DMSO) δ 8.27-8.20 (m, 2 H), 8.09 (s, 1 H), 7.33 (t, J = 5.5 Hz, 1 H), 6.96 (d, J = 6.2 Hz, 1 H), 3.88 (s, 3 H), 3.63-3.32 (m, 8 H), 3.27-3.13 (m, 3 H), 1.20-0.98 (m, 6 H).	0.0014

TABLE 6-continued

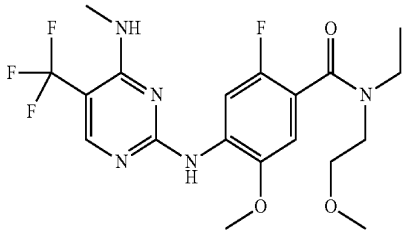
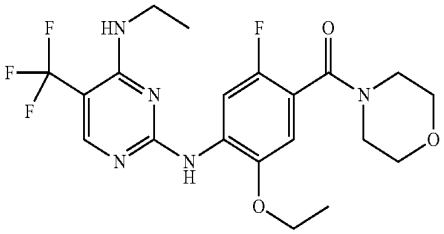
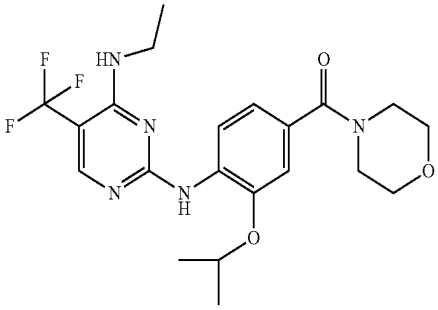
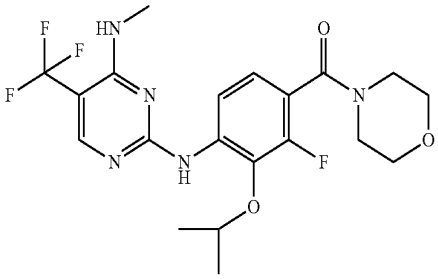
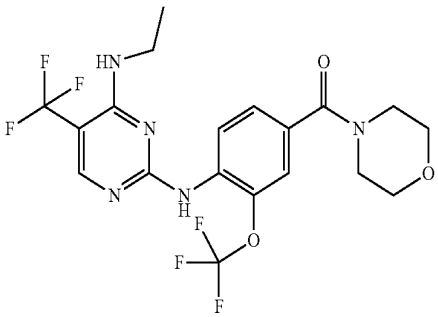
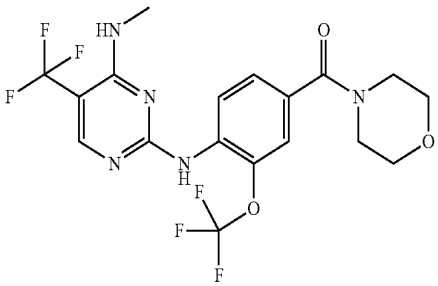
	Name	Structure	^{1}H NMR	K_1
308	N-Ethyl-2-fluoro-5-methoxy-N-(2-methoxy-ethyl)-4-(4-methylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-benzamide		^{1}H NMR (400 MHz, DMSO) δ 8.32-8.25 (m, 1 H), 8.24 (s, 1 H), 8.09 (s, 1 H), 7.34-7.27 (m, J = 4.2 Hz, 1 H), 6.96 (d, J = 6.2 Hz, 1 H), 3.88 (s, 3 H), 3.62-3.15 (m, 9 H), 2.93 (d, J = 4.4 Hz, 3 H), 1.18-0.97 (m, 3 H).	0.0035
309	[5-Ethoxy-4-(4-ethylamino-5-trifluoromethyl-pyrimidin-2-ylamino)-2-fluoro-phenyl]-morpholin-4-yl-methanone		^{1}H NMR (400 MHz, DMSO) δ 8.29 (d, J = 12.2 Hz, 1 H), 8.23 (s, 1 H), 8.04 (s, 1 H), 7.37 (t, J = 5.3Hz, 1 H), 7.02 (d, J = 6.2Hz, 1 H), 4.15 (q, J = 6.9Hz, 2 H), 3.71-3.44 (m, 9 H), 1.38 (t, J = 6.9 Hz, 3 H), 1.18 (t, J = 7.1 Hz, 3 H).	0.0021
310	(4-(4-(ethylamino)-5-(trifluoromethyl) pyrimidin-2-yl-amino)-3-isopropoxyphenyl) (morpholino) methanone		^{1}H NMR (400 MHz, DMSO) δ 8.38-8.31 (m, 1 H), 8.21-8.17 (s, 1 H), 7.97-7.92 (s, 1 H), 7.30-7.23 (t, J = 5.4 Hz, 1 H), 7.10-7.06 (d, J = 1.6 Hz, 1 H), 7.02-6.96 (dd, J = 8.3, 1.6 Hz, 1 H), 4.79-4.66 (m, 1 H), 3.64-3.56 (m, 4 H), 3.57-3.41 (m, 6 H), 1.35-1.29 (d, J = 6.0 Hz, 6 H), 1.21-1.09 (t, J = 7.1 Hz, 3 H).	0.0045
311	(2-fluoro-3-isopropoxy-4-(4-(methylamino)-5-(trifluoromethyl) pyrimidin-2-ylamino)phenyl) (morpholino) methanone		^{1}H NMR (400 MHz, DMSO) δ 8.22-8.20 (s, 1 H), 8.20-8.14 (m, 2 H), 7.32-7.27 (M, 1 H), 7.13-7.06 (dd, J = 8.4, 7.3 Hz, 1 H), 4.46-4.32 (m, 1 H), 3.67-3.59 (m, 4 H), 3.57-3.51 (m, 2 H), 3.29-3.23 (m, 2 H), 2.95-2.86 (d, J = 4.4 Hz, 3 H), 1.35-1.24 (d, J = 6.1 Hz, 6H).	
312	(4-(4-(ethylamino)-5-(trifluoromethyl) pyrimidin-2-ylamino)-3-(trifluoromethoxy) phenyl) (morpholino) methanone		^{1}H NMR (400 MHz, DMSO) δ 9.20-9.11 (s, 1 H), 8.19-8.11 (s, 1 H), 8.07-7.98 (d, J = 8.9 Hz, 1 H), 7.45-7.38 (m, 2 H), 7.22-7.12 (t, J = 5.6 Hz, 1 H), 3.66-3.56 (m, 4 H), 3.59-3.41 (m, 4 H), 3.42-3.35 (m, 2 H), 1.14-1.02 (t, J=7.0 Hz, 3 H).	0.028

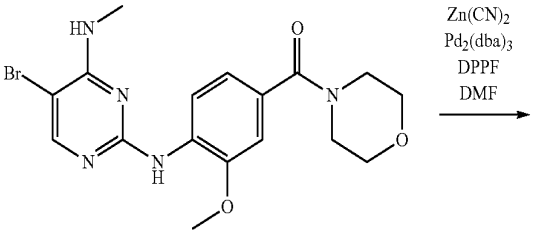
TABLE 6-continued

	Name	Structure	^{1}H NMR	K_1
313	(2-fluoro-3-isopropoxy-4-(4-(methylamino)-5-(trifluoromethyl) pyrimidin-2-ylamino)phenyl) (morpholino) methanone		^{1}H NMR (400 MHz, DMSO) δ 9.20-9.08 (s, 1 H), 8.20-8.14 (s, 1 H), 8.13-8.06 (d, J = 8.9 Hz, 1 H), 7.46-7.38 (m, 2 H), 7.23-7.15 (m, 1 H), 3.68-3.57 (m, 4 H), 3.57-3.37 (m, 4 H), 2.89-2.82 (d, J = 4.4 Hz, 3 H).	0.206

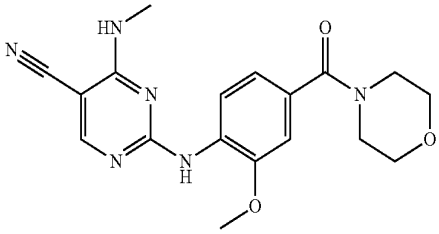
Example 11

2-[2-Methoxy-4-(morpholine-4-carbonyl)-phenylamino]-4-methylamino-pyrimidine-5-carbonitrile

[0567]



-continued



[0568] TA mixture of (4-(5-bromo-4-(methylamino)pyrimidin-2-ylamino)-3-methoxyphenyl)(morpholino)methanone (80 mg, 0.19 mmol), zinc cyanide (50 mg, 0 42 mmol), tris(dibenzylideneacetone)dipalladium (9 mg, 0.09 mmol), DPPF (11 mg, 0 02 mmol) in DMF (3 mL) was stirred at 105° C. in a pressure tube for 18 hours. The reaction mixture was filtered and concentrated. The crude product was purified by reverse phase HPLC to give the title compound (70 mg, 82%). Additional compounds made using the above procedure are shown in Table 7 below.

TABLE 7

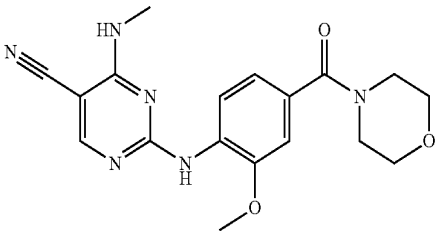
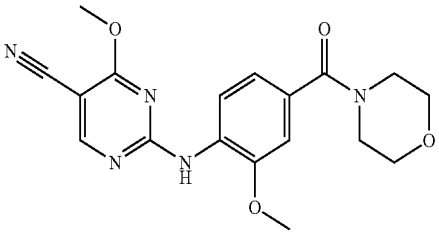
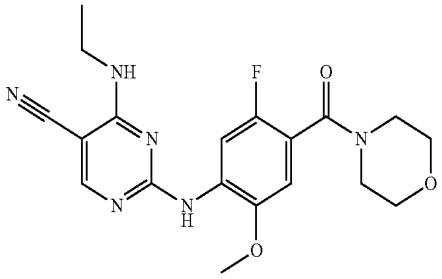
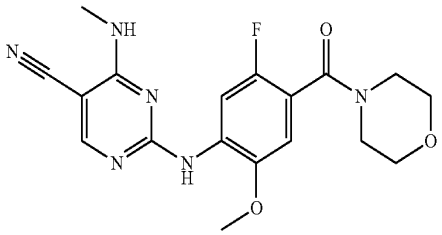
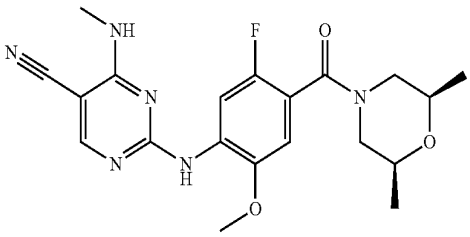
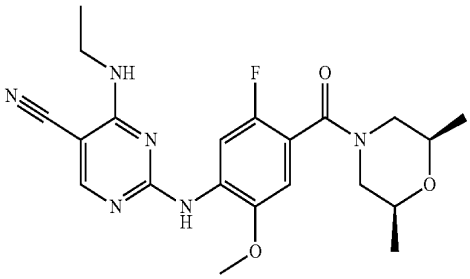
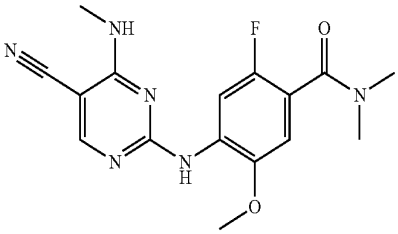
	Name	Structure	^{1}H NMR	K_1
314	2-(2-methoxy-4-(morpholine-4-carbonyl)phenylamino)-4-(methylamino) pyrimidine-5-carbonitrile		1H NMR (400 MHz, DMSO) δ 8.34 (s, 1 H), 8.33 (s, 1 H), 8.18 (d, J = 8.2, 1 H), 7.81-7.70 (m, 1 H), 7.08 (d, J = 1.5, 1 H), 7.01 (m, 1 H), 3.88 (s, 3 H), 3.60 (s, 4 H), 3.51 (s, 4 H), 2.88 (d, J = 4.5, 3 H)	0.0024
315	4-Methoxy-2-[2-methoxy-4-(morpholine-4-carbonyl)-phenylamino]-pyrimidine-5-carbonitrile		^{1}H NMR (400 MHz, DMSO): δ 9.27 (s, 1 H), 8.64 (s, 1 H), 7.85 (d, J = 7.9, 1 H), 7.11 (s, 1 H), 7.02 (d, J = 7.9, 1 H), 3.98 (s, 3 H), 3.85 (s, 3 H), 3.56 (m, 8 H).	0.0138

TABLE 7-continued

	Name	Structure	^{1}H NMR	K_1
316	4-Ethylamino-2-[5-fluoro-2-methoxy-4-(morpholine-4-carbonyl)-phenylamino]-pyrimdine-5-carbonitrile		^{1}H NMR (400 MHz, DMSO) δ 8.39 (s, 1 H), 8.32 (s, 1 H), 8.17 (d, J = 12.0 Hz, 1 H), 7.96-7.90 (m, 1 H), 7.04 (d, J = 6.2 Hz, 1 H), 3.88 (s, 4 H), 3.70-3.49 (m, 8 H), 3.48-3.38 (m, 3 H), 1.17 (t, J = 7.1 Hz, 4 H).	0.0065
317	2-[5-Fluoro-2-methoxy-4-(morpholine-4-carbonyl)-phenylamino]-4-methylamino-pyrimidine-5-carbonitrile		^{1}H NMR (400 MHz, DMSO) δ 8.39 (s, 1 H), 8.31 (s, 1 H), 8.22 (d, J = 11.9 Hz, 1 H), 7.88 (d, J = 3.8 Hz, 1 H), 7.04 (d, J = 6.2 Hz, 1 H), 3.88 (s, 4 H), 3.69-3.50 (m, 8 H), 2.91 (d, J = 4.5 Hz, 4 H).	0.0112
318	2-[4-((2R,6S)-2,6-Dimethyl-morpholine-4-carbonyl)-5-fluoro-2-methoxy-phenylamino]-4-methylamino-pyrimidine-5-carbonitrile		^{1}H NMR (400 MHz, DMSO) δ 8.40 (s, 1 H), 8.32 (s, 1 H), 8.23 (d, J = 12.0 Hz, 1 H), 7.89 (s, 1 H), 7.03 (d, J = 6.2 Hz, 1 H), 4.40 (d, J = 13.1 Hz, 1 H), 3.88 (s, 3 H), 3.52 (s, 2 H), 3.40-3.33 (m, J = 10.8 Hz, 1 H), 2.92 (d, J = 3.9 Hz, 3 H), 2.81 (t, J = 11.8 Hz, 1 H), 2.46 (d, J = 12.1 Hz, 1 H), 1.20-0.95 (m, 6 H).	0.0368
319	2-[4-((2R,6S)-2,6-Dimethyl-morpholine-4-carbonyl)-5-fluoro-2-methoxy-phenylamino]-4-ethylamino-pyrimidine-5-carbonitrile		^{1}H NMR (400 MHz, DMSO) δ 8.40 (s, 1 H), 8.33 (s, 1 H), 8.17 (d, J = 12.0 Hz, 1 H), 7.98-7.90 (m, 1 H), 7.03 (d, J = 6.2 Hz, 1 H), 4.40 (d, J = 12.9 Hz, 1 H), 3.88 (s, 3 H), 3.60-3.48 (m, 2 H), 3.48-3.39 (m, 2 H), 3.39-3.34 (m, 1 H), 2.81 (t, J = 11.9 Hz, 1 H), 2.49-2.42 (m, J = 12.0 Hz, 1 H), 1.21-0.97 (m, 9 H).	0.0194
320	4-(5-Cyano-4-methylamino-pyrimidin-2-ylamino)-2-fluoro-5-methoxy-N,N-dimethyl-benzamide		^{1}H NMR (400 MHz, DMSO) δ 8.39 (s, 1 H), 8.30 (s, 1 H), 8.19 (d, J = 11.9 Hz, 1 H), 7.90-7.83 (m, 1 H), 7.01 (d, J = 6.2 Hz, 1 H), 3.87 (s, 4 H), 2.99 (s, 3 H), 2.91 (d, J = 4.5 Hz, 3 H), 2.89 (s, 3 H).	0.0625

Example 12

In Vitro LRRK2 LabChip Assay

[0569] This assay was used to determine a compound's potency in inhibiting activity of LRRK2 by determining, Ki_{app}, IC_{50}, or percent inhibition values. In a polypropylene plate, LRRK2, fluorescently-labeled peptide substrate, ATP and test compound were incubated together. Using a LabChip 3000 (Caliper Life Sciences), after the reaction the substrate was separated by capillary electrophoresis into two populations: phosphorylated and unphosphorylated. The relative amounts of each were quantitated by fluorescence intensity. LRRK2 Ki was determined according to the equation:

$$Y=V0*(1-((x+Ki*(1+S/Km)+Et)/(2*Et)-(((x+Ki*(1+S/Km)+Et)\hat{}2-(4*Et*x))\hat{}0.5)/(2*Et))).$$

[0570] Ki values in Table 4 and elsewhere herein are shown in μM.

[0571] Assay conditions and materials used were as follows:

Final Assay Conditions:

[0572] LRRK2 G2019S in 5 mM $MgCl_2$: 5.2 nM (Invitrogen lot #567054A)

[0573] LRRK2 G2019S in 1 mM $MnCl_2$: 11 nM (Invitrogen lot #567054A)

[0574] LRRK2 Wild type in 5 mM $MgCl_2$: 15 nM (Invitrogen lot #500607F)

[0575] LRRK2 12020T in 5 mM $MgCl_2$: 25 nM (Invitrogen lot #43594)

[0576] Substrate: 1 μM

[0577] ATP: 130 μM

[0578] Kinase reaction time: 2 hours

[0579] Temperature: ambient

[0580] Total volume: 20 μl

ATP^{aPP} Kms:

[0581] G2019S in 5 mM $MgCl_2$: 130 μM

[0582] G2019S in 1 mM $MnCl_2$: 1 μM

[0583] Wild type in 5 mM $MgCl_2$: 80 μM

[0584] **12020**T in 5 mM $MgCl_2$: 14 μM

Materials:

[0585] Solid Support: Black 50 μL volume polypropylene 384 well plate (MatriCal cat #MP101-1-PP)

[0586] Kinase: LRRK2 G2019S (Invitrogen cat #PV4882).

[0587] LRRK2 Wild type (Invitrogen cat #PV4874).

[0588] Substrate: 5FAM-GAGRLGRDKYKTLRQIRQ-$CONH_2$

[0589] Non-binding plate: 384 well clear V-bottom polypropylene plates (Greiner cat #781280).

[0590] ATP: 10 mM ATP (Cell Signaling cat #9804).

[0591] Triton X-100: Triton X-100.

[0592] Brij-35: Brij-35 (Pierce cat #20150).

[0593] Coating Reagent #3: Coating Reagent #3 (Caliper).

[0594] DMSO: DMSO (Sigma cat #34869-100ML).

[0595] Complete Reaction Buffer: H_2O/25 mM Tris, pH 8.0/5 mM $MgCl_2$/2 mM DTT/0.01% Triton X-100.

[0596] Stop Solution: H_2O/100 mM HEPES, pH 7.2/0.015% Brij-35/0.2% Coating Reagent #3/20 mM EDTA.

[0597] Separation Buffer: H_2O/100 mM HEPES, pH 7.2/0.015% Brij-35/0.1% Coating Reagent #3/1:200 Coating Reagent #8/10 mM EDTA/5% DMSO.

Compound Plate Preparation:

[0598] For serial dilutions, 34.6 μl DMSO was added to columns 3-24. For the assay controls, 37.5 μl DMSO was added to columns 1 and 2 of rows A and P. a,d and 50 μl 25 μM G-028831 (Staurosporine) was added to columns 1 and 2, row B. For the samples: to start at 100 μM, 37.5 μl DMSO was to columns 1 and 2, then 12.5 μl 10 mM compound; to start at 10 μM, 78 μl DMSO was added to columns 1 & 2, then 2 μl 10 mM compound; and to start at 1 μM, 25 μM compound (2 μl 10 mM cmpd+798 μl DMSO) was added to empty columns 1 and 2. A Precision instrument was used to perform 1:3.16 serial dilutions ("PLK_BM_serial_halflog").

ATP Preparation:

[0599] ATP was diluted to 282.1 μM in Complete Kinase Buffer (final concentration was 130 μM).

Total and Blank Preparation:

[0600] In Complete Reaction Buffer, substrate was diluted to 4 μM. Equal volumes of Complete Reaction Buffer and 4 μM substrate were combined to obtain the blank. Equal volumes of Complete Reaction Buffer and 4 μM substrate were combined and to the combined solution was added 2× final LRRK2 concentration.

Assay Procedure:

[0601] To a 50 μl polypropylene plate, 5 μl/well buffer/substrate was added by hand to Blank wells. A Biomek FX was used to start the kinase reaction ("PLK SAR 23 ATP"). The following were added to the appropriate wells:

[0602] 2 μl compound+23 μl ATP;

[0603] 5 μl/well compound/ATP in Assay Plate;

[0604] 5 μl/well kinase/substrate in Assay Plate;

[0605] The plate was incubated for 2 hours in the dark. Biomek FX was used to stop the kinase reaction ("PLK Stop"), and 10 μl/well Stop solution was added to the Assay Plate. Results were read on the LabChip 3000.

Lab Chip 3000 Protocol:

[0606] The LabChip 3000 was run using the job "LRRK2 IC50" with the following job settings:

[0607] Pressure: −1.4 psi

[0608] Downstream voltage: −500 V

[0609] Upstream voltage: −2350 V

[0610] Post sample buffer sip time: 75 seconds

[0611] Post dye buffer sip time: 75 seconds

[0612] Final delay time: 200 seconds

Example 13

In Vitro LRRK2 Lanthascreen Binding Assay

[0613] This assay was used to determine a compound's potency in inhibiting activity of LRRK2 by determining, Ki_{app}, IC_{50}, or percent inhibition values. In 384 well proxiplates F black, shallow well plates LRRK2, Eu-anti-GST-antibody, Alexa Fluor® Kinase tracer 236 and test compound were incubated together.

[0614] Binding of the Alexa Fluor® "tracer" to a kinase was detected by addition of a Eu-labeled anti-GST antibody. Binding of the tracer and antibody to a kinase results in a high degree of FRET, whereas displacement of the tracer with a kinase inhibitor results in a loss of FRET.

[0615] Assay conditions and materials used were as follows:

Final Assay Conditions:

[0616] GST-LRRK2 G2019S 10 nM

[0617] Eu-anti-GST-antibody 2 nM

[0618] Kinase tracer 236 8.5 nM

[0619] Kinase reaction time: 1 hour

[0620] Temperature: ambient

[0621] Total volume: 15 μl

[0622] DMSO 1%

Materials:

[0623] 384 well proxiplates F black shallow well Perkin Elmer cat#6008260

[0624] Kinase: LRRK2 G2019S Invitrogen cat #PV4882 (LOT 567054A).

[0625] Eu-labeled anti-GST antibody Invitrogen cat #PV5594

[0626] Alexa Fluor® Kinase tracer 236 Invitrogen cat #PV5592

[0627] TRIS-HCl Sigma cat #T3253

[0628] EGTA Sigma cat #E3889

[0629] Brij-35: Sigma cat #B4184(30% w/v)

[0630] DMSO: Sigma cat #D8418

[0631] $MgCl_2$ Sigma cat #M9272

[0632] Reaction Buffer: H_2O/50 mM Tris, pH 7.4/10 mM $MgCl_2$/1 mM EGTA/0.01% Brij 35.

Compound Plate Preparation:

[0633] Serially dilute test compounds (10 mM stock) 1:3.16 (20 ul+43.2 ul) in 100% DMSO. 12pt curve. Dilute each concentration 1:33.3 (3 ul+97 ul) in reaction buffer. Stamp 5 ul to assay plate. Final top test concentration 100 uM.

Total and Blank Preparation:

[0634] In Reaction Buffer, 5 ul of DMSO(3%) was added to total and blank wells and 5 ul of Eu-labeled anti-GST antibody(6 nM) was added to blank wells.

Assay Procedure:

[0635] Add 5 ul LRRK2(30 nM)/Eu-labeled anti-GST antibody (6 nM) mix to compound and total wells. Add 5 ul kinase tracer (25.5 nM) to all wells. Incubate plates at room temperature for 1 hour on a plate shaker (gentle shaking). Read on Perkin Elmer EnVision reader HTRF protocol.

Data Handling:

[0636] Calculate ratio: (665/620)*10000. Substract mean background values from all data points. Calculate % of control for each test value. Plot % of control vs Compound concentration. Calculate Ki Value (xlfit curve fitting—Morrison equation).

[0637] Results expressed as a Ki in **82** M. The equation for Ki: Y=V0*(1−((x+Ki*(1+S/Km)+Et)/(2*Et)−(((x+Ki*(1+S/Km)+Et)^2−(4*Et*x))^0.5)/(2*Et)))

[0638] Where Et=4 nM

[0639] kd (Tracer)=8.5 nM

[0640] Tracer concentration (S)=8.5 nM.

Example 14

Parkinson's Disease Animal Model

[0641] Parkinson's disease can be replicated in mice and in primates by administration of 1-methyl-4-phenyl tetrahydropyridine (MPTP), a selective nigrostriatal dopaminergic neurotoxin that produces a loss of striatal dopamine (DA) nerve terminal markers. Compounds of the invention may be evaluated for effectiveness in treatment of Parkinson's disease using MPTP induced neurodegeneration following generally the protocol described by Saporito et al., *J. Pharmacology* (1999) Vol. 288, pp. 421-427.

[0642] Briefly, MPTP is dissolved in PBS at concentrations of 2-4 mg/ml, and mice (male C57 weighing 20-25 g) are given a subcutaneous injection of 20 to 40 mg/kg. Compounds of the invention are solubilized with polyethylene glycol hydroxystearate and dissolved in PBS. Mice are administered 10 ml/kg of compound solution by subcutaneous injection 4 to 6 h before MPTP administration, and then daily for 7 days. On the day of the last injection, mice are sacrificed and the midbrain blocked and postfixed in paraformaldehyde. Striata are dissected free, weighed, and stored at −70° C.

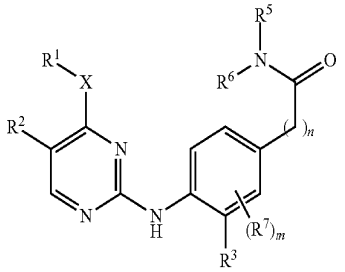
[0643] The striata thus collected are evaluated for content of dopamine and its metabolites dihydroxyphenylacetic acid and homovanillic acid, by HPLC with electrochemical detection as described by Sonsalla et al., *J. Pharmacol. Exp. Ther.* (1987) Vol. 242, pp. 850-857. The striata may also be evaluated using the tyrosine hydroxylase assay of Okunu et al., *Anal Biochem* (1987) Vol. 129, pp. 405-411 by measuring $^{14}CO_2$ evolution associated with tyrosine hydroxylase-mediated conversion of labeled tyrosine to L-dopa. The striata may further be evaluated using the Monoamine oxidase-B assay as described by White et al., *Life Sci.* (1984), Vol. 35, pp. 827-833, and by monitoring dopamine uptake as described by Saporito et al.,(1992) Vol. 260, pp. 1400-1409.

[0644] While the present invention has been described with reference to the specific embodiments thereof, it should be understood by those skilled in the art that various changes may be made and equivalents may be substituted without departing from the true spirit and scope of the invention. In addition, many modifications may be made to adapt a particular situation, material, composition of matter, process, process step or steps, to the objective spirit and scope of the present invention. All such modifications are intended to be within the scope of the claims appended hereto.

What is claimed is:

1. A compound of formula I:

I



or pharmaceutically acceptable salts thereof,

wherein:

m is from 0 to 3;

X is: —NR^a—; —O—; or —$S(O)_n$— wherein n is from 0 to 2 and R^a is hydrogen or C_{1-6}alkyl;

R^1 is: C_{1-6}alkyl; C_{2-6}alkenyl; C_{2-6}alkynyl; halo-C_{1-6}alkyl; C_{1-6}alkoxy-C_{1-6}alkyl; hydroxy-C_{1-6}alkyl; amino-C_{1-6}alkyl; C_{1-6}alkylsulfonyl-C_{1-6}alkyl; C_{3-6}cycloalkyl optionally substituted with C_{1-6}alkyl; C_{3-6}cycloalkyl-C_{1-6}alkyl wherein the C_{3-6}cycloalkyl portion is optionally substituted with C_{1-6}alkyl; tetrahydropyranyl; tetrahydrofuranyl; tetrahydrofuranyl-C_{1-6}alkyl; oxetanyl; or oxetan-C_{1-6}alkyl;

or R^1 and R^a together with the atoms to which they are attached may form a three to six membered ring that may optionally include an additional heteroatom selected from O, N and S, and which is substituted with oxo, halo or C_{1-6}alkyl;

R^2 is: halo; C_{1-6}alkoxy; cyano; C_{2-6}alkynyl; C_{2-6}alkenyl; halo-C_{1-6}alkyl; halo-C_{1-6}alkoxy; C_{3-6}cycloalkyl wherein the C_{3-6}cycloalkyl portion is optionally substituted with C_{1-6}alkyl; C_{3-6}cycloalkyl-C_{1-6}alkyl wherein the C_{3-6}cycloalkyl portion is optionally substituted with C_{1-6}alkyl; tetrahydrofuranyl; tetrahydrofuranyl-C_{1-6}alkyl; acetyl; oxetanyl; or oxetan-C_{1-6}alkyl;

R^3 is: —OR^4; halo; cyano; C_{1-6}alkyl; halo-C_{1-6}alkyl; C_{3-6}cycloalkyl optionally substituted with C_{1-6}alkyl; C_{3-6}cycloalkyl-C_{1-6}alkyl wherein the C_{3-6}cycloalkyl portion is optionally substituted with C_{1-6}alkyl; tetrahydrofuranyl; tetrahydrofuranyl-C_{1-6}alkyl; oxetanyl; or oxetan-C_{1-6}alkyl;

R^4 is: hydrogen; C_{1-6}alkyl; halo-C_{1-6}alkyl; C_{1-6}alkoxy-C_{1-6}alkyl; C_{3-6}cycloalkyl optionally substituted with C_{1-6}alkyl or halo; C_{3-6}cycloalkyl-C_{1-6}alkyl wherein the C_{3-6}cycloalkyl portion is optionally substituted with C_{1-6}alkyl or halo; tetrahydrofuranyl; tetrahydrofuranyl-C_{1-6}alkyl; oxetanyl; or oxetan-C_{1-6}alkyl;

R^5 is: hydrogen; or C_{1-6}alkyl;

n is 0 or 1;

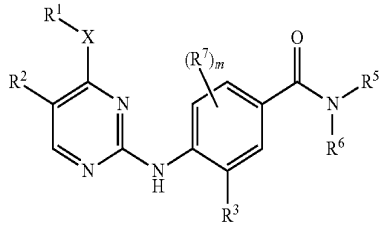
R^6 is: hydrogen; C_{1-6}alkyl; C_{1-6}alkoxy-C_{1-6}alkyl; hydroxy-C_{1-6}alkyl; amino-C_{1-6}alkyl; C_{3-6}cycloalkyl; C_{3-6}cycloalkyl-C_{1-6}alkyl; heterocyclyl; or heterocyclyl-C_{1-6}alkyl; wherein the C_{3-6}cycloalkyl, C_{3-6}cycloalkyl-C_{1-6}alkyl, heterocyclyl and heterocyclyl-C_{1-6}alkyl each may be optionally substituted with one, two, three or four groups groups independently selected from: C_{1-6}alkyl; halo-C_{1-6}alkyl; C_{1-6}alkoxy; halo-C_{1-6}alkoxy; hydroxy; hydroxy-C_{1-6}alkyl; halo; nitrile; C_{1-6}alkyl-carbonyl; C_{1-6}alkyl-sulfonyl; C_{3-6}cycloalkyl; C_{3-6}cycloalkyl-C_{1-6}alkyl; C_{3-6}cycloalkyl-carbonyl; amino; or heterocyclyl; or two of the groups together with the atoms to which they are attached may form a five or six-membered ring;

or R^5 and R^6 together with the nitrogen atom to which they are attached form a three- to seven-membered ring that optionally includes an additional heteroatom selected from O, N and $S(O)_n$, and which is optionally substituted with one, two, three or four groups independently selected from: C_{1-6}alkyl; halo-C_{1-6}alkyl; C_{1-6}alkoxy; halo-C_{1-6}alkoxy; hydroxy; C_{1-6}alkoxy-C_{1-6}alkyl; hydroxy-C_{1-6}alkyl; halo, nitrile; C_{1-6}alkyl-carbonyl; C_{1-6}alkyl-sulfonyl; C_{3-6}cycloalkyl; C_{3-6}cycloalkyl-C_{1-6}alkyl; C_{3-6}cycloalkyl-carbonyl; amino; or heterocyclyl; or two of the groups together with the atoms to which they are attached may form a five or six-membered ring; and

R^7 is: halo; C_{1-6}alkyl; C_{1-6}alkoxy; halo-C_{1-6}alkyl; or halo-C_{1-6}alkoxy.

2. The compound of claim **1**, wherein said compound is of formula II:

II



or a pharmaceutically acceptable salt thereof,

wherein:

m is from 0 to 3;

X is: —NR^a—; —O—; or —$S(O)_n$— wherein n is from 0 to 2 and R^a is hydrogen or C_{1-6}alkyl;

R^1 is: C_{1-6}alkyl; C_{2-6}alkenyl; C_{2-6}alkynyl; halo-C_{1-6}alkyl; C_{1-6}alkoxy-C_{1-6}alkyl; hydroxy-C_{1-6}alkyl; amino-C_{1-6}alkyl; C_{1-6}alkylsulfonyl-C_{1-6}alkyl; C_{3-6}cycloalkyl optionally substituted with C_{1-6}alkyl; C_{3-6}cycloalkyl-C_{1-6}alkyl wherein the C_{3-6}cycloalkyl portion is optionally substituted with C_{1-6}alkyl; tetrahydrofuranyl; tetrahydrofuranyl-C_{1-6}alkyl; oxetanyl; or oxetan-C_{1-6}alkyl;

R^2 is: halo; C_{1-6}alkoxy; cyano; C_{2-6}alkynyl; C_{2-6}alkenyl; halo-C_{1-6}alkyl; halo-C_{1-6}alkoxy; C_{3-6}cycloalkyl wherein the C_{3-6}cycloalkyl portion is optionally substituted with C_{1-6}alkyl; C_{3-6}cycloalkyl-C_{1-6}alkyl wherein the C_{3-6}cycloalkyl portion is optionally substituted with C_{1-6}alkyl; tetrahydrofuranyl; tetrahydrofuranyl-C_{1-6}alkyl; oxetanyl; or oxetan-C_{1-6}alkyl;

R^3 is: —OR^4; halo; cyano; C_{3-6}cycloalkyl optionally substituted with C_{1-6}alkyl; C_{3-6}cycloalkyl-C_{1-6}alkyl wherein the C_{3-6}cycloalkyl portion is optionally substituted with C_{1-6}alkyl; tetrahydrofuranyl; tetrahydrofuranyl-C_{1-6}alkyl; oxetanyl; or oxetan-C_{1-6}alkyl;

R^4 is: C_{1-6}alkyl; halo-C_{1-6}alkyl; C_{1-6}alkoxy-C_{1-6}alkyl; C_{3-6}cycloalkyl optionally substituted with C_{1-6}alkyl; C_{3-6}cycloalkyl-C_{1-6}alkyl wherein the C_{3-6}cycloalkyl portion is optionally substituted with C_{1-6}alkyl; tetrahydrofuranyl; tetrahydrofuranyl-C_{1-6}alkyl; oxetanyl; or oxetan-C_{1-6}alkyl;

R^5 is: hydrogen; or C_{1-6}alkyl;

R^6 is: hydrogen; C_{1-6}alkyl; C_{1-6}alkoxy-C_{1-6}alkyl; amino-C_{1-6}alkyl; C_{3-6}cycloalkyl; C_{3-6}cycloalkyl-C_{1-6}alkyl; heterocyclyl; or heterocyclyl-C_{1-6}alkyl; wherein the C_{3-6}cycloalkyl, C_{3-6}cycloalkyl-C_{1-6}alkyl, heterocyclyl and heterocyclyl-C_{1-6}alkyl each may be optionally substituted with one, two or three groups independently selected from: C_{1-6}alkyl; halo-C_{1-6}alkyl; C_{1-6}alkoxy; halo-C_{1-6}alkoxy; hydroxy; hydroxy-C_{1-6}alkyl; halo; nitrile; C_{1-6}alkyl-carbonyl; C_{1-6}alkyl-sulfonyl; C_{3-6}cycloalkyl; C_{3-6}cycloalkyl-C_{1-6}alkyl; C_{3-6}cycloalkyl-carbonyl; amino; or heterocyclyl; or two of the groups together with the atoms to which they are attached may form a five or six-membered ring;

or R^5 and R^6 together with the nitrogen atom to which they are attached form a three- to seven-membered ring that optionally includes an additional heteroatom selected from O, N and $S(O)_n$, and which is optionally substituted with one, two or three groups independently selected from: C_{1-6}alkyl; halo-C_{1-6}alkyl; C_{1-6}alkoxy; halo-C_{1-6}alkoxy; hydroxy; hydroxy-C_{1-6}alkyl; halo, nitrile; C_{1-6}alkyl-carbonyl; C_{1-6}alkyl-sulfonyl; C_{3-6}cycloalkyl; C_{3-6}cycloalkyl-C_{1-6}alkyl; C_{3-6}cycloalkyl-carbonyl; amino; or heterocyclyl; or two of the groups together with the atoms to which they are attached may form a five or six-membered ring; and

R^7 is: halo; C_{1-6}alkyl; C_{1-6}alkoxy; halo-C_{1-6}alkyl; or halo-C_{1-6}alkoxy.

3. The compound of claim **2** wherein m is 0 or 1.

4. The compound of claim **2** wherein X is —NR^a— or —O—.

5. The compound of claim **2** wherein X is —NR^a.

6. The compound of claim **2** wherein R^1 is C_{1-6}alkyl.

7. The compound of claim **2** wherein R^2 is: halo; halo-C_{1-6}alkyl; or cyano.

8. The compound of claim **2** wherein R^2 is: chloro, trifluoromethyl or cyano.

9. The compound of claim **2** wherein R^3 is: halo; or —OR^4.

10. The compound of claim **2** wherein R^3 is: halo; C_{1-6}alkoxy; or halo-C_{1-6}alkoxy.

11. The compound of claim **2** wherein R^3 is: R^3 is: methoxy; chloro; or fluoro.

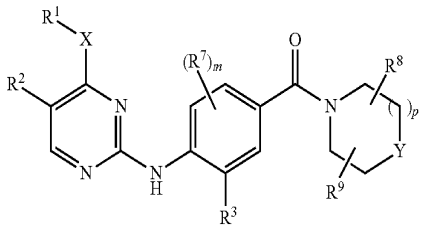
12. The compound of claim **2** wherein m is 1 and R^7 is halo or methoxy.

13. The compound of claim **2** wherein R^5 and R^6 together with the nitrogen atom to which they are attached form a three- to six-membered ring that is optionally includes an additional heteroatom selected from O, N and S, and which is optionally substituted with one, two or three groups independently selected from C_{1-6}alkyl, halo-C_{1-6}alkyl, C_{1-6}alkoxy, halo-C_{1-6}alkoxy, hydroxy, hydroxy-C_{1-6}alkyl, halo, nitrile, C_{1-6}alkyl-carbonyl, C_{1-6}alkyl-sulfonyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkyl-C_{1-6}alkyl, C_{3-6}cycloalkyl-carbonyl, amino, or heterocyclyl, or two of the groups together with the atoms to which they are attached may form a five or six-membered ring.

14. The compound of claim **2** wherein R^5 and R^6 together with the nitrogen atom to which they are attached form a morpholinyl group that is optionally substituted once or twice with groups independently selected from C_{1-6}alkyl, halo-C_{1-6}alkyl, C_{1-6}alkoxy, halo-C_{1-6}alkoxy, hydroxy, hydroxy-C_{1-6}alkyl, halo, nitrile, C_{1-6}alkyl-carbonyl, C_{1-6}alkyl-sulfonyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkyl-C_{1-6}alkyl, C_{3-6}cycloalkyl-carbonyl, amino, or heterocyclyl, or the two groups together with the atoms to which they are attached may form a five or six-membered ring.

15. The compound of claim **2** wherein said compound is of formula III

III



wherein:

p is from 0 to 2;

Y is: —O—; —$S(O)_n$—; —NR^{10}; or —$CR^{11}R^{12}$— when p is 1 or 2; and Y is —$CR^{11}R^{12}$— when p is 0;

R^8 and R^9 each independently is: hydrogen; C_{1-6}alkyl; halo-C_{1-6}alkyl; C_{1-6}alkoxy; halo-C_{1-6}alkoxy; hydroxy; hydroxy-C_{1-6}alkyl; halo; nitrile; C_{1-6}alkyl-carbonyl; C_{1-6}alkyl-sulfonyl; C_{3-6}cycloalkyl; C_{3-6}cycloalkyl-C_{1-6}alkyl; C_{3-6}cycloalkyl-carbonyl; amino; or heterocyclyl;

or R^8 and R^9 together with the atoms to which they are attached form a five- or six-membered ring;

R^{10} is: hydrogen; C_{1-6}alkyl; hydroxy-C_{1-6}alkyl; halo-C_{1-6}alkyl; hydroxy-C_{1-6}alkyl; C_{1-6}alkyl-carbonyl; C_{1-6}alkyl-sulfonyl; C_{3-6}cycloalkyl; C_{3-6}cycloalkyl-C_{1-6}alkyl; C_{3-6}cycloalkyl-carbonyl; heterocyclyl; or heterocyclyl-C_{1-6}alkyl;

or one of R^8 and R^9 together with R^{10} and the atoms to which they are attached form a five- or six-membered ring;

R^{11} is: hydrogen; C_{1-6}alkyl; or halo;

R^{12} is: hydrogen; C_{1-6}alkyl; halo-C_{1-6}alkyl; C_{1-6}alkoxy; halo-C_{1-6}alkoxy; hydroxy; hydroxy-C_{1-6}alkyl; halo; nitrile; C_{1-6}alkyl-carbonyl; C_{1-6}alkyl-sulfonyl; C_{3-6}cycloalkyl; C_{3-6}cycloalkyl-C_{1-6}alkyl; C_{3-6}cycloalkyl-carbonyl; amino; heterocyclyl; or heterocyclyl-C_{1-6}alkyl;

or R^{11} and R^{12} together with the atom to which they are attached may form a 3- to six-membered ring that optionally includes a heteroatom selected from O, N and S;

or one of R^8 and R^9 together with R^{10} and the atoms to which they are attached form a five- or six-membered ring;

or one of R^8 and R^9 together with R^{12} and the atoms to which they are attached form a five- or six-membered ring; and

m, n, X, R^1, R^2, R^3 and R^7 are as defined herein.

16. The compound of claim **2** wherein p is 1.

17. The compound of claim **2** wherein Y is —O—; —NR^{10}; or —$CR^{11}R^{12}$—.

18. The compound of claim **2** wherein Y is —O—.

19. A composition comprising:

(a) a pharmaceutically acceptable carrier; and

(b) a compound of claim **1**.

20. A method for treating Parkinson's disease, said method comprising administering to a subject in need thereof an effective amount of a compound of claim **1**.

* * * * *