(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) **EP 1 924 264 B9**

(12) **CORRECTED EUROPEAN PATENT SPECIFICATION**

(15) Correction information:
Corrected version no 1 (W1 B1)
Corrections, see
Claims EN 1-4, 6

(48) Corrigendum issued on:
19.02.2014 Bulletin 2014/08

(45) Date of publication and mention of the grant of the patent:
18.09.2013 Bulletin 2013/38

(21) Application number: **06778331.6**

(22) Date of filing: **23.08.2006**

(51) Int Cl.:
A61K 31/505 *(2006.01)* ***A61K 31/506*** *(2006.01)*
A61K 31/513 *(2006.01)* ***A61P 11/00*** *(2006.01)*
A61P 11/06 *(2006.01)* ***A61P 1/00*** *(2006.01)*

(86) International application number:
PCT/EP2006/065606

(87) International publication number:
WO 2007/025925 (08.03.2007 Gazette 2007/10)

(54) DIAMINOPYRIMIDINES AS P2X3 AND P2X2/3 MODULATORS

DIAMINOPYRIMIDINE ALS P2X3 UND P2X2/3 MODULATOREN

DIAMINOPYRIMIDINES COMME MODULATEURS P2X3 ET P2X2/3

(84) Designated Contracting States:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IS IT LI LT LU LV MC NL PL PT RO SE SI SK TR

(30) Priority: **01.09.2005 US 713548 P**

(43) Date of publication of application:
28.05.2008 Bulletin 2008/22

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WO-A2-03/040339 **US-A- 5 874 420**

- **GALLIGAN JAMES J: "Enteric P2X receptors as potential targets for drug treatment of the irritable bowel syndrome." BRITISH JOURNAL OF PHARMACOLOGY. APR 2004, vol. 141, no. 8, April 2004 (2004-04), pages 1294-1302, XP002411404 ISSN: 0007-1188**

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Description

[0001] This invention pertains to compounds and the use for the preparation of a medicament for the treatment of diseases associated with P2X purinergic receptors, and more particularly to uses of $P2X_3$ and/or $P2X_{2/3}$antagonists for treatment of respiratory diseases, conditions and disorders.

[0002] The urinary bladder is responsible for two important physiological functions: urine storage and urine emptying. This process involves two main steps: (1) the bladder fills progressively until the tension in its walls rises above a threshold level; and (2) a nervous reflex, called the micturition reflex, occurs that empties the bladder or, if this fails, at least causes a conscious desire to urinate. Although the micturition reflex is an autonomic spinal cord reflex, it can also be inhibited or mediated by centers in the cerebral cortex or brain.

[0003] Purines, acting via extracellular purinoreceptors, have been implicated as having a variety of physiological and pathological roles (See, Burnstock (1993) Drug Dev. Res. 28:195-206) ATP, and to a lesser extent, adenosine, can stimulate sensory nerve endings resulting in intense pain and a pronounced increase in sensory nerve discharge. ATP receptors have been classified into two major families, the P2Y- and P2X-purinoreceptors, on the basis of molecular structure, transduction mechanisms, and pharmacological characterization. The P2Y-purinoreceptors are G-protein coupled receptors, while the P2X-purinoreceptors are a family of ATP-gated cation channels. Purinergic receptors, in particular, P2X receptors, are known to form homomultimers or heteromultimers. To date, cDNAs for several P2X receptors subtypes have been cloned, including: six homomeric receptors, $P2X_1$; $P2X_2$; $P2X_3$; $P2X_4$; $P2X_5$; and $P2X_7$; and three heteromeric receptors $P2X_{2/3}$; $P2X_{4/6}$; $P2X_{1/5}$ (See, e.g., Chen et al. (1995) Nature 377:428-431; Lewis et al. (1995) Nature 377:432-435; and Burnstock (1997) Neurophamacol. 36:1127-1139). The structure and chromosomal mapping of mouse genomic $P2X_3$ receptor subunit has also been described (Souslova et al. (1997) Gene 195:101-111). In vitro, co-expression of $P2X_2$ and $P2X_3$ receptor subunits is necessary to produce ATP-gated currents with the properties seen in some sensory neurons (Lewis et al. (1995) Nature 377:432-435).

[0004] P2X receptor subunits are found on afferents in rodent and human bladder urothelium. Data exists suggesting that ATP may be released from epithelial/endothelial cells of the urinary bladder or other hollow organs as a result of distention (Burnstock (1999) J. Anatomy 194:335-342; and Ferguson et al. (1997) J. Physiol. 505:503-511). ATP released in this manner may serve a role in conveying information to sensory neurons located in subepithelial components, e.g., suburothelial lamina propria (Namasivayam et al. (1999) BJU Intl. 84:854-860). The P2X receptors have been studied in a number of neurons, including sensory, sympathetic, parasympathetic, mesenteric, and central neurons (Zhong et al. (1998) Br. J. Pharmacol. 125:771-781). These studies indicate that purinergic receptors play a role in afferent neurotransmission from the bladder, and that modulators of P2X receptors are potentially useful in the treatment of bladder disorders and other genitourinary diseases or conditions.

[0005] Recent evidence also suggests a role of endogenous ATP and purinergic receptors in nociceptive responses in mice (Tsuda et al. (1999) Br. J. Pharmacol. 128:1497-1504). ATP-induced activation of P2X receptors on dorsal root ganglion nerve terminals in the spinal cord has been shown to stimulate release of glutamate, a key neurotransmitter involved in nociceptive signaling (Gu and MacDermott, Nature 389:749-753 (1997)). $P2X_3$ receptors have been identified on nociceptive neurons in the tooth pulp (Cook et al., Nature 387:505-508 (1997)). ATP released from damaged cells may thus lead to pain by activating $P2X_3$ and/or $P2X_{2/3}$ containing receptors on nociceptive sensory nerve endings. This is consistent with the induction of pain by intradermally applied ATP in the human blister-base model (Bleehen, Br Pharmacol 62:573-577 (1978)). P2X antagonists have been shown to be analgesic in animal models (Driessen and Starke, Naunyn Schmiedebergs Arch Pharmacol 350:618-625 (1994)). This evidence suggests that $P2X_2$ and $P2X_3$ are involved in nociception, and that modulators of P2X receptors are potentially useful as analgesics.

[0006] There is accordingly a need for the use of compounds for the preparation of a medicament for treating respiratory diseases, conditions and disorders mediated by $P2X_3$ and/or $P2X_{2/3}$ receptors, as well as a need for compounds that act as modulators of P2X receptors, including antagonists of $P2X_3$ and $P2X_{2/3}$ receptors. The present invention satisfies these needs as well as others.

[0007] Other researchers have shown that $P2X_3$ receptors are expressed in human colon, and are expressed at higher levels in inflamed colon than in normal colon (Yiangou et al, Neuro-gastroenterol Mot (2001) 13:365-69). Other researchers have implicated the $P2X_3$ receptor in detection of distension or intraluminal pressure in the intestine, and initiation of reflex contractions (Bian et al., J Physiol (2003) 551.1:309-22), and have linked this to colitis (Wynn et al., Am J Physiol Gastrointest Liver Physiol (2004) 287:G647-57).

[0008] Inge Brouns et al. (Am J Respir Cell Mol Biol (2000) 23:52-61) found that $P2X_3$ receptors are expressed in pulmonary neuroepithelial bodies (NEBs), implicating the receptor in pain transmission in the lung. More recently, others have implicated $P2X_2$ and $P2X_3$ receptors in pO_2 detection in pulmonary NEBs (Rong et al., J Neurosci (2003) 23(36): 11315-21).

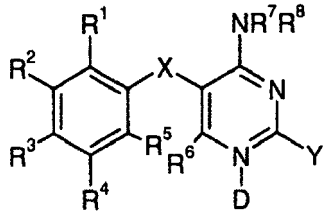
[0009] US5874420 provides methods of altering vagal tone in a patient by administering a therapeutically effective amount of a mediator of P2x-purinoceptors located on vagal afferent nerve terminals to the patient. Diagnostic applications are also provided.

[0010] WO03040339 relates to antisense oligonucleotides, compositions and methods useful for modulating the expression of P2X3. The compositions comprise antisense oligonucleotides, particularly antisense oligonucleotides targeted to nucleic acids encoding P2X3.

[0011] Galligan James J: "Enteric P2X receptors as potential targets for drug treatment of the irritable bowel syndrome." British Journal of Pharmacology. APR 2004, vol. 141, no. 8, April 2004 (2004-04), pages 1294-1302, XP002411404 ISSN: 0007-1188 provides insights into enteric P2X receptors as potential targets for drug treatment of the irritable bowel syndrome.

[0012] WO2005095359 defines compounds and methods for treating diseases mediated by a P2X3 and/or a P2X2/3 receptor antagonists.

[0013] The invention provides the use of a compound of formula I for the preparation of a medicament for treating a respiratory disease mediated by a $P2X_3$ or $P2X_{2/3}$ receptor antagonist:



(I)

or a pharmaceutically acceptable salt thereof,
wherein:

X	is $-CH_2-$; -O-; or -CHOH-;
Y	is hydrogen; or $-NR^dR^e$ wherein one of R^d and R^e is hydrogen, and the other is hydrogen; alkyl; cycloalkyl; cycloalkylalkyl; haloalkyl; haloalkoxy; hydroxyalkyl; alkoxyalkyl; acetyl; alkylsulfonyl; alkylsulfonylalkyl; aminocarbonyloxyalkyl; hydroxycarbonylalkyl; hydroxyalkyloxycarbonylalkyl; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl;
D	is an optional oxygen;
R^1	is alkyl; alkenyl; cycloalkyl; cycloalkenyl; halo; haloalkyl; hydroxyalkyl; or alkoxy;
R^2, R^3, R^4 and R^5	each independently is hydrogen; alkyl; alkenyl; amino; halo; amido; halo-alkyl; alkoxy; hydroxy; haloalkoxy; nitro; hydroxyalkyl; alkoxyalkyl; hydroxyalkoxy; alkynylalkoxy; alkylsulfonyl; arylsulfonyl; cyano; aryl; heteroaryl; heterocyclyl; heterocyclylalkoxy; aryloxy; heteroaryloxy; aralkyloxy; heteroaralkyloxy; optionally substituted phenoxy; $-(CH_2)_m-(Z)_n-(CO)-R^f$ or $-(CH_2)_m-(Z)_n-SO_2-(NR^g)_n-R^f$ where m and n each independently is 0 or 1, Z is O or NR^g, R^f is hydrogen, alkyl, hydroxy, alkoxy, amino, hydroxyalkyl or alkoxyalkyl, and each R^g is independently hydrogen or alkyl;
R^6	is hydrogen; alkyl; halo; haloalkyl; amino; or alkoxy; and
one of R^7 and R^8	is hydrogen, and the other is hydrogen; alkyl; cycloalkyl; cycloalkylalkyl; haloalkyl; haloalkoxy; hydroxyalkyl; alkoxyalkyl; acetyl; alkylsulfonyl; alkylsulfonylalkyl; aminocarbonyloxyalkyl; hydroxycarbonylalkyl; hydroxyalkyloxycarbonylalkyl; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl.

[0014] Exemplary respiratory diseases treatable with the invention include chronic obstructive pulmonary disease (COPD), asthma and bronchospasm. The invention also provides and pharmaceutical compositions and methods of preparing the same.

[0015] 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.

[0016] "Agonist" refers to a compound that enhances the activity of another compound or receptor site.

[0017] "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 methyl, ethyl, propyl, isopropyl, isobutyl, sec-butyl, tert-butyl, pentyl, n-hexyl, octyl and dodecyl.

[0018] "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 and propenyl.

[0019] "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 and propynyl.

[0020] "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 and pentylene.

[0021] "Alkoxy" means a moiety of the formula -OR, wherein R is an alkyl moiety as defined herein. Examples of alkoxy moieties include methoxy, ethoxy and isopropoxy.

[0022] "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 2-methoxyethyl, 3-methoxypropyl, 1-methyl-2-methoxyethyl, 1-(2-methoxyethyl)-3-methoxypropyl, and 1-(2-methoxyethyl)-3-methoxypropyl.

[0023] "Alkylcarbonyl" means a moiety of the formula -R'-R", where R' is oxo and R" is alkyl as defined herein.

[0024] "Alkylsulfonyl" means a moiety of the formula -R'-R", where R' is -SO_2- and R" is alkyl as defined herein.

[0025] "Alkylsulfonylalkyl" means a moiety of the formula -R'-R"-R"' where where R' is alkylene, R" is -SO_2- and R"' is alkyl as defined herein.

[0026] "Alkylamino" means a moiety of the formula -NR-R' wherein R is hyrdogen or alkyl and R' is alkyl as defined herein.

[0027] "Alkoxyamino" means a moiety of the formula -NR-OR' wherein R is hydrogen or alkyl and R' is alkyl as defined herein.

[0028] "Alkylsulfanyl" means a moiety of the formula -SR wherein R is alkyl as defined herein.

[0029] "Aminoalkyl" means a group -R-R' wherein R' is amino and R is alkylene as defined herein. "Aminoalkyl" includes aminomethyl, aminoethyl, 1-aminopropyl and 2-aminopropyl. The amino moiety of "aminoalkyl" may be substituted once or twice with alkyl to provide "alkylaminoalkyl" and "dialkylaminoalkyl" respectively. "Alkylaminoalkyl" includes methylaminomethyl, methylaminoethyl, methylaminopropyl and ethylaminoethyl. "Dialkylaminoalkyl" includes dimethylaminomethyl, dimethylaminoethyl, dimethylaminopropyl and N-methyl-N-ethylaminoethyl.

[0030] "Aminoalkoxy" means a group -OR-R' wherein R' is amino and R is alkylene as defined herein.

[0031] "Alkylsulfonylamido" means a moiety of the formula -NR'SO_2-R wherein R is alkyl and R' is hydrogen or alkyl.

[0032] "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.

[0033] "Alkynylalkoxy" means a group of the formula -O-R-R' wherein R is alkylene and R' is alkenyl as defined herein.

[0034] "Antagonist" refers to a compound that diminishes or prevents the action of another compound or receptor site.

[0035] "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 optionally substituted 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 and ethylenedioxyphenyl, including partially hydrogenated derivatives thereof.

[0036] "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 and 3-(3-chlorophenyl)-2-methylpentyl are examples of arylalkyl.

[0037] "Arylalkyl" means a group of the formula -R-R' wherein R is alkylene and R' is aryl as defined herein.

[0038] "Arylsulfonyl means a group of the formula -SO_2-R wherein R is aryl as defined herein.

[0039] "Aryloxy" means a group of the formula -O-R wherein R is aryl as defined herein.

[0040] "Aralkyloxy" means a group of the formula -O-R-R" wherein R is alkylene and R' is aryl as defined herein.

[0041] "Cyanoalkyl" " means a moiety of the formula -R'-R", where R' is alkylene as defined herein and R" is cyano or nitrile.

[0042] "Cycloalkyl" means a monovalent saturated carbocyclic moiety consisting of mono- or bicyclic rings. Cycloalkyl can optionally be substituted with one or more substituents, wherein each substituent is independently hydroxy, alkyl, alkoxy, halo, haloalkyl, amino, monoalkylamino, or dialkylamino, unless otherwise specifically indicated. Examples of cycloalkyl moieties include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, including partially unsaturated derivatives thereof.

[0043] "Cycloalkylalkyl" means a moiety of the formula -R'-R", where R' is alkylene and R" is cycloalkyl as defined herein.

[0044] "Heteroalkyl" means an alkyl radical as defined herein wherein one, two or three hydrogen atoms have been replaced with a substituent independently selected from the group consisting of -OR^a, -NR^bR^c, and -$S(O)_nR^d$ (where n is an integer from 0 to 2), with the understanding that the point of attachment of the heteroalkyl radical is through a carbon atom, wherein R^a is hydrogen, acyl, alkyl, cycloalkyl, or cycloalkylalkyl; R^b and R^c are independently of each other hydrogen, acyl, alkyl, cycloalkyl, or cycloalkylalkyl; and when n is 0, R^d is hydrogen, alkyl, cycloalkyl, or cycloalkylalkyl, and when n is 1 or 2, R^d is alkyl, cycloalkyl, cycloalkylalkyl, amino, acylamino, monoalkylamino, or dialkylamino. Representative examples include 2-hydroxyethyl, 3-hydroxypropyl, 2-hydroxy-1-hydroxymethylethyl, 2,3-dihydroxypropyl, 1-hydroxymethylethyl, 3-hydroxybutyl, 2,3-dihydroxybutyl, 2-hydroxy-1-methylpropyl, 2-aminoethyl, 3-aminopropyl,

2-methylsulfonylethyl, aminosulfonylmethyl, aminosulfonylethyl, aminosulfonylpropyl, methylamino-sulfonylmethyl, methylaminosulfonylethyl and methylaminosulfonylpropyl.

[0045] "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 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 and acridinyl, including partially hydrogenated derivatives thereof.

[0046] "Heteroarylalkyl" or "heteroaralkyl" means a group of the formula -R-R' wherein R is alkylene and R' is heteroaryl as defined herein.

[0047] "Heteroarylsulfonyl means a group of the formula -SO_2-R wherein R is heteroaryl as defined herein.

[0048] "Heteroaryloxy" means a group of the formula -O-R wherein R is heteroaryl as defined herein.

[0049] "Heteroaralkyloxy" means a group of the formula -O-R-R" wherein R is alkylene and R' is heteroaryl as defined herein.

[0050] The terms "halo", "halogen" and "halide", which may be used interchangeably, refer to a substituent fluoro, chloro, bromo, or iodo.

[0051] "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 and perfluoroalkyl (e.g., -CF_3).

[0052] "Haloalkoxy" means a moiety of the formula -OR, wherein R is a haloalkyl moiety as defined herein. An exemplary haloalkoxy is difluoromethoxy.

[0053] "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.

[0054] "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 optionally substituted piperidinyl, piperazinyl, homopiperazinyl, azepinyl, pyrrolidinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, pyridinyl, pyridazinyl, pyrimidinyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, quinuclidinyl, quinolinyl, isoquinolinyl, benzimidazolyl, thiadiazolylidinyl, benzothiazolidinyl, benzoazolylidinyl, dihydrofuryl, tetrahydrofuryl, dihydropyranyl, tetrahydropyranyl, thiamorpholinyl, thiamorpholinylsulfoxide, thiamorpholinylsulfone, dihydroquinolinyl, dihydrisoquinolinyl, tetrahydroquinolinyl and tetra-hydrisoquinolinyl.

[0055] "Heterocyclylalkyl" means a moiety of the formula -R-R' wherein R is alkylene and R' is heterocyclyl as defined herein.

[0056] "Heterocyclyloxy" means a moiety of the formula -OR wherein R is heterocyclyl as defined herein.

[0057] "Heterocyclylalkoxy" means a moiety of the formula -OR-R' wherein R is alkylene and R' is heterocyclyl as defined herein.

[0058] "Hydroxyalkoxy" means a moiety of the formula -OR wherein R is hydroxyalkyl as defined herein.

[0059] "Hydroxyalkylamino" means a moiety of the formula -NR-R' wherein R is hydrogen or alkyl and R' is hydroxyalkyl as defined herein.

[0060] "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.

[0061] "Hydroxycarbonylalkyl" or "carboxyalkyl" means a group of the formula -R-(CO)-OH where R is alkylene as defined herein.

[0062] "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.

[0063] "Hydroxyalkyl" means an alkyl moiety as defined herein, substituted with one or more, preferably one, two or three hydroxy groups, provided that the same carbon atom does not carry more than one hydroxy group. Representative examples include 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.

[0064] "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 2-, 3- and 4-hydroxycyclohexyl.

[0065] "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.

[0066] "Carbamate" means a group of the formula -O-C(O)-NR'R" wherein R' and R" each independently is hydrogen

or alkyl.

[0067] "Carboxy" means a group of the formula -O-C(O)-OH.

[0068] "Sulfonamido" means a group of the formula -SO_2-NR'R" wherein R', R" and R'" each independently is hydrogen or alkyl.

[0069] "Optionally substituted", when used in association with "aryl", "phenyl", "heteroaryl", "cycloalkyl," or "heterocyclyl", means an aryl, phenyl, heteroaryl, cyclohexyl or heterocyclyl which is optionally substituted independently with one to four substituents, preferably one or two substituents selected from alkyl, cycloalkyl, cycloalkylalkyl, heteroalkyl, hydroxyalkyl, halo, nitro, cyano, hydroxy, alkoxy, amino, acylamino, mono-alkylamino, di-alkylamino, haloalkyl, haloalkoxy, heteroalkyl, -COR (where R is hydrogen, alkyl, phenyl or phenylalkyl), -$(CR'R")_n$-COOR (where n is an integer from 0 to 5, R' and R" are independently hydrogen or alkyl, and R is hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, phenyl or phenylalkyl), or -$(CR'R")_n$-$CONR^aR^b$ (where n is an integer from 0 to 5, R' and R" are independently hydrogen or alkyl, and R^a and R^b are, independently of each other, hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, phenyl or phenylalkyl).

[0070] "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 halogen, alkane- or arylenesulfonyloxy, such as methanesulfonyloxy, ethanesulfonyloxy, thiomethyl, benzenesulfonyloxy, tosyloxy, and thienyloxy, dihalophosphinoyloxy, optionally substituted benzyloxy, isopropyloxy and acyloxy.

[0071] "Modulator" means a molecule that interacts with a target. The interactions include agonist and antagonist, as defined herein.

[0072] "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.

[0073] "Disease" and "Disease state" means any disease, condition, symptom, disorder or indication.

[0074] "Inert organic solvent" or "inert solvent" means the solvent is inert under the conditions of the reaction being described in conjunction therewith, including e.g., benzene, toluene,

[0075] acetonitrile, tetrahydrofuran, N,N-dimethylformamide, chloroform, methylene chloride or DCM, dichloroethane, diethyl ether, ethyl acetate, acetone, methyl ethyl ketone, methanol, ethanol, propanol, isopropanol, tert-butanol, dioxane and pyridine. Unless specified to the contrary, the solvents used in the reactions of the present invention are inert solvents.

[0076] "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.

[0077] "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. Such salts include:

acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid and phosphoric acid; or formed with organic acids such as acetic acid, benzenesulfonic acid, benzoic, camphorsulfonic acid, citric acid, ethanesulfonic acid, fumaric acid, glucoheptonic acid, gluconic acid, glutamic acid, glycolic acid, hydroxynaphtoic acid, 2-hydroxyethanesulfonic acid, lactic acid, maleic acid, malic acid, malonic acid, mandelic acid, methanesulfonic acid, muconic acid, 2-naphthalenesulfonic acid, propionic acid, salicylic acid, succinic acid, tartaric acid, p-toluenesulfonic acid and trimethylacetic acid; or

salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic or inorganic base. Acceptable organic bases include diethanolamine, ethanolamine, N-methylglucamine, triethanolamine and tromethamine. Acceptable inorganic bases include aluminum hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate and sodium hydroxide.

[0078] The preferred pharmaceutically acceptable salts are the salts formed from acetic acid, hydrochloric acid, sulphuric acid, methanesulfonic acid, maleic acid, phosphoric acid, tartaric acid, citric acid, sodium, potassium, calcium, zinc, and magnesium.

[0079] 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.

[0080] "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 trifluoroacetyl, acetamido, benzyl (Bn), benzyloxycarbonyl (carbobenzyloxy, CBZ), p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl and *tert*-butoxycarbonyl (BOC). 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.

[0081] "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.

[0082] "Subject" means mammals and non-mammals. Mammals means any member of the mammalia class including 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. Examples of non-mammals include birds. The term "subject" does not denote a particular age or sex.

[0083] "Respiratory disorder" or "respiratory disease" refers to chronic obstructive pulmonary disease (COPD), asthma and bronchospasm.

[0084] "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.

[0085] 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 preferred, more preferred and most preferred definitions, if any.

[0086] "Treating" or "treatment" of a disease state includes:

(i) preventing the disease state, i.e. causing the clinical symptoms of the disease state not to develop in a subject that may be exposed to or predisposed to the disease state, but does not yet experience or display symptoms of the disease state.
(ii) inhibiting the disease state, i.e., arresting the development of the disease state or its clinical symptoms, or
(iii) relieving the disease state, *i.e.,* causing temporary or permanent regression of the disease state or its clinical symptoms.

[0087] 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.

[0088] In general, the nomenclature used in this Application is based on AUTONOM™ v.4.0, a Beilstein Institute computerized system for the generation of IUPAC systematic nomenclature. Chemical structures shown herein were prepared using ISIS˙ version 2.2. Any open valency appearing on a carbon, oxygen or nitrogen atom in the structures herein indicates the presence of a hydrogen atom.

[0089] The respiratory disease is chronic obstructive pulmonary disease (COPD), asthma, or bronchospasm.

[0090] The disease is a respiratory disease selected from chronic obstructive pulmonary disease (COPD), asthma and bronchospasm.

[0091] In many embodiments of formula I Y is $-NR^dR^e$.

[0092] In certain embodiments of formula I R^5 and R^6 are hydrogen.

[0093] In certain embodiments of formula I R^2 is hydrogen.

[0094] In certain embodiments of formula I X is $-CH_2-$ or -O-. Preferably X is O.

[0095] In certain embodiments of formula I D is absent.

[0096] In certain embodiments of formula I R^1 is alkyl, alkenyl or cycloalkyl. Preferably, R^1 is ethyl, cyclopropyl, isopropenyl or isopropyl. More preferably R^1 is isopropyl.

[0097] In certain embodiments formula I one of R^7 and R^8 is hydrogen, and the other is: alkyl, cycloalkyl; cycloalkylalkyl; haloalkyl; hydroxyalkyl; alkoxyalkyl; alkylsulfonylalkyl; acetyl; alkylsulfonyl; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl.

[0098] In certain embodiments of formula I one of R^7 and R^8 is hydrogen and the other is alkyl, hydroxyalkyl or haloalkyl.

[0099] In certain embodiments formula I one of R^d and R^e is hydrogen, and the other is: alkyl, cycloalkyl; cycloalkylalkyl; haloalkyl; hydroxyalkyle; alkoxyalkyl; alkylsulfonylakyl; acetyl; alkylsulfonyl; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl.

[0100] In certain embodiments of formula I one of R^d and R^e is hydrogen and the other is alkyl, hydroxyalkyl or haloalkyl.

[0101] In certain embodiments of formula I R^3 and R^4 each independently is halo, alkoxy, haloalkoxy or alkylsulfonyl.

[0102] In certain embodiments of formula I R^3 is halo, alkoxy, haloalkoxy or hydroxy. Preferably R^3 is methoxy, fluoro,

or chloro. More preferably R^3 is methoxy. In certain embodiments R^3 is hydroxy.

[0103] In certain embodiments of formula I R^4 is halo, alkoxy, alkylsulfonyl or heteroaryl. Preferably R^4 is methoxy, iodo, methanesulfonyl or heteroaryl. More preferably R^4 is methoxy, bromo, chloro or iodo. In specific embodiments R^4 may be methoxy, while in other embodiments R^4 may be iodo.

[0104] In certain embodiments of formula I R^7, R^8, R^d and R^e are hydrogen.

[0105] In certain embodiments of formula I R^4 is heteroaryl. The heteroaryl may be, in certain embodiments, tetrazolyl, pyrazolyl, oxazolyl, imidazolyl, thiazolyl, thiophenyl, triazolyl, furanyl, isoxazolyl, oxadiazolyl, benzothiophenyl, pyridinyl, or pyrrolyl. More specifically, the heteroaryl maybe tetrazol-5-yl, pyrazol-1-yl, 3-methylpyrazol-1-yl, oxazol-2-yl, ox-azol-5-yl, imidazol-2-yl, thiazol-2-yl, thiazol-4-yl, thiophen-3-yl, 5-chloro-thiophen-2-yl, 1-methyl-imidazol-2-yl, imidazol-1-yl, pyrazol-3-yl, 2-methyl-thiazol-4-yl, furan-2-yl, 3,5-dimethyl-pyrazol-1-yl, 4,5-dihydrooxazol-2-yl, isoxazol-5-yl, [1,2,4]-ox-adiazol-3-yl, benzo[b]thiophen-3-yl, oxazol-4-yl, furan-3-yl, 4-methyl-thiophen-2-yl, thiazol-5-yl, tetrazol-1-yl, [1,2,4]tria-zol-1-yl, 2-methyl-thiazol-5-yl, 1-methyl-pyrazol-4-yl, 2-thiolyl-imidazol-1-yl, pyridin-2-yl, or 2,5-dimethyl-pyrrol-1-yl.

[0106] In one preferred embodiment of formula I X is -O-, R^1 is alkyl, alkenyl, cycloalkyl, or halo, R^2 is hydrogen, R^3 is alkoxy, hydroxy or halo, R^4 is alkoxy, halo, alkenyl, or heteroaryl selected from tetrazolyl, pyrazolyl, oxazolyl, imidazolyl, thiazolyl, thiophenyl, triazolyl, furanyl, isoxazolyl, oxadiazolyl, benzothiophenyl, pyridinyl and pyrrolyl, and R^5 and R^6 are hydrogen.

[0107] In another preferred embodiment of formula I X is -O-, R^1 is alkyl, alkenyl, cycloalkyl, or halo, R^2 is hydrogen, R^3 is alkoxy, hydroxy or halo, R^4 is alkoxy, halo, or alkenyl, and R^5 and R^6 are hydrogen.

[0108] In another preferred embodiment of formula I X is -O-, R^1 is alkyl, alkenyl, cycloalkyl, or halo, R^2 is hydrogen, R^3 is alkoxy, hydroxy or halo, R^4 is heteroaryl selected from tetrazolyl, pyrazolyl, oxazolyl, imidazolyl, thiazolyl, thiophenyl, triazolyl, furanyl, isoxazolyl, oxadiazolyl, benzothiophenyl, pyridinyl and pyrrolyl, and R^5 and R^6 axe hydrogen.

[0109] In another preferred embodiment of formula I X is -O-, R^1 is alkyl, alkenyl, cycloalkyl, or halo, R^2 is hydrogen, R^3 is alkoxy, hydroxy or halo, R^4 is alkoxy, halo, or alkenyl, R^5 and R^6 are hydrogen, R^7 and R^8 are hydrogen, and one of R^a and R^b is hydrogen and the other is hydrogen, alkyl, hydroxyalkyl or haloalkyl.

[0110] In another preferred embodiment of formula I X is -O-, R^1 is alkyl, alkenyl, cycloalkyl, or halo, R^2 is hydrogen, R^3 is alkoxy, hydroxy or halo, R^4 is heteroaryl selected from tetrazolyl, pyrazolyl, oxazolyl, imidazolyl, thiazolyl, thiophenyl, triazolyl, furanyl, isoxazolyl, oxadiazolyl, benzothiophenyl, pyridinyl and pyrrolyl, R^5 and R^6 are hydrogen, R^7 and R^8 are hydrogen, and one of R^a and R^b is hydrogen and the other is hydrogen, alkyl, acetyl, hydroxyalkyl or haloalkyl.

[0111] In another preferred embodiment of formula I X is -O- or $-CH_2-$, R^1 is isopropyl, isopropenyl, cyclopropyl or iodo, R^2 is hydrogen, R^3 is alkoxy, hydroxy or halo, R^4 is alkoxy or halo, and R^5 and R^6 are hydrogen.

[0112] In another preferred embodiment of formula I X is -O- or $-CH_2-$, R^1 is isopropyl, isopropenyl, cyclopropyl or iodo, R^2 is hydrogen, R^3 is alkoxy, hydroxy or halo, R^4 is alkoxy or halo, R^5 and R^6 are hydrogen, R^7 and R^8 are hydrogen, and one of R^a and R^b is hydrogen and the other is hydrogen, alkyl, hydroxyalkyl or haloalkyl.

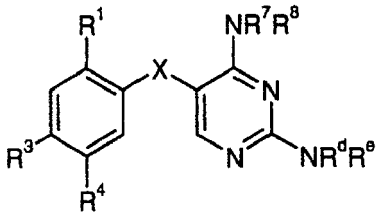
[0113] In another preferred embodiment of formula I X is -O- or $-CH_2-$, R^1 is isopropyl or iodo, R^2 is hydrogen, R^3 is methoxy, hydroxy, chloro, bromo or iodo, R^4 is methoxy, chloro, bromo or iodo, and R^5 and R^6 are hydrogen.

[0114] In another preferred embodiment of formula I X is -O- or $-CH_2-$, R^1 is isopropyl or iodo, R^2 is hydrogen, R^3 is methoxy, hydroxy, chloro, bromo or iodo, R^4 methoxy, chloro, bromo or iodo, R^5 and R^6 are hydrogen, R^7 and R^8 are hydrogen, and one of R^a and R^b is hydrogen and the other is hydrogen, alkyl, hydroxyalkyl or haloalkyl.

[0115] In another preferred embodiment of formula I X is -O- or $-CH_2-$, R^1 is isopropyl, R^2 is hydrogen, R^3 is methoxy, hydroxy, chloro, bromo or iodo, R^4 is methoxy, chloro, bromo or iodo, and R^5 and R^6 are hydrogen.

[0116] In another preferred embodiment of formula I X is -O- or $-CH_2-$, R^1 is isopropyl, R^2 is hydrogen, R^3 is methoxy, hydroxy, chloro, bromo or iodo, R^4 methoxy, chloro, bromo or iodo, R^5 and R^6 are hydrogen, R^7 and R^8 are hydrogen, and one of R^a and R^b is hydrogen and the other is hydrogen, alkyl, hydroxyalkyl or haloalkyl.

[0117] In certain embodiments the invention provides the use of a compound of formula II for the preparation of a medicament for treating a respiratory disease mediated by a $P2X_3$ or $P2X_{2/3}$ receptor antagonist



(II)

wherein:

X	is $-CH_2-$ or -O-;
R^1	is alkyl; alkenyl; cycloalkyl; cycloalkenyl; or halo;

R^3 and R^4	each independently is alkyl; alkenyl; amino; halo; amido; haloalkyl; alkoxy; hydroxy; haloalkoxy; nitro; hydroxyalkyl; alkoxyalkyl; hydroxyalkoxy; alkynylalkoxy; alkylsulfonyl; arylsulfonyl; cyano; aryl; heteroaryl; heterocyclyl; heterocyclylalkoxy; aryloxy; heteroaryloxy; aralkyloxy; heteroaralkyloxy; optionally substituted phenoxy; $-(CH_2)_m-(Z)_n-(CO)-R^f$ or $-(CH_2)_m-(Z)_n-SO_2-(NR^g)_n-R^f$ where m and n each independently is 0 or 1, Z is O or NR^g, R^f is hydrogen, alkyl, hydroxy, alkoxy, amino, hydroxyalkyl or alkoxyalkyl, and each R^g is independently hydrogen or alkyl;
one of R^7 and R^8	is hydrogen, and the other is hydrogen; alkyl; cycloalkyl; cycloalkylalkyl; haloalkyl; haloalkoxy; hydroxyalkyle; alkoxyalkyl; acetyl; alkylsulfonyl; alkylsulfonylalkyl; aminocarbonyloxyalkyl; hydroxycarbonylalkyl; hydroxyalkyloxycarbonylalkyl; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl; and
one of R^d and R^e	is hydrogen, and the other is hydrogen; alkyl; cycloalkyl; cycloalkylalkyl; haloalkyl; haloalkoxy; hydroxyalkyl; alkoxyalkyl; acetyl; alkylsulfonyl; alkylsulfonylalkyl; aminocarbonyloxyalkyl; hydroxycarbonylalkyl; hydroxyalkyloxycarbonylalkyl; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl.

[0118] In certain embodiments of formula II R^1 is alkyl, alkenyl or cycloalkyl. Preferably, R^1 is ethyl, cyclopropyl, isopropenyl or isopropyl. More preferably R^1 is isopropyl.

[0119] In certain embodiments formula II one of R^7 and R^8 is hydrogen, and the other is: alkyl, cycloalkyl; cycloalkylalkyl; haloalkyl; hydroxyalkyl; alkoxyalkyl; alkylsulfonylalkyl; acetyl; alkylsulfonyl; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl.

[0120] In certain embodiments of formula II one of R^7 and R^8 is hydrogen and the other is alkyl, hydroxyalkyl or haloalkyl.

[0121] In certain embodiments formula II one of R^d and R^e is hydrogen, and the other is: alkyl, cycloalkyl; cycloalkylalkyl; haloalkyl; hydroxyalky; alkoxyalkyl; alkylsulfonylalkyl; acetyl; alkylsulfonyl.; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl.

[0122] In certain embodiments of formula II one of R^d and R^e is hydrogen and the other is alkyl, hydroxyalkyl or haloalkyl.

[0123] In certain embodiments of formula II R^3 and R^4 each independently is halo, alkoxy, haloalkoxy or alkylsulfonyl.

[0124] In certain embodiments of formula II R^3 is halo, alkoxy, haloalkoxy or hydroxy. Preferably R^3 is methoxy, fluoro, or chloro. More preferably R^3 is methoxy. In certain embodiments R^3 is hydroxy.

[0125] In certain embodiments of formula II R^4 is halo, alkoxy, alkylsulfonyl or heteroaryl. Preferably R^4 is methoxy, iodo, methanesulfonyl or heteroaryl. More preferably R^4 is methoxy, bromo, chloro or iodo. In specific embodiments R^4 may be methoxy, while in other embodiments R^4 may be iodo.

[0126] In certain embodiments of formula II R^7, R^8, R^d and R^e are hydrogen.

[0127] In certain embodiments of formula II R^4 is heteroaryl. The heteroaryl may be, in certain embodiments, tetrazolyl, pyrazolyl, oxazolyl, imidazolyl, thiazolyl, thiophenyl, triazolyl, furanyl, isoxazolyl, oxadiazolyl, benzothiophenyl, pyridinyl, or pyrrolyl. More specifically, the heteroaryl may be tetrazol-5-yl, pyrazol-1-yl, 3-methylpyrazol-1-yl, oxazol-2-yl, oxazol-5-yl, imidazol-2-yl, thiazol-2-yl, thiazol-4-yl, thiophen-3-yl, 5-chloro-thiophen-2-yl, 1-methyl-imidazol-2-yl, imidazol-1-yl, pyrazol-3-yl, 2-methyl-thiazol-4-yl, furan-2-yl, 3,5-dimethyl-pyrazol-1-yl, 4,5-dihydrooxazol-2-yl, isoxazol-5-yl, [1,2,4]-oxadiazol-3-yl, benzo[b]thiophen-3-yl, oxazol-4-yl, furan-3-yl, 4-methyl-thiophen-2-yl, thiazol-5-yl, tetrazol-1-yl, [1,2,4]triazol-1-yl, 2-methyl-thiazol-5-yl, 1-methyl-pyrazol-4-yl, 2-thiolyl-imidazol-1-yl, pyridin-2-yl, or 2,5-dimethyl-pyrrol-1-yl.

[0128] In one preferred embodiment of formula II X is -O-, R^1 is alkyl, alkenyl, cycloalkyl, or halo, R^3 is alkoxy, hydroxy or halo, and R^4 is alkoxy, halo, alkenyl, or heteroaryl selected from tetrazolyl, pyrazolyl, oxazolyl, imidazolyl, thiazolyl, thiophenyl, triazolyl, furanyl, isoxazolyl, oxadiazolyl, benzothiophenyl, pyridinyl and pyrrolyl.

[0129] In another preferred embodiment of formula II X is -O-, R^1 is alkyl, alkenyl, cycloalkyl, or halo, R^3 is alkoxy, hydroxy or halo, and R^4 is alkoxy, halo, or alkenyl.

[0130] In another preferred embodiment of formula II X is -O-, R^1 is alkyl, alkenyl, cycloalkyl, or halo, R^3 is alkoxy, hydroxy or halo, and R^4 is heteroaryl selected from tetrazolyl, pyrazolyl, oxazolyl, imidazolyl, thiazolyl, thiophenyl, triazolyl, furanyl, isoxazolyl, oxadiazolyl, benzothiophenyl, pyridinyl and pyrrolyl.

[0131] In another preferred embodiment of formula II X is -O-, R^1 is alkyl, alkenyl, cycloalkyl, or halo, R^3 is alkoxy, hydroxy or halo, R^4 is alkoxy, halo, or alkenyl, R^7 and R^8 are hydrogen, and one of R^a and R^b is hydrogen and the other is hydrogen, alkyl, hydroxyalkyl or haloalkyl.

[0132] In another preferred embodiment of formula II X is -O-, R^1 is alkyl, alkenyl, cycloalkyl, or halo, R^3 is alkoxy, hydroxy or halo, R^4 is heteroaryl selected from tetrazolyl, pyrazolyl, oxazolyl, imidazolyl, thiazolyl, thiophenyl, triazolyl, furanyl, isoxazolyl, oxadiazolyl, benzothiophenyl, pyridinyl and pyrrolyl, R^7 and R^8 are hydrogen, and one of R^a and R^b is hydrogen and the other is hydrogen, alkyl, acetyl, hydroxyalkyl or haloalkyl.

[0133] In another preferred embodiment of formula II X is -O- or $-CH_2-$, R^1 is isopropyl, isopropenyl, cyclopropyl or iodo, R^3 is alkoxy, hydroxy or halo, and R^4 is alkoxy or halo.

[0134] In another preferred embodiment of formula II X is -O- or $-CH_2-$, R^1 is isopropyl, isopropenyl, cyclopropyl or iodo, R^3 is alkoxy, hydroxy or halo, R^4 is alkoxy or halo, R^7 and R^8 are hydrogen, and one of R^a and R^b is hydrogen and

the other is hydrogen, alkyl, hydroxyalkyl or haloalkyl.

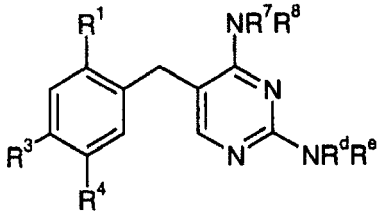
[0135] In another preferred embodiment of formula II X is -O- or -CH_2-, R^1 is isopropyl or iodo, R^3 is methoxy, hydroxy, chloro, bromo or iodo, and R^4 is methoxy, chloro, bromo or iodo.

[0136] In another preferred embodiment of formula II X is -O- or -CH_2-, R^1 is isopropyl or iodo, R^3 is methoxy, hydroxy, chloro, bromo or iodo, R^4 methoxy, chloro, bromo or iodo, R^7 and R^8 are hydrogen, and one of R^a and R^b is hydrogen and the other is hydrogen, alkyl, hydroxyalkyl or haloalkyl.

[0137] In another preferred embodiment of formula II X is -O- or -CH_2-, R^1 is isopropyl, R^3 is methoxy, hydroxy, chloro, bromo or iodo, and R^4 is methoxy, chloro, bromo or iodo.

[0138] In another preferred embodiment of formula II X is -O- or -CH_2-, R^1 is isopropyl, R^3 is methoxy, hydroxy, chloro, bromo or iodo, R^4 methoxy, chloro, bromo or iodo, R^7 and R^8 are hydrogen, and one of R^a and R^b is hydrogen and the other is hydrogen, alkyl, hydroxyalkyl or haloalkyl.

[0139] In certain embodiments the invention provides the use of a compound of formula III for the preparation of a medicament for treating a respiratory disease mediated by a $P2X_3$ or $P2X_{2/3}$ receptor antagonist

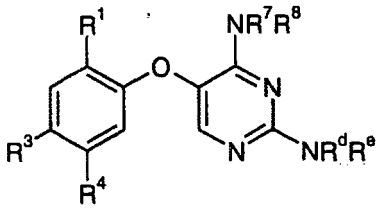


(III)

wherein:

R^1	is isopropyl; isopropenyl; cyclopropyl; or iodo;
R^3 and R^4	each independently is alkyl; alkenyl; amino; halo; amido; haloalkyl; alkoxy; hydroxy; haloalkoxy; nitro; hydroxyalkyl; alkoxyalkyl; hydroxyalkoxy; alkynylalkoxy; alkylsulfonyl; arylsulfonyl; cyano; aryl; heteroaryl; heterocyclyl; heterocyclylalkoxy; aryloxy; heteroaryloxy; aralkyloxy; heteroaralkyloxy; optionally substituted phenoxy; -$(CH_2)_m$-$(Z)_n$-(CO)-R^f or -$(CH_2)_m$-$(Z)_n$-SO_2-$(NR^g)_n$-R^f where m and n each independently is 0 or 1, Z is O or NR^g, R^f is hydrogen, alkyl, hydroxy, alkoxy, amino, hydroxyalkyl or alkoxyalkyl, and each R^g is independently hydrogen or alkyl;
one of R^7 and R^8	is hydrogen, and the other is hydrogen; alkyl; cycloalkyl; cycloalkylalkyl; haloalkyl; haloalkoxy; hydroxyalkyl; alkoxyalkyl; acetyl; alkylsulfonyl; alkylsulfonyl-alkyl; aminocarbonyloxyalkyl; hydroxycarbonylalkyl; hydroxyalkyloxycarbonylalkyl; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl; and
one of R^d and R^e	is hydrogen, and the other is hydrogen; alkyl; cycloalkyl; cycloalkylalkyl; haloalkyl; haloalkoxy; hydroxyalkyl; alkoxyalkyl; acetyl; alkylsulfonyl; alkylsulfonylalkyl; aminocarbonyloxyalkyl; hydroxycarbonylalkyl; hydroxyalkyloxycarbonylalkyl;
	aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl.

[0140] In other embodiments the invention provides the use of a compound of formula IV for the preparation of a medicament for treating a respiratory disease mediated by a $P2X_3$ or $P2X_{2/3}$ receptor antagonist



(IV)

wherein:

R^1	is alkyl; alkenyl; cycloalkyl; cycloalkenyl or halo;
R^3 and R^4	each independently is alkyl; alkenyl; amino; halo; amido; haloalkyl; alkoxy; hydroxy; haloalkoxy; nitro; hydroxyalkyl; alkoxyalkyl; hydroxyalkoxy; alkynylalkoxy; alkylsulfonyl; arylsulfonyl; cyano; aryl;

heteroaryl; heterocyclyl; heterocyclylalkoxy; aryloxy; heteroaryloxy; aralkyloxy; heteroaralkyloxy; optionally substituted phenoxy; $-(CH_2)_m-(Z)_n-(CO)-R^f$ or $-(CH_2)_m-(Z)_n-SO_2-(NR^g)_n-R^f$ where m and n each independently is 0 or 1, Z is O or NR^g, R^f is hydrogen, alkyl, hydroxy, alkoxy, amino, hydroxyalkyl or alkoxyalkyl, and each R^g is independently hydrogen or alkyl;

one of R^7 and R^8 is hydrogen, and the other is hydrogen; alkyl; cycloalkyl; cycloalkylalkyl; haloalkyl; haloalkoxy; hydroxyalkyl; alkoxyalkyl; acetyl; alkylsulfonyl; alkylsulfonyl-alkyl; aminocarbonyloxyalkyl; hydroxycarbonylalkyl; hydroxyalkyloxycarbonylalkyl; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl; and

one of R^d and R^e is hydrogen, and the other is hydrogen; alkyl; cycloalkyl; cycloalkylalkyl; haloalkyl; haloalkoxy, hydroxyalkyl; alkoxyalkyl; acetyl; alkylsulfonyl; alkylsulfonyl-alkyl; aminocarbonyloxyalkyl; hydroxycarbonylalkyl; hydroxyalkyloxycarbonylalkyl; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl.

[0141] In certain embodiments of formula IV R^1 is alkyl, alkenyl, cycloalkyl or halo. Preferably, R^1 is ethyl, cyclopropyl, isopropenyl, isopropyl or iodo. More preferably R^1 is isopropyl or iodo.

[0142] In certain embodiments formula III or formula IV one of R^7 and R^8 is hydrogen, and the other is: alkyl, cycloalkyl; cycloalkylalkyl; haloalkyl; hydroxyalkyl; alkoxyalkyl; alkyl-sulfonylalkyl; acetyl; alkylsulfonyl; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl.

[0143] In certain embodiments of formula III or formula IV one of R^7 and R^8 is hydrogen and the other is alkyl, hydroxyalkyl or haloalkyl.

[0144] In certain embodiments formula III or formula IV one of R^d and R^e is hydrogen, and the other is: alkyl, cycloalkyl; cycloalkylalkyl; haloalkyl; hydroxyalky; alkoxyalkyl; alkyl-sulfonylalkyl; acetyl; alkylsulfonyl; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl.

[0145] In certain embodiments of formula III or formula IV one of R^d and R^e is hydrogen and the other is alkyl, hydroxyalkyl or haloalkyl.

[0146] In certain embodiments of formula III or formula IV R^3 and R^4 each independently is halo, alkoxy, haloalkoxy or alkylsulfonyl.

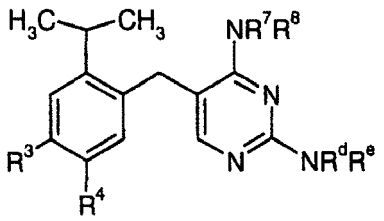
[0147] In certain embodiments of formula III or formula IV R^3 is halo, alkoxy, haloalkoxy or hydroxy. Preferably R^3 is methoxy, fluoro, or chloro. More preferably R^3 is methoxy. In certain embodiments R^3 is hydroxy.

[0148] In certain embodiments of formula III or formula IV R^4 is halo, alkoxy, alkylsulfonyl or heteroaryl. Preferably R^4 is methoxy, iodo, methanesulfonyl or heteroaryl. More preferably R^4 is methoxy, bromo, chloro or iodo. In specific embodiments R^4 may be meth-oxy, while in other embodiments R^4 may be iodo.

[0149] In certain embodiments of formula III or formula IV R^7, R^8, R^d and R^e are hydrogen.

[0150] In certain embodiments of formula III or formula IV R^4 is heteroaryl. The heteroaryl may be, in certain embodiments, tetrazolyl, pyrazolyl, oxazolyl, imidazolyl, thiazolyl, thiophenyl, triazolyl, furanyl, isoxazolyl, oxadiazolyl, benzothiophenyl, pyridinyl, or pyrrolyl. More specifically, the heteroaryl may be tetrazol-5-yl, pyrazol-1-yl, 3-methylpyrazol-1-yl, oxazol-2-yl, oxazol-5-yl, imidazol-2-yl, thiazol-2-yl, thiazol-4-yl, thiophen-3-yl, 5-chloro-thiophen-2-yl, 1-methyl-imidazol-2-yl, imidazol-1-yl, pyrazol-3-yl, 2-methyl-thiazol-4-yl, furan-2-yl, 3,5-dimethyl-pyrazol-1-yl, 4,5-dihydrooxazol-2-yl, isoxazol-5-yl, [1,2,4]-oxa-diazol-3-yl, benzo[b]thiophen-3-yl, oxazol-4-yl, furan-3-yl, 4-methyl-thiophen-2-yl, thiazol-5-yl, tetrazol-1-yl, [1,2,4]triazol-1-yl, 2-methyl-thiazol-5-yl, 1-methyl-pyrazol-4-yl, 2-thiolyl-imidazol-1-yl, pyridin-2-yl, or 2,5-dimethyl-pyrrol-1-yl.

[0151] In still other embodiments the invention provides the use of a compound of formula V for the preparation of a medicament for treating a respiratory disease mediated by a $P2X_3$ or $P2X_{2/3}$ receptor antagonist



(V)

wherein:

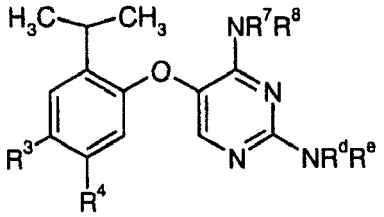
R^3 and R^4 each independently is alkyl; alkenyl; amino; halo; amido; haloalkyl; alkoxy; hydroxy; haloalkoxy; nitro; hydroxyalkyl; alkoxyalkyl; hydroxyalkoxy; alkynylalkoxy; alkylsulfonyl; arylsulfonyl; cyano; aryl; heteroaryl; heterocyclyl; heterocyclylalkoxy; aryloxy; heteroaryloxy; aralkyloxy; heteroaralkyloxy; optionally substituted phenoxy; $-(CH_2)_m-(Z)_n-(CO)-R^f$ or $-(CH_2)_m-(Z)_n\ SO_2-(NR^g)_n-R^f$ where m and

n each independently is 0 or 1, Z is O or NR^9, R^f is hydrogen, alkyl, hydroxy, alkoxy, amino, hydroxyalkyl or alkoxyalkyl, and each R^8 is independently hydrogen or alkyl;

one of R^7 and R^8 is hydrogen, and the other is hydrogen; alkyl; cycloalkyl; cycloalkylalkyl; haloalkyl; haloalkoxy; hydroxyalkyl; alkoxyalkyl; acetyl; alkylsulfonyl; alkylsulfonyl-alkyl; aminocarbonyloxyalkyl; hydroxycarbonylalkyl; hydroxyalkyloxycarbonylalkyl; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl; and

one of R^d and R^e is hydrogen, and the other is hydrogen; alkyl; cycloalkyl; cycloalkylalkyl; haloalkyl; haloalkoxy; hydroxyalkyl; alkoxyalkyl; acetyl; alkylsulfonyl; alkylsulfonyl-alkyl; aminocarbonyloxyalkyl; hydroxycarbonylalkyl; hydroxyalkyloxycarbonylalkyl; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl.

[0152] In other embodiments the subject uses may utilize compounds of the formula VI



(VI)

wherein:

R^3 and R^4 each independently is alkyl; alkenyl; amino; halo; amido; haloalkyl; alkoxy; hydroxy; haloalkoxy; nitro; hydroxyalkyl; alkoxyalkyl; hydroxyalkoxy; alkynylalkoxy; alkylsulfonyl; arylsulfonyl; cyano; aryl; heteroaryl; heterocyclyl; heterocyclylalkoxy; aryloxy; heteroaryloxy; aralkyloxy; heteroaralkyloxy; optionally substituted phenoxy; $-(CH_2)_m-(Z)_n-(CO)-R^f$ or $-(CH_2)_m-(Z)_n-SO_2-(NR^g)_n-R^f$ where m and n each independently is 0 or 1, Z is O or NR^g, R^f is hydrogen, alkyl, hydroxy, alkoxy, amino, hydroxyalkyl or alkoxyalkyl, and each R^g is independently hydrogen or alkyl;

one of R^7 and R^8 is hydrogen, and the other is: hydrogen; alkyl; cycloalkyl; cycloalkylalkyl; haloalkyl; haloalkoxy; hydroxyalkyl; alkoxyalkyl; acetyl; alkylsulfonyl; alkylsulfonylalkyl; aminocarbonyloxyalkyl; hydroxycarbonylalkyl; hydroxyalkyloxycarbonylalkyl; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl; and

one of R^d and R^e is hydrogen, and the other is hydrogen; alkyl; cycloalkyl; cycloalkylalkyl; haloalkyl; haloalkoxy; hydroxyalkyl; alkoxyalkyl; acetyl; alkylsulfonyl; alkylsulfonylalkyl; aminocarbonyloxyalkyl; hydroxycarbonylalkyl; hydroxyalkyloxycarbonylakyl; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl.

[0153] In certain embodiments formula (V) or formula (VI), one of R^7 and R^8 is hydrogen, and the other is alkyl, cycloalkyl; cycloalkylalkyl; haloalkyl; hydroxyalkyl; alkoxyalkyl; alkylsulf onylalkyl; acetyl; alkylsulfonyl; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroarylsulfonyl; heterocyclyl; or heterorcyclylalkyl.

[0154] In certain embodiments of formula (V) or formula (VI), one of R^7 and R^8 is hydrogen and the other is alkyl, hydroxyalkyl or haloalkyl.

[0155] In certain embodiments formula (V) or formula (VI), one of R^d and R^e is hydrogen, and the other is: alkyl, cycloalkyl; cycloalkylalkyl; haloalkyl; hydroxyalkyl; alkoxyalkyl; alkylsulfonylalkyl; acetyl; alkylsulfonyl; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl.

[0156] In certain embodiments of formula (V) or formula (VI), one of R^d and R^e is hydrogen and the other is alkyl, hydroxyalkyl or haloalkyl.

[0157] In certain embodiments of formula (V) or formula (VI), R^3 and R^4 each independently is halo, alkoxy, haloalkoxy or alkylsulfonyl.

[0158] In certain embodiments of formula (V) or formula (VI), R^3 is halo, alkoxy, haloalkoxy or hydroxy. Preferably R^3 is methoxy, fluoro, or chloro. More preferably R^3 is methoxy. In certain embodiments R^3 is hydroxy.

[0159] In certain embodiments of formula (V) or formula (VI), R^4 is halo, alkoxy, alkylsulfonyl or heteroaryl. Preferably R^4 is methoxy, iodo, methanesulfonyl or heteroaryl. More preferably R^4 is methoxy, bromo, chloro or iodo. In specific embodiments R^4 may be methoxy, while in other embodimets R^4 may be iodo.

[0160] In certain embodiments of formula (V) or formula (VI), R^7, R^8, R^d and R^e are hydrogen.

[0161] In certain embodiments of formula (V) or formula (VI), R^4 is heteroaryl. The heteroaryl may be, in certain embodiments, tetrazolyl, pyrazolyl, oxazolyl, imidazolyl, thiazolyl, thiophenyl, triazolyl, furanyl, isoxazolyl, oxadiazolyl,

benzothiophenyl, pyridinyl, or pyrrolyl. More specifically, the heteroaryl may be tetrazol-5-yl, pyrazol-1-yl, 3-methylpyrazol-1-yl, oxazol-2-yl, oxazol-5-yl, imidazol-2-yl, thiazol-2-yl, thiazol-4-yl, thiophen-3-yl, 5-chlorothiophen-2-yl, 1-methyl-imidazol-2-yl, imidazol-1-yl, pyrazol-3-yl, 2-methyl-thiazol-4-yl, furan-2-yl, 3,5-dimethyl-pyrazol-1-yl, 4,5-dihydrooxazol-2-yl, isoxazol-5-yl, [1,2,4]-oxadiazol-3-yl, benzo[b]thiophen-3-yl, oxazol-4-yl, furan-3-yl, 4-methyl-thiophen-2-yl, thiazol-5-yl, tetrazol-1-yl, [1,2,4]triazol-1-yl, 2-methyl-thiazol-5-yl, 1-methyl-pyrazol-4-yl, 2-thiolyl-imidazol-1-yl, pyridin-2-yl, or 2,5-dimethyl-pyrrol-1-yl.

[0162] In embodiments of the invention where any of R^7, R^8, R^d or R^e are heterocyclyl or a group that includes a heterocyclyl moiety, such heterocyclyl or heterocyclyl moiety may be piperidinyl, piperazinyl, tetrahydrofuranyl, tetrahydrothiopyranyl, or 1,1-dioxotetrahydro-thiopyranyl. More preferably, such heterocyclyl or heterocyclyl moiety may be piperidin-4-yl, 1-methyl-piperidine-4-yl, 1-methanesulfonyl-piperidin-4-yl, tetrahydropyran-4-yl, tetrahydrothiopyran-4-yl, or 1,1-dioxotrahydrothiopyran-4-yl.

[0163] Where any of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^c, R^d, R^e, R^f, R^g, or R^h is alkyl or contains an alkyl moiety, such alkyl is preferably lower alkyl, i.e. C_1-C_6alkyl, and more preferably C_1-C_4alkyl.

[0164] Representative compounds in accordance with the uses of the invention are shown in Table 1.

TABLE 1

#	Name
1	N^2-Isopropyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-N^4-methyl-pyrimidine-2,4-diamine
2	5-(2-Isopropyl-4,5-dimethoxy-phenoxy)-pyrimidine-2,4-diamine
3	5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N^4-isoxazol-5-ylmethyl-pyrimidine-2,4-diamine
4	N^2-Isopropyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine
5	5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N^4-(2-methoxy-ben2yl)-pyrimidine-2,4-diamine
6	5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N^2-(2,2,2-trifluoro-ethyl)-pyrimidine-2,4-diamine
7	3-[2-Amino-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidin-4-ylaminol-propane-1,2-diol
8	N-[4-Amino-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidin-2-yl]-acetamide
9	5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N^4-(4-methoxy-benzyl)-pyrimidine-2,4-diamine
10	5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N^4-phenyl-pyrimidine-2,4-diamine
11	5-(5-Chloro-2-isopropyl-4-methoxy-benzyl)-N^2-phenethyl-pyrimidine-2,4-diamine
12	5-(5-Chloro-2-isopropyl-4-methoxy-benzyl)-pyrimidine-2,4-diamine
13	N^4-Isobutyl-N^2-isopropyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine
14	5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N^2-phenyl-pyrimidine-2,4-diamine
15	N^2,N^4-Diisopropyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine
16	5-(5-Chloro-2-isopropyl-4-methoxy-benzyl)-N^2-isopropyl-pyrimidine-2,4-diamine
17	2-[2-Amino-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidin-4-ylamino]-ethanol
18	5-(2-Isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine
19	5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N^4-[2-(4-methoxy-phenyl)-ethyl]-pyri-midine-2,4-diamine
20	N^2-Benzyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine
21	5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N^4-(4-methanesulfonyl-cyclohexyl)-pyrimidine-2,4-diamine
22	N^2-Cyclopropyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine
23	N^4-Isopropyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine
24	N^2-Ethyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine
25	5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N^4-[2-(3-methoxy-phenyl)-ethyl]-pyrimidine-2,4-diamine
26	2-[4-Amino-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidin-2-ylamino]-ethanol
27	5-(2-sec-Butyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine
28	N^2-tert-Butyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine

(continued)

#	Name
29	N^2-Isobutyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine
30	5-(5-Chloro-2-isopropyl-4-methoxy-benzyl)-N^2-cyclopropyl-pyrimidine-2,4-diamine
31	5-(2-Isopropyl-4-methoxy-5-phenoxy-benzyl)-pyrimidine-2,4-diamine
32	N^4-Isobutyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine
33	N^4-Ethyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine
34	N^4-Benzyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine
35	5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N^4-(2,2,2-trifluoro-ethyl)-pyrimidine-2,4-diamine
36	5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N^2-(4-methoxy-phenyl)-pyrimidine-2,4-diamine
37	N^2-Isopropyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-N^4-phenyl-pyrimidine-2,4-diamine
38	N^4-Ethyl-N^2-isopropyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine
39	5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N^4-(1-methyl-piperidin-4-yl)-pyrimidine-2,4-diamine
40	5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N^2-(2-methoxy-phenyl)-pyrimidine-2,4-diamine
41	5-(4,5-Dichloro-2-isopropyl-benzyl)-pyrimidine-2,4-diamine
42	5-(5-Chloro-2-isopropyl-4-methoxy-benzyl)-N^2-ethyl-pyrimidine-2,4-diamine
43	5-(2-Isopropyl-4-methoxy-5-methyl-benzyl)-pyrimidine-2,4-diamine
44	5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N^2-pyrimidin-2-yl-pyrimidine-2,4-diamine
45	5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N^2-(2-methoxy-ethyl)-pyrimidine-2,4-diamine
46	N^4-Benzyl-N^2-isopropyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine
47	1-(4-{2-[4-Amino-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidin-2-ylamino]-propyl}-piperazin-1-yl)-ethanone
48	5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N^4-(tetrahydro-pyran-4-yl)-pyrimidine-2,4-diamine
49	N^4-Cyclopropyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine
50	5-(5-Ethoxy-2-isopropyl-4-methoxy-benzyl)-pyrimidine-2,4-diamine
51	N^2-(2,4-Dimethoxy-phenyl)-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine
52	N^2-Cyclobutyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine
53	N^2-(2-Chloro-phenyl)-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine
54	5-(4-Chloro-2-isopropyl-5-methoxy-benzyl)-pyrimidine-2,4-diamine
55	5-(5-Bromo-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine
56	5-(5-Chloro-2-isopropyl-4-methoxy-benzyl)-N^2-(3-methoxy-phenyl)-pyrimidine-2,4-diamine
57	5-(5-Chloro-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine
58	5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N^2,N^4-diphenyl-pyrimidine-2,4-diamine
60	5-(5-Chloro-2-isopropyl-4-methoxy-benzyl)-N^2-isobutyl-pyrimidine-2,4-diamine
62	5-(5-Chloro-2-isopropyl-4-methoxy-benzyl)-N^2-phenyl-pyrimidine-2,4-diamine
63	5-(2-Isopropyl-4-methoxy-5-methyl-phenoxy)-pyrimidine-2,4-diamine
64	5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N^2-methyl-pyrimidine-2,4-diamine
65	5-(2-Isopropyl-5-methyl-phenoxy)-pyrimidine-2,4-diamine
66	5-(5-Chloro-2-isopropyl-4-methoxy-benzyl)-N^2-methyl-pyrimidine-2,4-diamine
67	N^2-Benzyl-5-(5-chloro-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine

(continued)

#	Name
68	2-[2-Isopropylamino-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidin-4-yl-amino]-ethanol
69	5-(5-Chloro-2-isopropyl-4-methoxy-phenoxy)-N^2-(tetrahydro-pyran-4-yl)-pyrimidine-2,4-diamine
70	N^2-(4-Chloro-phenyl)-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine
71	5-(2-Isopropyl-phenoxy)-pyrimidine-2,4-diamine
72	5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N^4-methyl-pyrimidine-2,4-diamine
73	5-(5-Chloro-2-isopropyl-4-methoxy-phenoxy)-N^2-isopropyl-pyrimidine-2,4-diamine
74	5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N^4-(2-methoxy-ethyl)-pyrimidine-2,4-diamine
75	N^2-Isopropyl-5-(2-isopropyl-4,5-dimethoxy-phenoxy)-pyrimidine-2,4-diamine
76	5-(2-Ethyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine
77	5-(2-Isopropyl-4,5-dimethoxy-phenoxy)-N^2-phenyl-pyrimidine-2,4-diamine
78	N^2-tert-Butyl-5-(5-chloro-2-isopropyl-4-methoxy-benzyl)-pyrimidine-2,4-diamine
79	N^2-Benzyl-5-(2-isopropyl-4,5-dimethoxy-phenoxy)-pyrimidine-2,4-diamine
80	5-(2-Cyclopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine
81	N-[4-Amino-5-(2-isopropyl-4,5-dimethoxy-phenoxy)-pyrimidin-2-yl]-acetamide
82	N^2-Benzyl-5-(5-chloro-2-isopropyl-4-methoxy-benzyl)-pyrimidine-2,4-diamine
83	5-(2-Isopropyl-4,5-dimethoxy-phenoxy)-N^2-(2,2,2-trifluoro-ethyl)-pyrimidine-2,4-diamine
84	5-(2-Isopropyl-4,5-dimethoxy-phenoxy)-N^2-(2-methoxy-ethyl)-pyrimidine-2,4-diamine
85	5-(2-Isopropyl-4,5-dimethoxy-benzyl)-pyrimidin-4-ylamine
86	3-[4-Amino-5-(5-chloro-2-isopropyl-4-methoxy-phenoxy)-pyrimidin-2-ylamino]-pentane-1,5-diol
87	5-(5-Chloro-2-isopropyl-4-methoxy-benzyl)-N^2-cyclohexyl-pyrimidine-2,4-di-amine
88	2-[4-Amino-5-(5-chloro-2-isopropyl-4-methoxy-phenoxy)-pyrimidin-2-ylamino]-butan-1-ol
89	1-[5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-ethanone
90	5-[5-(1H-Imidazol-2-yl)-2-isopropyl-4-methoxy-phenoxy]-pyrimidine-2,4-diamine
91	(2,4-Diamino-pyrimidin-5-yl)-(2-isopropyl-4,5-dimethoxy-phenyl)-methanol
92	5-[5-Chloro-2-(2-fluoro-1-methyl-ethyl)-4-methoxy-phenoxy]-pyrimidine-2,4-diamine
93	(5-Chloro-2-isopropyl-4-methoxy-phenyl)-(2,4-diamino-pyrimidin-5-yl)-methanol
94	2-[4-Amino-5-(5-chloro-2-ethyl-4-methoxy-phenoxy)-pyrimidin-2-ylaminol-butan-1-ol
94	5-(5-Chloro-2-isopropyl-4-methoxy-phenoxy)-N^2-(3-ethanesulfonyl-1-methyl-propyl)-pyrimidine-2,4-diamine
95	5-(5-Bromo-2-ethyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine
96	5-(5-Chloro-2-ethyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine
97	5-(5-Chloro-2-cyclopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine
98	5-(2-Ethyl-5-methanesulfonyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine
99	5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-benzamide
100	5-(4,5-Dimethoxy-2-vinyl-phenoxy)-pyrimidine-2,4-diamine
101	5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-benzoic acid
102	5-(2-Cyclopropyl-4,5-dimethoxy-phenoxy)-pyrimidine-2,4-diamine
103	5-[2-Isopropyl-4-methoxy-5-(1H-tetrazol-5-yl)-phenoxy]-pyrimidine-2,4-diamine

(continued)

#	Name
104	5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-benzonitrile
105	4-[4-Amino-5-(5-chloro-2-isopropyl-4-methoxy-phenoxy)-pyrimidin-2-ylamino]-piperidine-1-carboxylic acid ethyl ester
106	[5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-urea
107	5-(5-Chloro-2-isopropyl-4-methoxy-phenoxy)-N^2-(1-cyclopropyl-ethyl)-pyrimidine-2,4-diamine
108	5-(5-Chloro-4-difluoromethoxy-2-isopropyl-phenoxy)-pyrimidine-2,4-diamine
109	5-(5-Amino-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine
110	N^4-Isopropyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-N^2-methyl-pyrimidine-2,4-diamine
111	N-[5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-acetamide
112	5-(2-Isopropyl-4-methoxy-5-tetrazol-1-yl-phenoxy)-pyrimidine-2,4-diamine
113	5-(2-Isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine
114	5-(2-Isopropyl-5-methanesulfonyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine
	5-(2-Isopropyl-4-methoxy-5-methyl-phenoxy)-N^2-phenyl-pyrimidine-2,4-diamine
115	5-(5-Chloro-2-isopropyl-4-methoxy-phenoxy)-N^2-(1,1-dioxo-hexahydro-λ^6-thiopyran-4-yl)-pyrimidine-2,4-diamine
116	Methyl-carbamic acid 2-[4-amino-5-(5-chloro-2-isopropyl-4-methoxy-phenoxy)-pyrimidin-2-ylamino]-propyl ester
117	5-(4-Chloro-2-isopropyl-5-methyl-phenoxy)-pyrimidine-2,4-diamine
118	5-(2-Isopropyl-4,5-dimethoxy-phenoxy)-6-methyl-pyrimidine-2,4-diamine
	1-(4-{2-[4-Amino-5-(5-chloro-2-isopropyl-4-methoxy-phenoxy)-pyrimidin-2-yl-amino]-propyl}-piperazin-1-yl)-ethanone
119	5-(5-Chloro-2-isopropyl-4-methoxy-phenoxy)-N^2-(1-methanesulfonyl-piperidin-4-yl)-pyrimidine-2,4-diamine
120	2-[4-Amino-5-(5-chloro-2-isopropyl-4-methoxy-phenoxy)-pyrimidin-2-ylamino]-(R)-propan-1-ol
121	5-(2-Ethyl-4,5-dimethoxy-phenoxy)-pyrimidine-2,4-diamin
122	5-(2-Isopropyl-5-methanesulfonyl-4-methoxy-phenoxy)-*N*^{2}-(tetrahydro-thiopyran-4-yl)-pyrimidine-2,4-diamine
123	5-(5-Chloro-2-isopropyl-4-methoxy-phenoxy)-*N*^{2}-(1,1-dioxo-hexahydro-1λ^6-thiopyran-4-yl)-pyrimidine-2,4-diamine 1-[5-(2,4-Diamino-pyrimidin-5-yloxy)-2-hydroxy-4-isopropyl-phenyl]-ethanone
124	5-(5-Iodo-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine
125	5-(2-Iodo-4,5-dimethoxy-phenoxy)-pyrimidine-2,4-diamine
126	5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-benzenesulfonamide
127	4-(2,4-Diamino-pyrimidin-5-yloxy)-2-iodo-5-isopropyl-phenol
128	5-(2,5-Diiodo-4-methoxy-phenoxy)-pyrimidine-2,4-diamine
129	3-[4-Amino-5-(5-bromo-2-isopropyl-4-methoxy-phenoxy)-pyrimidin-2-ylaminol - pentane-1,5-diol
130	5-(2-Ethyl-5-iodo-4-methoxy-phenoxy)-pyrimidine-2,4-diamine
131	5-(5-Iodo-2-isopropyl-4-methoxy-phenoxy)-l-oxy-pyrimidine-2,4-diamine
132	5-(2-Isopropyl-4methoxy-5-vinyl-phenoxy)-pyrimidine-2,4-diamine
133	5-(5-Iodo-2-isopropenyl-4-methoxy-phenoxy)-pyrimidine-2,4-diarnine

(continued)

#	Name
134	5-(2-Isopropyl-4-methoxy-5-pyrazol-1-yl-phenoxy)-pyrimidine-2,4-diamine
135	5-(5-Iodo-2-isopropyl-phenoxy)-pyrimidine-2,4-diamine
136	5- [2-Isopropyl-4-methoxy-5-(3-methyl-pyrazol-1-yl)-phenoxy] -pyrimidine-2,4-diamine
137	4-(2,4-Diamino-pyrimidin-5-ylmethyl)-2-iodo-5-isopropyl-phenol
138	5-(2-Isopropyl-4-methoxy-5-oxazol-2-yl-phenoxy)-pyrimidine-2,4-diamine
139	(S)-2-[4-Amino-5-(5-bromo-2-isopropyl-4-methoxy-phenoxy)-pyrimidin-2-yl-amino]-butan-1-ol
140	5-(4-Iodo-2-isopropyl-5-methoxy-phenoxy)-pyrimidine-2,4-diamine
141	5-(4-Bromo-2-isopropyl-5-methoxy-phenoxy)-pyrimidine-2,4-diamine
142	5-(2-Ethyl-5-iodo-phenoxy)-pyrimidine-2,4-diamine
143	5-(2-Isopropyl-4-methoxy-5-trifluoromethyl-phenoxy)-pyrimidine-2,4-diamine
144	5-(2-Isopropyl-4-methoxy-5-thiazol-4-yl-phenoxy)-pyrimidine-2,4-diamine
145	[4-(2,4-Diamino-pyrimidin-5-yloxy)-2-iodo-5-isopropyl-phenoxyl-acetonitrile
146	5-(2-Isopropyl-4-methoxy-5-thiophen-3-yl-phenoxy)-pyrimidine-2,4-diamine
147	(R)-2-[4-Amino-5-(2-isopropyl-5-methanesulfonyl-4-methoxy-phenoxy)-pyrimi-din-2-ylamino]-butan-1-ol
149	(S)-2-[4-Amino-5-(5-chloro-2-isopropyl-4-methoxy-phenoxy)-pyrimidin-2-yl-amino]-propionic acid
150	5-[5-(4,5-Dihydro-oxazol-2-yl)-2-isopropyl-4-methoxy-phenoxy]-pyrimidine-2,4-diamine
152	5-(2-Isopropyl-5-methanesulfonyl-4-methoxy-phenoxy)-N^2-(2,2,2-trifluoro-ethyl)-pyrimidine-2,4-diamine
153	5-(5-Iodo-2-isopropyl-4-methoxy-benzyl)-pyrimidine-2,4-diamine
154	5-(5-Bromo-2-cyclopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine
155	(S)-2-[4-Amino-5-(5-chloro-2-isopropyl-4-methoxy-phenoxy)-pyrimidin-2-yl-amino]-propionic acid 3-hydroxy-2-hydroxymethyl-2-methyl-propyl ester
156	5-[S-(5-Chloro-thiophen-2-yl)-2-isopropyl-4-methoxy-phenoxy]-pyrimidine-2,4-diamine
157	5-(2-Ethyl-4-methoxy-5-trifluoromethyl-phenoxy)-pyrimidine-2,4-diamine
158	5-[2-Isopropyl-4-methoxy-5-(1-methyl-1H-imidazol-2-yl)-phenoxy]-pyrimidine-2,4-diamine
159	5-[2-Isopropyl-4-methoxy-5-(2H-pyrazol-3-yl)-phenoxy]-pyrimidine-2,4-diamine
160	5-(5-Imidazol-l-yl-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine
161	N^2-Isopropyl-5-(2-isopropyl-5-methanesulfonyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine
162	2-[4-(2,4-Diamino-pyrimidin-5-yloxy)-2-iodo-5-isopropyl-phenoxy]-ethanol
163	5-(2-Isopropyl-5-methanesulfonyl-4-methoxy-phenoxy)-N^2-phenyl-pyrimidine-2,4-diamine
164	5-(4-Amino-2-ethylamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-benzamide
166	2-[4-Amino-5-(2-isopropyl-5-methanesulfonyl-4-methoxy-phenoxy)-pyrimidin-2-ylamino]-ethanol
167	5-[2-Isopropyl-4-methoxy-5-(2-methyl-thiazol-4-yl)-phenoxy]-pyrimidine-2,4-diamine
168	5-[5-Iodo-2-isopropyl-4-(pyrazin-2-ylmethoxy)-phenoxy]-pyrimidine-2,4-diamine
169	5-(2-Isopropyl-5-methanesulfonyl-4-methoxy-phenoxy)-N^2-(2-methoxy-ethyl)-pyrimidine-2,4-diamine
170	5-(2-Isopropyl-4-methoxy-5-[1,2,3]triazol-1-yl-phenoxy)-pyrimidine-2,4-diamine
171	5-(5-Furan-2-yl-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine
172	1-[5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-3-ethyl-urea

(continued)

#	Name
173	N^2-Cyclopropyl-5-(2-isopropyl-5-methanesulfonyl-4-methoxy-phenoxy)-pyrimi-dine-2,4-diamine
174	2-[4-(2,4-Diamino-pyrimidin-5-yloxy)-2-iodo-5-isopropyl-phenoxy]-acetamide
175	5-[5-(3,5-Dimethyl-pyrazol-1-yl)-2-isopropyl-4-methoxy-phenoxy]-pyrimidine-2,4-diamine
176	N^2-Benzyl-5-(2-isopropyl-5-methanesulfonyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine
177	N^2-Ethyl-5-(2-isopropyl-5-methanesulfonyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine
178	5-(2-Isopropyl-5-methanesulfonyl-4-methoxy-phenoxy)-N^2-(1-methanesulfonyl-piperidin-4-yl)-pyrimidine-2,4-diamine
179	1-[4-Amino-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidin-2-ylamino]-2-methyl-propan-2-ol
180	N^2-Isobutyl-5-(2-isopropyl-5-methanesulfonyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine
181	5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-N-methyl-benzamide
183	5-(2-Isopropyl-5-isoxazol-5-yl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine
185	N^4-(4-Fluoro-phenyl)-5-(2-isopropyl-5-methanesulfonyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine
186	5-(5-Chloro-2-isopropyl-4-methoxy-benzyl)-N^2-(2,2,2-trifluoro-ethyl)-pyrimidine-2,4-diamine
187	5-(2-Isopropyl-4-methoxy-5-[1,2,4]oxadiazol-3-yl-phenoxy)-pyrimidine-2,4-di-amine
188	5-(2-Isopropyl-5-methanesulfonyl-4-methoxy-phenoxy)-N^2-(tetrahydro-pyran-4-yl)-pyrimidine-2,4-diamine
189	1-[5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-ethanol
191	5-(2,5-Diisopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine
192	5-(5-Benzo[b]thiophen-3-yl-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine
193	5-[2-Isopropyl-4-methoxy-5-(1-methoxy-ethyl)-phenoxy]-pyrimidine-2,4-diamine
194	5-(2-Isopropyl-4-methoxy-5-oxazol-4-yl-phenoxy)-pyrimidine-2,4-diamine
196	5-[5-(5-Chloro-thiophen-2-yl)-2-isopropyl-4-methoxy-benzyl]-pyrimidine-2,4-diamine
197	5-(2-Isopropyl-4-methoxy-5-thiazol-2-yl-phenoxy)-pyrimidine-2,4-diamine
198	5-(2-Isopropyl-4-methoxy-5-thiophen-3-yl-benzyl)-pyrimidine-2,4-diamine
199	5-(5-Furan-3-yl-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine
200	5-(2-Isopropyl-5-methoxy-phenoxy)-pyrimidine-2,4-diamine
201	5-[5-Iodo-2-isopropyl-4-(pyrimidin-2-ylmethoxy)-phenoxy]-pyrimidine-2,4-diamine
202	5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N^2-pyridin-2-yl-pyrimidine-2,4-diamine
204	5-(2-Isopropyl-4-methoxy-5-thiophen-2-yl-phenoxy)-pyrimidine-2,4-diamine
205	1-[5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-3-phenyl-urea
206	5-(5-Chloro-2-isopropyl-4-methoxy-benzyl)-*N*^{2}-(2-methoxy-ethyl)-pyrimidine-2,4-diamine
207	5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-N-methyl-benzene-sulfonamide
208	5-(2-Isopropyl-5-methanesulfonyl-4-methoxy-phenoxy)-N^2-methyl-pyrimidine-2,4-diamine
209	5-[5-Iodo-2-isopropyl-4-(pyridin-2-ylmethoxy)-phenoxy]-pyrimidine-2,4-diamine
210	*N*-[2-Acetylamino-5-(2-isopropyl-4-methoxy-5-methyl-benzyl)-pyrimidin-4-yl)-acetamide
211	5-[4-(2-Fluoro-benzyloxy)-5-iodo-2-isopropyl-phenoxy]-pyrimidine-2,4-diamine
212	5-(2-Isopropyl-4-methoxy-5-pyrrol-1-yl-phenoxy)-pyrimidine-2,4-diamine

(continued)

#	Name
213	5-(2-Isopropyl-4-methoxy-5-trifluoromethoxy-phenoxy)-pyrimidine-2,4-diamine
214	2-[4-(2,4-Diamino-pyrimidin-5-ylmethyl)-2-iodo-5-isopropyl-phenoxy]-ethanol
216	5-[5-(4,5-Dihydro-oxazol-2-yl)-2-isopropyl-4-methoxy-benzyl]-pyrimidine-2,4-diamine
217	5'-(2,4-Diamino-pyrimidin-5-yloxy)-4'-isopropyl-2'-methoxy-biphenyl-3-carbonitrile
218	5-[2-Isopropyl-4-methoxy-5-(4-methyl-thiophen-2-yl)-phenoxy]-pyrimidine-2,4-diamine
221	5-(5-Chloro-2-isopropyl-4-methoxy-phenoxy)-N^2-[(S)-1-(4-methyl-2,6,7-trioxa-bicyclo[2.2.2]oct-1-yl)-ethyl]-pyrimidine-2,4-diamine
222	5-(5-Iodo-2-isopropyl-4-prop-2-ynyloxy-phenoxy)-pyrimidine-2,4-diamine
223	5-(2-Isopropyl-4-methoxy-5-nitro-phenoxy)-pyrimidine-2,4-diamine
224	5-(4-Ethoxy-5-iodo-2-isopropyl-phenoxy)-pyrimidine-2,4-diamine
225	5-[5-Iodo-2-isopropyl-4-(pyridin-3-ylmethoxy)-phenoxy]-pyrimidine-2,4-diamine
226	5-(4-Benzyloxy-5-iodo-2-isopropyl-phenoxy)-pyrimidine-2,4-diamine
227	5-(4-Isopropyl-6-methoxy-biphenyl-3-yloxy)-pyrimidine-2,4-diamine
229	5-(5-Furan-2-yl-2-isopropyl-4-methoxy-benzyl)-pyrimidine-2,4-diamine
230	5-(2-Isopropyl-4-methoxy-5-thiazol-5-yl-phenoxy)-pyrimidine-2,4-diamine
231	1-[5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-pyrrolidin-2-one
232	5-(2-Isopropyl-5-methanesulfonyl-4-methoxy-benzyl)-pyrimidine-2,4-diamine
233	5-[5-Chloro-2-(1-fluoro-1-methyl-ethyl)-4-methoxy-phenoxy]-pyrimidine-2,4-diamine
234	5-[5-Iodo-2-isopropyl-4-(2-methoxy-ethoxy)-phenoxy]-pyrimidine-2,4-diamine
235	5-(2-Isopropyl-4-methoxy-5-oxazol-5-yl-phenoxy)-pyrimidine-2,4-diamine
236	1-[4-Chloro-2-(2,4-diamino-pyrimidin-5-yloxy)-5-methoxy-phenyl]-ethanol
237	1-[4-Chloro-2-(2,4-diaeno-pyrimidin-5-yloxy)-5-methoxy-phenyl]-ethanol
238	2-[2-(2,4-Diamino-pyrimidin-5-yloxy)-4-iodo-5-methoxy-phenyl]-propan-1-ol
240	5-[5-Iodo-2-isopropyl-4-(2-methoxy-benzyloxy)-phenoxy]-pyrimidine-2,4-diamine
241	5-[5-Iodo-2-isopropyl-4-(2,2,2-trifluoro-ethoxy)-phenoxy]-pyrimidine-2,4-diamine
242	5-[5-Iodo-2-isopropyl-4-(3,4,5-trimethoxy-benzyloxy)-phenoxy]-pyrimidine-2,4-diamine
243	2-[2-(2,4-Diamino-pyrimidin-5-yloxy)-4-iodo-5-methoxy-phenyl]-propan-2-ol
244	5-[2-Isopropyl-4-methoxy-5-(4-methyl-thiophen-3-yl)-phenoxy]-pyrimidine-2,4-diamine
245	5-(2-Isopropyl-4-methoxy-5-nitro-phenoxy)-pyrimidine-2,4-diamine
246	5-[5-Iodo-2-isopropyl-4-(1-methyl-piperidin-2-ylmethoxy)-phenoxy]-pyrimidine-2,4-diamine
247	5-[5-Iodo-2-isopropyl-4-(tetrahydro-pyran-2-ylmethoxy)-phenoxy]-pyrimidine-2,4-diamine
248	5-(2-Isopropyl-4-methoxy-5-[1,2,4]triazol-1-yl-phenoxy)-pyrimidine-2,4-diamine
249	5-(2-Isopropyl-4,5-dimethoxy-phenoxy)-N^2-(2-methoxy-ethyl)-pyrimidine-2,4-diamine
250	5-(4'-Fluoro-4-isopropyl-6-methoxy-biphenyl-3-yloxy)-pyrimidine-2,4-diamine
251	5-(5-Chloro-2-isopropyl-4-methoxy-phenoxy)-N^2-(2,2,2-trifluoro-ethyl)-pyrimidine-2,4-diamine
252	5-(2,4-Diamino-pyrimidin-5-ylmethyl)-4-isopropyl-2-methoxy-benzonitrile
253	5-[2-Isopropyl-4-methoxy-5-(2-methyl-thiazol-5-yl)-phenoxy]-pyrimidine-2,4-diamine
254	5-(2-Isopropyl-4-methoxy-6-methyl-phenoxy)-pyrimidine-2,4-diamine

(continued)

#	Name
255	5-(5-Ethanesulfonyl-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine
256	5-(2-Isopropyl-4-methoxy-5-thiazol-5-yl-benzyl)-pyrimidine-2,4-diamine
257	1-[5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-1*H*-imid-azole-2-thiol
258	5-[2-Isopropyl-4-methoxy-5-(1-methyl-1*H*-pyrazol-4-yl)-phenoxy]-pyrimidine-2,4-diamine
259	5-[5-Iodo-2-isopropyl-4-(pyridin-4-ylmethoxy)-phenoxy]-pyrimidine-2,4-diamine
260	5-(4-Iodo-2-isopropyl-phenoxy)-pyrimidine-2,4-diamine
261	5-(5-Iodo-4-isopropyl-2-methoxy-benzyl)-pyrimidine-2,4-diamine
262	5-(5-Fluoro-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine
263	5-(4'-Fluoro-5-isopropyl-2-methoxy-biphenyl-4-yloxy)-pyrimidine-2,4-diamine
264	5-[4-(3-Fluoro-benzyloxy)-5-iodo-2-isopropyl-phenoxy]-pyrimidine-2,4-diamine
265	5-(4-Bromo-2-isopropyl-phenoxy)-pyrimidine-2,4-diamine
266	5-(4-Furan-2-yl-2-isopropyl-5-methoxy-phenoxy)-pyrimidine-2,4-diamine
267	2-[5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-propan-2-ol
269	5-[4-(2,6-Difluoro-benzyloxy)-5-iodo-2-isopropyl-phenoxy]-pyrimidine-2,4-di-amine
270	5-(5-Iodo-2-isopropyl-4-phenethyloxy-phenoxy)-pyrimidine-2,4-diamine
271	5-(2-Isopropyl-4-methoxy-5-pyridin-4-yl-phenoxy)-pyrimidine-2,4-diamine
272	5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N^2-(1-methyl-piperidin-4-yl)-pyrimidine-2,4-diamine
273	5-(2,4-Diamino-pyrimidin-5-yloxy)-N-ethyl-4-isopropyl-2-methoxy-benzenesulf-onamide
274	5-[2-Isopropyl-5-(4-methanesulfonyl-piperazin-1-yl)-4-methoxy-phenoxyl -pyri-midine-2,4-diamine
275	5-(2-Isopropyl-4-methoxy-5-pyridin-3-yl-phenoxy)-pyrimidine-2,4-diamine
276	5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-N,N-dimethyl-benz-amide
277	5-[5-(2,5-Dimethyl-pyrrol-1-yl)-2-isopropyl-4-methoxy-phenoxy]-pyrimidine-2,4-diamine
278	5-(2-Ethyl-3-methoxy-benzyl)-pyrimidine-2,4-diamine
279	5-(2-Bromo-4,5-dimethoxy-phenoxy)-pyrimidine-2,4-diamine

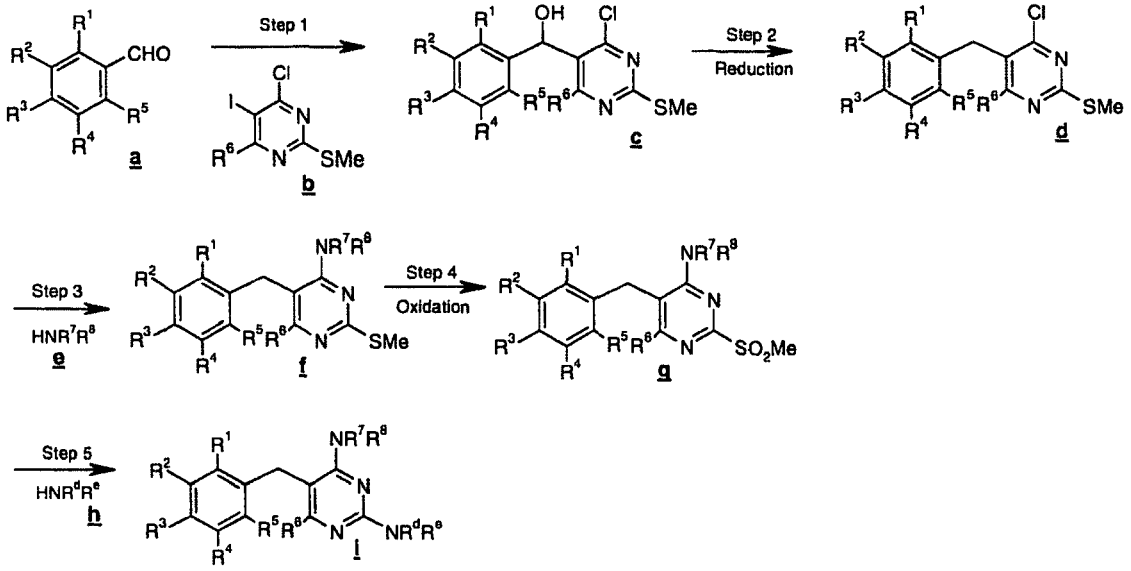
[0165] Compounds of the present invention can be made by a variety of methods depicted in the illustrative synthetic reaction schemes shown and described below.

[0166] 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.

[0167] The starting materials and the intermediates of the synthetic reaction schemes can be isolated and purified if desired using conventional techniques, including filtration, distillation, crystallization and chromatography. Such materials can be characterized using conventional means, including physical constants and spectral data.

[0168] Unless specified to the contrary, the reactions described herein preferably are conducted under an inert atmosphere at atmospheric pressure at a reaction temperature range of from about -78°C to about 150°C, more preferably from about 0°C to about 125°C, and most preferably and conveniently at about room (or ambient) temperature, e.g., about 20°C.

[0169] Scheme A below illustrates one synthetic procedure usable to prepare specific compounds of formula (I) wherein X is methylene, Y is $-NR^dR^e$, and R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^d, and R^e are as defined herein.



SCHEME A

[0170] In Step 1 of Scheme A, benzaldehyde **a** is alkylated with the Grignard reagent derived from 4-chloro-5-iodo-2-methylsulfanyl-pyrimidine **b** or like iodopyrimidine to provide an alpha-hydroxy benzyl pyrimidine **c**. The iodopyrimidine used in this step may be prepared according to the procedure described by Sakamoto et al., Chem. Pharm. Bull., 34 1986, p. 2719. Numerous substituted benzaldehydes **a** are commercially available or are readily prepared by techniques well known to those skilled in the art. In many instances, a "masked aldehyde", such as an imine or oxazoline, may be used used to allow introduction of desired functionalities to benzaldehyde **a** after which the masked aldehyde is deprotected to provide the free aldehyde group. Aldehyde protection schemes of this sort are shown in the experimental examples below.

[0171] The reaction of step 1 may be carried out in the presence of an alkyl magnesium bromide under dry polar aprotic solvent conditions.

[0172] In step 2, alpha-hydroxy benzyl pyrimidine **c** is reduced to provide benzyl pyrimidine **d**. The reduction of step 2 may be achieved using triethylsilane and trifluoroacetic acid under polar solvent conditions.

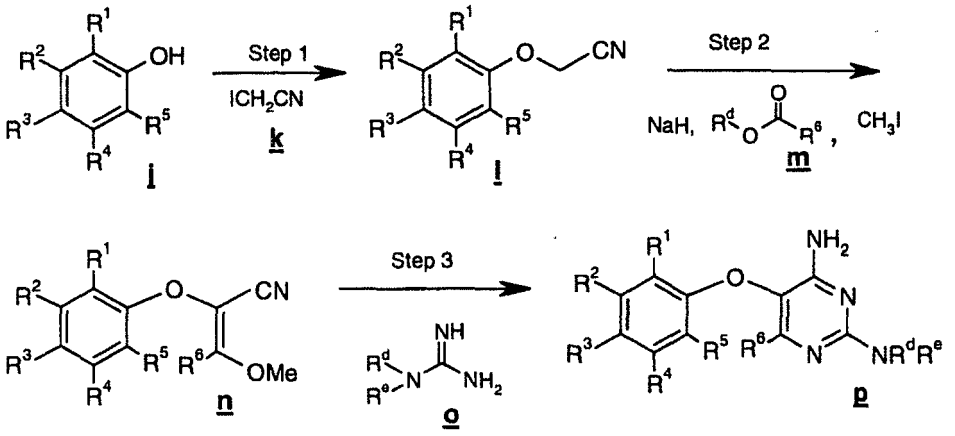
[0173] In step 3, a first amination by reaction of amine **e** with benzyl pyrimidine **d** yields benzyl aminopyrimidine **f**. Amine **e** may comprise any suitable primary or secondary amine having functionalities R^7 or R^8 in accordance with the invention. Amine **e** may comprise, e.g., ammonia, methylamine, ethylamine, isopropylamine, aniline, benzylamine, phenylethylamine, cyclopropylamine, dimethylamine, aziridine, pyrrolidine, piperidine, or the like. The amination of step 3 may be carried out by heating benzyl pyrimidine **d** in the presence of excess amine **e** under sealed conditions.

[0174] In step 4, an oxidation of the methylsulfanyl group of benzyl aminopyrimidine **f** is carried out to afford amino methanesulfonyl benzylpyrimidine **g**. The oxidation of step 4 may be carried out using metachloroperbenzoic acid (mCPBA), OXONE·, or like oxidizing agent under mild, polar solvent conditions.

[0175] A second amination occurs in step 6 in which amino methanesulfonyl benzylpyrimidine **g** is treated with amine **h** to displace the methanesulfonyl group and provide diamino benzylpyrimidine **i.** The diamino benzylpyrimidine **i** is a compound of formula (I) and is usable in the methods of the invention. The amination of step 6 may be achieved by heating amino methanesulfonyl benzylpyrimidine **g** in the presence of excess amine **h** under mild pressure and polar solvent conditions.

[0176] Numerous variations on the above procedure are possible and will suggest themselves to those skilled in the art upon review of this disclosure. For example, various pyrimidine reagents may be used in place of iodopyrimidine **b** in step 1. In such variation, described in the experimental examples below, benzaldehyde **a** may be treated with 5-lithio-2,6-di-methoxypyrimidine (Mathson et al., JOC 55(10) 1990 3410-12) to form a dimethoxy benzyl pyrimidine alchohol which is subsequently oxidized with MnO_2. The resultant ketone can then be aminated to displace the methoxy groups to yield a diamino benzylpyrimidine in accordance with the invention.

[0177] Scheme B below illustrates another synthetic procedure usable to prepare specific compounds of formula (I) above, wherein X is O, Y is $-NR^dR^e$, R^7 and R^8 are hydrogen, and R^1, R^2, R^3, R^4, R^5, R^d, and R^e are as defined herein.



SCHEME B

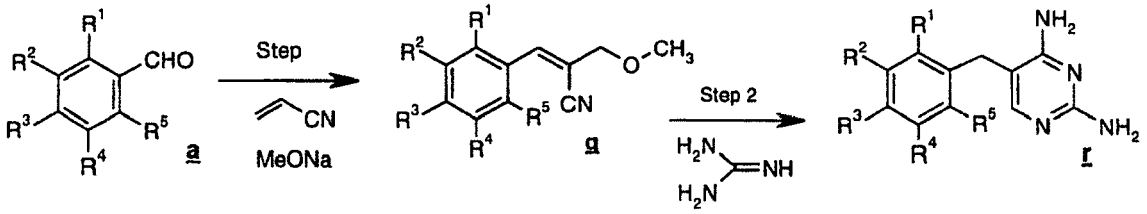
[0178] In step 1 of Scheme B, an O- alkylation is carried out by reaction of phenol **j** with a halo-acetonitrile such as iodoacetonitrile **k** to afford cyano ether **1**. Numerous substituted phenols j are either commercially available or may be prepared by techniques well known in the art for use in step 1. For example, the substituted benzaldehydes **a** of Scheme A above may be converted to the corresponding phenols **j** via Baeyer- Villiger oxidation using peracid such as mCPBA, as illustrated in the experimental examples below. The alkylation of step 1 may be effected in the presence of mild base under polar aprotic solvent conditions.

[0179] In step 2, a cyano enol ether compound **n** is formed by treatment of cyano ether **l** with a strong base such as sodium hydride, followed by introduction of ester **m** to form an enolate (not shown), that in turn is alkylated by addition of iodomethane or other alkyl halide. This step may be carried out under polar aprotic solvent conditions.

[0180] In step 3 cyano enol ether **n** is reacted with guanidine compound **o** in the presence of base, under polar aprotic conditions, to yield diaminopyrimidine (VI). The diaminopyrimidine (VI) is a compound of formula (I) usable in the methods of the invention.

[0181] As in the case of Scheme A discussed above, numerous variations on the procedure of Scheme B are possible and will be readily apparent to those skilled in the art. For example, selective amination of the $-NH_2$ group of diamino pyrimidine **p**, using reductive amination or like technique, may be used to introduce R^7 and R^8 functionalities in accordance with formula (I).

[0182] Yet another procedure usable for preparation of the subject compounds is shown in Scheme C, wherein R^1, R^2, R^3, R^4 and R^5 are as defined herein. Scheme C represents the well-known synthesis of "ormetoprim" and "trimethoprim" antibacterials. This synthetic procedure is reported by Manchand et al., J. Org. Chem. 1992, 57, 3531-3535.



SCHEME C

[0183] In the procedure of Scheme C, benzaldehyde **a** is treated with acrylonitrile in the presence of sodium methoxide in step 1 to afford a phenyl methoxymethyl cinnamonitrile com-pound **q**, which in turn is reacted with guanidine in step 2 to yield the diaminopyrimidine **r**. Diamino pyrimidine **r** is a compound of formula (I) in which X is $-CH_2-$, Y is $-NN_2$ and R^6, R^7 and R^8 are hydrogen.

[0184] The procedure of Scheme C is effective for use with benzaldehydes **a** in which groups R^1 and R^5 are small such that the aldehyde functionality in step 1, and methoxymethyl cinnamonitrile functionality in step 2, are relatively unhindered. However, the introduction, e.g., of R^1 as an isopropyl or larger alkyl group, reduces the yield of step 1 nominally to zero. Table 2 below summarizes the relative yields provided by Scheme C for various benzaldehyde starting

materials.

Table 2

	R^1	R^2	R^3	R^4	R^5	Yield %
1	H	-H	-OMe	-OMe	-H	67%
2	-OMe	-H	-OMe	-OMe	-H	37%
3	$-CH_3$	-H	-OMe	-OMe	-H	34%
4	-Et	-H	-OMe	-OMe	-H	18%
5	-Isopropyl	-H	-OMe	-OMe	-H	<1%

[0185] The commercially available benzaldehydes represented by compounds 1-3 of Table 2 all result in effective synthesis of diaminopyrimidines. Introduction of an ethyl group as R^1 significantly reduced yield of Scheme C, and introduction of an isopropyl are larger group as R^1 resulted in essentially no product from the reaction of Scheme C.

[0186] Specific details for producing compounds of the invention are described in the Examples section below.

[0187] The compounds of the invention are useful for treating respiratory disorders, including chronic obstructive pulmonary disorder (COPD), asthma and bronchospasm.

[0188] 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.

[0189] 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, preferably 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.

[0190] Compounds of the invention may be administered as pharmaceutical formulations in-cluding 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. The preferred manner of administration is generally oral using a convenient daily dosage regimen which can be adjusted according to the degree of affliction.

[0191] 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.

[0192] 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 preferably contain from about one (1) to about seventy (70) percent of the active compound. Suitable carriers include magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatine, tragacanth, methylcellulose, sodium car-

boxymethylcellulose, a low melting wax and cocoa butter. The term "preparation" is intended to include the formulation of the active compound with encapsulating material 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.

[0193] 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, e.g., in aqueous propylene glycol solutions or may contain emulsifying agents, e.g., 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 and solubilizing agents.

[0194] The compounds of the invention may be formulated for parenteral administration (e.g., by injection, e.g. 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, e.g. 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.

[0195] 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, e.g., 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.

[0196] 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, e.g., by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and to solidify.

[0197] 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.

[0198] The subject compounds may be formulated for nasal administration. The solutions or suspensions are applied directly to the nasal cavity by conventional means, e.g., 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 e.g. by means of a metering atomizing spray pump.

[0199] The compounds of the invention may be formulated for aerosol administration, particular-ly to the respiratory tract and including intranasal administration. The compound will generally have a small particle size e.g. of the order of five (5) microns or less. Such a particle size may be obtained by means known in the art, e.g. by micronization. The active ingredient is provided in a pressurized pack with a suitable propellant such as a chlorofluorocarbon (CFC), e.g., 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, e.g. 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 e.g. in capsules or cartridges of e.g., gelatine or blister packs from which the powder may be administered by means of an inhaler.

[0200] 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 transder-

mal 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.

[0201] The pharmaceutical preparations are preferably 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.

[0202] Other suitable pharmaceutical carriers and their formulations are described in Remington: The Science and Practice of Pharmacy 1995, edited by Martin, Mack Publishing Company, 19th edition, Easton, Pennsylvania. Representative pharmaceutical formulations containing a compound of the present invention are described below.

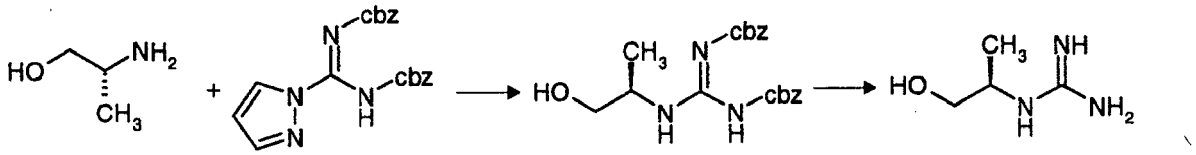
EXAMPLES

[0203] The following preparations and examples are given to enable those skilled in the art to more clearly understand and to practice the present invention.

[0204] The following abbreviations may be used in the Examples: DCM: dichloromethane/- methylene chloride; DMF: N,N-dimethylformamide; TEA: triethylamine; THF: tetrahydrofuran; RT: room (ambient) temperature; min: minutes

Preparation 1: N-(2-(R)-Hydroxy-1-methyl-ethyl)-guanidine

[0205]



Step 1 Bis-benzyloxycarbonyl-N-(2-(R)-Hydroxy-1-methyl-ethyl)-guanidine

[0206] To a solution of R-(-)-2-amino-1-propanol (0.59 g, 8.0 mmol) in 50 mL THF was added pyrrazole carboxamidine (3.0 g, 8.0 mmol, prepared as described by Berbatowicz et al., Tetrahedron 34 1993 p.3389). After 16 hours the mixture was concentrated in vacuo. Purification via flash chromatography (93:7 ethyl acetate/CH_2Cl_2) afforded bis-benzyloxycarbonyl- N-(2-(R)-hydroxy-1-methyl-ethyl)-guanidine (3.0 g, 97%) as a white solid.

Step 2 N-(2-(R)-Hydroxy-1-methyl-ethyl)-guanidine

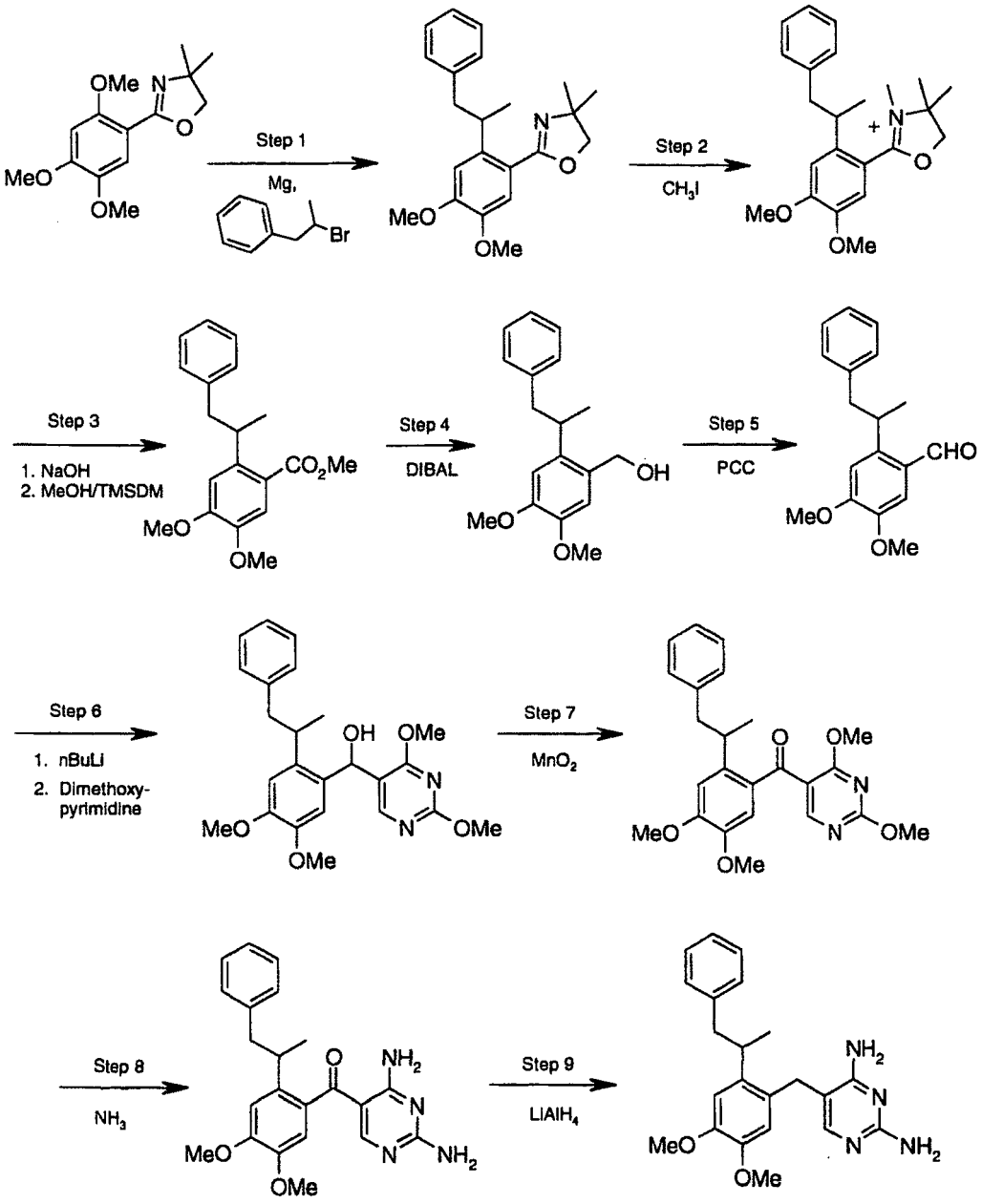
[0207] To a solution of bis-benzyloxycarbonyl- N-(2-(R)-hydroxy-1-methyl-ethyl)-guanidine in 75 mL EtOH was added 10% Pd/C (0.10 g). The mixture was stirred under 1 Atmosphere of H_2. After 16 hours the mixture was filtered through a pad of celite and concentrated in vacuo to give N-(2-(R)-hydroxy-1-methyl-ethyl)-guanidine (0.44 g, 69%).

[0208] Using the appropriate amines with the above procedure, the following guainidine compounds were also prepared:

N-(3-Ethanesulfonyl-1-methyl-propyl)-guanidine;
4-Guanidino-piperidine-1-carboxylic acid ethyl ester;
N-(1-Cyclopropyl-ethyl)-guanidine;
N-(Tetrahydro-thiopyran-4-yl)-guanidine;
N-[2-(4-Acetyl-piperazin-1-yl)-1-methyl-ethyl]-guanidine;
N-(1-Hydroxymethyl-propyl)-guanidine
N-(1-Methanesulfonyl-piperidin-4-yl)-guanidine; and
N-[3-Hydroxy-1-(2-hydroxy-ethyl)-propyl]-guanidine.

Example 1: 5-[4,5-Dimethoxy-2-(1-methyl-2-phenyl-ethyl)-benzyl]-pyrimidine-2,4-diamine

[0209] The synthetic procedure used in this Example is outlined in Scheme D.



Scheme D

Step 1. 2-[4,5-Dimethoxy-2-(1-methyl-2-phenyl-ethyl)-phenyl]-4,4-dimethyl-4,5-di-hydro-oxazole

[0210] The 4,4-dimethyl-2-(2,4,5-trimethoxy-phenyl)-4,5-dihydro-oxazole oxazoline used in this step was prepared according to the procedure reported by Meyers et al., J Org Chem 43 1978, pp.1372-1379.

[0211] To a rapidly stirring suspension of magnesium turnings (1.32 g, 54.5 mol) and in 35 mL THF was added 1,2-dibromoethane (0.10 mL) in one portion. 2-bromo-1-phenylpropane (10.86 g, 54.5 mmol) was added at a rate that maintained the internal temperature at 40°C. After 2.5 hours the cloudy suspension was transferred via canula to a solution of 4,4-di-methyl-2-(2,4,5-trimethoxy-phenyl)-4,5-dihydro-oxazole oxazoline (10.013 g, 36.4 mmol) in 50 mL THF. After 18 hours the solution cooled to 0°C and quenched by the slow addition of 10% NH_4Cl. 500 mL H_2O was added and the mixture was extracted with ethyl acetate, washed with H_2O, and washed with brine. The combined organics were dried over Na_2SO_4, filtered and concentrated in vacuo to give a crude solid. Purifications via flash chromatography (4:1 hexane/ethyl acetate) afforded 2-[4,5-dimethoxy-2-(1-methyl-2-phenyl-ethyl)-phenyl]-4,4-dimethyl-4,5-dihydro-oxazole as a clear viscous oil (7.833 g, 41%).

Step 2. 2-[4.5-Dimethoxy-2-(1-methyl-2-phenyl-ethyl)-phenyl]-3,4,4-trimethyl-4.5-dihydro-oxazolium iodide

[0212] To a solution of 2-[4,5-dimethoxy-2-(1-methyl-2-phenyl-ethyl)-phenyl]-4,4-dimethyl-4,5-dihydro-oxazole (7.515 g, 21.3 mmol) in 50 mL NO_2CH_3 was added iodomethane (2.65 mL, 42.5 mmol). The solution was warmed to 110°C. After 3 hours the solution was cooled and concentrated in vacuo to give 2-[4,5-dimethoxy-2-(1-methyl-2-phenyl-ethyl)-phenyl]-3,4,4-trimethyl-4,5-dihydro-oxazolium iodide (10.108 g) as an orange solid.

Step 3. 4,5-Dimethoxy-2-(1-methyl-2-phenyl-ethyl)-benzoic acid ethyl ester

[0213] To a solution of 2-[4,5-dimethoxy-2-(1-methyl-2-phenyl-ethyl)-phenyl]-3,4,4-trimethyl-4,5-dihydro-oxazolium iodide (5.132 g, 10.4 mmol) in 52 mL methanol was added 4 M NaOH (5.2 mL, 20.7 mmol). The solution was warmed to reflux. After 16 hours the solution was cooled to 0°C and acidified to pH=1 with concentrated HCl. The mixture was extracted with ethyl acetate, washed with H_2O and washed with brine. The combined organics were dried over Na_2SO_4, filtered and concentrated in vacuo to give a crude acid (3.228 g). A portion of this acid (2.919 g, 9.73 mmol) was dissolved in a mixture of 70 mL benzene and 20 mL MeOH. Trimethylsilyldiazomethane (6.3 mL, 2.0 M in hexanes) was added drop-wise. After 30 min the solution was concentrated in vacuo to give 4,5-dimethoxy-2-(1-methyl-2-phenyl-ethyl)-benzoic acid methyl ester as an oil (2.886 g).

Step 4. [4,5-Dimethoxy-2-(1-methyl-2-phenyl-ethyl]-phenyl]-methanol

[0214] Diisobutyl aluminum hydride (22.9 mL, 1.0 M in THF) was added to a solution of 4,5-di-methoxy-2-(1-methyl-2-phenyl-ethyl)-benzoic acid methyl ester (2.886 g, 9.2 mmol) in 100 mL THF at - 78°C over 10 min. The mixture was allowed to stir for 1 h and warmed to RT. After 1.5 hours the mixture was quenched by the slow addition of 50 mL saturated Rochelle's salt. After rapidly stirring for 30 min the mixture was filtered through a pad of celite and concentrated in vacuo. H_2O was added and the slurry was extracted with ethyl acetate, washed with H_2O and washed with brine. The combined organics were dried over Na_2SO_4, filtered and concentrated in vacuo to give a crude oil. Purification via flash chro-matography (3:1 hexane/ethyl acetate) afforded [4,5-dimethoxy-2-(1-methyl-2-phenyl-ethyl)-phenyl]-methanol as a clear oil (1.269 g, 48%).

Step 5. 4,5- Dimethoxy-2-(1-methyl-2-phenyl-ethyl)-benzaldehyde

[0215] A solution of pyridinium chlorochromate (1.253 g, 5.8 mmol) in 40 mL CH_2Cl_2 was cooled to 0°C. [4,5-Dimethoxy-2-(1-methyl-2-phenyl-ethyl)-phenyl]-methanol (1.110 g, 3.88 mmol) in 5.0 mL CH_2Cl_2 was added drop-wise and allowed to stir for 45 min. The mixture was diluted in 200 mL Et_2O, filtered through celite and concentrated in vacuo to afford a dark brown oil. Purification via flash chromatography (9:1 hexane/ethyl acetate) gave 4,5-dimethoxy-2-(1-methyl-2-phenyl-ethyl)-benzaldehyde (0.840 g, 76%) as a clear oil.

Step 6. [4,5-Dimethoxy-2-(1-methyl-2-phenyl-ethyl)-phenyl]-(2,4-dimethoxy-pyrimidin-5-yl)-methanol

[0216] Freshly distilled 2,2,6,6-tetramethyl piperidine (0.85 mL, 5.0 mmol) was dissolved in 20 mL THF and cooled to 0°C. n-Butyllithium (2.0 mL, 2.5 M in hexanes) was added dropwise over 5 min and the mixture was allowed to stir for 30 min and then cooled to -78°C. 2,4-Dimethoxypyrimidine (0.353 g, 2.52 mmol) was added dropwise over 5 min. After 45 min the solution was transferred via a dry ice cooled cannula to a solution of 4,5-dimethoxy-2-(1-methyl-2-phenyl-ethyl)-benzaldehyde (0.717 g, 2.52 mmol) in 20 mL THF at -78°C. After stirring for 1 hour the solution was warmed to RT and quenched by the slow addition of 50 mL 10% NH_4Cl. After 100 mL of H_2O was added the mixture was extracted with ethyl acetate, washed with H_2O and washed with brine. The combined organics were dried over Na_2SO_4, filtered and concentrated in vacuo to give an orange oil. Purification via flash chromatography (3:2 hexane/ethyl acetate) afforded [4,5-dimethoxy-2-(1-methyl-2-phenyl-ethyl)-phenyl]-(2,4-dimethoxy-pyrimidin-5-yl)-methanol (0.551 g, 52%) as a clear oil.

Step 7. [4,5-Dimethoxy-2-(1-methyl-2-phenyl-ethyl)-phenyl]-(2,4-dimethoxy-pyrimidin-5-yl)-methanone

[0217] To a solution of [4,5-dimethoxy-2-(1-methyl-2-phenyl-ethyl)-phenyl]-(2,4-dimethoxy-pyrimidin-5-yl)-methanol (0.418 g, 0.9 mmol) in 20 mL toluene was added MnO_2 (0.335 g, 4.7 mmol). The mixture was warmed to reflux and H_2O was removed via a Dean-Stark trap. After 1 hour the mixture was cooled, filtered through a pad of celite and concentrated in vacuo to give a crude oil. Purification via flash chromatography (7:3 hexane/ethyl acetate) afforded [4,5-dimethoxy-2-(1-methyl-2-phenyl-ethyl)-phenyl]-(2,4-dimethoxy-pyrimidin-5-yl)-methanone (0.258 g, 62%) as a clear oil.

Step 8. (2,4-Diamino-pyrimidin-5-yl)-[4,5-dimethoxy-2-(1-methyl-2-phenyl-ethyl)-pheny]-methanone

[0218] A solution of [4,5-dimethoxy-2-(1-methyl-2-phenyl-ethyl)-phenyl]-(2,4-dimethoxy-pyri-midin-5-yl)-methanone (0.212 g, 0.5 mmol) in 5.0 mL MeOH was added to ammonia (15 mL, 7.0M in MeOH) in a sealed tube. The mixture was heated to 80°C. After 16 hours the solution was cooled and concentrated in vacuo to give a dark solid. Purification via flash chromatography (95:5 CH_2Cl_2/MeOH) afforded (2,4-diamino-pyrimidin-5-yl)-[4,5-dimethoxy-2-(1-methyl-2-phenyl-ethyl)-phenyl]-methanone (0.162 g, 86%) as a white solid.

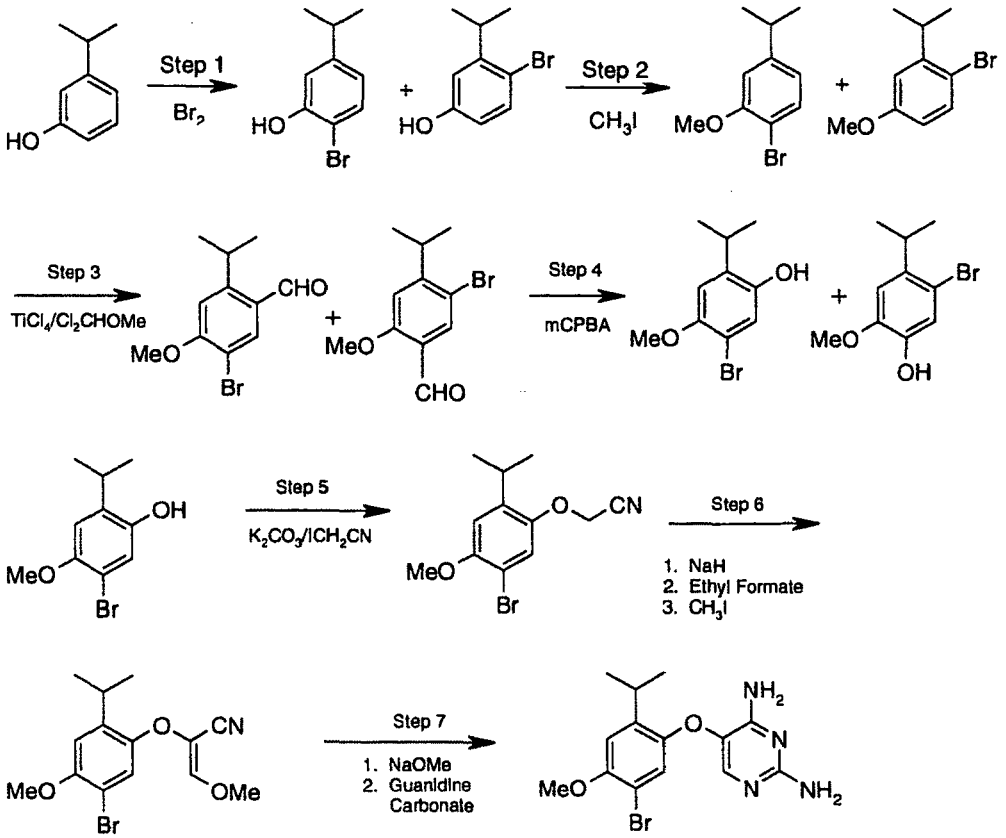
Step 9. 5-[4,5-dimethoxy-2-(1-methyl-2-phenyl-ethyl)-benzyl]-pyrimidine-2,4-diamine

[0219] To a solution of (2,4-diamino-pyrimidin-5-yl)-[4,5-dimethoxy-2-(1-methyl-2-phenyl-ethyl)-phenyl]-methanone (0.413 g, 0.4 mmol) in 10 mL THF was added $LiAlH_4$ (0.73 mL, 1.0 M in THF) over 5 min. After gas evolution ceased the mixture was warmed to reflux. After 3 h the mixture was cooled to 0°C and quenched by the Fieser method. After 30 min the mixture was filtered through a pad of celite and concentrated in vacuo to give a crude white solid. To a solution of this solid in 5 mL CH_2Cl_2 was added trifluoroacetic acid (1.1 mL, 14.0 mmol) followed by triethylsilane (0.4 mL, 2.8 mmol). After 30 min 50 mL 10% K_2CO_3 was as added and the mixture was extracted with ethyl acetate and washed with brine. The combined organics were dried over Na_2SO_4, filtered and concentrated in vacuo. Purification via flash chromatography (95:5 CH_2Cl_2) afforded 5-[4,5-dimethoxy-2-(1-methyl-2-phenyl-ethyl)-benzyl]-pyrimidine-2,4-diamine (0.066 g, 58%) as a white foam; melting point (HCl salt) 227.1-227-4°C.

[0220] Using the procedure of Example 1 described above, but replacing 2-bromo-1-phenyl propane in step 1 with 2-bromopropane or other alkyl bromides, and replacing ammonia in step 8 with various alkyl or benzyl amines, afforded a variety of compounds under essential the same reaction conditions. Additional compounds are prepared using the procedure outlined in Example 1 are shown in Table 1.

Example 2: 5-(5-Bromo-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine

[0221] The synthetic procedure used in this Example is outlined in Scheme E.



Scheme E

Step 1. 2-Bromo-5-isopropyl-phenol

[0222] A solution of 3-isopropyl phenol (4.975 g, 36.5 mmol) in 37 mL of CCl_4, was cooled to -20°C. Bromine (1.9 mL, 38.4 mmol) was dissolved in 5.0 mL CCl_4, and added dropwise at such a rate that the internal temperature was maintained below -10°C. The mixture was allowed to warm to RT. After 12 hours the mixture was taken up in 100 mL CH_2Cl_2, washed with H_2O and then with brine. The combined organics were dried over Na_2SO_4, filtered and concentrated in vacuo to give 8.663 g of a 1:1 mixture of 2-bromo-5-isopropyl-phenol and 4-bromo-5-isopropyl phenol as a dark oil). These two isomers were inseparable and were used together in step 2 below.

Step 2. 1-Bromo-4-isopropyl-2-methoxy-benzene

[0223] To a mixture of 2-bromo-5-isopropyl-phenol and 4-bromo-5-isopropyl phenol from step 1 (8.663 g, 40.3 mmol), K_2CO_3 (16.710 g, 120.9 mmol) in 50 mL DMF, was added iodomethane (3.0 mL, 48.3 mmol) with mechanical stirring. The mixture was warmed to 50°C for 4 hours. After cooling to RT 300 mL H_2O was added and the solution was extracted with diethyl ether (Et_2O), washed with H_2O and washed with brine. The combined organics were dried over $MgSO_4$ filtered and concentrated in vacuo to give 1-bromo-4-isopropyl-2-methoxy-benzene and 1-bromo-2-isopropyl-4-methoxy-benzene (6.621 g, 72%) as a 1:1 inseparable mixture in the form of a pale yellow oil. This mixture of regioisomers was used directly in step 3 below.

Step 3. 5-Bromo-2-isopropyl-4-methoxy-benzaldehyde

[0224] To a solution of 1-bromo-4-isopropyl-2-methoxy-benzene and 1-bromo-2-isopropyl-4-methoxy-benzene from step 2 (6.621 g, 28.9 mmol) in 100 mL 1,2 dichloroethane was added $TiCl_4$ (6.3 mL, 57.8 mmol) at 0°C. After 10 min, dichloromethoxymethane (Cl_2CHOMe) (2.6 mL, 28.9 mmol) was added and the mixture was warmed to reflux. After 3 hours the mixture was cooled poured over ice and acidified with 50 mL 2 M HCl. The resulting slurry was extracted with CH_2Cl_2, and washed with brine. The combined organics were dried over $MgSO_4$, filtered and concentrated in vacuo to give a dark-green oil. Purification via flash chromatography (96:4 hexane/ethyl acetate) afforded 5-bromo-2-isopropyl-4-methoxy-benzaldehyde and 5-bromo-4-isopropyl-2-methoxy-benzaldehyde (2.876 g, 39%, 6.621 g, 72%) as a 1:1 mixture of inseparable isomers in the form of an orange oil, which was used directly in step 4.

Step 4. 5-Bromo-2-isopropyl-4-methoxy-phenol

[0225] To a solution of 5-bromo-2-isopropyl-4-methoxy-benzaldehyde and 5-bromo-4-iso-propyl-2-methoxy-benzaldehyde from step 3 (2.87 g, 11.2 mmol) in 25 mL CH_2Cl_2 was added mCPBA (2.31 g, 13.4 mmol). After 16 hours the mixture was taken up in 150 ml CH_2Cl_2 and washed with sat $NaHCO_3$, and then with brine. The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo to give an oil that was taken up in 50 mL MeOH and 30 mL 4M NaOH. After 2 hours the mixture was evaporated, diluted with water and acidified to pH = 1 with concentrated HCl. The mixture was extracted with ethyl acetate (3X 100 mL) and washed with 100 mL brine. The combined organics were dried over Na_2SO_4, filtered and evaporated to give a mixture of 5-bromo-2-isopropyl-4-methoxy-phenol and 2-bromo-5-isopropyl-4-methoxy-phenol as an orange residue. These regioisomers were separable by flash chromatography (gradient: hexane, 7:3, 1:1 hexane/- CH_2Cl_2) to afford 5-bromo-2-isopropyl-4-methoxy-phenol (0.929, 34%) as a yellow oil which was used in the following step, and 2-bromo-5-isopropyl-4-methoxy-phenol (0.404 g, 15%) as a yellow solid.

Step 5. (5-Bromo-2-isopropyl-4-methoxy-phenoxy)-acetonitrile

[0226] To a mixture of 5-bromo-2-isopropyl-4-methoxy-phenol from step 4 (0.831 g, 3.4 mmol) and K_2CO_3 (0.562 g, 4.1 mmol) in 17 mL dimethyl formamide (DMF) was added iodoacetonitrile (0.594 g, 3.6 mmol). The mixture was warmed to 60°C for 30 min and then allowed to cool to RT. After cooling to RT the mixture was taken up in 50 mL of H_2O and extracted with 1:1 toluene/ethyl acetate, washed with H_2O and then with brine. The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo to give a crude solid. Purification via flash chromatography (1:1 hexane/CH_2Cl_2) afforded (5-bromo-2-isopropyl-4-methoxy-phenoxy)-acetonitrile (0.611 g, 63%) as a while solid.

Step 6. 2-(5-Bromo-2-isopropyl-4-methoxy-phenoxy)-3-methoxy-acrylnitrile

[0227] Sodium hydride (0.122 g, 5.0 mmol, 60% w/w) was washed with dry hexanes and evaporated under a stream of nitrogen. 10 mL THF was added and the mixture was cooled to 0°C. (5-Bromo-2-isopropyl-4-methoxy-phenoxy)-acetonitrile (0.577 g, 2.03 mmol) was added in portions. After 30 min ethyl formate (4.9 mL, 60.9 mmol) was added and the solution was warmed to 80°C. After 4.5 hours the mixture was cooled and 5.0 mL iodomethane was added in one

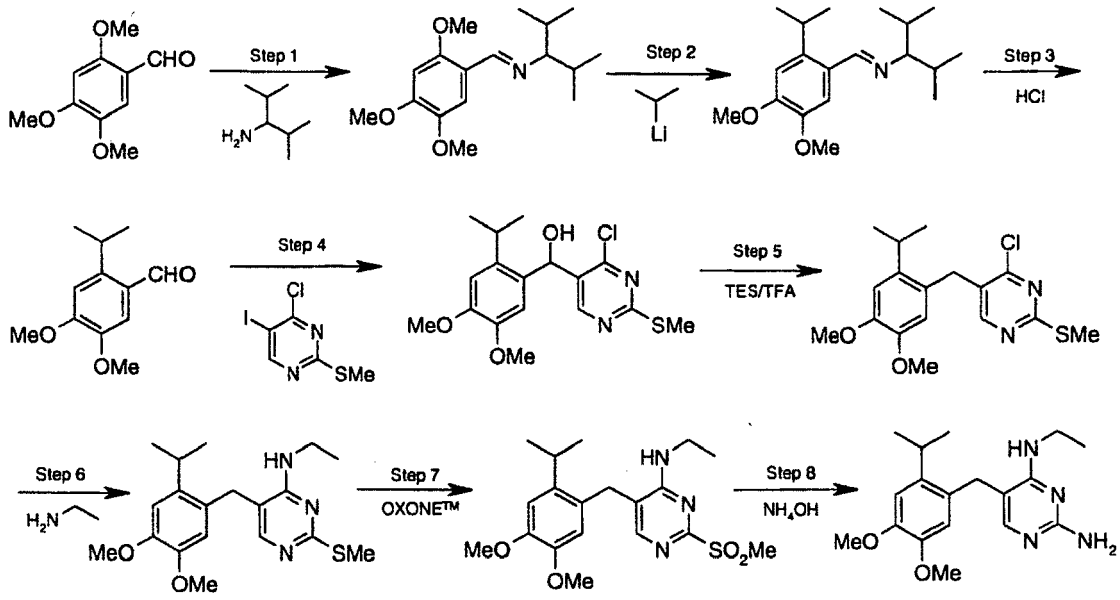
portion. After 16 hours the solution was quenched with H_2O, concentrated in vacuo, extracted with ethyl acetate, washed with H_2O and then washed with brine. The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. Purification via flash chromatography (9:1 hexane/ethyl acetate) afforded 2-(5-bromo-2-isopropyl-4-methoxy-phenoxy)-3-methoxy-acrylonitrile (0.319 g, 48%) as a white solid.

Step 7. 5-(5-Bromo-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine

[0228] To a solution of 2-(5-bromo-2-isopropyl-4-methoxy-phenoxy)-3-methoxy-acrylonitrile (0.282 g, 0.9 mmol) and guanidine carbonate (0.078 g, 0.4 mmol) in 10.0 mL dimethyl sulfoxide (DMSO) was added sodium methoxide (1.0 mL, 1.0M in MeOH). The mixture was warmed to 120°C. The methanol was collected via a short-path condenser. After 3 h the mixture was cooled and concentrated in vacuo to give a crude oil. Purification via flash chromatography (95:5 CH_2Cl_2/MeOH) afforded 17 (0.246 g, 77%) as a pink solid; Mass Spec M+H = 352. The above procedure may be used with various different phenols in step 1 and/or substituted guanidines in step 7 under essentially the same reaction conditions to produce additional compounds. Additional compounds made according to the procedure of Example 2 are shown in Table 1.

Example 3: N^4-Ethyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine

[0229] The synthetic procedure used in this Example is outlined in Scheme F.



Scheme F

Step 1. (1-Isopropyl-2-methyl-propyl)-(2,4,5-trimethoxy-benzylidene)-amine

[0230] To a solution of 2,4,5-trimethoxybenzaldehyde (20.10 g, 102.4 mmol) in 200 mL of toluene was added 2,4-dimethylpentyl-3-amine and *p*-toluene sulfonic acid (0.1 g). The mixture was warmed to reflux. The generated H_2O was removed with a Dean-Stark trap. After 3 h, the solution was cooled, washed with 50 mL saturated $NaHCO_3$, dried over Na_2SO_4 and filtered. The solution was concentrated in vacuo to give a yellow syrup. Purification via Kügel-Rhor distillation (80°C, 200 mTorr) gave (1-isopropyl-2-methyl-propyl)-(2,4,5-trimethoxy-benzylidene)-amine (28.70 g, 96%) as a pale yellow solid.

Step 2. (2-Isopropyl-4,5-dimethoxy-benzylidene)-(1-isopropyl-2-methyl-propyl)-amine

[0231] To a solution of (1-isopropyl-2-methyl-propyl)-(2,4,5-trimethoxy-benzylidene)-amine (1.024 g, 3.5 mmol) in 35 ml THF at -78°C was added isopropyllithium (6.0 mL, 0.7 M in pentane) dropwise over 5 min. The solution was allowed to stir 30 min at -78°C. After warming to RT over 45 min the mixture was quenched by the addition of 5 mL of 10% NH_4Cl and concentrated in vacuo. 100 mL of H_2O was added and the mixture was extracted with ethyl acetate, washed with

H_2O and then brine. The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo to give (2-isopropyl-4,5-dimethoxy-benzylidene)-(1-isopropyl-2-methyl-propyl)-amine as a yellow oil.

Step 3. 2-Isopropyl-4,5-dimethoxy-benzaldehyde

[0232] (2-Isopropyl-4,5-dimethoxy-benzylidene)-(1-isopropyl-2-methyl-propyl)-amine was dissolved in 30 ml of THF. HCl (4.1 mL, 4 M) was added and the mixture was warmed to reflux. After 3 hours the mixture was cooled concentrated in vacuo. 100 mL of H_2O was added and the mixture was extracted with ethyl acetate, washed with H_2O and then with brine. The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo to give an orange oil. Purification via flash chromatography (85:15 hexane/ethyl acetate) gave 2-isopropyl-4,5-dimethoxy-benzaldehyde (0.331g, 43%) as a clear oil

Step 4. (4-Chloro-2-methylsulfanyl-pyrimidin-5-yl)-(2-isopropyl-4,5-dimethoxy-phenyl)-methanol

[0233] The 4-chloro-5-iodo-2-methylsulfanyl-pyrimidine used in this step was prepared according to the procedure described by Sakamoto et al., Chem. Pharm. Bull., 34 1986, p. 2719. To a solution of 4-chloro-5-iodo-2-methylsulfanyl-pyrimidine (1.10 g, 3.9 mmol) in 20 mL THF at - 40°C was added isopropyl magnesium bromide (2.3 mL, 2 M in THF)) over 5 min. After 30 min, 2-isopropyl-4,5-dimethoxy-benzaldehyde from step 3 (1.04 g, 4.6 mmol) was added and the solution was warmed to RT. The mixture was quenched by the addition of brine, and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. Purification via flash chromatography (ethyl acetate) afforded (4-chloro-2-methylsulfanyl-pyrimidin-5-yl)-(2-isopropyl-4,5-dimethoxy-phenyl)-methanol (1.168 g, 82%) as a light yellow solid.

Step 5. 4-Chloro-5-(2-isopropyl-4,5-dimethoxy-benzyl)-2-methylsulfanyl-pyrimidine

[0234] To a solution of (4-chloro-2-methylsulfanyl-pyrimidin-5-yl)-(2-isopropyl-4,5-dimethoxyphenyl)-methanol (6.5 g, 17.6 mmol) in 200 mL CH_2Cl_2 was added triethylsilane (28.0 mL, 176 mmol) and trifluoroacetic acid (TFA) (70 mL, 881 mmol). After 2 hours the solution was concentrated in vacuo, 10% K_2CO_3 was added and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. Purification via flash chromatography (4:1 hexanes/ethyl acetate) afforded 4-chloro-5-(2-isopropyl-4,5-dimethoxy-benzyl)-2-methylsulfanyl-pyrimidine (5.60 g, 91%) as a clear oil.

Step 6. Ethyl-[5-(2-isopropyl-4,5-dimethoxy-benzyl)-2-methylsulfanyl-pyrimidin-4-yl]-amine

[0235] To a glass pressure vessel containing 4-chloro-5-(2-isopropyl-4,5-dimethoxy-benzyl)-2-methylsulfanyl-pyrimidine (0.212 g, 0.6 mmol) was added 5.0 mL ethyl amine via a cold finger condenser. The vessel was capped and warmed to 50°C. After 16 hours the solution was cooled to RT, evaporated and taken up in H_2O. The mixture was extracted with ethyl acetate, washed with H_2O and then washed with brine. The combined organic layers were dried over Na_2SO_4, filtered and evaporated in vacuo. Purification via flash chromatography (4:1 hexane/ethyl acetate) afforded ethyl-[5-(2-isopropyl-4,5-dimethoxy-benzyl)-2methylsulfanyl-pyrimidin-4-yl]-amine (0.136 g, 63%) as a white solid.

Step 7. Ethyl-[5-(2-isopropyl-4,5-dimethoxy-benzyl)-2-methanesulfonyl-pyrimidin-4-yl]-amine

[0236] To a solution of ethyl-[5-(2-isopropyl-4,5-dimethoxy-benzyl)-2-methylsulfanyl-pyrimidin-4-yl]-amine (0.129 g, 0.4 mmol) in 20 mL 1:1 H_2O/THF was added OXONE˙ (0.461 g, 0.8 mmol) in 4.0 mL H_2O. After 2 hours, 50 mL H_2O was added and the mixture was extracted with ethyl acetate, washed with H_2O and washed with brine. The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo to give ethyl-[5-(2-isopropyl-4,5-dimethoxy-benzyl)-2-methanesulfonyl-pyrimidin-4-yl]-amine (0.131 g, 92%) as a white foam.

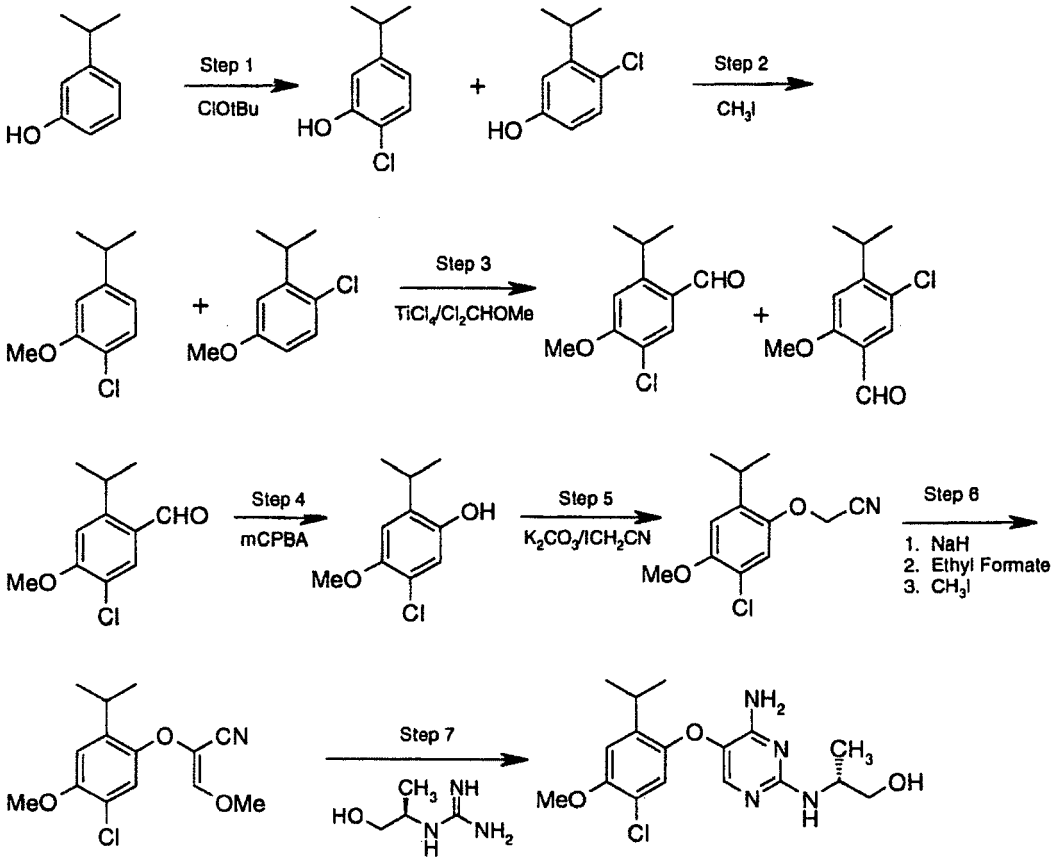
Step 8. N^4-Ethyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine

[0237] To ethyl-[5-(2-isopropyl-4,5-dimethoxy-benzyl)-2-methanesulfonyl-pyrimidin-4-yl]-amine (0.078g, 0.2 mmol) in microwave reactor vial was added 2.0 mL dimethoxy ethane and 0.5 mL concentrated NH_4OH. The vial was capped and placed in a microwave reactor. The internal temperature was warmed to 145°C. After 2 hours an additional portion of 0.4 mL concentrated NH_4OH was added and the mixture was heated an additional 2 hours. The mixture was cooled and concentrated in vacuo. Purification via flash chromatography (96:4 CH_2Cl_2/MeOH) afforded N^4-ethyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine (0.031 g, 47%) as a pale yellow solid; Mass Spec M+H = 329. Use of different alkyllithium reagents in step 1 and/or different substituted amines in steps 6 and 8 of the above procedure

afforded additional compounds under the same or very similar reaction conditions. Additional compounds made by the procedure of Example 3 are shown in Table 1.

Example 4: 2-[4-Amino-5-(5-chloro-2-isopropyl-4-methoxy-phenoxy)-pyrimidin-2-ylamino]-(R)-propan-1-ol

[0238] The synthetic procedure used in this Example is outlined in Scheme G.



Scheme G

Step 1. 2-Chloro-5-isopropyl-phenol

[0239] A solution of 3-isopropyl phenol (10.0 g, 73.4 mmol) in 350 mL 9:1 benzene/$CHCl_3$ was cooled to 0°C. Hypochlorous acid *tert*-butyl ester (8.77 g, 80.8 mmol) was added dropwise over 5 min and the mixture was allowed to warm to RT. After 16 h the mixture was concentrated in vacuo to give a crude oil. Purification via flash chromatography afforded 2-chloro-5-isopropyl-phenol and 4-chloro-3-isopropyl-phenol (6.540 g, 52%) as a 7:3 inseparable mixture of isomers in the form of a pale yellow oil. The combined regioisomers were used together in the following step.

Step 2. 1-Chloro-4-isopropyl-2-methoxy-benzene

[0240] To a solution of 2-chloro-5-isopropyl-phenol and 4-chloro-3-isopropyl-phenol from step 1 (8.694 g, 47.1 mmol) in 50 mL DMF was added K_2CO_3. Iodomethane (3.5 mL, 56.5 mmol) was added and the mixture was warmed to 50°C. After 4 hours H_2O was added. The mixture was extracted with ethyl acetate, washed with H_2O, washed and washed with brine. The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo to give 1-chloro-4-isopropyl-2-methoxy-benzene and 1-chloro-2-isopropyl-4-methoxybenzene (9.289 g) as a 7:3 inseparable mixture in the form of a pale yellow oil, which was used directly in the following step.

Step 3. 5-Chloro-2-isopropyl-4-methoxy-benzaldehyde

[0241] Using the procedure of step 3 of Example 2, the combined 1-chloro-4-isopropyl-2-methoxy-benzene and 1-

chloro-2-isopropyl-4-methoxy-benzene (3.715 g, 20.1 mmol) were treated with $TiCl_4$ followed by Cl_2CHOMe to give a mixture of 5-chloro-2-isopropyl-4-methoxy-benzaldehyde and 5-chloro-4-isopropyl-2-methoxy-benzaldehyde as a yellow oil. These regioisomers were separable by flash chromatography (gradient: hexane, 7:3, 1:1 hexane/CH_2Cl_2) to afford 5-chloro-2-isopropyl-4-methoxy-benzaldehyde (1.269 g, 30%) as a pale yellow solid.

Step 4. 5-Chloro-2-isopropyl-4-methoxy-phenol

[0242] Using the procedure of step 4 from Example 2 described above, 5-chloro-2-isopropyl-4-methoxy-benzaldehyde (3.203 g, 15.1 mmol) afforded 5-chloro-2-isopropyl-4-methoxy-phenol (1.768 g, 58%) as s clear oil.

Step 5. (5-Chloro-2-isopropyl-4-methoxy-phenoxy)-acetonitrile

[0243] To a solution of 5-chloro-2-isopropyl-4-methoxy-phenol (10.36 g, 51.6 mmol) in 40 mL DMF was added K_2CO_3 (8.55 g, 62.0 mmol) and the mixture was heated to 65°C. After 15 min iodoacetonitrile (9.05 g, 54.2 mmol) was added and the mixture was heated to 80°C for 1 hour. The mixture was cooled, poured into an ice/H_2O mixtue and extracted with 1:1 toluene/hexane. The combined organics were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by passing through a short plug of silica to afford (5-chloro-2-isopropyl-4-methoxy-phenoxy)-acetonitrile (11.97 g, 97%) as a white solid.

Step 6. 2-(5-Chloro-2-isopropyl-4-methoxy-phenoxy)-3-methoxy-acrylonitrile

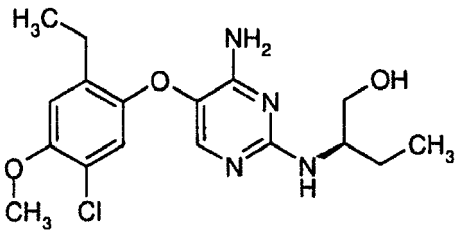
[0244] To a solution of (5-chloro-2-isopropyl-4-methoxy-phenoxy)-acetonitrile (1.44 g, 6.0 mmol) and ethyl formate (2.2 g, 29.2 mmol) in 7 mL 1,2-dimethoxyethane at 5°C was added 95% NaH (0.15 g, 6.0 mmol) in one portion. The mixture was warmed to RT. After 1 hour 95% NaH (0.15 g, 6.0 mmol) was added in one portion. After 1 hour 10 mL iodomethane was added and the mixture was allowed to stir for 16 hour. The mixture was concentrated in vacuo, 1N HCl was added and the mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. Purification via flash chromatography (85:15 hexane/ethyl acetate) afforded 2-(5-chloro-2-isopropyl-4-methoxy-phenoxy)-3-methoxy-acrylonitrile (1.41 g, 84%) as a white solid.

Step 7. 2-[4-Amino-5-(5-chloro-2-isopropyl-4-methoxy-phenoxy)-pyrimidin-2-ylamino]-(R)-propan-1-ol

[0245] To a solution of 2-(5-chloro-2-isopropyl-4-methoxy-phenoxy)-3-methoxy-acrylonitrile (0.20 g, 0.7 mmol) in 1 mL DMSO was added N-(2-(R)-hydroxy-1-methyl-ethyl)-guanidine from Preparation 1 (0.10 g, 0.8 mmol). The solution was warmed to 120°C. After 45 min the solution was cooled, taken up in H_2O, and extracted with ethyl acetate. The combined organic layers were washed with H_2O, dried over $NaSO_4$, filtered and concentrated in vacuo. Purification via flash chromatography (95:5 CH_2Cl_2/MeOH) afforded 2-[4-Amino-5-(5-chloro-2-isopropyl-4-methoxy-phenoxy)-pyrimidin-2-ylamino]-(R)-propan-1-ol (0.128 g, 50 %) as a solid; Mass Spec M+H = 366.

Example 5: 2-[4-Amino-5-(5-chloro-2-ethyl-4-methoxy-phenoxy)-pyrimidin-2-yl-amino]-butan-1-ol

[0246]



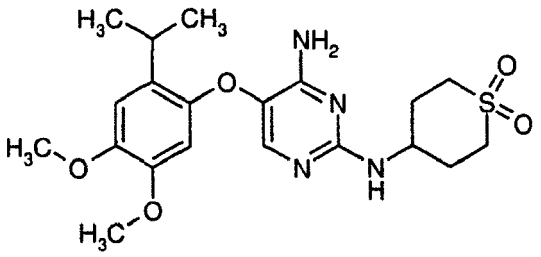
[0247] To a solution of N-(2-(R)-hydroxy-1-methyl-ethyl)-guanidine from Preparation 1 (0.15 g, 1.1 mmol) in 1 mL of dry DMSO was added 2-(5-chloro-2-isopropyl-4-methoxy-phenoxy)-3-methoxy-acrylonitrile (0.23 g, 0.9 mmol) from step 6 of Example 4. The mixture was heated at 120°C for 3.0 hours. The reaction mixture was cooled and 20 mL of water was added and was extracted with EtOAc (2 X 50 mL). The combined organic solution was then washed with water (3 X 50 mL), then with Brine. The solution was dried over $MgSO_4$, filtered and concentrated. The compound was purified by column chromatography on Silica Gel using 2% MeOH/DCM. The fractions containing the product were combined and evaporated under reduced pressure to give crude product. This product was suspended in 2 mL of ether, and 0.6

mL of 1M HCl/ether (1.5 eq.) was added. 30 min later, the solid was filtered and washed with ether to give 160 mg of2-[4-amino-5-(5-chloro-2-isopropyl-4-methoxy-phenoxy)-pyrimidin-2-ylamino]-(R)-propan-1-ol as a hydrochloride salt: Mass Spec M+H = 367; MP; 111.4-116.9°C.

[0248] The above procedure was used with various different phenols and amino guanidines under essentially the same reaction conditions to produce additional compounds, which are shown in Table 1.

Example 6: N2-(1,1-Dioxo-hexahydro-1λ6-thiopyran-4-yl)-5-(2-isopropyl-4,5-dimethoxy-phenoxy)-pyrimidine-2,4-diamine

[0249]

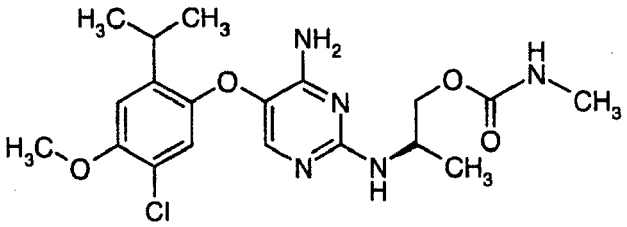


[0250] 5-(2-Isopropyl-4,5-dimethoxy-phenoxy)-N^2-(tetrahydro-thiopyran-4-yl)-pyrimidine-2,4-diamine was prepared according to the procedure of example 5, using 2-(2-isopropyl-4,5-dimethoxy-phenoxy)-3-methoxy-acrylonitrile (prepared using the procedure of Example 4) together with N-(tetrahydro-thiopyran-4-yl)-guanidine from Preparation 1.

[0251] To a mixture of 5-(2-isopropyl-4,5-dimethoxy-phenoxy)-N^2-(tetrahydro-thiopyran-4-yl)-pyrimidine-2,4-diamine (0.19 g, 0.46 mmol) in 25 mL of methanol and 25 mL of water was added the OXONE (1.73 g, 1.4 mmol). This mixture was stirred at RT overnight. The reaction mixture was diluted with water (50 mL) and extracted with EtOAc (3 X 50 mL). The organic solution was washed with Brine, dried over $MgSO_4$. The solution was filtered and concentrated. The residue was purified on one preparative TLC plate (20 x 40 cm) eluting with EtOAc. Product recovered was stirred with 1.5 eq of 1M HCl/ether to afford 25 mg of N^2-(1,1-dioxo-hexahydro-1λ6-thiopyran-4-yl)-5-(2-isopropyl-4,5-dimethoxy-phenoxy)-pyrimidine-2,4-diamine HCl salt): MS (M+H); 441: MP; 255.1 - 257.8°C.

Example 7: Methyl-carbamic acid 2-[4-amino-5-(5-chloro-2-isopropyl-4-methoxy-phenoxy)-pyrimidin-2-ylamino]-propyl ester

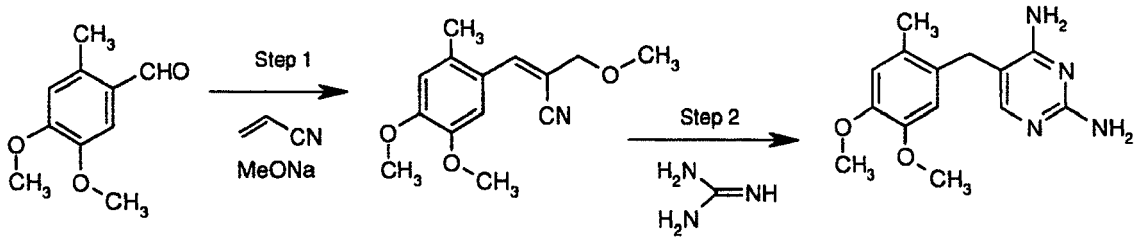
[0252]



[0253] 1,1-Carbonyldiimidazole (0.97 g, 6 mmol) was added to a solution of 2-[4-Amino-5-(5-chloro-2-isopropyl-4-methoxy-phenoxy)-pyrimidin-2-ylamino]-(R)-propan-1-ol from Example 4 (0.22 g, 0.6 mmol) in 20 mL of THF at RT. The mixture was stirred for 2 hours and methylamine (3 mL, 2M/THF, 0.6 mmol) was added. The reaction mixture was stirred overnight and concentrated under reduced pressure, diluted with water (75 mL), and extracted with EtOAc (2 X 75 mL). The organic phase was washed with Brine and dried with $MgSO_4$. The solution was filtered and concentrated. The residue was purified on two Silica preparative TLC plates (20 X 40 cm) eluting with 5% MeOH/DCM affording 143 mg of methyl-carbamic acid 2-[4-amino-5-(5-chloro-2-isopropyl-4-methoxy-phenoxy)-pyrimidin-2-ylamino]-propyl ester: MS (M+H); 424: MP; 63.5 - 69.4°C.

Example 8: 5-(4,5-Dimethoxy-2-methyl-benzyl)-pyrimidine-2,4-diamine

[0254] The synthetic procedure used in this Example is outlined in Scheme H.



Scheme H

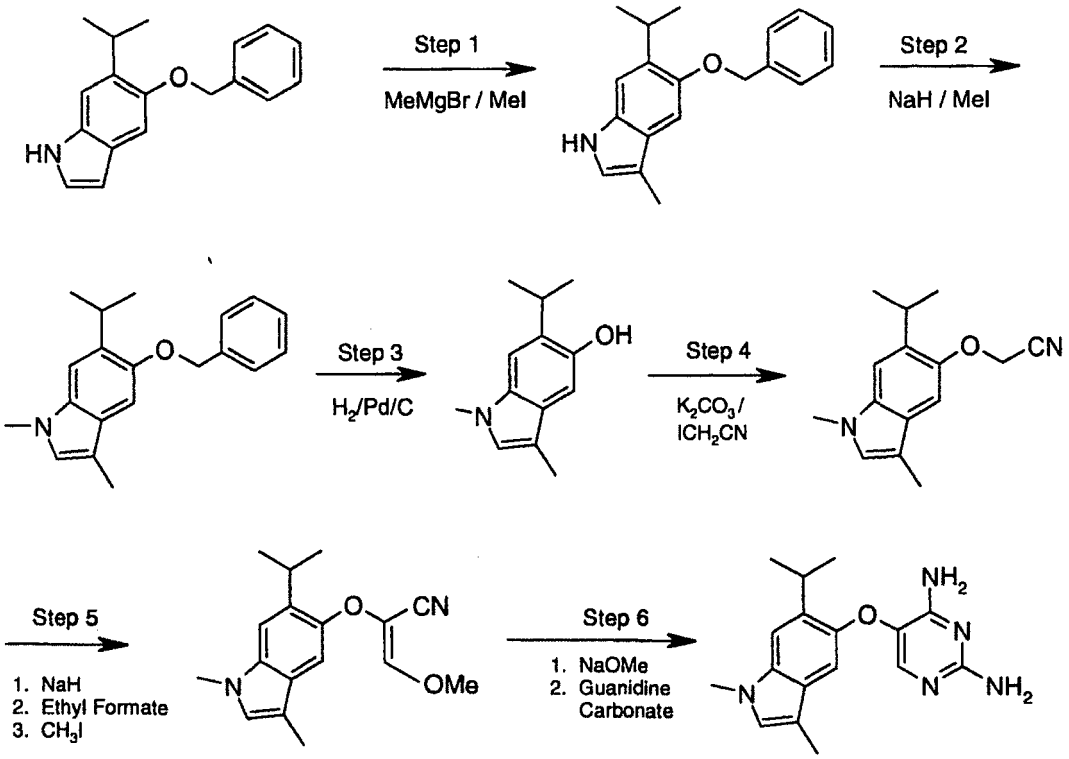
[0255] This Example follows the procedure described by Manchand et al., J. Org. Chem. 1992, 57, 3531-3535. Briefly, in step 1 4,5-dimethoxy-2-methyl-benzaldehyde and sodium methoxide were dissolved in cold methanol and stirred under nitrogen at RT for 18 hours. The mixture was cooled to -15°C, and crude 3-(4,5-dimethoxy-2-methyl-phenyl)-2-methoxymethyl-acrylonitrile was collected as filtrate.

[0256] In step 2, 3-(4,5-dimethoxy-2-methyl-phenyl)-2-methoxymethyl-acrylonitrile and sodium methoxide were dissolved in dry DMSO and stirred for 3.5 hours at 85°C under nitrogen. Guanidine carbonate was then added to the stirring solution, after which the temperature was raised to 125°C for three hours, during which methanol removed via a Dean-Stark trap. The solution was cooled to RT, diluted with water, and the crude filtrate was recrystallized in DMF to yield 5-(4,5-dimethoxy-2-methyl-benzyl)-pyrimidine-2,4-diamine as a white solid. Mp: 232°C. Mass Spec (M+H): 275.

[0257] Additional compounds made by Example 8 are shown in Table 1.

Example 9: 5-(6-Isopropyl-1,3-dimethyl-1H-indol-5-yloxy)-pyrimidine-2,4-diamine

[0258] The synthetic procedure used in this Example is outlined in Scheme I.



SCHEME I

[0259] The 5-benzyloxy-6-isopropyl-1H-indole utilized in step 1 of this Example was prepared from 1-{2-[(5-benzyloxy)-4-(1-methylethyl)-2-nitrophenyl]ethenyl}-pyrrolidine according to the procedure reported by Leonardi et al., Eur. J. Med. Chem. (1994), 29, 551-559. The methylation of step 3 below also follows the procedure described by Leonardi et al.

Step 1. 5-Benzyloxy-6-isopropyl-3-methyl-1H-indole

[0260] The methylation carried out in this step follows the procedure for indole alkylation reported by Marino et al., J. Am. Chem. Soc. (1992), 114, 5566-5572. 5-Benzyloxy-6-isopropyl-1H-indole (0.855 g, 3.22 mmol) was dissolved in 20 mL of dry THF, and the resulting solution was cooled in an ice bath. Ethyl magnesium bromide (4.9 ml, 4.9 mmol in ether) was added dropwise to the solution, and the solution was then stirred for 4 hours at RT. Methyl iodide (1.42 g, 10 mmol) was then added, and stirring was continued for an additional 18 hours at RT. The reaction mixture was poured into ice water and extracted with ethyl acetate. The combined organic layers were washed with saturated ammonium chloride, dried ($MgSO_4$), and concentrated *in vacuo.* The resulting residue was purified with flash chromatography (ethyl acetate/hexanes = 1/9) to yield 325 mg of 5-benzyloxy-6-isopropyl-3-methyl-1H-indole Mass Spec (M+H): 280.

Step 2. 5-Benzyloxy-6-isopropyl-1,3-dimethyl-1H-indole

[0261] 5-Benzyloxy-6-isopropyl-3-methyl-1H-indole (0.320 g, 1.15 mmol), KOH (0.264 g, 4.7 mmol), benzyl tributylammonium chloride (0.071g, 0.230 mmol), and methyl iodide (0.107 mL, 1.72 mmol) were added to 3 mL of toluene. The resulting mixture was stirred for 4 hours at 90°C, cooled to RT, poured into water, and extracted with ethyl acetate 2 times. The combined organic layers were washed with water, dried ($MgSO_4$), and evaporated *in vacuo* to provide a crude oil that was was purified with flash chromatography (ethyl acetate/hexanes = 1/9); yield 270 mg of 5-benzyloxy-6-isopropyl-1,3-dimethyl-1H-indole.

Step 3. 6-Isopropyl-1,3-dimethyl-1H-indol-5-ol

[0262] 5-Benzyloxy-6-isopropyl-1,3-dimethyl-1H-indole (0.270 g, 1.30 mmol) and Pd/C 10% (0.150 g) were added to 10 mL of methanol, and the mixture was hydrogenated in a Parr apparatus for 1.5 hours at 55 psi, at RT. The catalyst was removed by filtration and the solvent was removed *in vacuo.* The residue was purified with flash chromatography (5% ethyl acetate in hexanes) to yield 210 mg of 6-isopropyl-1,3-dimethyl-1H-indol-5-ol.

Step 4. (6-Isopropyl-1,3-dimethyl-1H-indol-5-yloxy)-acetonitrile

[0263] (6-Isopropyl-1,3-dirnethyl-1H-indol-5-yloxy)-acetonitrile was prepared from 6-isopropyl-1,3-dimethyl-1H-indol-5-ol by treatment with iodoacetonitrile using the procedure of step 5 of Example 2 above.

Step 5. 2-(6-Isopropyl-1,3-dimethyl-1H-indol-5-yloxyl-4-methoxy-but-2-enenitrile

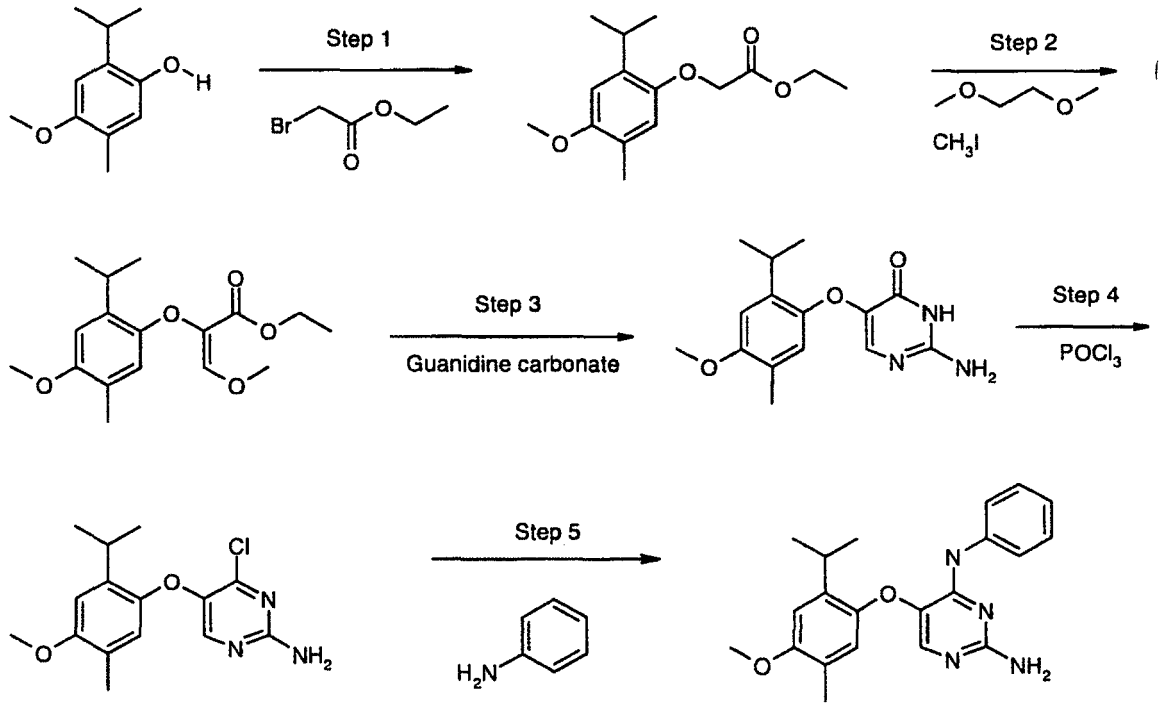
[0264] 2-(6-Isopropyl-1,3-dimethyl-1H-indol-5-yloxy)-4-methoxy-but-2-enenitrile was prepared from (6-isopropyl-1,3-dimethyl-1H-indol-5-yloxy)-acetonitrile by treatment with sodium hydride and methyl iodide using the procedure of step 6 of Example 2 above.

Step 6. 5-(6-Isopropyl-1,3-dimethyl-1H-indol-5-yloxy)-pyrimidine-2,4-diamine

[0265] 5-(6-Isopropyl-1,3-dimethyl-1H-indol-5-yloxy)-pyrimidine-2,4-diamine was prepared from 2-(6-isopropyl-1,3-dimethyl-1H-indol-5-yloxy)-4-methoxy-but-2-enenitrile by treatment with guanidine carbonate and sodium methoxide using the procedure of step 7 of Example 2 above. This material was dissolved in 2.5 ml absolute ethanol, and 820 ml of 1 N HCl in diethyl ether was added with stirring. Diethyl ether was added slowly until small crystals formed, and the solution was then placed in a -10°C freezer for 18 hours. The solid that had formed was collected by filtration, washed with diethyl ether, and dried under vacuum at 45°C to give 171 mg. of the hydrochloride salt, Mp: 185.1°C. 5-(6-Isopropyl-1-methyl-1H-indol-5-yloxy)-pyrimidine-2,4-diamine was also prepared using the above procedure, but omitting the 3-methylation of step 1. MS (M+H): 298.

Example 10: 5-(2-Isopropyl-4-methoxy-5-methyl-phenoxy)-N^4-phenyl-pyrimidine-2,4-diamine

[0266] The synthetic procedure used in this Example is outlined in Scheme J.



Scheme J

Step 1. (2-Isopropyl-4-methoxy-5-methyl-phenoxyl-acetic acid ethyl ester

[0267] To a solution of 2-isopropyl-4-methoxy-5-methyl-phenol (3.933 g, 21.8 mmol) in acetone (100 ml) was added potassium carbonate (20 g, 145 mmol) and ethyl bromoacetate (5ml, 45.1 mmol). The mixture was refluxed over night and was filtered through celite. The filtrate was concentrated under reduced pressure and the residue was partitioned between ethyl acetate and water. The organic phase was washed with brine and dried over anhydrous sodium sulfate. After removal of drying agent, the organic solution was concentrated under reduced pressure. The residue was purified with silica gel chromatography (10% to 15% methylene chloride in hexane) to yield (2-isopropyl-4-methoxy-5-methyl-phenoxy)-acetic acid ethyl ester as white solid (4.78 g, 82%).

Step 2. 2-(2-Isopropyl-4-methoxy-5-methyl-phenoxy)-3-methoxy-acrylic acid ethyl ester

[0268] To a solution of (2-isopropyl-4-methoxy-5-methyl-phenoxy)-acetic acid ethyl ester (4.42 g, 16.6 mmol) in anhydrous 1,2-dimethoxy ethane (60 ml) was added sodium hydride (60% in mineral oil, 3.5 g, 87.5 mmol) at RT. After 5 min of stirring, ethyl formate (40 ml, 495 mmol) was added. The mixture was heated at 85°C for 7 hours. After cooling to RT, iodomethane was added and stirring was continued overnight. Solvent was concentrated under reduced pressure and the residue was partitioned between ethyl acetate and water. The organic phase was washed with brine and dried over anhydrous sodium sulfate. After removal of drying agent, the organic solution was concentrated under reduced pressure. The residue was purified with silica gel chromatography (10% to 30% ethyl acetate in hexane) to yield 2-(2-isopropyl-4-methoxy-5-methyl-phenoxy)-3-methoxy-acrylic acid ethyl ester as a pale yellow oil (1.19 g, 23%).

Step 3. 2-Amino-5-(2-isopropyl-4-methoxy-5-methyl-phenoxy)-3H-pyrimidin-4-one

[0269] To a solution of NaOMe [prepared from sodium (0.05 g, 2.17 mmol) in anhydrous methanol (5 ml)], was added guanidine carbonate. After 5 min, a solution of 2-(2-isopropyl-4-methoxy-5-methyl-phenoxy)-3-methoxy-acrylic acid ethyl ester (0.22 g, 0.713 mmol) in anhydrous DMSO (10 ml) was added. The mixture was heated at 120°C for 3 hours and was cooled and partitioned between ethyl acetate and water. The organic phase was washed with brine and dried over anhydrous sodium sulfate. After removal of drying agent, the organic solution was concentrated under reduced pressure. The residue was purified with silica gel chromatography (5% methanol in methylene chloride /0.1% concentrated NH_4OH) to yield 2-amino-5-(2-isopropyl-4-methoxy-5-methyl-phenoxy)-3H-pyrimidin-4-one as pale yellow solid (0.045 g, 22%). MS M+H=290.

Step 4. 4-Chloro-5-(2-isopropyl-4-methoxy-5-methyl-phenoxy)-pyrimidin-2-ylamine

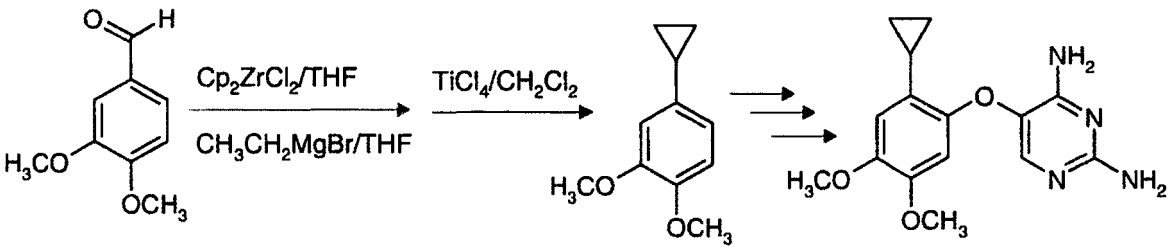
[0270] A mixture of 2-amino-5-(2-isopropyl-4-methoxy-5-methyl-phenoxy)-3H-pyrimidin-4-one in phosphorus oxychloride (5 ml) was heated at 110°C for 40 min and stirred at RT over night. Solvent was removed under reduced pressure and ice water was added. The aqueous solution was basified with potassium carbonate to pH 9, and extracted with methylene chloride. The organic phase was washed with brine and dried over anhydrous sodium sulfate. After removal of drying agent, the organic solution was concentrated under reduced pressure to yield 4-chloro-5-(2-isopropyl-4-methoxy-5-methyl-phenoxy)-pyrimidin-2-ylamine as yellow solid (0.043 g, 88%). MS M+H = 308.

Step 5. 5-(2-Isopropyl-4-methoxy-5-methyl-phenoxy)-N^4-phenyl-pyrimidine-2,4-diamine

[0271] A suspension of 4-chloro-5-(2-isopropyl-4-methoxy-5-methyl-phenoxy)-pyrimidin-2-yl-amine (0.043 g, 0.14 mmol) in aniline (4 ml) was placed in a sealed tube and heated at 100°C over night. Methylene chloride was added and insoluble solid was removed by filtration through celite. The combined methylene chloride filtrate was washed with water and dried over anhydrous sodium sulfate. After removal of the drying agent, the organic phase was concentrated under reduced pressure. The residue was purified with silica gel chromatography (2% methanol in methylene chloride) to yield a yellow oily residue, which was further purified with preparative TLC and HPLC (5 to 100%acetonitrile in water with 0.1% trifluoroacetic acid to yield 5-(2-Isopropyl-4-methoxy-5-methyl-phenoxy)-N^4-phenyl-pyrimidine-2,4-diamine, M+H: 365.

Example 11: 5-(2-Cyclopropyl-4,5-dimethoxy-phenoxy)-pyrimidine-2,4-diamine

[0272]



Step 1. 4-Cyclopropyl-1,2-dimethoxy-benzene

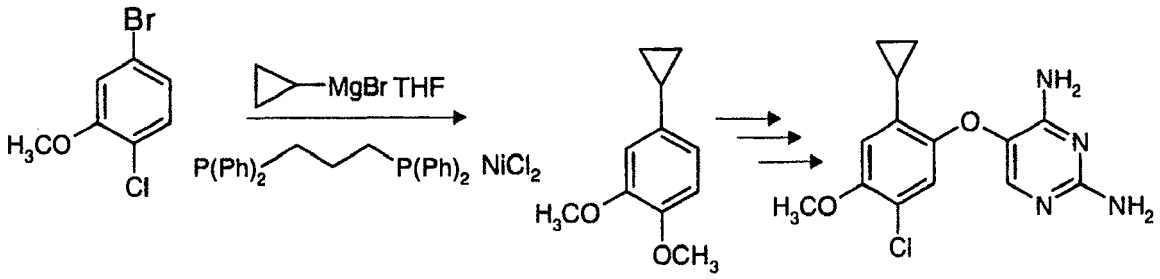
[0273] To a solution of zirconocene dichloride (1.76 g, 6.02 mmols) in dry THF (25 ml), was slowly added ethylmagnesium bromide (12 ml, 1 M in THF, 12 mmol) at -78°C. The green solution was stirred for 15 min at -78°C and then warmed to 2°C until the reaction color turned red (15 min). A solution of 3,4-dimethoxy-benzaldehyde (1.00 g, 6.02 mmol) in dry THF (20 ml) was added and the reaction was allowed to warm up to RT over 1.5 hours. Solvent was removed under reduced pressure, and DCM (20 ml) was added. The reaction mixture was cooled to 0°C and titanium chloride (IV) (6 ml, 1M in dichloromethan, 6 mmol) was added. The reaction was allowed to warm up to RT over 30 min, and quenched with saturated ammonium chloride solution. The mixture was filtered through celite and portioned between DCM and water. The combined DCM was washed with saturated aqueous solution of ammonium chloride, saturated aqueous sodium bicarbonate and brine. The organic phase was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (gradient: 8% to 30%ethyl acetate in hexane) to yield 4-cyclopropyl-1,2-dimethoxy-benzene as yellow oily residue (0.2 g, 19%). Ref: Vincent Gandon et al. Eur. J. Org. Chem. 2000, 3713.

Step 2. 5-(2-Cyclopropyl-4,5-dimethoxy-phenoxy)-pyrimidine-2,4-diamine

[0274] 5-(2-Cyclopropyl-4,5-dimethoxy-phenoxy)-pyrimidine-2,4-diamine was prepared from 4-cyclopropyl-1,2-dimethoxy-benzene following the procedure of step 1 and steps 3-7 of Example 2 above.

Example 12: 5-(5-Chloro-2-cyclopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine

[0275]



Step 1. 1-Chloro-4-cyclopropyl-2-methoxy-benzene

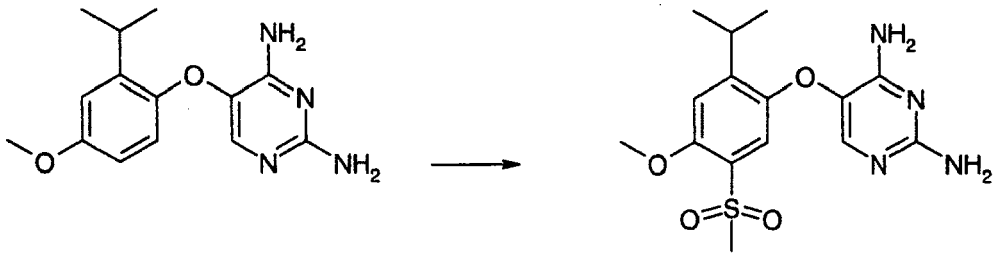
[0276] To a solution of 4-bromo-1-chloro-2-methoxy-benzene (1.45 g, 6.55 mmol) in dry THF (10 ml), was added {1,3-bis (diphenylphosphino)-propane} dichloronickel (II) and cyclopropylmagnesium bromide (46 ml, 0.5 M in THF, 23 mmols) at RT. The solution was stirred at RT for 2 hours, and then heated at 65°C for 48 hours. Aqueous hydrochloric acid solution (1 N, 20 mL) was aded, and the mixture was then cooled to RT and stirred for 30 min. The reaction mixture was partitioned between ethyl acetate and water. The combined organic phase was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (2% ethyl acetate in hexane) to yield 1-chloro-4-cyclopropyl-2-methoxybenzene as yellow oily residue (0.81 g, 67%).

Step 2. 5-(5-Chloro-2-cyclopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine

[0277] 5-(5-Chloro-2-cyclopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine was prepared from 4-cyclopropyl-1,2-dimethoxy-benzene following the procedure of step 1 and steps 3-7 of Example 2 above.

Example 13: 5-(2-Isopropyl-5-methanesulfonyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine

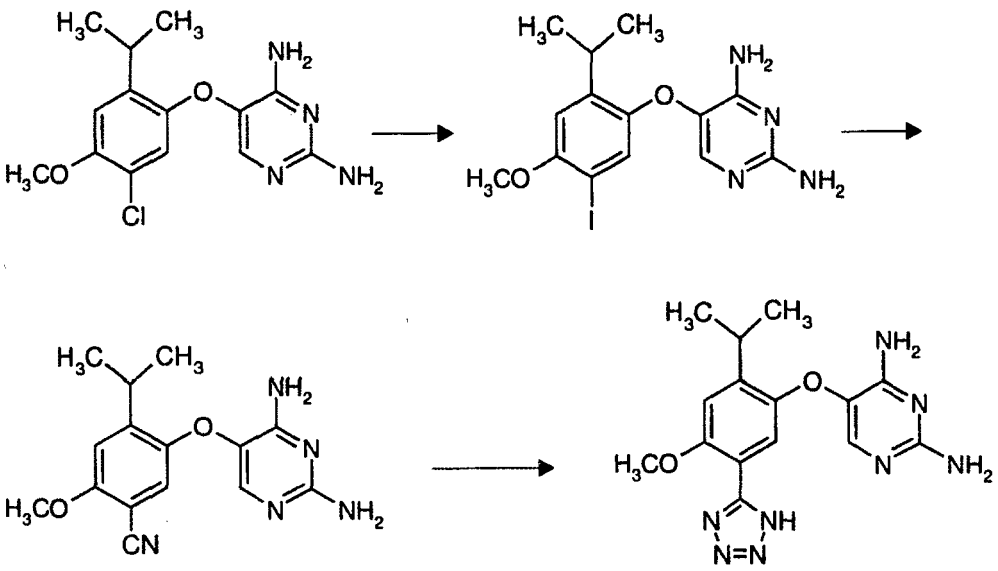
[0278]



[0279] To a mixture of 5-(2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine (0.32g, 1.17mmol), prepared according to Example 2, and methanesulfonic anhydride (0.81g, 4.67mmol) was added trifluoromethanesulfonic acid (0.45g, 3.00 mmol), and the mixture was heated at 80°C for 16 hrs. The reaction mixture was poured into ice water, basified with saturated $NaHCO_3$ solution and extracted into DCM, which was dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified via flash chromatography on silica gel (3%CH_3OH in CH_2Cl_2 with 0.1%NH_4OH) gave 5-(2-isopropyl-5-methanesulfonyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine as a white solid (0.248 g, 90%; 0.107 g), MS (M+H): 353.

Example 14: 5-[5-(2,3-Dihydro-1H-tetrazol-5-yl)-2-isopropyl-4-methoxy-phenoxy]-pyrimidine-2,4-diamine

[0280]



Step 1 5-(5-Iodo-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine

[0281] To a solution of 5-(2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine (0.40 g, 1.44 mmol) in glacial acetic acid (4 ml) at RT was added a solution of iodine monochloride (0.28 g, 1.76 mmol) in glacial acetic acid (4 ml). Water (6 ml) was also added, and the reaction was stirred for 16 hours, after which another portion of iodine monochloride (0.4g, 2.47mmol) in glacial acetic acid (4ml) was added. The reaction mixture was stirred for an additional hour at RT. The acidic mixture was basified with saturated $NaHCO_3$ solution and extracted into DCM. The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified via flash chromatography (5%CH_3OH in CH_2CL_2 with 0.1% NaOH) to give 5-(5-iodo-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine as beige colored solid (0.536 g, 92%). M+H 400.

Step 2. 5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-benzonitrile

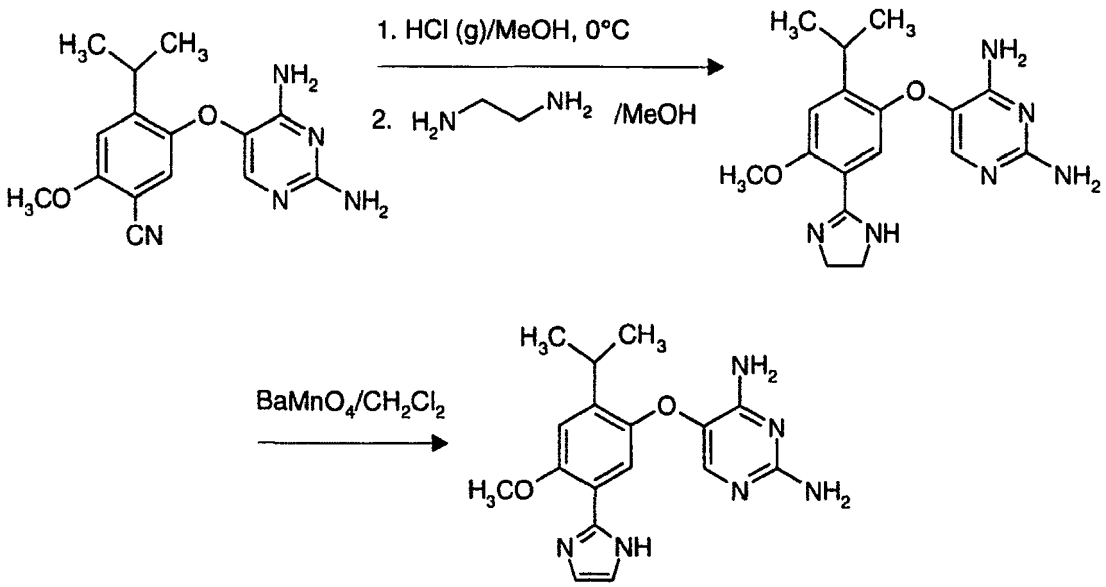
[0282] A mixture of 5-(5-iodo-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine (0.37g, 0.925 mmol) and CuCN (0.12 g, 1.39 mmol) in DMF (5 ml) was heated at 120°C for 3 hours. Water (100 ml) was added, and the precipitate was collected. The residue was triturated with methanolic DCM (10% CH_3OH in CH_2Cl_2 with 0.1% NH_4OH) to release the product from its copper complex and filtered. The filtrate was concentrated and purified via flash chromatography (3%CH_3OH in CH_2Cl_2 with 0.1% NH_4OH) to give 5-(2,4-diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-benzonitrile as white solid (0.12 g, 44%): M+H 300.

Step 3. 5-[5-(2,3-Dihydro-1H-tetrazol-5-yl)-2-isopropyl-4-methoxy-phenoxy]-pyrimidine-2,4-diamine

[0283] To a hot solution of 5-(2,4-diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-benzonitrile (0.2 g, 0.67mmol) in xylene (15 ml) at 120°C was added azidotributyltin (1.10 g, 0.67 mmol), and the reaction mixture was heated for two hours. Another portion of azidotributyltin (1.10 g, 3.34 mmol) was added, and the mixture was heated for another five hours. The reaction mixture was cooled to 0°C and bubbled with HCl gas for five min. The solid formed was collected by filtration and washed with CH_2Cl_2 (3 x 5 ml). Purification of the solid by preparative HPLC (15-95%CH_3CN in water, 10 minute gradient) gave 5- [5-(2,3-dihydro-1H-tetrazol-5-yl)-2-isopropyl-4-methoxy-phenoxy]-pyrimidine-2,4-diamine HCl salt, as white solid (62 mg, 25%). M+H 343.

Example 15: 5-[5-(1H-Imidazol-2-yl)-2-isopropyl-4-methoxy-phenoxy]-pyrimidine-2,4-diamine

[0284]



Step 1. 5-[5-(4,5-Dihydro-1H-imidazol-2-yl)-2-isopropyl-4-methoxy-phenoxy]-pyrimidine-2,4-diamine

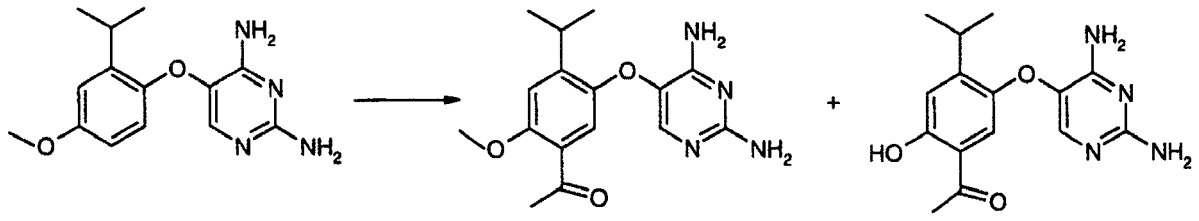
[0285] To a cooled (0°C) suspension of 5-(2,4-diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-benzonitrile (0.138 g, 0.461 mmol) in dry methanol (15 ml) was bubbled with HCl gas for 10 min and refrigerated overnight. Solvent was evaporated under reduced pressure to give a yellow solid which was redissolved in dry methanol (10 ml). Ethylene diamine (0.034 ml, 0.509mmol) was added and the reaction mixture was refluxed for 20 hours and concentrated under reduced pressure. The residue was purified by silica gel chromatography (gradient: 7- 50% methanol in methylene chloride /0.1% concentrated NH_4OH) to yield 5-[5-(4,5-dihydro-1H-imidazol-2-yl)-2-isopropyl-4-methoxy-phenoxy]-pyrimidine-2,4-diamine which was crystalized from methanol /ethyl acetate /ether as a white solid, (0.053g, 33%).

Step 2. 5-[5-(1H-Imidazol-2-yl)-2-isopropyl-4-methoxy-phenoxy]-pyrimidine-2,4-diamine

[0286] To a solution of 5-[5-(4,5-dihydro-1H-imidazol-2-yl)-2-isopropyl-4-methoxy-phenoxy]-pyrimidine-2,4-diamine (0.033 g, 0,096 mmol) in dry methylene chloride (25 ml) was added barium manganate (0.4 g, 1.56 mmol). The reaction mixture was refluxed over night, after which more of barium manganate (0.1 g) was added, and the mixture was refluxed for another 6 hours. The reaction mixture was filtered through celite, and the filtrate was concentrated under reduced pressure. The residue was purified with preparative TLC (8% methanol in methylene chloride /0.1% concentrated ammonium hydroxide) to yield 5-[5-(1H-imidazol-2-yl)-2-isopropyl-4-methoxy-phenoxy]-pyrimidine-2,4-diamine as pale yellow solid (0.026 g, 41%).

Example 16: 1-[5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-ethanone and 1-[5-(2,4-Diamino-pyrimidin-5-yloxy)-2-hydroxy-4-isopropyl-phenyl]-ethanone

[0287]

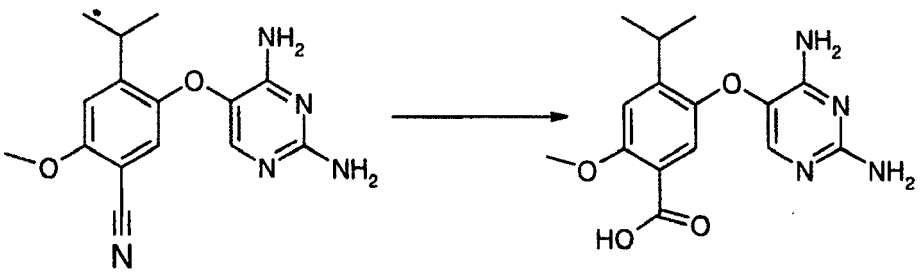


[0288] 5-(2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine in anhydrous dichloroethane (20 mL) was added to trifluoroacetic acid (0.06 mL, 0.77 mmol), acetyl chloride (0.31 mL, 4.37 mmol), and aluminum trichloride (583 mg, 4.37 mmol). After stirring for 22 hours at RT, water (1.2 mL) was added to the reaction at 0°C. The mixture was dried using anhydrous sodium sulfate and concentrated in vacuo. Aqueous sodium hydroxide (0.2M, 10 mL) was added to the residue and the mixture was heated at 100°C for 1 hour. After cooling, the reaction was extracted with DCM. The

DCM layer was dried using anhydrous magnesium sulfate, concentrated, and purified with silica gel column chromatography eluting with 96/4/0.1 DCM / methanol/ ammonium hydroxide to yield 1-[5-(2,4-diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-ethanone (72 mg, 31%) as off-white solid, MS (M+H) = 317. Also recovered was 1-[5-(2,4-diamino-pyrimidin-5-yloxy)-2-hydroxy-4-isopropyl-phenyl]-ethanone (43 mg, 20%) as pale yellow solid, MS (M+H) = 303.

Example 17: 5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-benzoic acid

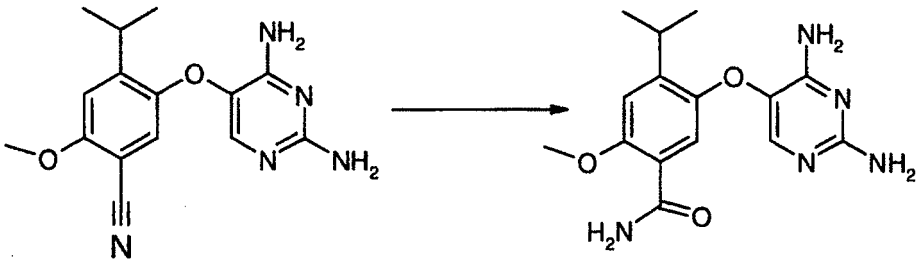
[0289]



[0290] To a suspension of 5-(2,4-diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-benzonitrile (50 mg, 0.17 mmol, from Example 15) in ethanol (1 mL) was added sodium hydroxide (174 mg, 4.34 mmol, dissolved in 1 mL water). After refluxing overnight, the reaction was cooled in an ice bath. Aqueous hydrochloric acid (3M) was added until the pH of the reaction was 7. The white solid precipitate was collected, washed with small amounts of water and DCM, and dried to yield 5-(2,4-diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-benzoic acid: (51 mg, 96%, MS (M+H) = 319), which was converted to the hydrochloride salt.

Example 18: 5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-benzamide

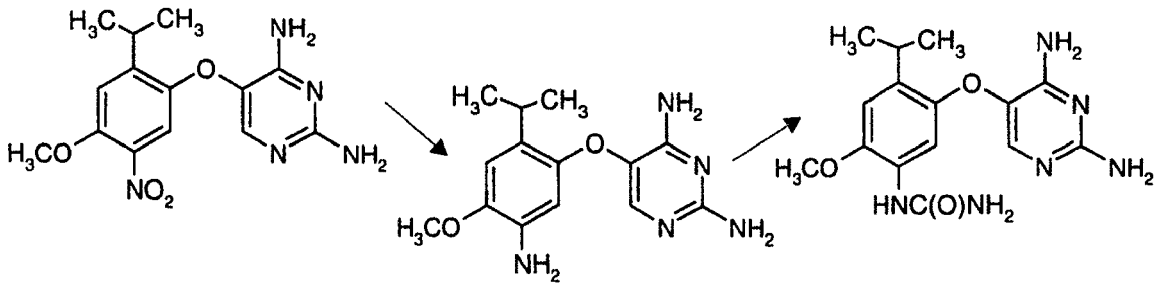
[0291]



[0292] To 5-(2,4-diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-benzonitrile (49 mg, 0.16 mmol, from Example 15) suspended in ethanol (1 mL) was added sodium hydroxide (64 mg, 1.60 mmol, dissolved in 1 mL water). The reaction was heated at 110°C for 5 hours, cooled, and washed with DCM (25 mL). The DCM layer was concentrated and purified by preparatory TLC plates (92/8/0.5 DCM / methanol/ ammonium hydroxide) to yield 5-(2,4-diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-benzamide as white solid (9 mg, 17%, MS (M+H) = 318), which was converted to the hydrochloride salt.

Example 19: [5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-urea

[0293]



Step 1. 5-(5-Amino-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine

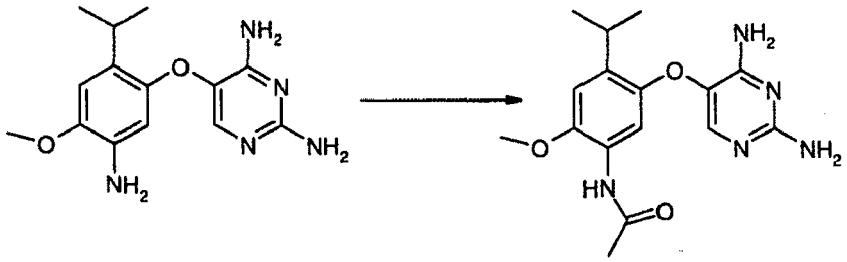
[0294] To 5-(2-isopropyl-4-methoxy-5-nitro-phenoxy)-pyrimidine-2,4-diamine (2.1 g, 6.58 mmol) suspended in ethanol (150 mL) in a Parr bomb, was added 10% palladium on charcoal (210 mg). After hydrogenation in the Parr hydrogenator overnight at 35 psi, the reaction was filtered through celite. The celite pad was washed with ethanol and ethyl acetate and the filtrate was concentrated. Purification with silica gel column chromatography (92/810.1 DCM / methanol/ ammonium hydroxide) gave 5-(5-amino-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine as a pale orange solid (468 mg, 25%, $(M+H)^+$ = 290), which was converted to the hydrochloride salt.

Step 2. [5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-urea

[0295] To 5-(5-amino-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine (314 mg, 1.09 mmol) suspended in water (3 mL) was added acetic acid (0.25 mL, 4.34 mmol). Once all solids had dissolved, sodium cyanate (71 mg, 1.09 mmol, dissolved in 1.5 mL water) was added dropwise. After 30 min, the reaction was concentrated and purified with silica gel column chromatography eluting with 92/8/0.1 DCM / methanol/ ammonium hydroxide to yield [5-(2,4-diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-urea as an off-white solid (244 mg, 68%, $(M+H)^+$ = 333), which was converted to a hydrochloride salt.

Example 20: N-[5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-acetamide

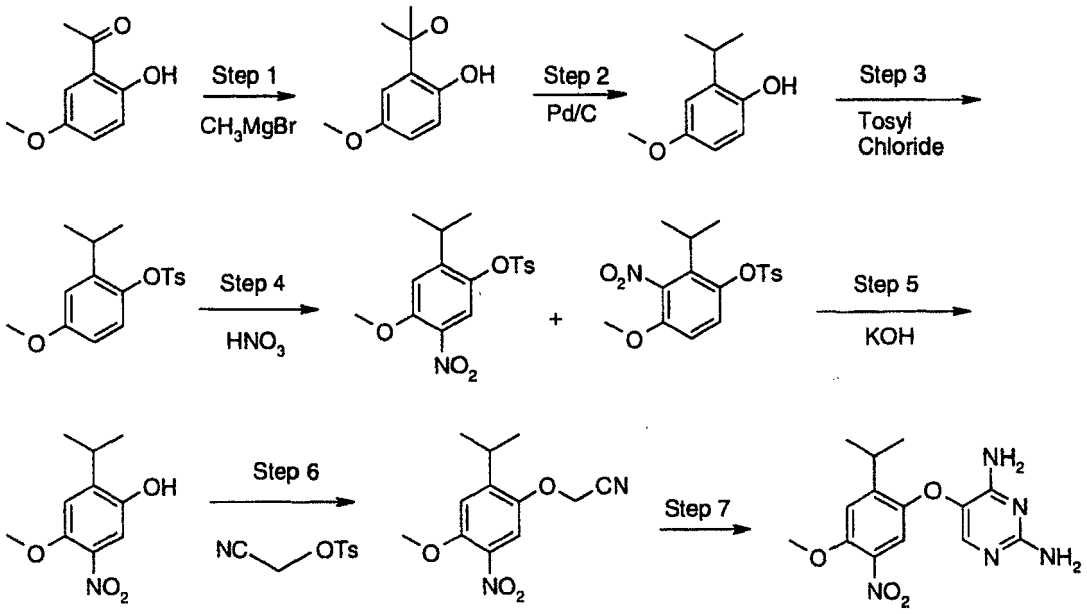
[0296]



[0297] To 5-(5-amino-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine (100 mg, 0.35 mmol, from Example 17) dissolved in anhydrous DCM (10 mL) was added anhydrous pyridine (0.03 mL, 0.38 mmol). To this reaction mixture at 0°C was added acetyl chloride (0.03 mL, 0.38 mmol). After stirring at RT for 1 hour, the reaction was concentrated and purified with preparatory TLC (93/7/0.5 DCM / methanol/ ammonium hydroxide) to yield an off-white solid (74 mg mixture of bis- and tris-acetylated products). To this solid was added aqueous sodium hydroxide (0.2 M, 2 mL), and the mixture was refluxed for 1 hour, cooled, and washed with DCM (10 mL). The DCM layer was dried using anhydrous magnesium sulfate and concentrated in vacuo to yield N-[5-(2,4-diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-acetamide as a white solid (53 mg, 46%, $(M+H)^+$ =332) which was converted to a hydrochloride salt:

Example 21: 5-(2-Isopropyl-4-methoxy-5-nitro-phenoxy)-pyrimidine-2,4-diamine

[0298] The synthetic procedure used in this Example is outlined in Scheme K



SCHEME K

Step 1. 2-(1-Hydroxy-1-methyl-ethyl)-4-methoxy-phenol

[0299] To a solution of methylmagnesium bromide (221 ml, 665 mmol) in 800 ml THF at 0°C was added 1-(2-hydroxy-5-methoxy-phenyl)-ethanone (20.21 g, 302 mmol) in portions over 30 min. The mixture was allowed to warm to RT. After 16 h the mixture was quenched by the slow addition of 10% NH_4Cl, carefully acidified to pH = 1 (slow addition) with concentrated HCl and extracted with Et_2O. The combined organics were washed with H_2O, washed with brine, died over $MgSO_4$, filtered and concentrated in vacuo to give 2-(1-hydroxy-1-methyl-ethyl)-4-methoxy-phenol (50.57 g, 100%) as a tan solid.

Step 2. 2-Isopropyl-4-methoxy-phenol

[0300] To a solution of 2-(1-hydroxy-1-methyl-ethyl)-4-methoxy-phenol (50.57 g, 278 mmol) in 550 ml AcOH was added 10% Pd/C (as a slurry in 20 ml H_2O). Ammonium formate (87.52 g, 1388 mmol) was added in portions. The mixture was warmed to 100°C for 1 hour, cooled and filtered through a pad of celite. The celite pad was washed with ethyl acetate. The mother liquor was mixed with H_2O and extracted with ethyl acetate. The combined organics were washed with H_2O, washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo to give 2-isopropyl-4-methoxy-phenol (44.74 g, 97%) as a pale yellow oil.

Step 3. Toluene-4-sulfonic acid 2-isopropyl-4-methoxy-phenyl ester

[0301] To a solution of 2-isopropyl-4-methoxy-phenol (56.91 g, 342 mmol) TEA (57.3.0 ml, 411 mmol) in 750 ml CH_2Cl_2 was cooled to 0°C. p-Toluenesulfonyl chloride (68.54 g, 360 mmol) in 250 ml CH_2Cl_2 was added dropwise at a rate that maintained the internal temperature < 10°C. The mixture was allowed to warm to RT. After 16 h, H_2O was added and the mixture was extracted with CH_2Cl_2. The combined organics were washed with brine, dried with Na_2SO_4, filtered and concentrated in vacuo to afford a crude solid. Recrystallization from hexanes afforded toluene-4-sulfonic acid 2-isopropyl-4-methoxy-phenyl ester (81.67 g, 74%) as white needles.

Step 4. Toluene-4-sulfonic acid 2-isopropyl-4-methoxy-5-nitro-phenyl ester

[0302] To a solution of toluene-4-sulfonic acid 2-isopropyl-4-methoxy-phenyl ester (19.00 g, 59 mmol) in 118 mL AcOH was added 236 ml fuming HNO_3 over 20 min. After 16 h the solution was pouring into a rapidly stirring slurry of 21 of ice/H_2O. After 15 min the precipitate was filtered, washed with H_2O and dried under vacuum (50°C) to give toluene-4-sulfonic acid 2-isopropyl-4-methoxy-5-nitro-phenyl ester (21.27 g, 98 %) and toluene-4-sulfonic acid 2-isopropyl-4-methoxy-3-nitro-phenyl ester and as a pale yellow solid (7:1 inseperable mixture).

Step 5. 2-Isopropyl-4-methoxy-5-nitro-phenol

[0303] A solution of toluene-4-sulfonic-acid 2-isopropyl-4-methoxy-5-nitro-phenyl ester and 2-isopropyl-4-methoxy-3-nitro-phenyl ester (21.20 g, 58 mmol) and 175 mL 2M KOH in 350 mL EtOH was warmed to 100°C. After 45 min the mixture was cooled, evaporated and taken up in 11 of water. The solution was acidified to pH = 1 with 12 M HCl and extracted with ethyl acetate. The combined organics were washed with H_2O, brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The crude oil was purified via flash chromatography (gradient: 95:5 to 4:1 hexane/ethyl acetate) to afford 3-amino-2-isopropyl-5-nitro-phenol (10.03 g, 81%) as a yellow solid and 3-amino-2-isopropyl-3-nitro-phenol (1.32 g, 11%) as a yellow oil.

Step 6. (2-Isopropyl-4-methoxy-5-nitro-phenoxy)-acetonitrile

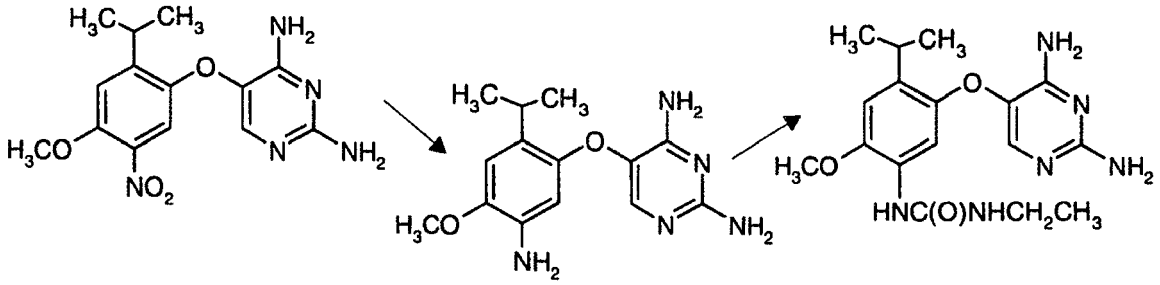
[0304] A mixture of 3-amino-2-isopropyl-5-nitrophenol (9.94 g, 47 mmol), K_2CO_3 (13.00 g, 94 mmol) and toluenenesulfonic acid cyanomethyl ester (10.93 g, 52 mmol) in 500 mL DMF was warmed to 50°C. After 16 h the mixture was cooled, poured into 500 mL H_2O and extracted with toluene/ethyl acetate (1:1). The combined organics were washed with H_2O, washed with brine, filtered and concentrated in vacuo. The crude solid was recrystallized from EtOH to afford (2-isopropyl-4-methoxy-5-nitro-phenoxy)-acetonitrile (8.95 g, 76%) as a yellow crystalline solid.

Step 7. 5-(2-Isopropyl-4-methoxy-5-nitro-phenoxy)-pyrimidine-2,4-diamine

[0305] A mixture of (2-isopropyl-4-methoxy-5-nitro-phenoxy)-acetonitrile (8.785 g, 35.5 mmol) and Brederick's reagent (14.6 mL, 70.9 mmol) was warmed to 100°C. After 45 min the mixture was evaporated under reduced pressure (50°C, 50 mtorr) to give an orange solid. The solid was added to a solution of aniline hydrochloride (9.19 g, 70.9 mmol) in 150 mL of EtOH. The mixture was warmed to reflux. After 16 hr additional aniline hydrochloride (4.596 g, 35.5 mmol) was added mixture was continued at reflux for 4 h. The solution was concentrated in vacuo and poured into H_2O. The mixture was extracted with ethyl acetate, washed with H_2O, washed with brine, dried over Na_2SO_4, and concentrated in vacuo to afford a yellow-green solid. This crude product was added to a mixture of 200 mL NMP and guanidine carbonate (17.70 g, 98 mmol) and warmed to 130°C. After 5 hours the mixture was cooled then poured onto 21 of an ice/H_2O mixture. The resulting precipitate was filtered, washed with H_2O and dried under vacuum (50°C). The crude solid was recrystallized from EtOH to afford 5-(2-isopropyl-4-methoxy-5-nitro-phenoxy)-pyrimidine-2,4-diamine (8.14 g, 63%, 3 steps) as a yellow crystalline solid (solvated 1:1 with EtOH). $(M+H)^+ = 320$.

Example 22: 1-[5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-3-ethyl-urea

[0306]



Step 1. 5-(5-Amino-2-Isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine

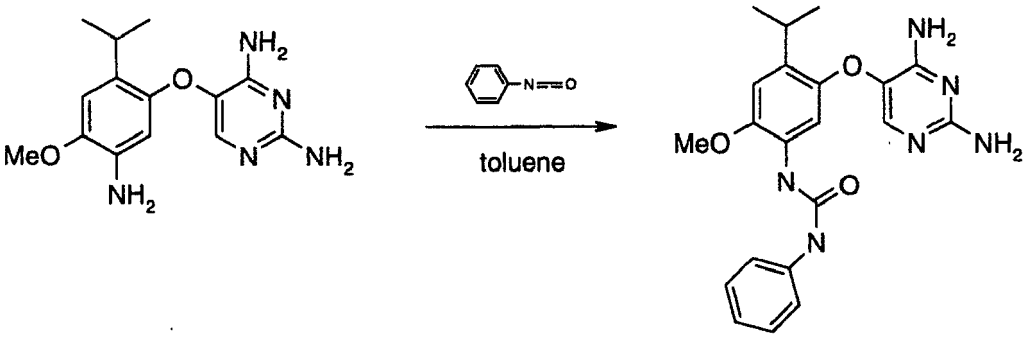
[0307] To a solution of 5-(2-isopropyl-4-methoxy-5-nitro-phenoxy)-pyrimidine-2,4-diamine (2.953 g, 9.2 mmol) in 250 mL EtOH and 25 AcOH was added 10% Pd/C. The mixture was placed under 50 psi of H_2 via a Parr hydrogenator. After 2.5 h the mixture was filtered through a pad of celite. The pad was washed with ethyl acetate and the solution was partially concentrated in vacuo. The residue was taken up in 500 mL H_2O and cooled to 0°C. The solution was adjusted to pH = 12 with 50% NaOH extracted with ethyl acetate. The combined organics were washed with H_2O, washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo to afford 5-(5-amino-2-Isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine (2.156 g, 82%) as a dark-orange solid.

Step 2. 1-[5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-3-ethyl-urea

[0308] A solution of 5-(5-amino-2-Isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine (0.117 g, 0.4 mmol) and ethyl isocyanate (0.034 g, 0.5 mmol) in 4 mL of toluene was heated to 100°C in a sealed tube. After 5 h the solution was cooled and concentrated in vacuo and gave a brown solid. Purification via flash chromatography (CH_2Cl_2/MeOH 97:3) afforded 1-[5-(2,4-diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-3-ethyl-urea (0.120 g, 83%) as a white solid; (M+H) = 361.

Example 23: 1-[5-(2,4-diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-3-phenyl-urea

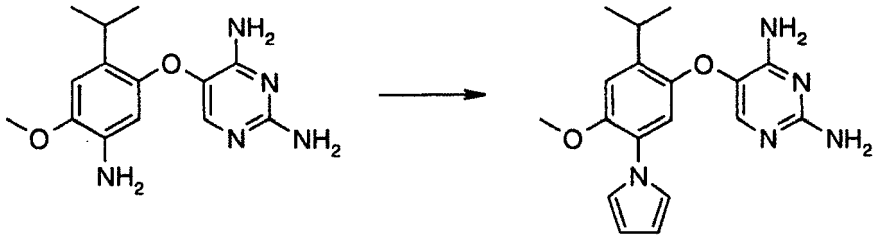
[0309]



[0310] 5-(5-amino-2-Isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine (0.309 g, 1.1 mmol) was converted, as described in the above procedure, to 1-[5-(2,4-diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-3-phenyl-urea (0.122 g, 28%) as white solid; $[MH]^+$ = 408.

Example 24: 5-(2-Isopropyl-4-methoxy-5-pyrrol-1-yl-phenoxy)-pyrimidine-2,4-diamine

[0311]

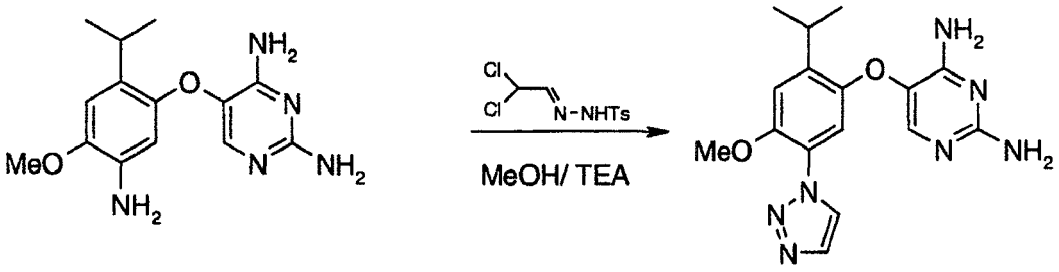


[0312] To a solution of 5-(5-amino-2-Isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine (0.303 g, 1.0 mmol) in 15 mL AcOH was added 2,5-dimethoxypyran (0.152 g, 1.2 mmol). The solution was warmed to reflux. After 2 h the solution was cooled and poured over ice/H_2O. The solution was converted to pH = 8 with 50% NaOH and extracted with ethyl acetate (3x75 mL). The combined organics were washed with H_2O, washed with brine, dried with Na_2SO_4, filtered and concentrated in vacuo to give a brown solid. Purification via flash chromatography (CH_2Cl_2/MeOH 97:3) afforded 5-(2-isopropyl-4-methoxy-5-pyrrol-1-yl-phenoxy)-pyrimidine-2,4-diamine (0.244 g, 72%) as a pale yellow solid. (M+H) = 340.

[0313] Similarly prepared from 5-(5-amino-2-Isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine (0.313 g, 1.1 mmol) and 2,5-hexanedione (0.14 ml, 1.2 mmol) was 5-[5-(2,5-dimethyl-pyrrol-1-yl)-2-isopropyl-4-methoxy-phenoxy]-pyrimidine-2,4-diamine, (0.259 g, 64 %). (M+H) = 368.

Example 25: 5-(2-Isopropyl-4-methoxy-5-[1,2,3]triazol-1-yl-phenoxy)-pyrimidine-2,4-diamine

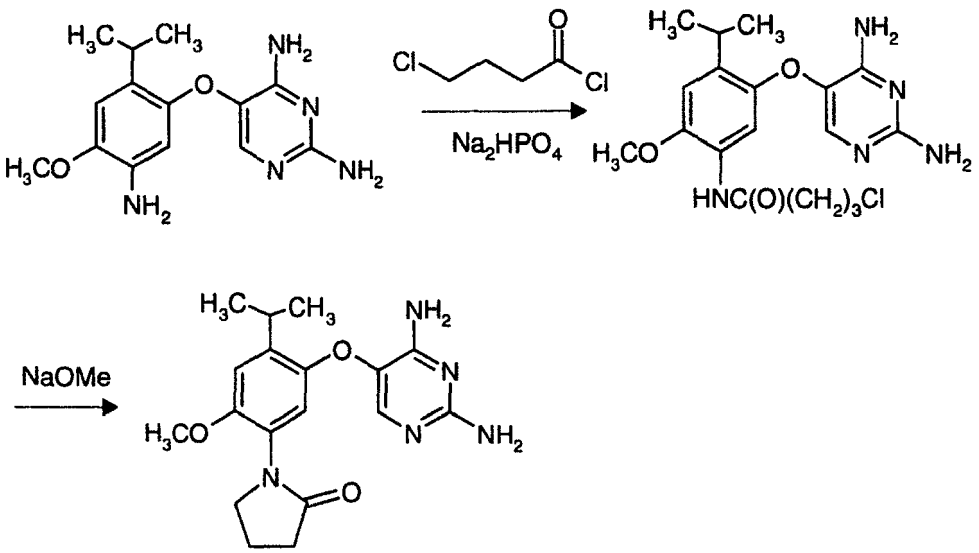
[0314]



[0315] Following the procedure of Harada et al., Heterocycles 1998, 48, 695-702, to a solution of 5-(5-amino-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine (0.400 g, 1.8 mmol) in 5 ml methanol at 0°C was added trimethylamime (0.308 g, 3.0 mmol) and hydrazine 1,1-dichloroethyl hydrazine tosylate (0.388 g, 1.4 mmol). The solution was warmed to 50°C. After 4 h the mixture was concentrated in vacuo and extracted with CH_2Cl_2. The combined organics were washed with H_2O, washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification via flash chromatography (94:6 CH_2Cl_2/MeOH) afforded 5-(2-sopropyl-4-methoxy-5-[1,2,3]triazol-1-yl-phenoxy)-pyrimidine-2,4-diamine (0.145 g, 31%) as a white solid; $[MH]^+$= 342.

Example 26: 1-[5-(4-Amino-2-methyl-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-pyrrolidin-2-one

[0316]



Step 1. 4-Chloro-N-[5-(2,4-diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-butyramide

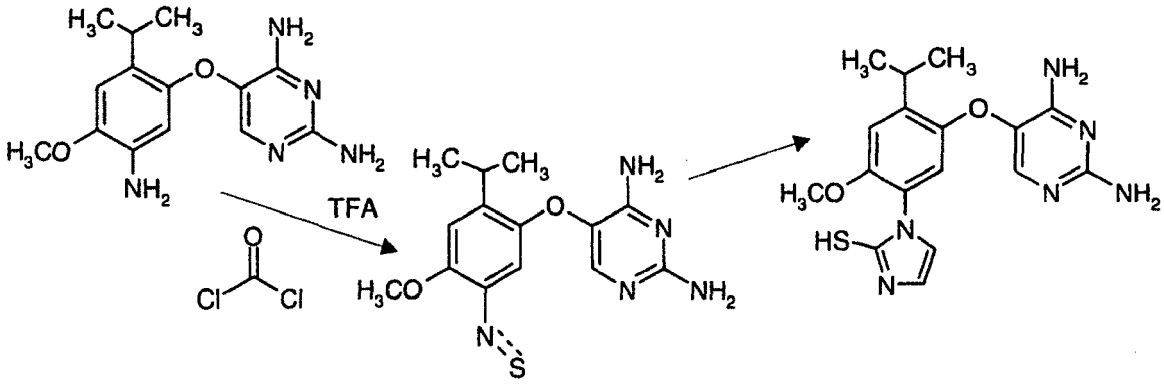
[0317] To a solution of 5-(5-amino-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine (0.400 g, 1.4 mmol) in 15 ml $CHCl_3$ and Na_2HPO_4 (0.392 g, 2.8 mmol) was added 4-chlorobutyryl chloride (0.194 g, 1.4 mmol) dropwise. After 4.5 h, H_2O and CH_2Cl_2 were added and the mixture was allowed to stir 15 min. The mixture was neutralized with 2N Na_2CO_3 and extracted with CH_2Cl_2. The combined organics were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo to afford 4-chloro-N-[5-(2,4-diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-butyramide (0.495 g, 91%) as brown foam; $[MH]^+$= 394.

Step 2. 1-[5-(4-Amino-2-methyl-pyrimidin-5-yloxy)-4-isopropyl-2-methozy-phenyl]-pyrrolidin-2-one

[0318] To a solution of 5 ml 1.9 M NaOMe in MeOH was added 4-Chloro-N-[5-(2,4-diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-butyramide (0.495 g, 1.3 mmol). After 6 h the solution was concentrated in vacuo. The residue was taken up in ethyl acetate, washed with H_2O, washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo to give 1-[5-(4-amino-2-methyl-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-pyrrolidin-2-one (0.230 g, 47%) as white solid; $[MH]^+$ = 358; mp (HCl salt) > 300°C.

Example 27: 1-[5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-1H-imidazole-2-thiol

[0319]



Step 1. 5-(2-Isopropyl-5-isothiocyanato-4-methoxy-phenoxy)-pyrimidine-2,4-diamine

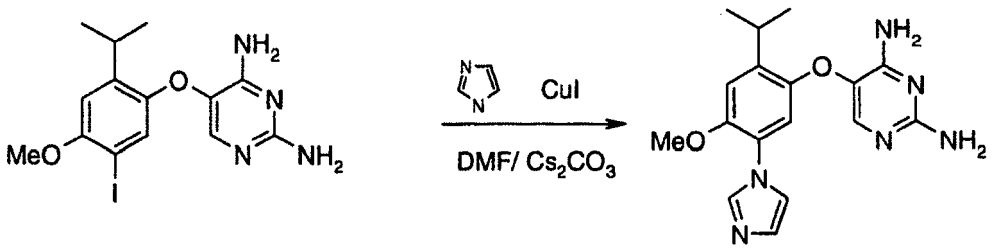
[0320] To a solution of 5-(5-amino-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine (0.100 g, 0.4 mmol) in 1 ml H_2O and TFA (0.040 g, 0.4 mmol) was added thiophosgene (0.040 g, 0.4 mmol). After 1 h the mixture was neutralized with 2M NaOH and extracted with CH_2Cl_2. The combined organics were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo to afford 5-(2-isopropyl-5-isothiocyanato-4-methoxy-phenoxy)-pyrimidine-2,4-diamine (0.042 g, 36%) as brown foam $[MH]^+$ = 334.

Step 2. 1-[5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-1H-imidazole-2-thiol

[0321] To a solution of amino acetal (0.173 g, 1.3 mmol) in 10 ml EtOH was added a solution of thio-isocyanate (0.430 g, 1.3 mmol) in 2 ml EtOH. The mixture was warmed to reflux. After 30 min the mixture was cooled, concentrated in vacuo and suspended in 1M HCl and refluxed again for another 30 min reaction was neutralized with saturated $NaHCO_3$ and extracted with CH_2Cl_2. The combined organics were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo to afford 1-[5-(2,4-diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-1H-imidazole-2-thiol (0.298 g, 50%) as white solid $[MH]^+$ = 373.

Example 28: 5-(5-Imidazol-1-yl-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine

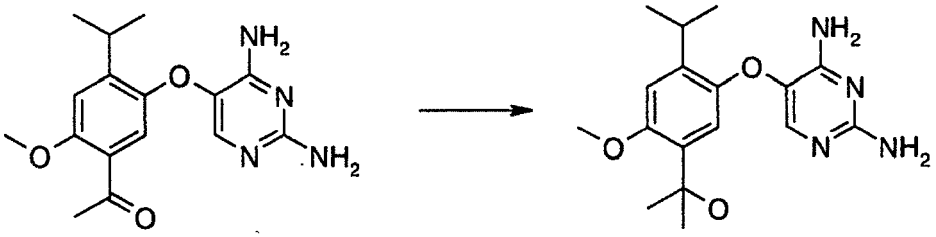
[0322]



[0323] A suspension of 5-iodo-diaminopyrimidine (0.294 g, 0.74 mmol), imidazole (0.120 g, 1.8 mmol), CuI (0.070 g, 0.4 mmol), and Cs_2CO_3 (0.616 g, 1.9 mmol) in 4 ml DMF was heated to 100°C. After 72 hours the mixture was cooled, diluted with H_2O and extracted with ethyl acetate. The combined organics were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. Purification via preparative TLC (94:6 CH_2Cl_2/MeOH) afforded 5-(5-imidazol-1-yl-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine (0.020 g, 8%) as a white solid; $[MH]^+$= 341.

Example 29: 2-[5-(2,4-Diaminopyrimidin-5-yloxy)-4-isopropyl-2methoxy-phenyl]-propan-2-ol

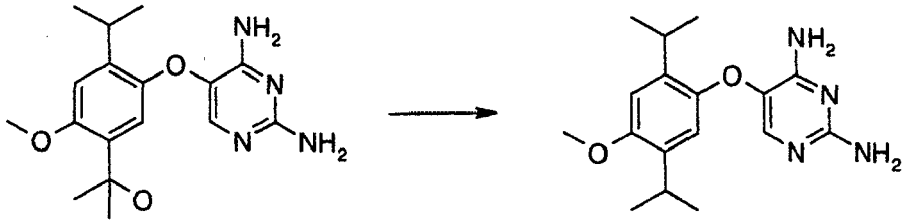
[0324]



[0325] To a solution of methylmagnesium bromide (83.4 mmol, 27.8 ml, 3.0 M in Et_2O) in 83 mL THF at 0°C was added 1-[5-(2,4-diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-ethanone (2.523 g, 8.3 mmol, from Example 16) in portions. After 16 h the mixture was cooled to 0°C and was quenched by the addition 10% NH_4Cl. H_2O was added and the mixture was extracted with ethyl acetate. The combined organics were washed with H_2O, washed with brine, dried over $NaHCO_3$, filtered and concentrated in vacuo. The crude solid was taken up in 31 ml DMF. K_2CO_3 (0.65 g, 4.7 mmol) and iodomethane (0.098 ml, 1.6 mmol) were added and the mixture was warmed to 50°C. Additional portions of iodomethane (0.019 mL, 0.6 mmol) was added at 1, 2 and 3 hr. After 16 h the mixture was cooled and 10% NH_4Cl and extracted with ethyl acetate. The combined organics were washed with H_2O, washed with brine, dried with Na_2SO_4, filtered and concentrated in vacuo to give 2-[5-(2,4-diaminopyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-propan-2-ol (0.711 g, yiled) as a white solid. $[MH]^+$= 333.

Example 30: 5-(2,5-Diiosopropyl-methoxy-phenoxy)-pyrimidine-2,4-diamine

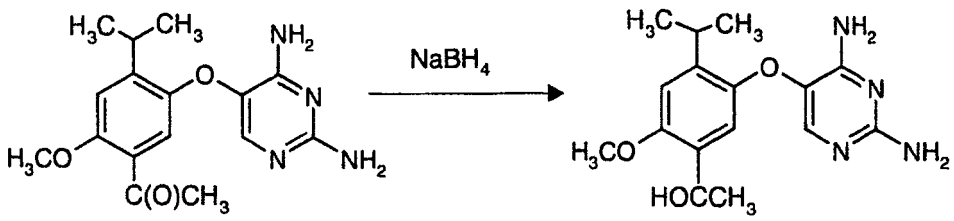
[0326]



[0327] To a solution of 2-[5-(2,4-diaminopyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-propan-2-ol: (0.350 g, 1.1 mmol) in 10 ml CH_2Cl_2 was added trifluoroacetic acid (4.0 ml, 52.6 mmol) and triethylsilane (1.7 ml, 10.5 mmol). After 30 min saturated $NaHCO_3$ was added and the mixture was extracted with ethyl acetate. The combined organics were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo to give a crude oil. Purification via flash chromatography (96:4 CH_2Cl_2/MeOH) gave 5-(2,5-diiosopropyl-methoxy-phenoxy)-pyrimidine-2,4-diamine (0.225 g, 68%) as a white solid. $[MH]^+$ = 317.

Example 31: 1-[5-(2,4-Diamino-pyrimidine-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-ethanol

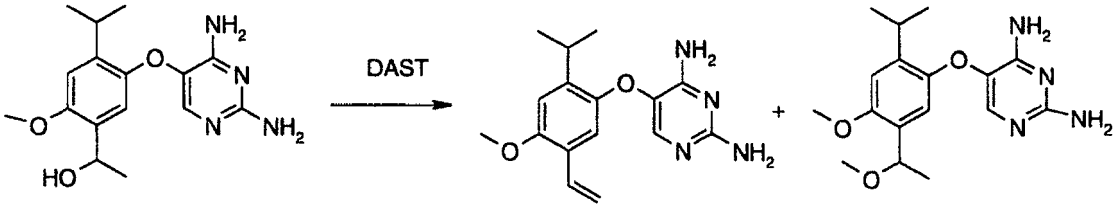
[0328]



[0329] To a solution of 1-[5-(2,4-diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-ethanone (2.500 g, 8.3 mmol) in 100 ml MeOH was slowly added $NaBH_4$ (1.566 g, 41.4 mmol) at 0°C. The solution was allowed to warm to RT. After 20 h, the saturated NH_4Cl was added, the mixture was concentrated in vacuo and extracted with ethyl acetate. The combined organics were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. Purification via silica gel column chromatography (9:1 CH_2Cl_2/MeOH) afforded to 1-[5-(2,4-diamino-pyrimidine-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-ethanol (1.613 g, 60%) as white foam; $[MH]^+$= 301.

Example 32: 5-(2-Isopropyl-4-methoxy-5-vinyl-phenoxy)-pyrimidine-2,4-diamine and 5-[2-Isopropyl-4-methoxy-5-(1-methoxy-ethyl)-phenoxy]-pyrimidine-2,4-diamine

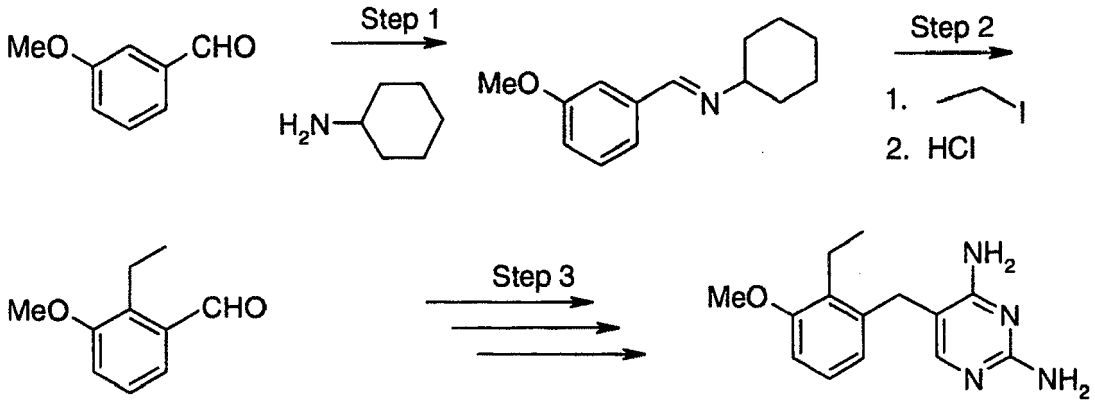
[0330]



[0331] To a solution of 1-[5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-ethanol (1.613 g, 5.3 mmol) in 30 ml CH_2Cl_2 at -78°C was added DAST (0.935 g, 5.8 mmol). After stirring 1.5 h, saturated $NaHCO_3$ was added and the mixture was extracted by CH_2Cl_2. The combined organics were washed with brine and dried Na_2SO_4, filtered and concentrated in vacuo. Purification via silica gel chromatography (95:5 CH_2Cl_2/MeOH) gave 5-(2-Isopropyl-4-methoxy-5-vinyl-phenoxy)-pyrimidine-2,4-diamine (0.044 g, 3%) as a foam ($[MH]^+$ = 301) and 5-[2-Isopropyl-4-methoxy-5-(1-methoxy-ethyl)-phenoxy]-pyrimidine-2,4-diamine(0.075 g, 4%) as foam. $[MH]^+$ = 303.

Example 33: 5-(2-Ethyl-3-methoxy-benzyl)-pyrimidine-2,4-diamine

[0332] The synthetic procedure used in this Example is outlined in Scheme M.



SCHEME M

Step 1. Cyclohexyl-(3-methoxy-benzylidene)-amine

[0333] 3-Methoxy benzaldehyde (10.105 g, 74.2 mmol) was converted, as described in step 1 of Example 3, to Cyclohexyl-(3-methoxy-benzylidene)-amine (15.08 g, 94%) as a clear oil.

Step 2. 2-Ethyl-3-methoxy benzaldehyde

[0334] To a solution of 2,2,6,6-tetramethylpiperidine (4.67 g, 33 mmol) in 75 ml THF at -15°C was added n-butyllithium (12.6 ml, 32 mmol, 2.5 in hexanes) dropwise maintaining the internal temperature below -10°C. After 15 min a solution of cyclohexyl-(3-methoxybenzylidene)-amine (3.259 g, 15.0 mmol) in 5.0 ml THF was added and the solution was allowed to stir at -15°C. After 1 h the solution was cooled to -78°C. Iodoethane (11.9 ml, 150 mmol) was added in one portion and the solution was allowed to warm to RT over 45 min, poured into 10% NH_4Cl, and extracted with Et_2O. The combined organics were washed with H_2O, washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to give a crude imine as an oil. The oil was taken up in 90 ml of THF and HCl (22 ml, 89 mmol, 4.0 M) and warmed to reflux. After 2 the solution was cooled. H_2O was added and the mixture was extracted with ethyl acetate. The combined organics were washed with H_2O, washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo to give a crude oil. Purification via flash chromatography (98:2 hexane/ethyl acetate) gave 2-ethyl-3-methoxy benzaldehyde (1.543 g, 63%,

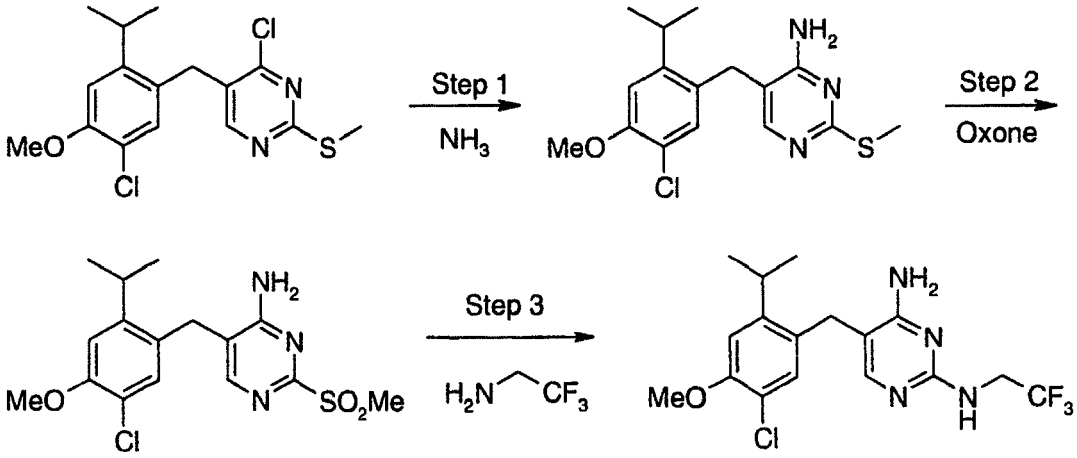
2 steps) as a clear oil.

Step 3. 5-(2-Ethyl-3-methoxy-benzyl)-pyrimidine-2,4-diamine

[0335] Following the procedure of steps 4-8 of Example 3, 2-ethyl-3-methoxy benzaldehyde (1.025 g, 6.24 mmol) afforded 5-(2-Ethyl-3-methoxy-benzyl)-pyrimidine-2,4-diamine (0.154 g, 10 %, 2 steps) as a pale yellow solid. $[MH^+]$ = 259

Example 34: 5-(5-Chloro-2-isopropyl-4-methoxy-benzyl)-N^2-(2,2,2-trifloro-ethyl)-pyrimidine-2,4-diamine

[0336] The synthetic procedure used in this Example is outlined in Scheme M.



SCHEME M

Step 1. 5-(5-Chloro-2-isopropyl-4-methoxy-benzyl)-2-methylsulfanyl-pyrimidin-4-yl-amine

[0337] To 25 ml of saturated NH_3 in EtOH was added 4-chloro-5-(5-chloro-2-isopropyl-4-methoxy-benzyl)-2-methylsulfanyl-pyrimidine (0.580 g, 1.6 mmol). The solution was warmed to 85°C in a sealed reaction vessel. After 3 days the solution was cooled, concentrated in vacuo and suspended in CH_2Cl_2. The precipitate was filtered and the mother liquor was concentrated in vacuo. Purification via flash chromatography (7:3 hexane/ethyl acetate) afforded 5-(5-chloro-2-isopropyl-4-methoxy-benzyl)-2-methylsulfanyl-pyrimidin-4-yl-amine (0.504 g, 92%) as a white solid.

Step 2. 5-(5-Chloro-2-isopropyl-4-methoxy-benzyl)-2-methylsulfonyl-pyrimidine-4-yl-amine

[0338] To a solution of 4-chloro-5-(5-chloro-2-isopropyl-4-methoxy-benzyl)-2-methylsulfanyl-pyrimidine (0.320 g, 0.9 mmol) in 15 ml THF and 15 ml H_2O was added Oxone (1.227 g, 2 mmol) in portions. After 16 h the solution was concentrated in vacuo and extracted with ethyl acetate. The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification via flash chromatography afforded 5-(5-chloro-2-isopropyl-4-methoxy-benzyl)-2-methylsulfonyl-pyrimidine-4-ylamine (0.333, 96%) as a white solid.

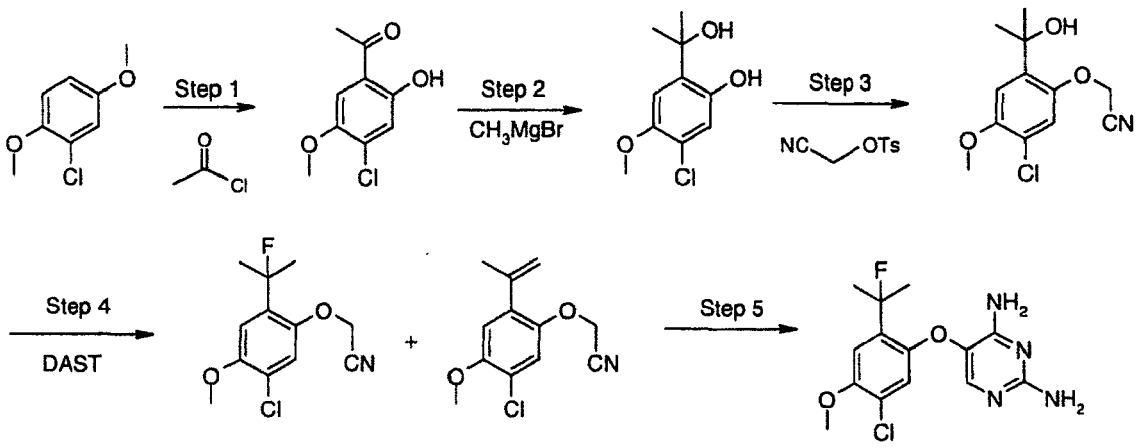
Step 3. 5-(5-Chloro-2-isopropyl-4-methoxy-benzyl)-N^2-(2,2,2-trifloro-ethyl)-pyrimidine-2,4-diamine

[0339] To a solution of 5-(5-chloro-2-isopropyl-4-methoxy-benzyl)-2-methylsulfonyl-pyrimidine-4-ylamine (0.050 g, 0.1 mmol) in 3 ml DME was added 0.5 ml 2,2,2-trifluoroethyl amine. The mixture was heated in the microwave (130°C, 10 barr). After 22 h the mixture was concentrated in vacuo. Purification via reverse phase preparative HPLC afforded the TFA salt of 5-(5-chloro-2-isopropyl-4-methoxy-benzyl)-N^2-(2,2,2-trifluoro-ethyl)-pyrimidine-2,4-diamine (0.010 g, 19%) as a white solid); $[MH]^+$= 389.

[0340] Similarly prepared from 5-(5-chloro-2-isopropyl-4-methoxy-benzyl)-2-methylsulfonyl-pyrimidine-4-ylamine (0.100 g, 0.3 mmol) but using 2-methoxyethylamine was 5-(5-chloro-2-isopropyl-4-methoxy-benzyl)-N^2-(2-methoxy-ethyl)-pyrimidine-2,4-diamine (0.068 g, 63%) as a white solid; $[MH]^+$ = 365.

Example 35: 5-[5-Chloro-2-(1-fluoro-1-methyl-ethyl)-4-methoxy-phenoxy]-pyrimidine-2,4-diamine

[0341] The synthetic procedure used in this Example is outlined in Scheme N.



SCHEME N

Step 1. 1-(4-Chloro-2-hydroxy-5-methoxy-phenyl]-ethanone

[0342] To a mixture of $AlCl_3$ (8.89 g, 59 mmol) in CH_2Cl_2 at -10°C was added acetyl chloride (4.1 ml, 58 mmol) dropwise while maintaining the internal temperature below 0°C. After 20 min 2-chloro-1,4-dimethoxybenzene (10.0 g, 8.3 mmol) was dissolved in 8 ml CH_2Cl_2 and added to the above solution dropwise while maintaining the internal temperature below 0°C. After 20 min the mixture was warmed to RT for 1 hour then warmed to reflux. After 21 h the solution was cooled, poured over a mixture of ice and concentrated HCl and extracted with DCM. The combined organics were concentrated in vacuo and recrystallized from H_2O/EtOH to afford 1-(4-chloro-2-hydroxy-5-methoxy-phenyl)-ethanone (8.78 g, 85%) as a solid.

Step 2. 5-Chloro-2-(1-hydroxy-1-methyl-ethyl)-4-methoxy-phenol

[0343] To a solution of 1-(4-chloro-2-hydroxy-5-methoxy-phenyl)-ethanone (9.80 g, 49 mmol) in 90 mL THF at 0°C was added methyl magnesium bromide (37 mL, 112 mmol, 3.0 M in Et_2O. After 2 h the reaction was quenched by the addition of 10% NH_4Cl. The mixture was adjusted to pH = 1 with 2M HCl and extracted with ethyl acetate. The combined organics were washed with H_2O, washed with brine, dried with $MgSO_4$, filtered and concentrated in vacuo to give a crude solid. Purification via flash chromatography afforded alcohol 5-chloro-2-(1-hydroxy-1-methyl-ethyl)-4-methoxy-phenol (11.85 g, more than 100%) as a yellow solid.

Step 3. [5-Chloro-2-(1-hydroxy-1-methyl-ethyl)-4-methoxy-phenoxy]-pyrimidine-2,4-diamine

[0344] To a mixture of 5-chloro-2-(1-hydroxy-1-methyl-ethyl)-4-methoxy-phenol (2.00 g, 9 mmol) and K_2CO_3 (2.55 g, 19 mmol) in 50 mL DMF was added toluenesulfonyl cyano ethyl ester (2.34 g, 11 mmol). The mixture was allowed to stir at RT. After 16 h the mixture was poured into 200 ml water and extracted with ethyl acetate. The combined organics were washed with water, washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo to give a crude solid. Purification via flash chromatography (7:3 hexane/ethyl acetate) to afford [5-chloro-2-(1-hydroxy-1-methyl-ethyl)-4-methoxy-phenoxy]-pyrimidine-2,4-diamine (1.62 g, 69%) as a white solid.

Step 4. 5-[5-Chloro-2-(1-fluoro-1-methyl-ethyl)-methoxy-phenoxy]-acetonitrile

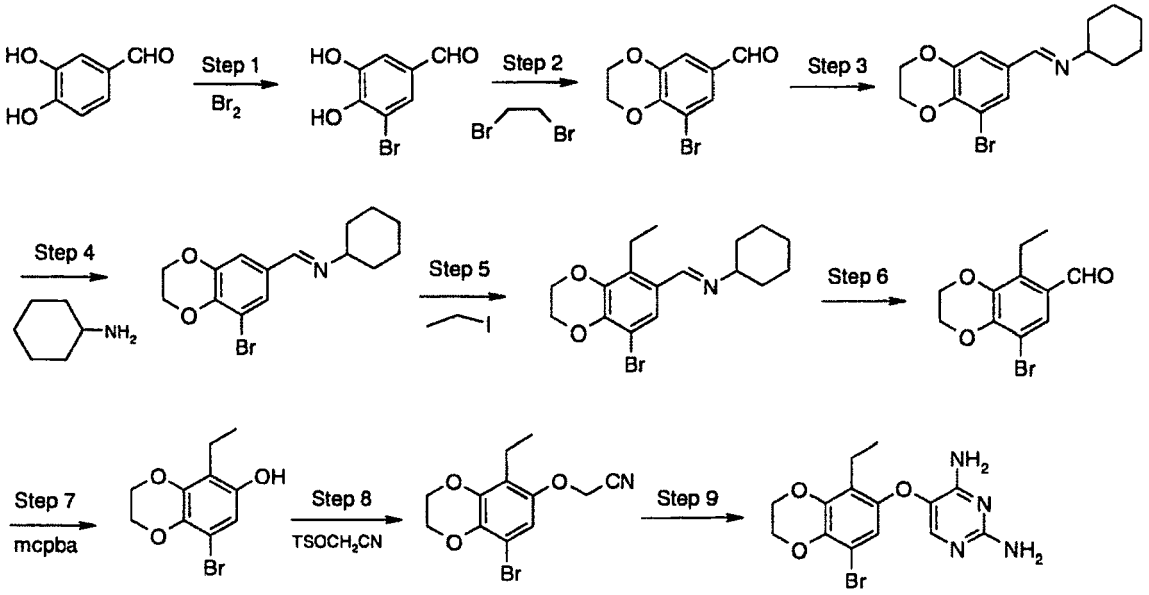
[0345] To a solution of [5-chloro-2-(1-hydroxy-1-methyl-ethyl)-4-methoxy-phenoxy]-pyrimidine-2,4-diamine (1.432 g, 5.6 mmol) in 50 ml CH_2Cl_2 at -78°C was added DAST (0.77 ml, 5.9 mmol) dropwise. After 1.5 the solution was warmed to RT and quenched by the addition of saturated $NaHCO_3$ solution and extracted with CH_2Cl_2. The combined organics were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo to give an inseparable mixture (9:1) of 5-[5-chloro-2-(1-fluoro-1-methyl-ethyl)-methoxy-phenoxy]-acetonitrile (1.543 g) and (5-Chloro-2-isopropenyl-4-methoxy-phenoxy)-acetonitrile as a pale brown oil.

Step 5. 5-[5-Chloro-2-(1-fluoro-1-methyl-ethyl)-methoxy-phenoxy]-pyrimidine-2,4-diamine

[0346] 5-[5-Chloro-2-(1-fluoro-1-methyl-ethyl)-methoxy-phenoxy]-acetonitrile (1.447 g, 4.2 mmol) was converted, as describe in steps 6 and 7 of Example 2, to 5-[5-chloro-2-(1-fluoro-1-methyl-ethyl)-methoxy-phenoxy]-pyrimidine-2,4-diamine (0.263 g, 10 % for three steps) as a yellow solid; mp = 220.1-220.6°C (HCl salt); $[MH]^+$ = 328. Similarly prepared, but starting with 3-fluoro-1,4-dimethoxybenzene, and using hydrogenation with Pd/C in step 4 instead of DAST, was 5-(5-fluro-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine (0.778 g, 42%); mp (HCl salt) = 239-241°C; $[MH]^+$= 293.

Example 36: 5-(8-Bromo-5-ethyl-2,3-dihydro-benzo[1,4]dioxin-6-yloxy)-pyrimidine-2,4-diamine

[0347] This compound is not covered by the claims. The synthetic procedure used in this Example is outlined in Scheme O.



SCHEME O

Step 1. 3-Bromo-4,5-dihydroxy-benzaldehyde

[0348] To a solution of 3,4-dihydroxy benzaldehyde (15.48 g, 112 mmol) in 500 ml AcOH was added bromine (6.1 ml, 118 mmol) dropwise in 50 ml AcOH over 10 min. After 4 h the mixture was poured into cold H_2O. The precipitate was filtered, washed with cold H_2O and dried in vacuum to give 3-bromo-4,5-dihydroxy-benzaldehyde (11.64 g, 48%) as a grey solid.

Step 2. 8-Bromo-2,3-dihydro-benzo[1,4]dioxine-6-carboxaldehyde

[0349] To a solution of 3-bromo-4,5-dihydroxy-benzaldehyde (20.78 g, 95 mmol) in 480 ml DMF was added K_2CO_3 (52.95 g, 383 mmol) followed by 1,2-dibromoethane (8.7 ml, 101 mmol). The mixture was warmed to 100°C. After 18 additional 1,2 dibromoethane (1.0 mL) was added. After 2 h the mixture was poured into water and extracted with ethyl acetate. The combined organics were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The crude solid was purified via flash chromatography (9:1 hexane/ethyl acetate) to give 8-bromo-2,3-dihydro-benzo[1,4] dioxine-6-carboxaldehyde (15.82 g, 99 %) as a white solid.

Step 3. (8-Bromo-2,3-dihydro-benzo[1.4]dioxine-6-ylmethylene)-cyclohexyl-amine

[0350] According to the procedure in example 3 (step 1), 8-Bromo-2,3-dihydro-benzo[1,4]dioxine-6-carboxaldehyde (15.63 g, 64 mmol)) and cyclohexylamine (7.02 g, 71 mmol) gave 8-Bromo-2,3-dihydro-benzo[1,4]dioxine-6-ylmethylene)-cyclohexyl-amine (24.2 g) as a viscous oil which was used in the following step without purification.

Step 4. 8-Bromo-5-ethyl-2,3-dihydro-benzo[1,4]dioxine-6-carboxaldehyde

[0351] According to the procedure of step 2 of Example 33, 8-bromo-2,3-dihydro-benzo[1,4]dioxine-6-ylmethylene)-cyclohexyl-amine (23.09 g, 71 mmol) gave 8-bromo-5-ethyl-2,3-dihydro-benzo[1,4]dioxine-6-carboxaldehyde (3.67 g, 24 %).

Step 5. 8-Bromo-5-ethyl-2,3-dihydro-benzo[1,4]dioxin-6-ol

[0352] 8-Bromo-5-ethyl-2,3-dihydro-benzo[1,4]dioxine-6-carboxaldehyde (3.674 g, 13.5 mmol), using the procedure described in Example 2 (step 4), was converted to 8-Bromo-5-ethyl-2,3-dihydro-benzo[1,4]dioxin-6-ol (3.182 g, 91%) as a white solid.

Step 6. (8-Bromo-5-ethyl-2,3-dihydro-benzo[1.4]dioxin-6-yloxy)-acetonitrile

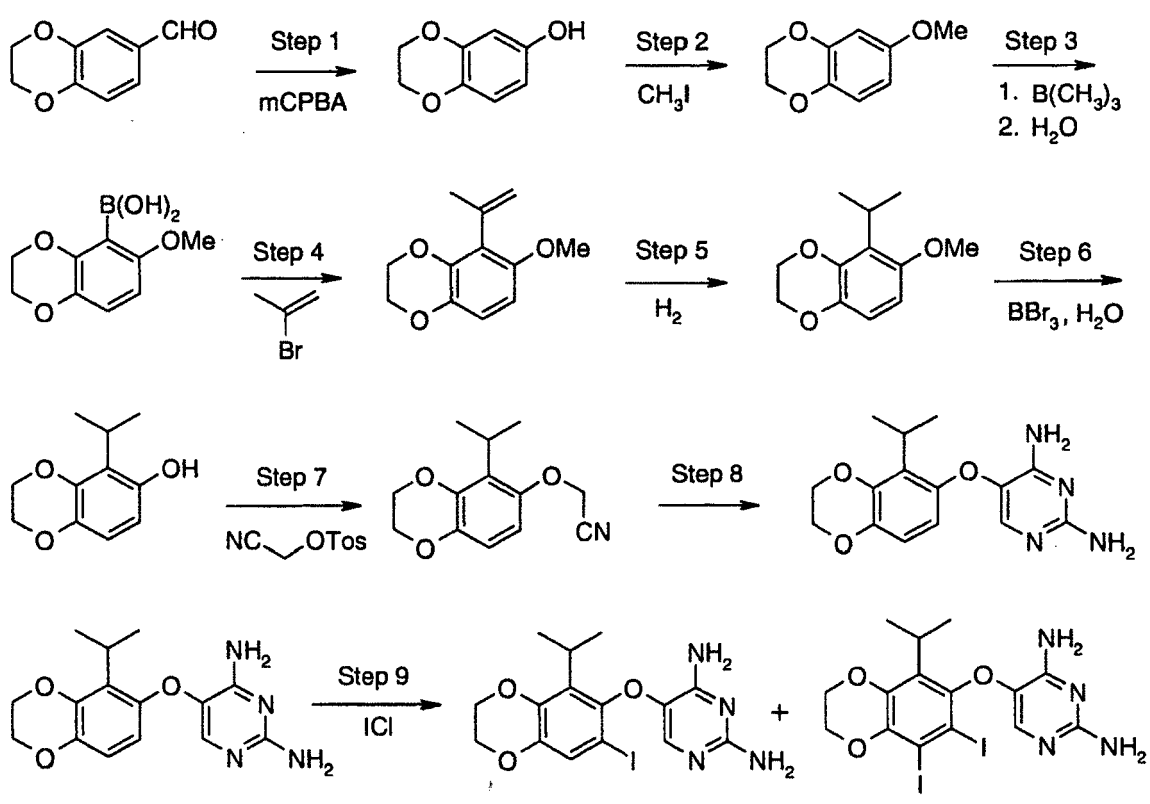
[0353] 8-Bromo-5-ethyl-2,3-dihydro-benzo[1,4]dioxin-6-ol (3.182 g, 12.3 mmol), as described in the procedure of Step 6 of Example 21, was converted to cyanomethyl ether 8-Bromo-5-ethyl-2,3-dihydro-benzo[1,4]dioxin-6-yloxy)-acetonitrile (2.30 g, 63%).

Step 7. 5-(8-Bromo-5-ethyl-2,3-dihydro-benzo[1.4]dioxin-6-yloxy)-pyrimidine-2,4-diamine

[0354] 8-Bromo-5-ethyl-2,3-dihydro-benzo[1,4]dioxin-6-yloxy)-acetonitrile (2.30 g, 8.7 mmol), using the procedure of steps 6 and 7 of Example 2, was converted to 5-(8-Bromo-5-ethyl-2,3-dihydro-benzo[1.4]dioxin-6-yloxy)-pyrimidine-2,4-diamine (0.951 g, 32%) as yellow solid; mp = 291-293°C; $[MH]^+$= 368.

Example 37: 5-(7-Iodo-5-isopropyl-2,3-dihydro-benzo[1,4]dioxin-6-yloxy)-pyrimidine-2,4-diamine

[0355] The synthetic procedure used in this Example is outlined in Scheme P. This compound is not covered by the claims.



SCHEME P

Step 1. 2.3-Dihydro-benzo[1,4]dioxin-6-ol

[0356] To a solution of 2,3-dihydro-benzo[1,4]dioxin-6-carboxaldehyde (30.0 g, 183 mmol) in 500 ml CH_2Cl_2 was added mCPBA (37.85 g, 219 mmol). The suspension was heated to 50°C. After 16 h saturated $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2. The combined organics were concentrated in vacuo and taken up in MeOH and 200 ml 4M NaOH was added. After 2 h the mixture was acidified with 4M HCl and extracted with ethyl acetate. The combined organics were washed with saturated $NaHCO_3$, washed with brine, concentrated in vacuo, and taken up in CH_2Cl_2. The solution was filtered to remove the precipitate. The resulting solution was stirred with saturated $NaHCO_3$ for 1 h, separated, dried over $MgSO_4$, filtered and concentrated in vacuo to give 2,3-dihydro-benzo-[1,4]dioxin-6-ol (26.92 g, 94%).

Step 2. 6-Methoxy-2,3-dihydro-benzo[1,4]dioxine

[0357] To a mixture of K_2CO_3 (47.54 g, 344 mmol) and Bu_4NI (1.256 g, 3.4 mmol) in DMF was added 2,3-dihydro-benzo[1,4]dioxin-6-ol (26.2 g, 172 mmol) followed by iodomethane (16.1 ml, 258 mmol). After 16 hours the mixture was filtered. The solution was mixed with H_2O and extracted with ethyl acetate. The combined organics were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. Purification via flash chromatography (95:5 hexane/ethyl acetate) afforded methyl 6-methoxy-2,3-dihydro-benzo-[1,4]dioxine (24.23 g, 85%) as a clear oil.

Step 3. 6-Methoxy-2,3-dihydro-benzo[1,4]dioxin-5-yl-boronic acid

[0358] To a solution of methyl ether X (10.0 g, 60 mmol) in 50 ml THF at -78°C *n*-butyllithium (36 ml, 90 mmol, 2.5 M in hexanes) was added dropwise. After 1 h the solution was warmed to RT. After 1 h the solution was cooled to -78°C and trimethyl borate (13.6 ml, 120 mmol) was added. The solution was warmed to RT. After 16 h the mixture was quenched by the addition of water and resulting mixture was acidified with AcOH and extracted with ethyl acetate. The combined organics were washed with saturated $NaHCO_3$, dried with $MgSO_4$, filtered and concentrated in vacuo. The resulting oil was azeotroped with toluene to afford 6-methoxy-2,3-dihydro-benzo[1,4]dioxin-5-yl-boronic acid (13.72 g, 98%) as an oil.

Step 4. 5-Isopropenyl-6-methoxy-2,3-dihydro-benzo[1,4]dioxine

[0359] To a solution of 2-bromopropene (5.4 ml, 59 mmol) in 200 mL DME was added $Pd(Ph_3P)_4$ (3.116, 2.8 mmol). After 30 min 6-methoxy-2,3-dihydro-benzo[1,4]dioxin-5-yl-boronic acid (13.320 g, 58.6 mmol) and K_2CO_3 (8.099 g, 58.6 mmol) was added. The mixture was warmed to reflux. After 16 hours the mixture was cooled, filtered through a pad of celite and concentrated in vacuo. The residue was dissolved in H_2O and extracted with ethyl acetate. The combined organics were washed with saturated $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated in vacuo. Purification via flash chromatography afforded isoprene 5-isopropenyl-6-methoxy-2,3-dihydro-benzo[1,4]dioxine (5.542 g, as an inseparable mixture of product/sm 1:1) as an oil.

Step 5. 5-Isopropyl-6-methoxy-2,3-dihydro-benzo[1,4]dioxine

[0360] To a solution of 5-isopropenyl-6-methoxy-2,3-dihydro-benzo[1,4]dioxine (5.00 g, x mmol) in 80 ml MeOH was added 10% Pd/C (0.18 g). The mixture was placed under 50 psi of H_2. After 16 hours the mixture was filtered through a pad of celite. The solution was concentrated in vacuo. Purification via flash chromatography (97:3 hexane/ethyl acetate) afforded isopropyl 5-isopropyl-6-methoxy-2,3-dihydro-benzo[1,4]dioxine (2.458 g, 21% from boronic acid) as a clear oil.

Step 6. 5-Isopropyl-6 hydroxy-2,3-dihydro-benzo[1,4]dioxine

[0361] To a solution of 5-isopropyl-6-methoxy-2,3-dihydro-benzo[1,4]dioxine (1.011 g, 4.9 mmol) in 15 ml CH_2Cl_2 at -78°C was added BBr_3 (7.3 ml, 7.3 mmol). The solution was allowed to warm to RT. After 16 hours the solution was cooled to -78°C, quenched with H_2O, warmed to RT and extracted with CH_2Cl_2. The combined organics were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. Purification via flash chromatography (7:3 hexane/ethyl acetate) afforded 5-isopropyl-6 hydroxy-2,3-dihydro-benzo-[1,4]dioxine (0.622 g, 63%) as a pale yellow oil.

Step 7. 5-Isopropyl-2,3-dihydro-benzo[1,4]dioxin -6-yloxy)acetonitrile

[0362] 5-Isopropyl-6 hydroxy-2,3-dihydro-benzo[1,4]dioxine (0.622 g, 3.2 mmol) was converted, as described in Example 2 (step 5), to 5-isopropyl-2,3-dihydro-benzo[1,4]dioxin-6-yloxy)-acetonitrile (0.544 g, 72%) as a clear oil.

Step 8. 5-(5-Isopropyl-2,3-dihydro-benzo[1,4]dioxin-6-yloxyl-pyrimidine-2,4-diamine

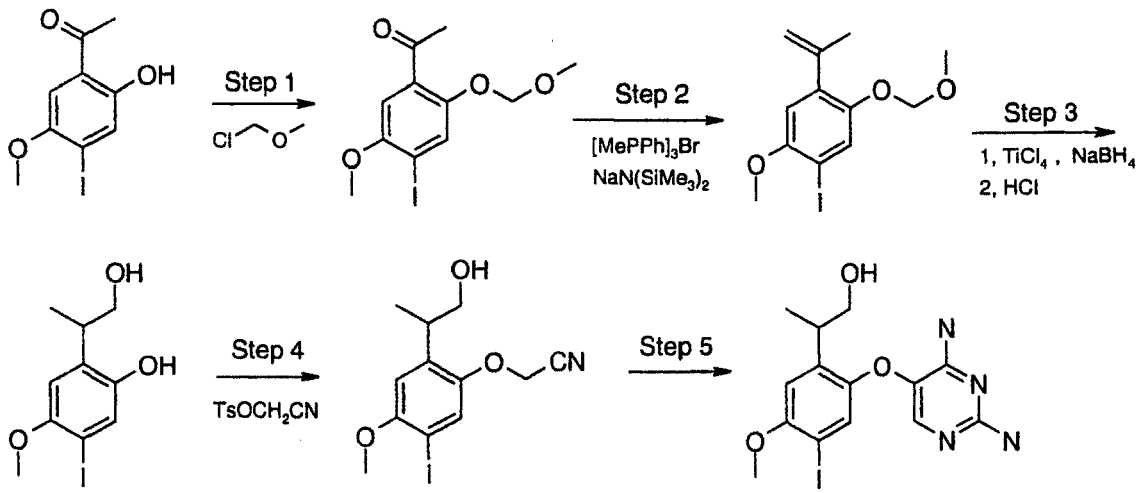
[0363] 5-Isopropyl-2,3-dihydro-benzo[1,4]dioxin -6-yloxy)acetonitrile (0.544 g, 2.3 mmol) was converted, as described in step 6 of Example 21, to 5-(5-isopropyl-2,3-dihydro-benzo[1,4]-dioxin-6-yloxy)-pyrimidine-2,4-diamine (0.560 g, 86%) as a yellow foam.

Step 9. 5-(7-Iodo-5-isopropyl-2,3-dihydro-benzo[1,4]dioxin-6-yloxy)-pyrimidine-2,4-diamine and 5-(7,8-Diiodo-5-isopropyl-2,3-dihydro-benzo[1,4]dioxin-6-yloxy)-pyrimidine-2,4-diamine

[0364] To a solution of 5-(5-isopropyl-2,3-dihydro-benzo[1,4]dioxin-6-yloxy)-pyrimidine-2,4-diamine (250 mg, 0.83 mmol) in acetic acid (2 ml) was added ICl (0.670 g, 4.13 mmol) in 3 ml AcOH and 2 ml H_2O. After 20 h the reaction was neutralized with Na_2CO_3 and extracted with CH_2Cl_2. The combined organics were washed with washed 10% $NaHSO_3$, washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. Purification via flash chromatography (97:3 CH_2Cl_2/MeOH) afforded 5-(7,8-diiodo-5-isopropyl-2,3-dihydro-benzo[1,4]dioxin-6-yloxy)-pyrimidine-2,4-diamine (0.049 g, 10%) as yellow solid ($[MH]^+$= 555) and 5-(7-iodo-5-isopropyl-2,3-dihydro-benzo[1,4]dioxin-6-yloxy)-pyrimidine-2,4-diamine (0.050 g, 14%) as a foam. $[MH]^+$=429.

Example 38: 2-[2-(2,4-Diamino-pyrimidin-5-yloxy)-4-iodo-5-methoxy-phenyl]-propan-1-ol

[0365] The synthetic procedure used in this Example is outlined in Scheme Q.



SCHEME Q

Step 1. 1-(2-Hydroxy-4-iodo-5-methoxy-phenyl)-ethanone

[0366] To a suspension of sodium hydride (0.044 g, 1.1 mmol, 60% in mineral oil) in 0.5 ml DMF was added sodium 5-iodo-2-acetyl,4-methoxyphenol (0.292 g, 1 mmol, prepared as described in Example 35) as a solution in 1.5 ml DMF. After 10 min chloromethoxy methane (0.079 g, 1.0 mmol) was added. After 30 min the mixture was extracted with CH_2Cl_2. The combined organics were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. Purification via flash chromatography (88:12= hexane/ethyl acetate) afforded 1-(2-hydroxy-4-iodo-5-methoxy-phenyl)-ethanone (0.314 g, 85%) as yellow solid; $[MH]^+$= 337.

Step 2. 1-Iodo-4-iosprenyl-2-methoxy-5-methoxymethoxy-benzene

[0367] To a suspension of methyl triphenylphosphonium bromide (0.457 g, 1.3 mmol) in 8 ml THF was added sodium hexamethyldisilazide (1.3 ml, 1.29 mmol, 1.0 M in THF). After 1.5 h 1-(2-hydroxy-4-iodo-5-methoxy-phenyl)-ethanone (0.288 g, 0.9 mmol) as a solution in 8 ml THF was added dropwise. After 20 h the mixture was filtered through a pad of celite and extracted with CH_2Cl_2. The combined organics were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. Purification via flash chromatography (95:5 hexane/ethyl acetate) afforded 1-iodo-4-iosprenyl-2-methoxy-5-methoxymethoxy-benzene (0.224 g, 78%) as colorless liquid; $[MH]^+$ = 335.

Step 3. 2-(2-Hydroxy-1-methyl-ethyl)-5-iodo-4-methoxy-phenol

[0368] To a mixture of $NaBH_4$ (0.051 g, 1.3 mmol) in 4 ml DME was added $TiCl_4$ (0.67 ml, 0.67 mmol, 1.0 M in CH_2Cl_2). After 1 hour, 2-methyl 1-iodo-4-iosprenyl-2-methoxy-5-methoxymethoxy-benzene (0.224 g, 0.7 mmol) in 4 ml DME was added. After 20 h the mixture was quenched with H_2O and extracted with ethyl acetate. The combined organics were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo to give an oil. To a solution of this oil in 3 ml isopropanol was added 3 ml 6M HCl. After 3 h the mixture was neutralized with saturated $NaHCO_3$ and extracted with ethyl acetate. The combined organics were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo to give an oil. Purification via preparative TLC (70:30 hexane/ethyl acetate) afforded 2-(2-hydroxy-1-methyl-ethyl)-5-iodo-4-methoxy-phenol (0.080 g, 30%) as a clear oil; $[MH]^+$ = 309.

Step 4. [2-(2-Hydroxy-methyl-ethyl)-5-iodo-4-methoxy-phenoxyl-acetonitrile

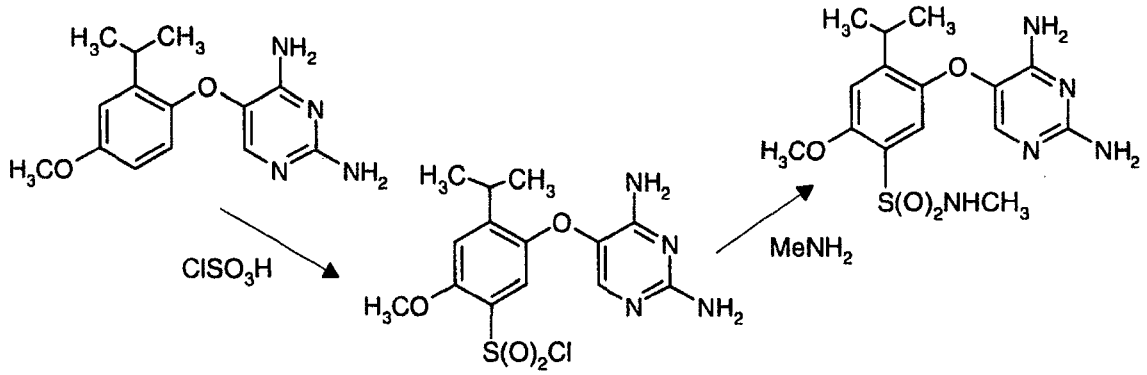
[0369] 2-(2-Hydroxy-1-methyl-ethyl)-5-iodo-4-methoxy-phenol (0.080 g, 0.3 mmol) was converted, as described in step 6 of Example 21, to [2-(2-hydroxy-methyl-ethyl)-5-iodo-4-methoxy-phenoxy]-acetonitrile (0.076 g, 84%) as white solid; $[MH]^+$= 348.

Step 5. 2-[2-(2,4-Diaminopyrimidin-5-yloxy)-4-iodo-5- methoxy-phenyl]-propan-1-ol

[0370] [2-(2-hydroxy-methyl-ethyl)-5-iodo-4-methoxy-phenoxy]-acetonitrile (0.488 g, 1.4 mmol), using the procedure of step 7 of Example 21, was converted to 2-[2-(2,4-diamino-pyrimidin-5-yloxy)-4-iodo-5-methoxy-phenyl]-propan-1-ol (0.459 g, 79%) as a white solid; mp (HCl salt) = 290.1-292.2°C; $[MH]^+$= 417.

Example 39: 5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-N-methyl-benzenemethylsulfonamide

[0371]



Step 1. 5-(2,4-Diamino-pyrimidin-5-yloxyl-4-isopropyl-2-methoxy-benzenesulfonyl chloride

[0372] A mixture of pyrimidine (0.400 g, 1.5 mmol) in 2 ml chlorosulfonic acid was allowed to stir 20 min. The mixture was poured over ice. The precipitate was filtered, washed by cold H_2O and dried under vacuum to afford 5-(2,4-diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-benzenesulfonyl chloride (0.515 g, 95%) as a white solid; $[MH]^+$= 373.

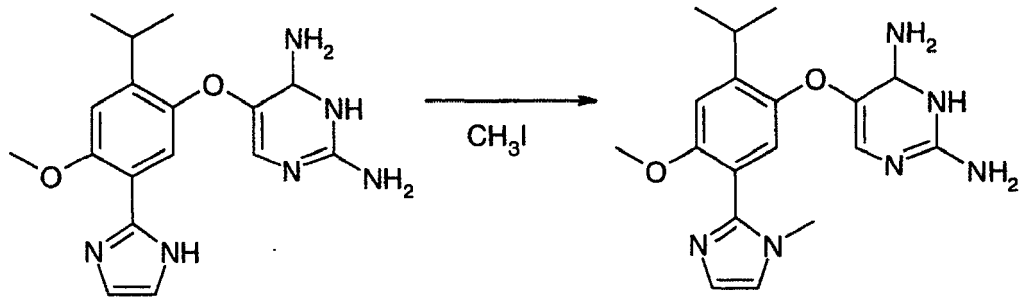
Step 2. 5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-N-methyl-benzene-methylsulfonamide

[0373] To 10 ml methyl amine -78°C in a screw-capped tube was added 5-(2,4-diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-benzenesulfonyl chloride (0.300 g, 0.8 mmol). The mixture was allowed to warm to RT. After 20 hours the mixture was evaporated, washed with H_2O, and dried under vacuum to afford 5-(2,4-diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-N-methyl-benzenemethylsulfonamide (0.170 g, 57%) as a white solid; mp (HCl salt) = 252.3-252.9°C; $[MH]^+$ = 367.

[0374] Similarly prepared, replacing methylamine with ethylamine, was 5-(2,4-diamino-pyrimidin-5-yloxy)-N-ethyl-4-isopropyl-2-methoxy-benzenesulsonamide (0.186 g, 61%) as a white solid; mp (HCl salt)= 260-265 °C; $[MH]^+$= 382.

Example 40: 5-[2-Isopropyl-4-methoxy-5-(1-methyl-1H-imidazol-2-yl)-phenoxy]-3,4-dihydro-pyrimidine-2,4-diamine

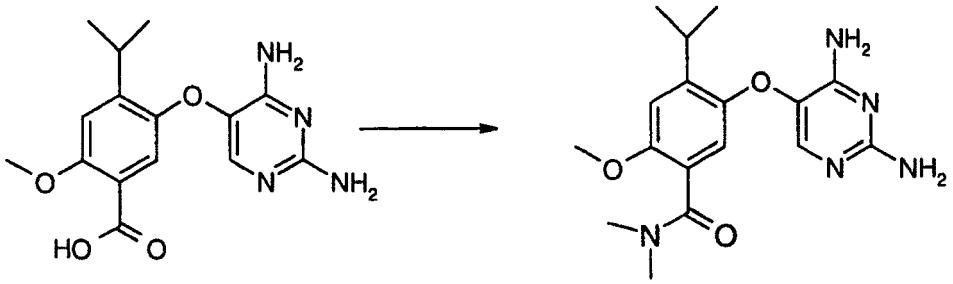
[0375]



[0376] To a solution of 5-[5-(1H-Imidazol-2-yl)-2-isopropyl-4-methoxy-phenoxy]-3,4-dihydro-pyrimidine-2,4-diamine (0.044g, 0.129 mmols) and iodomethane (9 ul, 0.145 mmols) in acetone (5 ml) was added KOH (0.055g, 0.98 mmols), the mixture was heated at 30°C for 20 min, the mixture was filtered through celite, washed with CH_2Cl_2, the combined organic solution was concentrated in vacuo. The residue was purified via preparative TLC silica plates, eluted with 5% $MeOH/CH_2Cl_2/NH_4OH$ four times to give 5-[2-isopropyl-4-methoxy-5-(1-methyl-1H-imidazol-2-yl)-phenoxy]-3,4-dihydro-pyrimidine-2,4-diamine (0.024g, 52%). Mass Spec: M+H: 355.

Example 41: 5-(2,4-Diamino-pyrimidin-5-yloxy)4-isopropyl-2-methoxy-N,N-dimethyl-benzamide

[0377]

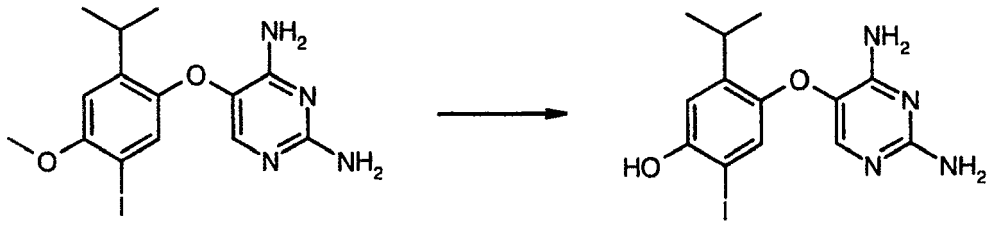


[0378] To a suspension of 5-(2,4-diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-benzoic acid (180 mg, 0.57 mmol, from Example 17) in anhydrous DCM (5.6 mL) was added trifluoroacetic acid (0.08 mL, 1.14 mmol) and then thionyl chloride (0.36 mL, 5.65 mmol). After 1 hour the reaction was concentrated. To the residue was added anhydrous DCM (4.5 mL) and dimethylamine (2.84 mL of a 2M solution in THF, 5.65 mmol). After 2 hours stirring at RT, the reaction was filtered and concentrated. Purification via silica gel column chromatography eluting with 95/5/0.1 to 93/7/0.1 DCM / methanol/ ammonium hydroxide yielded 5-(2,4-diamino-pyrimidin-5-yloxy)4-isopropyl-2-methoxy-N,N-dimethyl-benzamide (40 mg, 20%) as pale yellow solid, MS (M+H) = 346.

[0379] Similarly prepared using methylamine instead of dimethylamine, 5-(2,4-diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-N-methyl-benzamide (23 mg, 15%) was prepared as pale yellow solid, MS (M+H) = 332.

Example 42: 4-(2,4-Diamino-pyrimidin-5-yloxy)-2-iodo-5-isopropyl-phenol

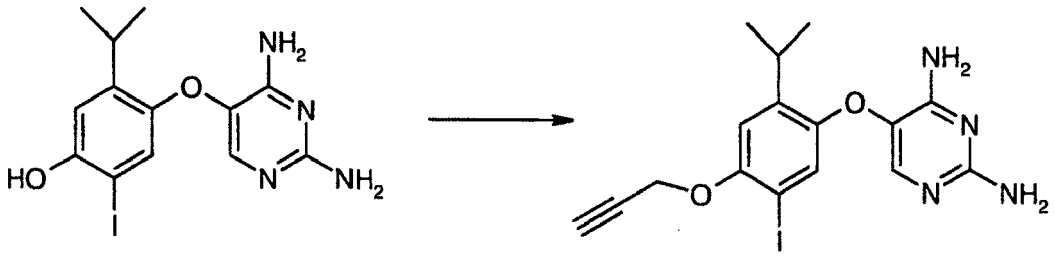
[0380]



[0381] To a cold suspension of 5-(5-iodo-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine (0.21g, 0.52mmol) in DCM (15ml) at 0°C was added BBr_3(0.26g, 1.05mmol). The reaction mixture was stirred at RT for 16 hrs., quenched with water and basified with sat. $NaHCO_3$. The insoluble solid was collected by filtration. The filtrate was washed with water, dried over Na_2SO_4, filtered and concentrated in vacuo. The combined residue was purified via flash chromatographed on silica gel (3 to 5% methanol in DCM with 0.1% NH_4OH) gave desired product (0.174g, 86%), (M+H) = 387.

Example 43: 5-(5-Iodo-2-isopropyl-4-prop-2-ynyloxy-phenoxy)-pyrimidine-2,4-diamine

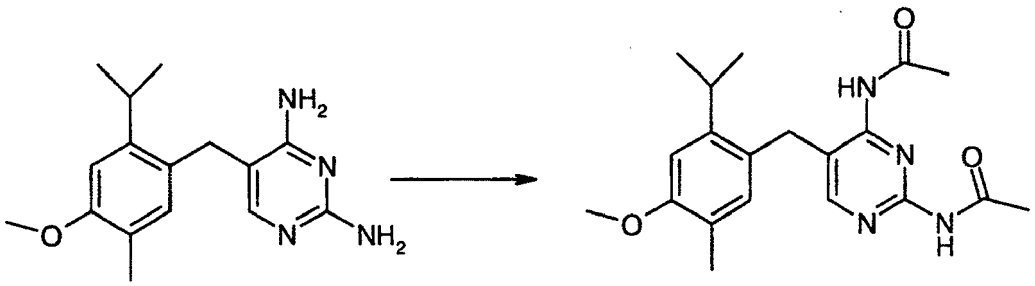
[0382]



[0383] To 4-(2,4-diamino-pyrimidin-5-yloxy)-2-iodo-5-isopropyl-phenol (200 mg, 0.43 mmol) dissolved in anhydrous DMF (2 mL) was added anhydrous potassium carbonate (414 mg, 3.00 mmol) and propargyl chloride (0.03 mL, 0.43 mmol). After stirring at RT overnight, the reaction was extracted with DCM, water and brine. The DCM layer was dried using anhydrous magnesium sulfate, concentrated, and purified via silica gel column chromatography (95/5/0.1 DCM / methanol/ ammonium hydroxide) to yield 5-(5-iodo-2-isopropyl-4-prop-2-ynyloxy-phenoxy)-pyrimidine-2,4-diamine as white solid (131 mg, 71%), MS (M+H) = 425.

Example 44: N-[2-Acetylamino-5-(2-isopropyl-4-methoxy-5-methyl-benzyl)-pyrimidin-4-yl] -acetamide

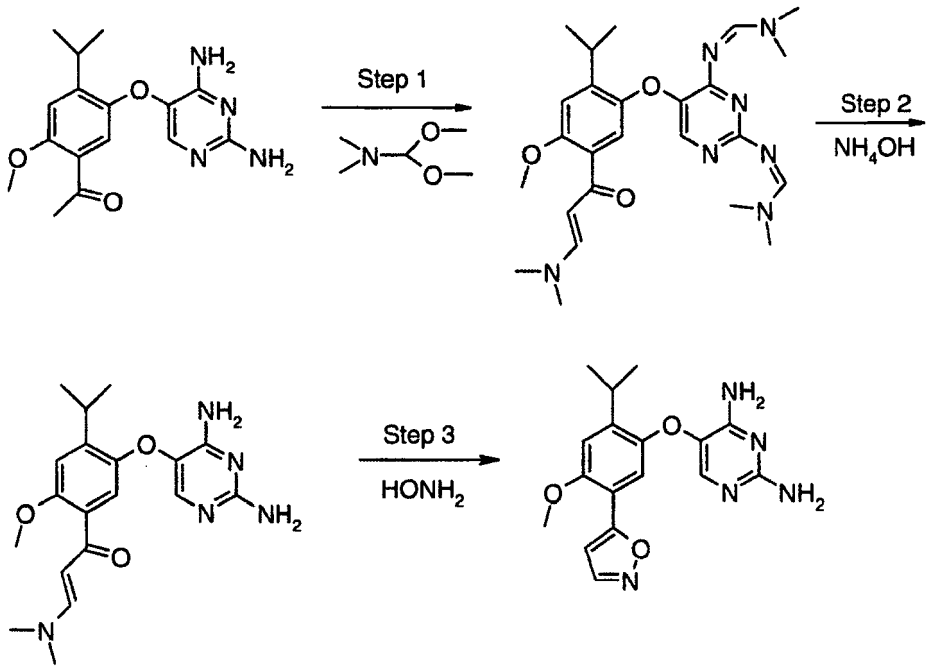
[0384]



[0385] To 5-(2-sopropyl-4-methoxy-5-methyl-benzyl)-pyrimidine-2,4-diamine (30 mg, 0.10 mmol) dissolved in anhydrous pyridine (1 mL) was added acetyl chloride (0.04 mL, 0.44 mmol). After stirring 30 min at RT, the reaction was concentrated. The residue was dissolved in DCM, washed with water, and concentrated in vacuo. Purification via preparative TLC (95/ 5 DCM / methanol) yielded N-[2-acetylamino-5-(2-isopropyl-4-methoxy-5-methyl-benzyl)-pyrimidin-4-yl]-acetamide (7 mg, 18%), MS (M+H) = 371.

Example 45: 5-(2-Isopropyl-5-isoxazol-5-yl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine

[0386] The synthetic procedure used in this Example is outlined in Scheme Q.



SCHEME Q

Step 1. N'-[5-[5-(3-Dimethylamino-acryloyl)-2-isopropyl-4-methoxy-phenoxy]-4-(dimethylamino-methyleneamino)-pyrimidin-2-yl]-N,N-dimethyl-formamidine

[0387] To 1-[5-(2,4-diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-ethanone (100 mg, 0.32 mmol, from Example 16) dissolved in anhydrous DMF (0.6 mL) was added DMF dimethyl acetal (0.17 mL, 1.26 mmol) and the reaction was heated at 114°C overnight. Concentration of the reaction mixture yielded N'-[5-[5-(3-Dimethylamino-acryloyl)-2-isopropyl-4-methoxy-phenoxy]-4-(dimethylamino-methyleneamino)-pyrimidin-2-yl]-N,N-dimethyl-formamidine.

Step 2. 1-[5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-3-dimethylamino-propenone

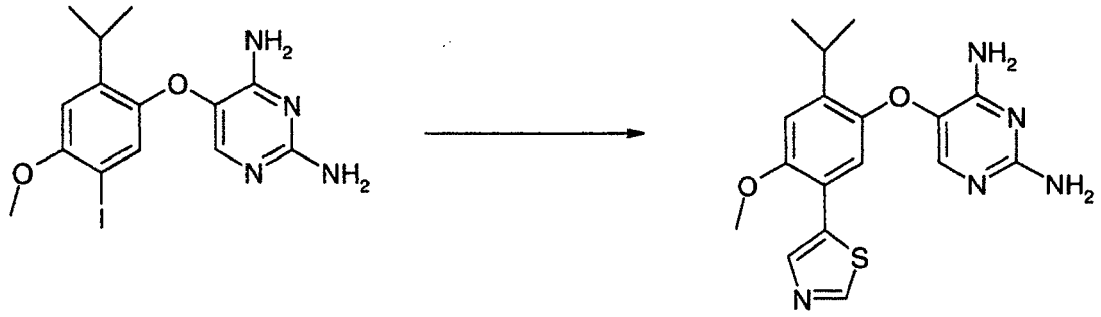
[0388] The N'-[5-[5-(3-Dimethylamino-acryloyl)-2-isopropyl-4-methoxy-phenoxy]-4-(dimethyl-amino-methyleneamino)-pyrimidin-2-yl]-N,N-dimethyl-formamidine from step 1 was dissolved in methanol (1 mL) and ammonium hydroxide (1 mL). After stirring 5 days at RT, the reaction was concentrated and purified by preparatory TLC plates (92/ 8/ 0.5 DCM / methanol/ ammonium hydroxide) to yield 1-[5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-3-dimethylamino-propenone (34 mg, 29%) as white solid.

Step 3. 5-(2-Isopropyl-5-isoxazol-5-yl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine

[0389] To 1-[5-(2,4-Diamina-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-3-dimethyl-amino-propenone (30 mg, 0.08 mmol) dissolved in a mixture of methanol (1.5 mL) and water (0.4 mL) was added hydroxylamine hydrochloride (14 mg, 0.20 mmol) and the reaction was refluxed for 1 hour. Purification by preparatory TLC plates (92/ 8/ 0.5 DCM / methanol/ ammonium hydroxide) yielded 5-(2-isopropyl-5-isoxazol-5-yl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine (8 mg, 29%) as white solid, MS (M+H) = 342.

Example 45: 5-(2-Isopropyl-4-methoxy-5-thiazol-5-yl-phenoxy)-pyrimidme-2,4-diamine

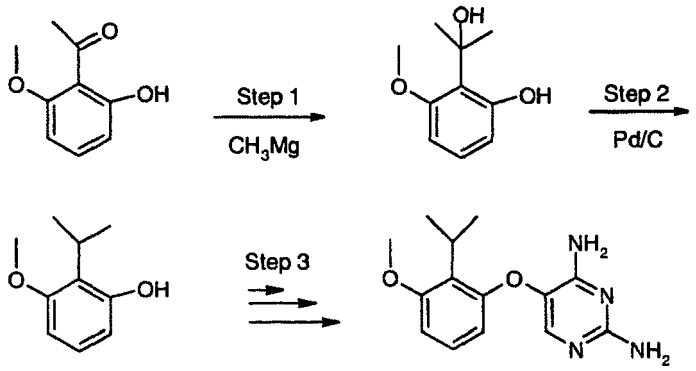
[0390]



[0391] To 5-(5-Iodo-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine (600 mg, 1.5 mmol, from Example 14, Step 1) dissolved in N,N-dimethylacetamide (4.8 mL) was added potassium acetate (221 mg, 2.24 mmol), thiazole (0.53 mL, 7.5 mmol) and tetrakis(triphenylphosphine)palladium(0) (70 mg, 0.06 mmol). After heating at 115°C overnight the cooled reaction was extracted with DCM (100 mL) and water (2 x 100 mL). The DCM layer was dried using anhydrous sodium sulfate, concentrated and purified by silica gel column chromatography eluting with 95/5/0.1 DCM / methanol/ ammonium hydroxide to yield 5-(2-isopropyl-4-methoxy-5-thiazol-5-yl-phenoxy)-pyrimidine-2,4-diamine (49 mg, 9%) as pale yellow solid, MS (M+H) = 358.

Example 46: 5-(2-Isopropyl-3-methoxy-phenoxy)-pyrimidine-2,4-diamine

[0392] The synthetic procedure used in this Example is outlined in Scheme R.



SCHEME R

Step 1. 2-(1-Hydroxy-1-methyl-ethyl)-3-methoxy-phenol

[0393] To a solution of methyl magnesium bromide (24 mL of a 3M solution in diethyl ether, 72.2 mmol) in anhydrous THF (20 mL) at 0°C was added a solution of 2'-hydroxy-6'-methoxy-acetophenone (4 g, 24.1 mmol) in anhydrous THF (40 mL), maintaining the temperature below 11°C during the addition. After stirring for 1.5 hours at RT, a solution of 10% ammonium chloride (30 mL) was added slowly maintaining the temperature below 22°C with the use of an ice bath. Water (300 mL) was slowly added and the reaction was extracted twice with ethyl acetate. The combined ethyl acetate layers were washed with water, brine, dried using anhydrous sodium sulfate and concentrated to give 2-(1-hydroxy-1-methyl-ethyl)-3-methoxy-phenol (4.52 g) as pale yellow solid.

Step 2. 2-Isopropyl-3-methoxy-phenol

[0394] To a solution of 2-(1-Hydroxy-1-methyl-ethyl)-3-methoxy-phenol dissolved in acetic acid (50 mL) was added 10% palladium on charcoal (500 mg), water (6 mL), and ammonium formate (7.82 g, 124 mmol). After refluxing for 1 hour, the reaction was cooled and filtered through celite. The celite pad was washed with ethyl acetate (500 mL). Water (300 mL) was added to the filtrate, and the mixture was basified (pH = 8) using solid sodium bicarbonate. The ethyl acetate layer was collected and washed with water, brine, dried using anhydrous sodium sulfate and concentrated to yield 2-Isopropyl-3-methoxy-phenol (3.68 g, 92%) as pale yellow solid.

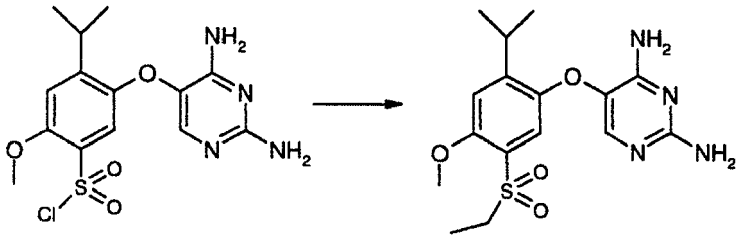
Step 3. 5-(2-Isopropyl-3-methoxy-phenoxy)-pyrimidine-2,4-diamine

[0395] Using the 2-Isopropyl-3-methoxy-phenol of step 3 above, and following the procedure of steps 5-7 of Example 2,5-(2-isopropyl-3-methoxy-phenoxy)-pyrimidine-2,4-diamine was prepared. MS (M+H) = 275.

[0396] Similarly prepared was 5-(2-Isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine. MS (M+H) = 275.

Example 47: 5-(5-Ethanesulfonyl-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine

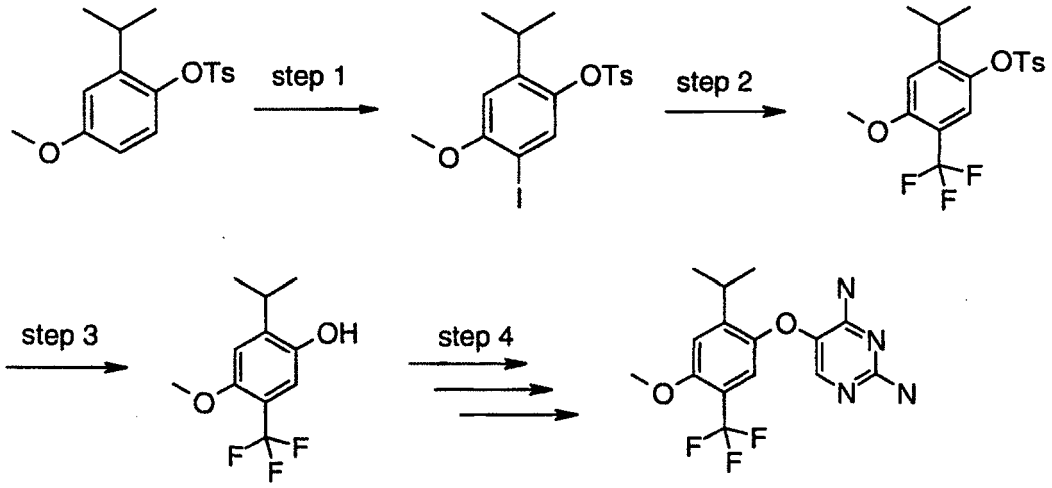
[0397]



[0398] To a solution of sodium sulfite (541 mg, 4.29 mmol) in water (20 mL) was added 5-(2,4-diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-benzenesulfonyl chloride (400mg, 1.07 mmol) and the reaction was heated at 80°C for 1 hour. Sodium bicarbonate (361 mg, 4.29 mmol-dissolved in 5 mL water), dioxane (20 mL), and ethyl iodide (0.10 mL, 1.29 mmol) were added and the reaction was heated at 80°C for 2 hours. The reaction was concentrated, extracted with dichloromethane (150 mL) and water (20 mL). The DCM layer was dried using anhydrous sodium sulfate, concentrated, and purified via silica gel column chromatography (95/5/0.1 DCM / methanol/ ammonium hydroxide) to yield 5-(5-ethanesulfonyl-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine (77 mg, 20%) as white solid, MS (M+H) = 367.

Example 48: 5-(2-Isopropyl-4-methoxy-5-trifluoromethyl-phenoxy)-pyrimidine-2,4-diamine

[0399] The synthetic procedure used in this Example is outlined in Scheme S.



SCHEME S

Step 1. 1-Iodo-4-isopropyl-2-methoxy-5-(toluene-4-sulfonyl)-benzene

[0400] To a solution of 2-Isopropyl-4-methoxy-1-(toluene-4-sulfonyl)-benzene (10 g, 31.25 mmol) in HOAc (10ml) was added a solution of ICl (9.6g, 59.26mmol) in HOAc (10 ml) and H_2O (5 ml). The reaction mixture was stirred at RT for 16 hrs and basified by saturated $NaHCO_3$ solution. The aqueous solution was extracted into EtOAc which was washed with water, brine, dried over Na_2SO_4, filtered and concentrated in vacuo to give 1-Iodo-4-isopropyl-2-methoxy-5-(toluene-4-sulfonyl)-benzene (12.35g, 89%).

Step 2. 1-Isopropyl-5-methoxy-2-(toluene-4-solfonyl)-4-trifluoromethyl-benzene

[0401] To a hot mixture of 1-iodo-4-isopropyl-2-methoxy-5-(toluene-4-sulfonyl)-benzene (0.5 g, 1.12 mmol), CuI, KF in anhydrous DMF (10 ml) at 120°C oil bath temperature, was added trifluoromethyl iodide (0.64g, 4.48mmol) in portions over 30 min. The reaction mixture was heated for 4 hrs and poured into H_2O (100 ml). The insoluble solid, which was collected by filtration was triturated with methylene chloride, filtered and concentrated to give 1-isopropyl-5-methoxy-2-(toluene-4-sulfonyl)-4-trifluoromethyl-benzene (0.45 g, 100%) as a solid.

Step 3. 2-Isopropyl-4-methoxy-5-trifluoromethyl-phenol

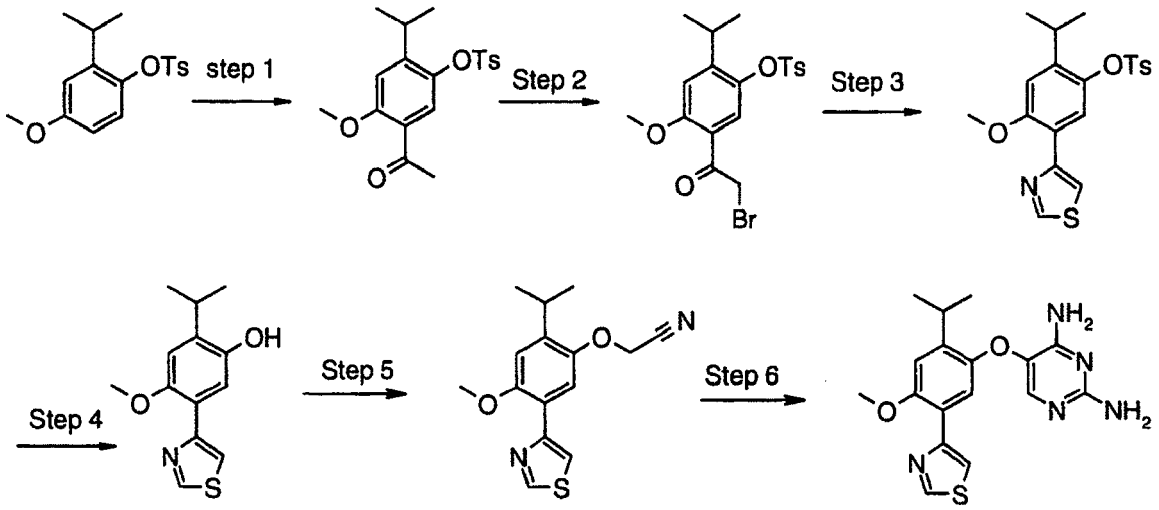
[0402] A solution of 1-isopropyl-5-methoxy-2-(toluene-4-sulfonyl)-4-trifluoromethyl-benzene (0.40 g, 1.03 mmol) and NaOH (0.5 g, 12.5 mmol) in MeOH(5ml) and H_2O (5ml) was heated at 90°C for 2 hrs. The cooled reaction mixture was acidified with 3N HCl and extracted into methylene chloride. The combined extract was dried with Na_2SO_4, filtered and concentrated to give the desired 2-isopropyl-4-methoxy-5-trifluoromethyl-phenol (0.194 g, 81%) as an oil.

Step 4. 5-(2-Isopropyl-4-methoxy-5-trifluoromethyl-phenoxy)-pyrimidine-2,4-diamine

[0403] Following the procedure of Example 2 steps 5-7,2-isopropyl-4-methoxy-5-trifluoromethyl-phenol was converted to 5-(2-isopropyl-4-methoxy-5-trifluoromethyl-phenoxy)-pyrimidine-2,4-diamine. (M+H) = 343

Example 49: 5-(2-Isopropyl-4-methoxy-5-thiazol-4-yl-phenoxy)-pyrimidine-2,4-diamine

[0404] The synthetic procedure used in this Example is outlined in Scheme T.



SCHEME T

Step 1. 1-[4-Isopropyl-2-methoxy-5-(toluene-4-sulfonyl)-phenyl]-ethanone

[0405] To a clear solution of 2-isopropyl-4-methoxy-1-(toluene-4-sulfonyl)-benzene (5.3 g, 16.56 mmol) in DCE (50 ml) was added acetyl chloride (2.0 g, 24.84 mmol) and $AlCl_3$ (3.3 g, 24.84 mmol) at RT. The reaction mixture was stirred at RT for 16 hrs and quenched by H_2O (10 ml). Ten min after quenching, the aqueous solution was extracted into CH_2Cl_2. The combined extract was washed with H_2O, dried over Na_2SO_4, filtered and concentrated. Flashed chromatography on silica gel (0 to 30% EtOAc in Hex) gave 1-[4-isopropyl-2-methoxy-5-(toluene-4-sulfonyl)-phenyl]-ethanone (4.7g, 79%) as white solid.

Step 2. 2-Bromo-1-[4-isopropyl-2-methoxy-5-(toluene-4-sulfonyl)-phenyl]-ethanone

[0406] To a hot mixture of $CuBr_2$ (0.25 g, 1.10 mmol) in EtOAc (1 ml) was added a solution of 1-[4-Isopropyl-2-methoxy-5-(toluene-4-sulfonyl)-phenyl]-ethanone (0.2 g, 0.55 mmol) in $CHCl_3$ (1 ml). The reaction mixture was refluxed for 16 hours, filtered, and concentrated to give 2-Bromo-1-[4-isopropyl-2-methoxy-5-(toluene-4-sulfonyl)-phenyl]-ethanone

(0.23 g, 95%) as an oil.

Step 3. 4-[4-Isopropyl-2-methoxy-5-(toluene-4-sulfonyl)-phenyl]-thiazole

[0407] To a solution of 2-Bromo-1-[4-isopropyl-2-methoxy-5-(toluene-4-sulfonyl)-phenyl]-ethanone (0.23 g, 0.51 mmol) in anhydrous dioxane (5 ml) was added Na_2CO_3 (1.1 g, 10.12 mmol) and thioamide (5 ml, 0.31g, 5.06 mmol). The reaction mixture was refluxed for 3 hrs and partitioned between H_2O and methylene chloride. The combined organic extracts was dried over Na_2SO_4, filtered and concentrated. Flash chromatography on silica (30% EtOAc in Hex) gave 4-[4-Isopropyl-2-methoxy-5-(toluene-4-sulfonyl)-phenyl]-thiazole (0.19g, 95%)as oil.

Step 4. 2-Isopropyl-4-methoxy-5-thiazol-4-yl-phenol

[0408] A mixture of 4-[4-Isopropyl-2-methoxy-5-(toluene-4-sulfonyl)-phenyl]-thiazole (1.0 g, 2.27 mmol) and K_2CO_3 (1.6 g, 11.34 mmol) in anhydrous MeOH (10 ml) was refluxed for 8 hrs. Solvent was removed in vacuo and the residue was partitioned between methylene chloride and water. The combined organic extract was dried over Na_2SO_4, filtered, and concentrated to give 2-Isopropyl-4-methoxy-5-thiazol-4-yl-phenol.

Step 5. (2-Isopropyl-4-methoxy-5-thiazol-4-yl-phenoxy)-acetonitrile

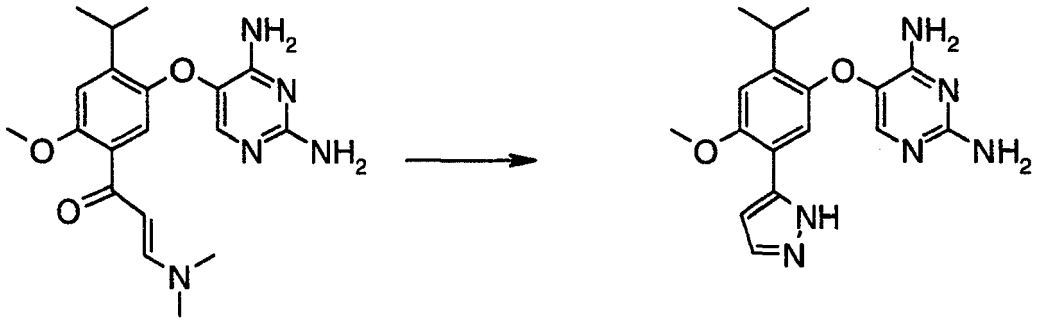
[0409] The crude 2-Isopropyl-4-methoxy-5-thiazol-4-yl-phenol from step 4 and bromoacetonitrile (0.33 g, 2.72 mmol) together with K_2CO_3 (0.94 g, 6.81 mmol) in anhydrous acetonitrile (30 ml) was heated at 60°C for 3 hrs. The reaction mixture was partitioned between EtOAc and water. The combined organic extract was dried over Na_2SO_4, filtered and concentrated. Flash chromatography on silica (10 to 20%% EtOAc in Hexanes) gave (2-Isopropyl-4-methoxy-5-thiazol-4-yl-phenoxy)-acetonitrile (0.47 g, 72%) as an oil.

Step 6. 5-(2-Isopropyl-4-methoxy-5-thiazol-4-yl-phenoxy)-pyrimidine-2,4-diamine

[0410] A mixture of (2-Isopropyl-4-methoxy-5-thiazol-4-yl-phenoxy)-acetonitrile (0.27 g, 0.94 mmol) and Brederick's reagent (0.35 g, 2.01 mmol) was heated at 100°C for 2 hrs. Excess Brederick's reagent was removed under reduced pressure. The residue was dissolved in anhydrous EtOH (10 ml) and aniline HCl (0.38 g, 2.93 mmol) was added. The reaction mixture was heated at 80°C for 18 hrs and partitioned between EtOAc and water. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. Guanidine carbonate (0.27 g,1.49 mmol) and NMP (10 ml) were added and heated to 120°C for 10 hrs. The reaction mixture was poured into water and extracted into EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. Flash chromatography on silica (3% MeOH in methylene chloride with 0.1%NH_4OH) gave 5-(2-Isopropyl-4-methoxy-5-thiazol-4-yl-phenoxy)-pyrimidine-2,4-diamine (0.15g, 68%) as a solid. (M+H) = 358.

Example 50: 5-[5-(N'-Allylidene-hydrazinomethyl)-2-isopropyl-4-methoxy-phenoxy]-pyrimidine-2,4-diamine

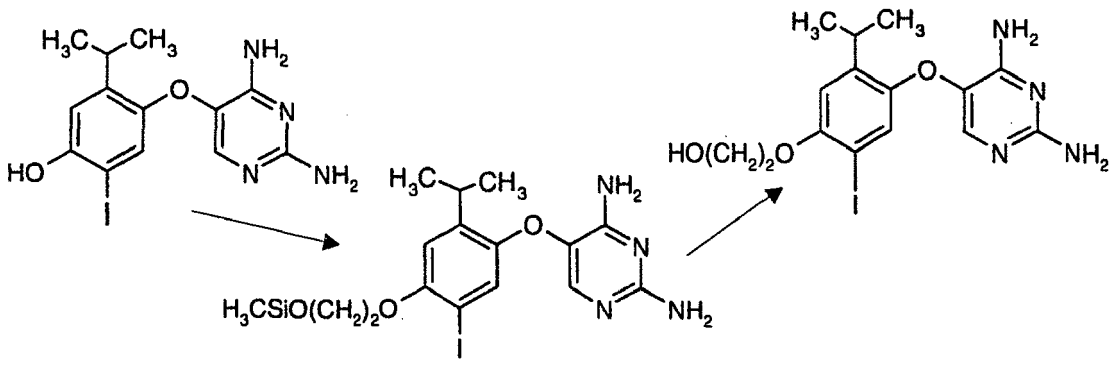
[0411]



[0412] To a solution of 1-[5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-3-dimethylamino-propenone (0.25 g, 0.67 mmol) in EtOH (6 ml) was added hydrazine hydrate (0.076 g,1.2 mmol). The reaction mixture was stirred at RT for 16 hrs and concentrated. Recrystallization of the crude residue in EtOH/EtOAc gave 5-[5-(N'-Allylidene-hydrazinomethyl)-2-isopropyl-4-methoxy-phenoxy]-pyrimidine-2,4-diamine (0.228 g, 100%). (M+H) = 341.

Example 51: 2-[4-(2,4-Diamino-pyrimidin-5-yloxy)-2-iodo-5-isopropyl-phenoxy]-ethanol

[0413]



Step 1. 5-[5-Iodo-2-isopropyl-4-(2-trimethylsilanyloxy-ethoxy)-phenozy]-pyrimidine-2,4-diamine

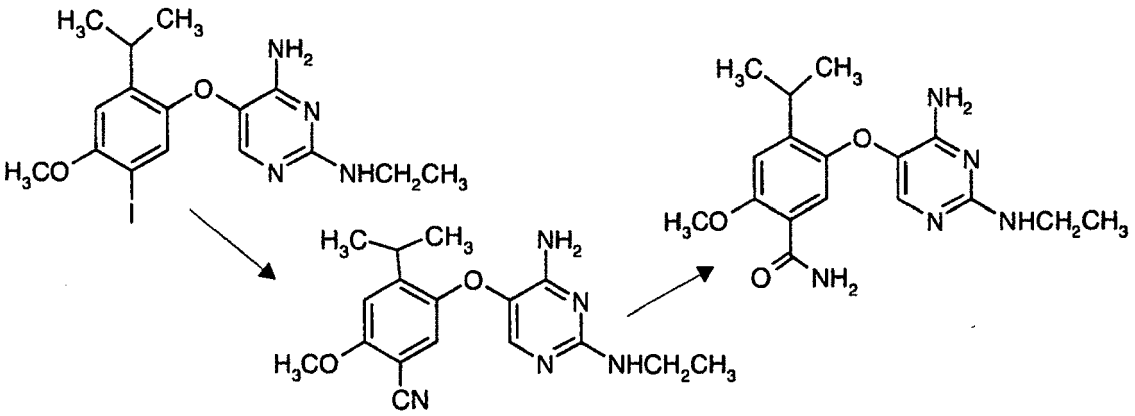
[0414] A mixture of 4-(2,4-Diamino-pyrimidin-5-yloxy)-2-iodo-5-isopropyl-phenol (0.3 g, 0.78 mmol), (2-bromoethoxy)-tert-butyl-dimethyl silane (0.28 g, 1.17 mmol), and K_2CO_3 (0.22 g, 1.56 mmol) in anhydrous DMF (5 ml) was heated at 50°C for 16 hrs. Solvent was removed in vacuo. The residue was partitioned between methylene chloride and water. The combined organic extract was washed with water, dried over Na_2SO_4, filtered and concentrated. Flash chromatography on silica(3%MeOH in methylene chloride with 0.1% NH_4OH) gave 5-[5-Iodo-2-isopropyl-4-(2-trimethylsilanyloxy-ethoxy)-phenoxy]-pyrimidine-2,4-diamine (0.38 g, 90%) as a solid.

Step 2. 2-[4-(2,4-Diamino-pyrimidin-5-yloxy)-2-iodo-5-isopropyl-phenoxy]-ethanol

[0415] 5-[5-Iodo-2-isopropyl-4-(2-trimethylsilanyloxy-ethoxy)-phenoxy]-pyrimidine-2,4-diamine (0.38 g, 0.69 mmol) in a solution of HOAc/THF/H_2O in a ratio of 3:1:1.95 ml) was heated at 65°C for 16 hrs. The pH of the reaction mixture was adjusted to pH = 9 and extracted into methylene chloride. The combined extract was dried over Na_2SO_4, filtered and concentrated. Flash chromatography on silica (5% MeOH in methylene chloride with 0.1% NH_4OH) gave 2-[4-(2,4-diamino-pyrimidin-5-yloxy)-2-iodo-5-isopropyl-phenoxy]-ethanol (0.25 g, 86%) as a white solid. (M+H) = 431

Example 52: 5-(4-Amino-2-ethylamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-benzamide

[0416]



Step 1. 5-(4-Amino-2-ethylamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-benzonitrile

[0417] To a solution of N*2*-Ethyl-5-(5-iodo-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine (1.65 g, 4.12 mmol) in anhydrous DMF (10 ml) was added CuCN, and the reaction mixture was heated to 120°C for 3 hrs. The reaction mixture was poured into water (200 ml) and the insoluble portion was collected by filtration. The solid was triturated with

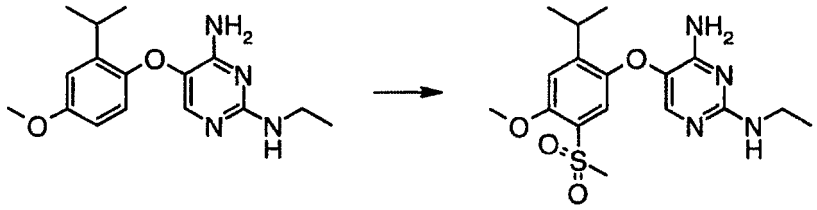
10% MeOH/methylene chloride/0.1% NH_4OH solution (100 ml) and filtered again. The filtrate was concentrated and flash chromatographed on silica (3% MeOH in methylene chloride with 0.1%NH_4OH) to give 5-(4-Amino-2-ethylamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-benzonitrile (0.87 g, 71%) as a white solid.

Step 2. 5-(4-Amino-2-ethylamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-benzamide

[0418] To a solution of 5-(4-Amino-2-ethylamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-benzonitrile (0.3 g, 0.92 mmol) in EtOH/H_2O (1:1,10 ml) was added a solution of NaOH (0.37 g, 9.17 mmol) in H_2O (1 ml). The reaction mixture was heated at 100°C for 24 hrs and neutralized with 3N HCl. Ethanol was removed in vacuo and the remaining aqueous solution was extracted into methylene chloride. The combined extract was washed with water, dried over Na_2SO_4, filtered and concentrated. Flash chromatography on silica gel (3 to 8% EtOAc in Hexanes) gave 5-(4-Amino-2-ethylamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-benzamide (0.086g, 27%) as a white solid. (M+H) = 346.

Example 53: N^2-Ethyl-5-(2-isopropyl-5-methanesulfonyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine

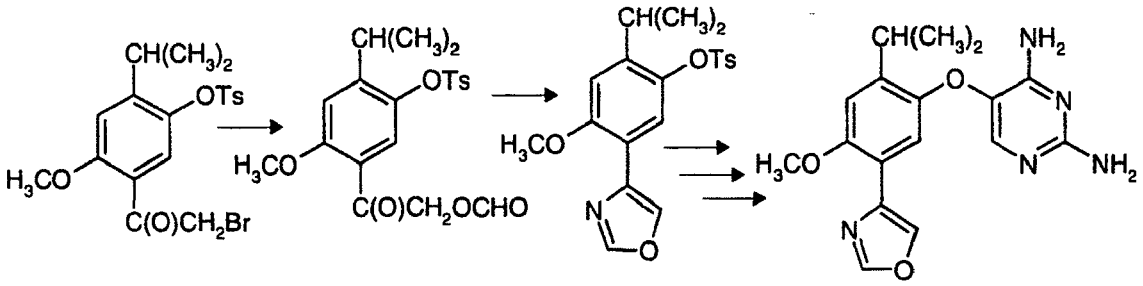
[0419]



[0420] A mixture of N^2-Ethyl-5-(2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine (0.30 g, 0.99 mmol), methanesulfonic anhydride (1.0 g, 5.96 mmol) and trifluoromethane-sulfonic acid (0.37 g, 2.48 mmol) was heated at 70°C for two hrs. The hot reaction mixture was poured into ice water and basified with sat. $NaHCO_3$ solution. The aqueous solution was then extracted into methylene chloride. The combined organic extract was washed with H_2O, dried over Na_2SO_4, filtered and concentrated. Flash chromatography on silica (1% MeOH in methylene chloride with 1% NH_4OH) gave N^2-Ethyl-5-(2-isopropyl-5-methanesulfonyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine (87 mg, 23%) as a solid. (M+H)=381.

Example 54: 5-(2-Isopropyl-4-methoxy-5-oxazol-4-yl-phenoxy)-pyrimidine-2,4-diamine

[0421]



Step 1. Toluene-4-sulfonic acid 5-(2-formyloxy-acetyl)-2-isopropyl-4-methoxy-phenyl ester

[0422] A mixture of 2-Bromo-1-[4-isopropyl-2-methoxy-5-(toluene-4-sulfonyl)-phenyl]-ethanone (0.2 g, 0.45 mmol) and sodium formate (0.040 g, 0.60 mmol) in anhydrous DMF (3 ml) was stirred at RT for 16 hours. The reaction mixture was poured into H_2O and extracted into EtOAc. The combined organic extract was dried over Na_2SO_4, filtered and concentrated to yield toluene-4-sulfonic acid 5-(2-formyloxy-acetyl)-2-isopropyl-4-methoxy-phenyl ester.

Step 2. 4-[4-Isopropyl-2-methoxy-5-(toluene-4-sulfonyl)-phenyl]-oxazole

[0423] A solution of the crude toluene-4-sulfonic acid 5-(2-formyloxy-acetyl)-2-isopropyl-4-methoxy-phenyl ester from

above and ammonium acetate (0.17 g, 2.25 mmol) in HOAc (5 ml) was heated at 100°C for 2 hrs. The reaction mixture was partitioned between methylene chloride and sat. $NaHCO_3$ solution. The combined organic extract was dried over Na_2SO_4, filtered and concentrated. Flash chromatography on silica (30 to 50% EtOAc in Hexanes) gave 4-[4-Isopropyl-2-methoxy-5-(toluene-4-sulfonyl)-phenyl]-oxazole (25 mg, 14%) as a white solid.

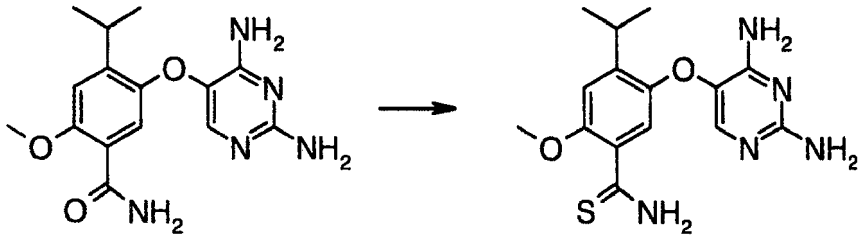
Step 3. 5-(2-Isopropyl-4-methoxy-5-oxazol-4-yl-phenoxyl-pyrimidine-2,4-diamine

[0424] 4-[4-Isopropyl-2-methoxy-5-(toluene-4-sulfonyl)-phenyl]-oxazole was converted, using the procedure of steps 4-6 of Example 49, to 5-(2-Isopropyl-4-methoxy-5-oxazol-4-yl-phenoxy)-pyrimidine-2,4-diamine. (M+H) = 342.

Example 55: 5-(2-Isopropyl-4-methoxy-5-thiazol-2-yl-phenoxy)-pyrimidine-2,4-diamine

Step 1. 5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-thiobenzamide

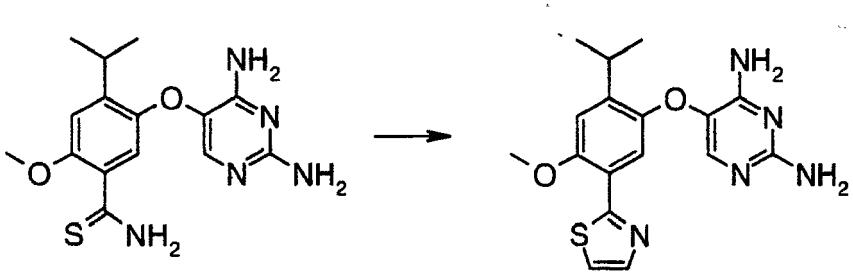
[0425]



[0426] A mixture of 5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-benzamide (0.25 g, 0.79 mmol, prepared according to the procedure of Example 52) and Lawesson's reagent (0.96 g, 2.37 mmol) in anhydrous THF (20 ml) was stirred at RT for 16 hrs and concentrated in vacuo. Flash chromatography on silica (5%CH_3OH in methylene chloride with 1% NH_4OH) gave 5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-thiobenzamide (0.201 g, 76%) as a yellow solid.

Step 2. 5-(2-Isopropyl-4-methoxy-5-thiazol-2-yl-phenoxy)-pyrimidine-2,4-diamine

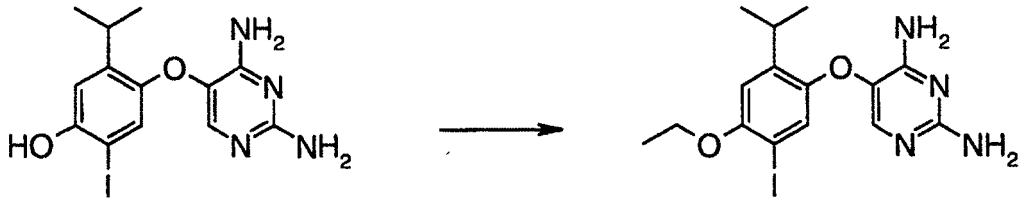
[0427]



[0428] To a solution of 5-(2,4-diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-thiobenzamide (0.23 g, 0.69 mmol) in HOAc (5 ml) was added bromoacetaldehyde diethylacetal (0.18 g, 0.9 mmol) and TsOH (5 mg) as a catalyst. The reaction mixture was heated at 110°C for 16 hrs and basified with sat. $NaHCO_3$ solution. The aqueous solution was extracted into methylene chloride. The combined organic extract was dried over Na_2SO_4, filtered and concentrated. Flash chromatography on silica (5% MeOH in methylene chloride with 1% NH_4OH) gave 5-(2-Isopropyl-4-methoxy-5-thiazol-2-yl-phenoxy)-pyrimidine-2,4-diamine (0.070 g, 28%) as a yellow solid. (M+H) = 358.

Example 56: 5-(4-Ethoxy-5-iodo-2-isopropyl-phenoxy)-pyrimidine-2,4-diamine

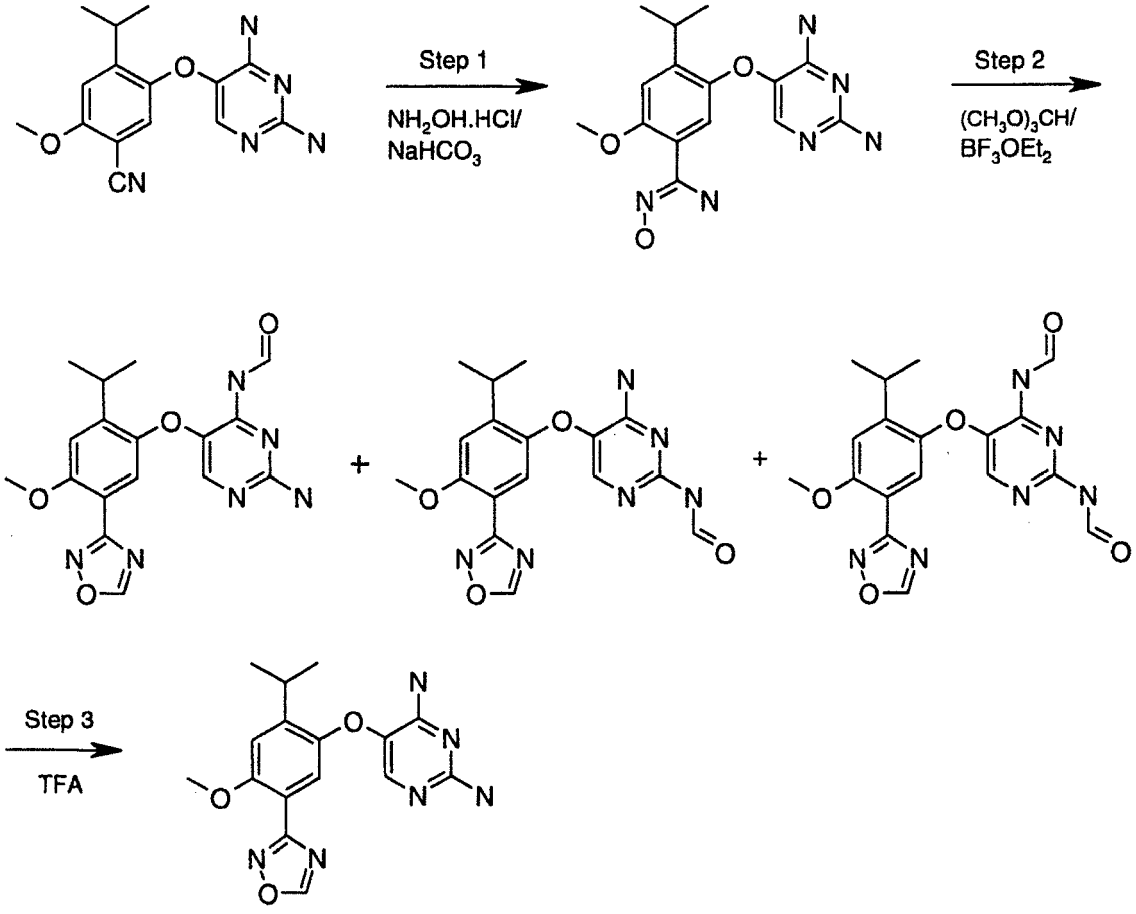
[0429]



[0430] To a solution of 4-(2,4-Diamino-pyrimidin-5-yloxy)-2-iodo-5-isopropyl-phenol (0.2 g, 0.52 mmol) in anhydrous DMF (2 ml) was added EtBr (57 mg, 0.52 mmol) in portions. The reaction mixture was partitioned between EtOAc and H_2O. The organic extract was dried over Na_2SO_4, filtered and concentrated. Flash chromatography on silica (3% MeOH in methylene chloride with 1% NH_4OH) gave 5-(4-Ethoxy-5-iodo-2-isopropyl-phenoxy)-pyrimidine-2,4-diamine (0.17 g, 28%) as a yellow solid. (M+H) = 415.

Example 57: 5-(2-Isopropyl-4-methoxy-5-[1,2,4]oxadiazol-3-yl-phenoxy)-pyrimidine-2,4-diamine

[0431] The synthetic procedure used in this Example is outlined in Scheme U.



SCHEME U

[0432] The 5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-benzonitrile utilized in step 1 of this Example was prepared as described in Scheme 1.

Step 1 5-(2,4-Diamino-pyrimidin-5-yloxy)-N-hydroxy-4-isopropyl-2-methoxy-benzamidine

[0433] The benzamidination carried out in this step follows the procedure reported by Meyer et al., Synthesis 2003, 6, pp.899-905. To a stirred mixture of hydroxylamine hydrochloride (0.099 g, 1.43 mmol) and sodium hydrogen carbonate

(0.119 g, 1.42 mmol) in ethanol (1.4 ml) and water (0.3 ml) was added 5-(2,4-diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-benzonitrile (0.385 g, 1.29 mmol) and the mixture heated at reflux for 5 hours. A second portion of hydroxylamine hydrochloride (0.049 g, 0.71 mmol) and sodium hydrogen carbonate (0.060 g, 0.71 mmol) was added. After a further 2 hours the mixture was cooled, concentrated *in vacuo,* then diluted with water (10 ml) and extracted with ethyl acetate. The combined organic extracts were washed with brine then dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield 5-(2,4-diamino-pyrimidin-5-yloxy)-N-hydroxy-4-isopropyl-2-methoxy-benzamidine (355 mg) as a yellow foam. This material was used directly without further purification.

Step 2 N-[2-Amino-5-(2-isopropyl-4-methoxy-5-[1,2,4]oxadiazol-3-yl-phenoxy)-py$_i$imidin-4-yl]formamide, N-[4-amino-5-(2-isopropyl-4-methoxy-5-[1,2,4]oxadiazol-3-yl-phenoxy)-pyrimidin-2-yl]formamide and N-[4-formylamino-5-(2-isopropyl-4-methoxy-5-[1,2,4]oxadiazol-3-yl-phenoxy)-pyrimidin-2-yl]-formamide

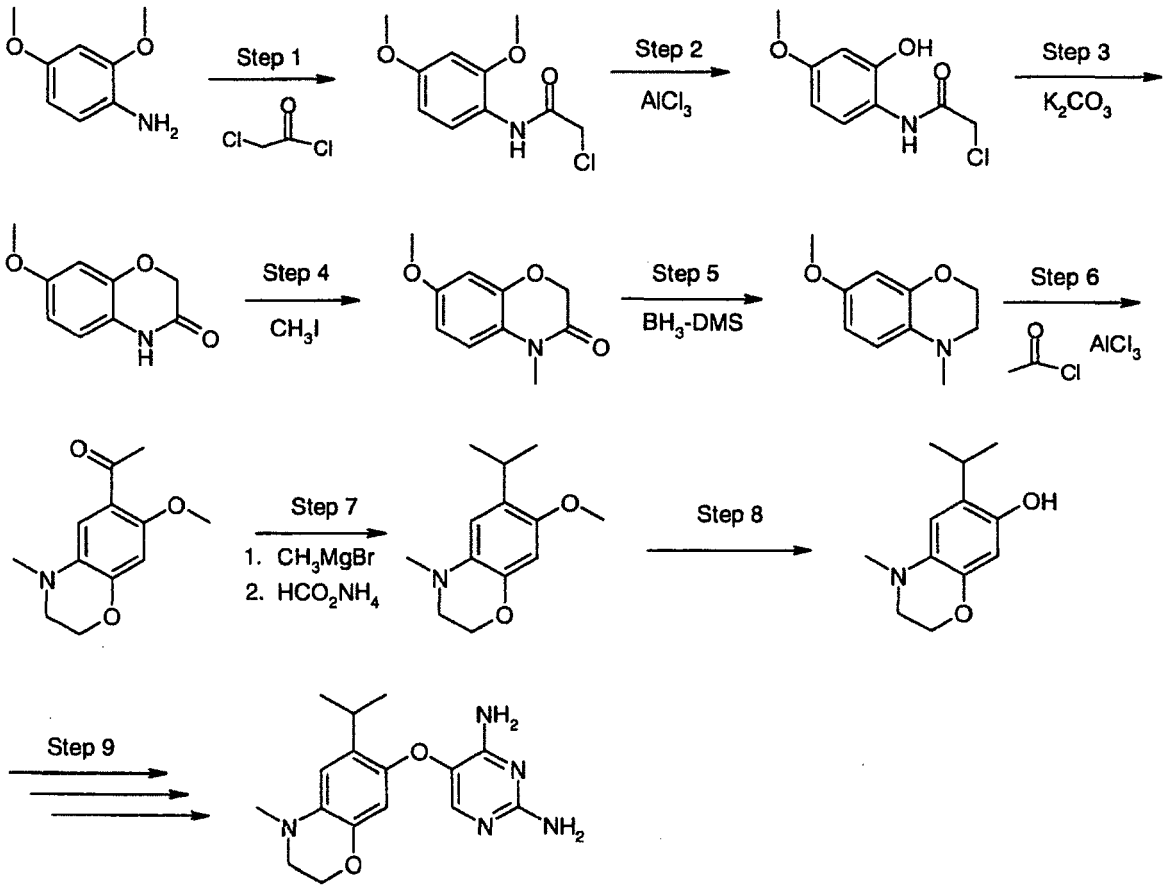
[0434] The formylation carried out in this step follows the procedure reported by Kitamura et al. Chem. Pharm. Bull. 2001, 49, pp.268-277. To a suspension of 5-(2,4-diamino-pyrimidin-5-yloxy)-N-hydroxy-4-isopropyl-2-methoxy-benzamidine (0.350 g, 1.05 mmol) in trimethylorthoformate (1.12 g, 10.5 mmol) at RT and under nitrogen was added boron trifluoride diethyl etherate (1 drop) then the mixture heated at reflux for 1 ½ hours. The resultant mixture was cooled, diluted with DCM (60 ml), then washed with water (20 ml), brine (20 ml) and then dried ($MgSO_4$) filtered and concentrated *in vacuo* to provide a mixture of N-[2-amino-5-(2-isopropyl-4-methoxy-5-[1,2,4]oxadiazol-3-yl-phenoxy)-pyrimidin-4-yl] formamide, N- [4-amino-5-(2-isopropyl-4-methoxy-5- [1,2,4]oxadiazol-3-yl-phenoxy)-pyrimidin-2-yl]formamide and N-[4-formylamino-5-(2-isopropyl-4-methoxy-5-[1,2,4]oxadiazol-3-yl-phenoxy)-pyrimidin-2-yl]-formamide as a yellow solid (260 mg). This material was used directly without further purification.

Step 3 5-(2-Isopropyl-4-methoxy-5-[1,2,4]oxadiazol-3-yl-phenoy)-pyrimidine-2,4-diamine

[0435] A mixture of N-[2-amino-5-(2-isopropyl-4-methoxy-5-[1,2,4]oxadiazol-3-yl-phenoxy)-pyrimidin-4-yl]formamide, N-[4-amino-5-(2-isopropyl-4-methoxy-5-[1,2,4]oxadiazol-3-yl-phenoxy)-pyrimidin-2-yl]formamide and N-[4-formylamino-5-(2-isopropyl-4-methoxy-5-[1,2,4]oxadiazol-3-yl-phenoxy)-pyrimidin-2-yl]-formamide (0.164 g) in trifluoroacetic acid (10 mL) was heated at reflux for 24 h. The mixture was then cooled and concentrated *in vacuo.* The residue was purified by flash chromatography (0 - 5% methanol in DCM) to yield 76 mg of 5-(2-isopropyl-4-methoxy-5-[1,2,4]oxadiazol-3-yl-phenoxy)-pyrimidine-2,4-diamine as its trifluoroacetic acid salt. $(M+H)^+$ =343; MP 135 - 138.5°C.

Example 58: 5-(6-Isopropyl-4-methyl-3,4-dihydro-2H-benzo[1,4]oxazin-7-yloxy)-pyrimidine-2,4-diamine

[0436] The synthetic procedure used in this Example is outlined in Scheme V. This compound is not covered by the claims.



SCHEME V

Step 1. 2-Chloro-N-(2,4-dimethoxy-phenyl)-acetamide

[0437] A mixture of 2,4-dimethoxy aniline (30.6 g, 0.2 mol), TEA (27.9 mL, 0.2 mol) in 600 mL methylene chloride was stirred at 0°C under nitrogen. Chloroacetyl chloride (16 mL, 0.2 mol) was added dropwise, and the reaction mixture was stirred for 15 min at 0°C, and then stirred for an additional two hours during which time the reaction mixture was allowed to warm to RT. The reaction was quenched by addition of 1N HCl, followed by saturated aqueous sodium bicarbonate. The aqueous mixture was partitioned with EtOAc, and the organic phase was separated, dried ($MgSO_4$), filtered, and evaporated under reduced pressure to give 45.58 g of crude 2-chloro-N-(2,4-dimethoxy-phenyl)-acetamide. MS (M+H) = 230.

Step 2. 2-Chloro-N-(2-hydroxy-4-methoxy-phenyl)-acetamide

[0438] 2-Chloro-N-(2,4-dimethoxy-phenyl)-acetamide (45.8 g, 0.2 mol) was dissolved in 1000 mL methylene chloride, and the reaction mixture was stirred at 0°C under nitrogen. Aluminum trichloride (78.9 g, 0.6 mol) was added in portions over 30 min, and the reaction mixture was allowed to stir for 17 hours at RT. The reaction mixture was concentrated to 200 mL volume under reduced pressure, and then poured onto ice. Solids were removed by filtration, and the liquid was taken up in EtOAc, washed with brine, dried ($MgSO_4$), filtered, and evaporated under reduced pressure to yield 39.67 g of 2-Chloro-N-(2-hydroxy-4-methoxy-phenyl)-acetamide. MS (M+H) = 216.

Step 3. 7-Methozy-4H-benzo[1,4]oxazin-3-one

[0439] 2-Chloro-N-(2-hydroxy-4-methoxy-phenyl)-acetamide (390.0 g, 0.18 mol) and powdered potassium carbonate (27.6 g, 0.2 mol) were added to 1000 mL acetone, and the reaction mixture was refluxed under nitrogen for eight hours. The reaction mixture was cooled, solids were removed by filtration, and the liquid was concentrated under reduced pressure to give 32.56 g of crude 7-Methoxy-4H-benzo[1,4]oxazin-3-one. (M+H) = 180.

Step 4. 7-Methoxy-4-methyl-4H-benzo[1,4]oxazin-3-one

[0440] 7-Methoxy-4H-benzo[1,4]oxazin-3-one (11.61 g, 0.065 mol) in 100 mL dry DMF was stirred at 0°C under nitrogen. Sodium hydride (60%, 2.85 g, 0.072 mol) was added in portions over 30 min, after which methyl iodide (4.44 mL, 0.071 mol) was added dropwise. The reaction mixture was stirred at 0°C for 2.5 hours, then poured into 1400 mL water. The resulting aqueous mixture was extracted four times with 400 mL EtOAc, and the combined organic layers were washed with water, then brine, dried ($MgSO_4$), filtered, and evaporated under reduced pressure to provide 13.07 g of 7-Methoxy-4-methyl-4H-benzo-[1,4]oxazin-3-one. (M+H) = 194.

Step 5. 7-Methoxy-4-methyl-3,4-dihydro-2H-benzo[1,4]oxazine

[0441] 7-Methoxy-4-methyl-4H-benzo[1,4]oxazin-3-one (13.07 g, 0.68 mol) was added to 100 mL dry THF, and the reaction mixture was refluxed under nitrogen. Borane-dimethyl sulfide (13.6 mL, 0.136 mol) was added dropwise over one hour, and the reaction mixture was allowed to reflux for two hours. The reaction mixture was cooled and then quenched by addition of 50 mL of 10% aqueous HCl. Precipitate was removed by filtration, and the liquid was concentrated under reduced pressure to give 11.17 g of 7-Methoxy-4-methyl-3,4-dihydro-2H-benzo[1,4]oxazine. (M+H) = 180.

Step 6. 1-(7-Methoxy-4-methyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)-ethanone

[0442] 7-Methoxy-4-methyl-3,4-dihydro-2H-benzo[1,4]oxazine (11.17 g, 0.625 mol) in 400 mL of 1,2-dichloroethane was stirred at 0°C under nitrogen. Aluminum trichloride (8.3 g, 0.625 mol) was added in portions, followed by dropwise addition of acetyl chloride (4.9 mL, 0.678 mol). The reaction mixture was stirred at 0°C for 2.5 hours. Aluminum trichloride (3 g) was added, and the reaction mixture was stirred at RT for 24 hours. The reaction mixture was poured into ice and 550 mL 3N HCl was added. The aqueous mixture was extracted with methylene chloride, and the combined organic layers were dried ($MgSO_4$), filtered, and evaporated under reduced pressure to yield 10.48 g of 1-(7-Methoxy-4-methyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)-ethanone. (M+H) = 222.

Step 7. 6-Isopropyl-7-methoxy-4-methyl-3,4-dihydro-2H-benzo[1,4]oxazine

[0443] 1-(7-Methoxy-4-methyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)-ethanone (10.48 g, 0.473 mol) was dissolved in 25 mL dry THF and the reaction mixture was stirred at 0°C under nitrogen. Methyl magnesium bromide (22 mL of 3M solution in Et_2O, 0.15 mol) was added dropwise, and the reaction mixture was stirred at 0°C for two hours. The reaction was quenched by dropwise addition of 50 mL 10% aqueous ammonium chloride, followed by water. The aqueous mixture was extracted with EtOAc, and the combined organic layers were dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The residue was taken up in 95 mL acetic acid, and the reaction mixture was stirred at RT under nitrogen. Ammonium formate (14.92 g) and 10% Palladium on activated carbon (1.0 g) were added, and the reaction mixture was heated to 120°C for three hours. The reaction mixture was cooled, solids were removed by filtration, and the filtrate was diluted with water, and made neutral by addition of solid sodium bicarbonate. The resulting aqueous solution was extracted with EtOAc, and the combined organic layers were dried ($MgSO_4$), filtered, and evaporated under reduced pressure to yield 9.97 g of 6-Isopropyl-7-methoxy-4-methyl-3,4-dihydro-2H-benzo[1,4]oxazine.

Step 8. 5-(6-Isopropyl-4-methyl-3,4-dihydro-2H-benzo[1,4]oxazin-7-yloxy)-pyrimidine-2,4-diamine

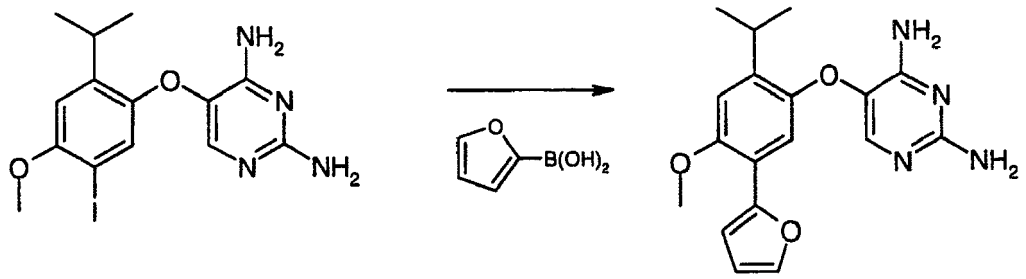
[0444] 6-Isopropyl-7-methoxy-4-methyl-3,4-dihydro-2H-benzo[1,4]oxazine (2.21 g, 0.01 mol) was dissolved in 20 mL methylene chloride, and the reaction mixture was cooled to -65°C. Boron tribromide (12 mL of 1M solution in methylene chloride, 0.012 mol) was added dropwise over 15 min, and the reaction mixture was stirred for 5.5 hours, during which time the reaction mixture was allowed to warm to 0°C. The reaction mixture was then stirred for 24 hours at RT. The reaction mixture was cooled to 0°C, and methanol was slowly added until exotherm stopped. The reaction mixture was partitioned between water and methylene chloride, and the organic phase was dried ($MgSO_4$), filtered, and evaporated under reduced pressure to yield 1.38 g of 5-(6-Isopropyl-4-methyl-3,4-dihydro-2H-benzo-[1,4]oxazin-7-yloxy)-pyrimidine-2,4-diamine. (M+H) = 208.

Step 9. 5-(6-Isopropyl-4-methyl-3,4-dihydro-2H-benzo[1,4]oxazin-7-yloxy)-pyrimidine-2,4-diamine

[0445] 5-(6-Isopropyl-4-methyl-3,4-dihydro-2H-benzo[1,4]oxazin-7-yloxy)-pyrimidine-2,4-diamine was converted, using the procedure of steps 4-6 of Example 49, to 5-(6-Isopropyl-4-methyl-3,4-dihydro-2H-benzo[1,4]oxazin-7-yloxy)-pyrimidine-2,4-diamine. (M+H) = 316. Mp = 167.3-170.1°C.

Example 59: 5-(5-Furan-2-yl-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine

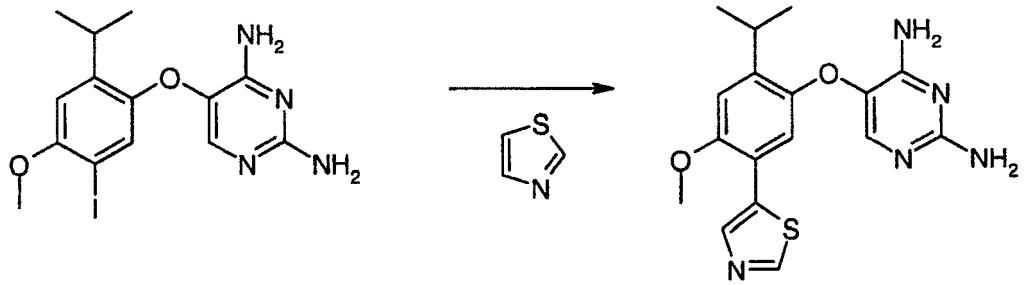
[0446]



[0447] 5-(5-Iodo-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine (400 mg, 1 mmol), furan 2-boronic acid (285 mg, 1.5 mmol) and $Pd(Ph_3)_2Cl_2$ (50 mg) were taken up in 13 mL of degassed dioxane in a screw cap pressure flask. Sodium bicarbonate (2 mL of 2M aqueous solution) was added, and the reaction mixture was heated to 105°C for 40 hours. The reaction mixture was cooled and partitioned between water and ethyl acetate. The organic phase was separated, dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography (3% to 5% MeOH in methylene chloride with 1% ammonium hydroxide) to yield 53 mg of 5-(5-Furan-2-yl-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine. (M+H) = 339. Mp = 253.7-254.6°C.

Example 60: 5-(5-Furan-2-yl-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine

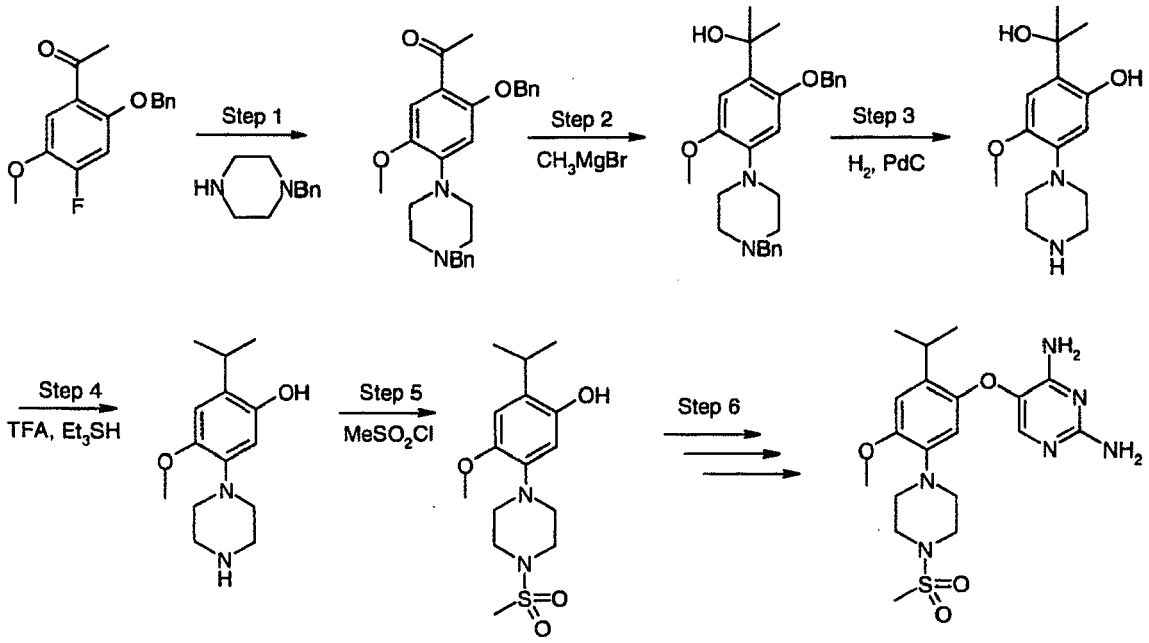
[0448]



[0449] 5-(5-Iodo-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine (400 mg, 1.0 mmol), potassium acetate ((147 mg), $Pd(Ph_3)_2Cl_2$ (40 mg in 2 mL dimethyl acetamide) and thiazole were added to a screw cap pressure vial and heated to 155°C for 40 hours. The reaction mixture was cooled and partitioned between water and ethyl acetate. The organic phase was separated, dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography (3% to 5% MeOH in methylene chloride with 1% ammonium hydroxide) to yield 61 mg of 5-(5-Furan-2-yl-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine. (M+H)=356. Mp = 199.1-203.3°C.

Example 61: 5-[2-Isopropyl-5-(4-methanesulfonyl-piperazin-1-yl)-4-methoxy-phenoxy] -pyrimidine-2,4-diamine

[0450] The synthetic procedure used in this Example is outlined in Scheme W.



SCHEME W

Step 1. 1-[4-(4-Benzyl-piperazin-1-yl)-2-hydroxy-5-methoxy-phenyl]-ethanone

[0451] To a solution of 1-(2-Benzyloxy-4-fluoro-5-methoxy-phenyl)-ethanone (4.25 g, 15.5 mmol) in 3 mL DMF was added 1-benzyl-piperazine (5.4 mo, 30.9 mmol) and potassium carbonate (4.28 g, 30.9 mmol). The reaction mixture was heated under nitrogen to 130-140°C for 18 hours. The reaction mixture was cooled to RT, poured into ice water, and extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$) filtered, and evaporated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel (hexanes:ethyl acetate 8.5:1.5) to yield 4.5 g (73%) of 1-[4-(4-Benzyl-piperazin-1-yl)-2-hydroxy-5-methoxy-phenyl]-ethanone as a solid. MP = 90-92°C.

Step 2. 2-[2-Benzyloxy-4-(4-benzyl-piperazin-1-yl)-5-methoxy-phenyl]-propan-2-ol

[0452] 1-[4-(4-Benzyl-piperazin-1-yl)-2-hydroxy-5-methoxy-phenyl]-ethanone (4.25 g, 11.3 mmol) was dissolved in 100 mL dry THF, and the resulting solution was cooled to 0°C and stirred under nitrogen. Methyl magnesium bromide (5.6 mL, 16.9 mmol) was added dropwise, and the reaction mixture was stirred for 30 min at 0°C. The reaction mixture was stirred for an additional 12 hours at RT, then poured into ice water and extracted with EtOAc. The combined organic layers were washed with saturated aqueous ammonium chloride, dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel (hexanes: ethyl acetate 8:2) to yield 4.73 g (94%) of 2-[2-Benzyloxy-4-(4-benzyl-piperazin-1-yl)-5-methoxy-phenyl]-propan-2-ol as a solid. MP = 94-96°C.

Step 3. 2-(1-Hydroxy-1-methyl-ethyl)-4-methoxy-5-piperazin-1-yl-phenol

[0453] A mixture of 2-(2-Benzyloxy-4-(4-benzyl-piperazin-1-yl)-5-methoxy-phenyl]-propan-2-ol (2.01 g, 4.5 mmol) 10 % Pd/C (0.28 g) in EtOH (60 mL) was hydrogenated at 50 psi at RT for 12 hours. The reaction mixture was filtered to remove the catalyst, and the filtrate was concentrated uner reduced pressure to yield 1.1g (92%) of 2-(1-Hydroxy-1-methyl-ethyl)-4-methoxy-5-piperazin-1-yl-phenol.

Step 4. 2-Isopropyl-4-methoxy-5-piperazin-1-yl-phenol

[0454] To a stirred suspension of 2-(1-Hydroxy-1-methyl-ethyl)-4-methoxy-5-piperazin-1-yl-phenol (0.5 g, 1.9 mmol) in DCM under nitrogen at RT was aded trifluoroacetic acid (7.2 mL, 93.86 mmol) followed by triethyl silane (3.0 mL, 18.8 mmol). The reaction mixture was stirred for 18 hours at RT, and then was evaporated under reduced pressure. The residue was partitioned between DCM and saturated aqueous potassium carbonate. The organic layer was separated, washed with water, dried ($MgSO_4$), filtered, and evaporated under reduced pressure to afford 0.47 g (99%) of 2-Isopropyl-

4-methoxy-5-piperazin-1-yl-phenol as an oil.

Step 5. 2-Isopropyl-5-(4-methanesulfonyl-piperazin-1-yl)-4-methoxy-phenol

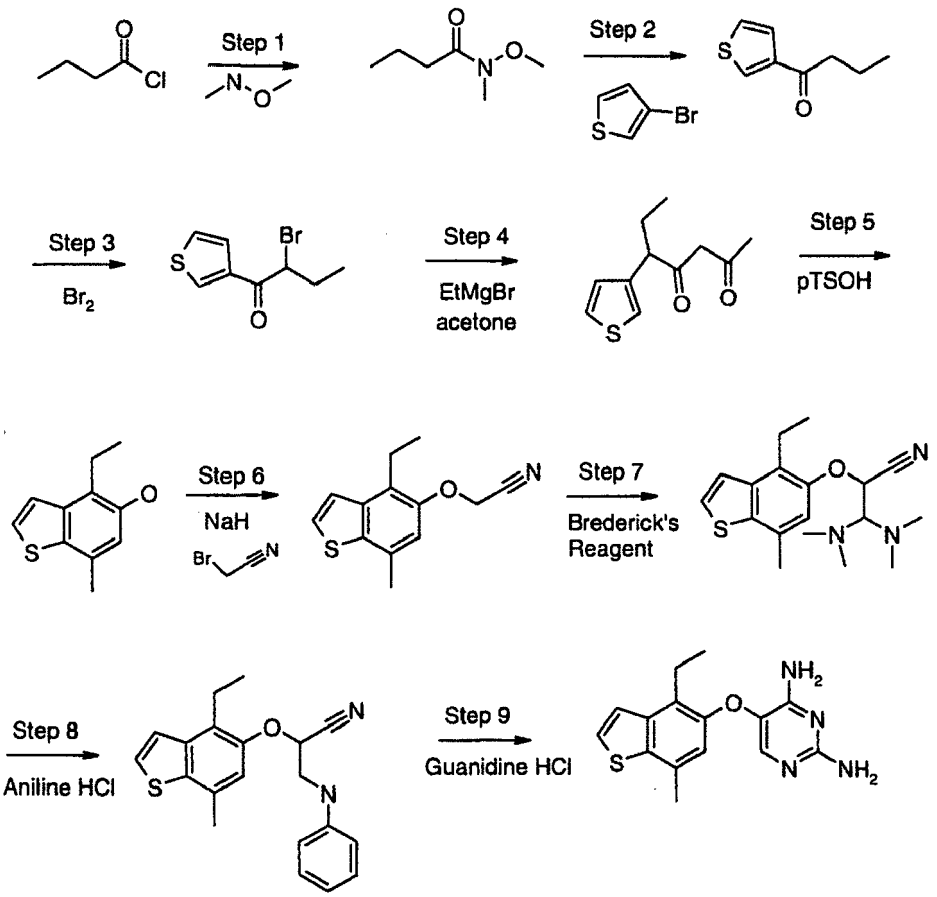
[0455] To a stirring solution of 2-Isopropyl-4-methoxy-5-piperazin-1-yl-phenol (0.47 g, 1.88 mmol) in DCM at 0°C under nitrogen was added TEA (0.26 mL, 1.89 mmol), followed by methanesulfonyl chloride (0.15 mL, 1.89 mmol). The reaction mixture was stirred at 0°C for 5 min, and then allowed to warm to RT. The reaction mixture was partitioned between DCM and water, and the organic layer was separated, washed with water, dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The residue was purified via flash chromatography (hexanes:EtOAc 3:2) to afford 0.1 g (16%) of 2-Isopropyl-5-(4-methane-sulfonyl-piperazin-1-yl)-4-methoxy-phenol as an oil.

Step 6. 5-[2-Isopropyl-5-(4-methanesulfonyl-piperazin-1-yl)-4-methoxy-phenoxy]-pyrimidine-2,4-diamine

[0456] 2-Isopropyl-5-(4-methanesulfonyl-piperazin-1-yl)-4-methoxy-phenol was converted, using the procedure of steps 4-6 of Example 49, to 5-[2-Isopropyl-5-(4-methanesulfonyl-piperazin-1-yl)-4-methoxy-phenoxy]-pyrimidine-2,4-diamine. (M+H) = 437. Mp = 115-117°C.

Example 62: 5-(4-Ethyl-7-methyl-benzo[b]thiophen-5-yloxy)-pyrimidine-2,4-diamine

[0457] This compound is not covered by the claims. The synthetic procedure used in this Example is outlined in Scheme X.



SCHEME X

Step 1 N-Methoxy-N-methyl-butyramide

[0458] Pyridine (100 mL) was cooled to 0°C, and N,O-dimethylhydroxylamine hydrochloride (20.14g, 206 mmol) was

added with stirring. This solution was stirred for 10 min, and then a solution of butyryl chloride (19.5 ml, 20g, 188 mmol) dissolved in 50 ml methylene chloride was added via addition funnel over 30 min. A precipitate formed after 5 min. This suspension was stirred and allowed to warm to RT. Stirring was continued for 2.0 hours, and the reaction was diluted with water, extracted with methylene chloride twice. The methylene chloride layers were combined and washed with 1 N HCl twice and once with brine. Diethyl ether (100 mL) was added to facilitate emulsion separation, and the organic layer was separated and washed with saturated bicarbonate solution, brine, and dried over magnesium sulfate. The solution was filtered and the solvent removed in vacuo to give N-Methoxy-N-methyl-butyramide as an oil (22.1 g, 89%).

Step 2. 1-Thiophen-3-yl-butan-1-one

[0459] 3-Bromothiophene (11 g, 67 mmol) dissolved in hexanes (110 ml) was cooled to -20°C in acetone/water bath, and n-BuLi (28 ml, 71 mmol, 2.5 N solution in hexanes)was added slowly, over 10 min, then stirred 10 min at -20°C. THF was added (10 ml) over 5 min with rapid stirring. Precipitate formed after about 2/3 of addition. After adding all of the THF, the reaction mixture was stirred 20 min at -20°C, then 20 ml hexanes was added and the reaction mixture was allowed to warm to 0°C. N-Methoxy-N-methyl-butyramide (9.29 g, 71 mmol) dissolved in 20 ml hexanes was added via cannula over 5 min, and the reaction mixture was stirred at 0°C for 1.5 hours. The reaction mixture was quenched with water, then 1 N HCl (75 ml), extracted twice with ether, washed 1 N HCl, brine, and dried over magnesium sulfate. Solvent was removed under reduced pressure to give an oil, which was chromatographed by flash chromatography (5% EtOAc/hexanes) to give 6.7 g, 64% of 1-Thiophen-3-yl-butan-1-one as an oil.

Step 3. 2-Bromo-1-thiophen-3-yl-butan-1-one

[0460] 1-Thiophen-3-yl-butan-1-one (6.7 g. 43 mmol) in 210 mL diethyl ether was cooled to 0°C, and 0.6 ml glacial acetic acid was added dropwise, followed by bromine (2.26 ml, 46 mmol) dropwise. The reaction mixture was allowed to warm to RT over hours. The reaction mixture was washed with water, 1 N sodium thiosulfate, brine, and then dried over magnesium sulfate. Solvent was removed under reduced pressure to give an oil which was chromatographed (5% EtOAc/Hexanes) to give 6.1 g 2-Bromo-1-thiophen-3-yl-butan-1-one, 79%, as an oil.

Step 4. 5-Thiophen-3-yl-heptane-2,4-dione

[0461] EtMgBr (6.69 ml, 13 mmol, 2 M in ethyl ether) in benzene (10 ml) was cooled to 0°C, and tBuOH (1.28 ml, 13 mmol) was slowly added. The reaction mixture was stirred at 0°C for 5 min, then acetone (530 ul, 7 mmol) was added, followed by a solution of 2-bromo-1-thiophen-3-yl-butan-1-one (1.3 g, 6 mmol) in 3 ml benzene via cannula. The reaction mixture was heated to reflux for 1 hour, and acetone (250 ul) was added. The reaction mixture was heated 2 hours more at reflux. The reaction was cooled, quenched with 1 N HCl (10 ml), extracted three times with diethyl ether, washed with brine, and dried over magnesium sulfate. The solvent was removed in vacuo and the residue chromatographed (5% ethyl acetate/hexanes) to give 247 mg of 2-bromo-1-thiophen-3-yl-butan-1-one starting material and 520 mg of 5-thiophen-3-yl-heptane-2,4-dione, 44%.

Step 5. 4-Ethyl-7-methyl-benzo[b]thiophen-5-ol

[0462] 5-Thiophen-3-yl-heptane-2,4-dione (410 mg, 2 mmol) was dissolved inin 15 ml benzene, and p-toluene sulfonic acid monohydrate (408 mg, 2 mmol) was added. The reaction mixture was heated to reflux for 30 min, cooled, diluted with diethy ether, washed with saturated sodium bicarbonate, water, brine, and dried over magnesium sulfate. Concentration in vacuo 370 mg of 4-Ethyl-7-methyl-benzo[b]thiophen-5-ol, 98 %, as a white solid.

Step 6. (4-Ethyl-7-methyl-benzo[b]thiophen-5-yloxy)-acetonitrile

[0463] 4-Ethyl-7-methyl-benzo[b]thiophen-5-ol (438 mg, 2 mmol) was dissolved in 10 ml DMF, and the reaction mixture was cooled to 0°C. Sodium hydride (66 mg, 3 mmol) was added and the reaction mixture was stirred 30 min at 0°C. Bromoacetonitrile (170 ul, 3 mmol) was addeed, and the reaction mixture was stirred 10 min at 0°C, then allowed to warm to RT. The reaction was quenched after 1 hour at RT with water, diluted with ethyl acetate, washed with water, brine, and dried over magnesium sulfate. Solvent was removed in vacuo, and the residue chromatographed (10% ethyl acetate in hexanes) to give 422 mg of (4-Ethyl-7-methyl-benzo[b]thiophen-5-yloxy)-acetonitrile as an oil, 80%.

Step 7. 3,3-Bis-dimethylamino-2-(4-ethyl-7-methyl-benzo[b]thiophen-5-yloxy)-propionitrile

[0464] 3,3-Bis-dimethylamino-2-(4-ethyl-7-methyl-benzo[b]thiophen-5-yloxy)-propionitrile (422 mg, 2 mmol) was dis-

solved in 2.5 ml tert-butoxybis(dimethylamino)methane, and the reaction mixture was heated to 100°C for 1 hour. The reaction was cooled to RT and the volume reduced under 1 mm vacuum while heating at 60°C. The residue was then placed on a high vacuum pump for 1 hour to give 3,3-Bis-dimethylamino-2-(4-ethyl-7-methyl-benzo[b]thiophen-5-yloxy)-propionitrile, 595 mg, 98 %, as an oil.

Step 8. 2-(4-Ethyl-7-methyl-benzo[b]thiophen-5-yloxy)-3-phenylamino-acrylonitrile

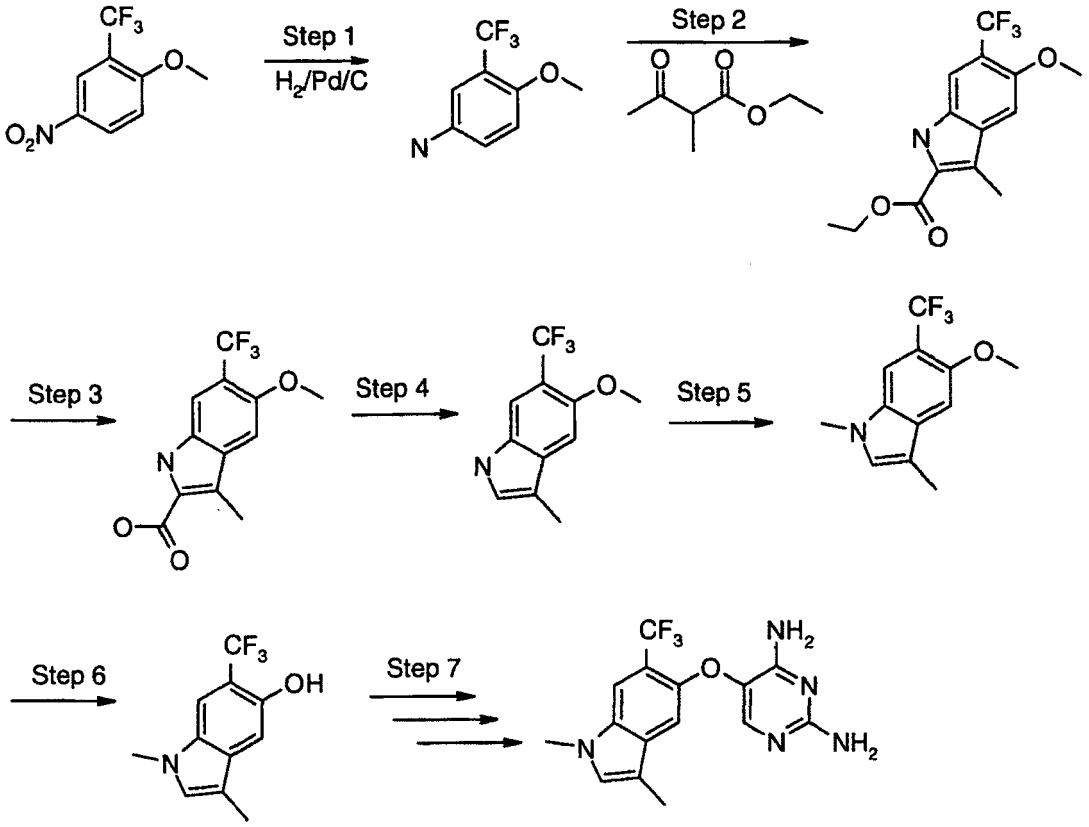
[0465] 3,3-Bis-dimethylamino-2-(4-ethyl-7-methyl-benzo[b]thiophen-5-yloxy)-propionitrile (590 mg, 2 mmol) and aniline HCl (1.1g, 9 mmol) in 5 mL absolute ethanol were heated at reflux for 2.0 hours. In a separate flask, guanidine HCl (0.850 mg., 9 mmol) and sodium methoxide solution (1.83 ml, 9 mmol, 4.9 molar solution in methanol) were mixed in 1 ml ethanol. The guanidine solution was added to the reaction mixture via pipette, and the reaction mixture was heated to reflux for 5 hours, then cooled. Solvent was removed in vacuo, and the residue was, chromatographed (5% MeOH/ methylene chloride/1%NH_4OH) to give 368 mg 2-(4-ethyl-7-methyl-benzo[b]thiophen-5-yloxy)-3-phenylamino-acrylonitrile, 61%. Also present was 50 mg of 5-(4-Ethyl-7-methyl-benzo[b]thiophen-5-yloxy)-pyrimidine-2,4-diamine, 9%.

Step 9. 5-(4-Ethyl-7-methyl-benzo[b]thiophen-5-yloxy)-pyrimidine-2,4-diamine

[0466] 2-(4-Ethyl-7-methyl-benzo[b]thiophen-5-yloxy)-3-phenylamino-acrylonitrile (360 mg, 1 mmol), guanidine HCl (411 mg, 4 mmol) and sodium methoxide (880 ul, 4 mmol, 4.9 M solution in methanol) in 5 mL absolute ethanol were heated to reflux in 5 ml absolute ethanol for 2 hours. Premixed guanidine HCl (411 mg, 4 mmol) and sodium methoxide (880 ul, 4 mmol, 4.9 M solution in methanol) in 1 ml EtOH was added via pipette, and the reaction mixture was heated to reflux for 2 hours. The reaction mixture was cooled, diluted with water, extracted twice with EtOAc, washed with brine, and dried over magnesium sulfate. Solvent was removed in vacuo to give 241 mg of 5-(4-ethyl-7-methyl-benzo-[b] thiophen-5-yloxy)-pyrimidine-2,4-diamine as a white solid (74%). Mass Spec M+H = 301, M.P. = 181°C. Recrystallization of 175 mg of this product from MeOH and HCl/diethyl ether afforded 98 mg of the corresponding HCl salt 49%. Mass Spec M+H = 301, M.P. > 300 C.

Example 63: 5-(1,3-Dimethyl-6-trifluoromethyl-1H-indol-5-yloxy)-pyrimidine-2,4-diamine

[0467] The synthetic procedure used in this Example is outlined in Scheme Y. This compound is not covered by the claims.



SCHEME Y

Step 1. 4-Methoxy-3-trifluoromethyl-phenylamine

[0468] 1-Methoxy-4-nitro-2-trifluoromethyl-benzene (10g, 45 mmol) was hydrogenated in a Paar apparatus with shaking at 50 psi for 4 hours, with 1 g 10 wt % Pd/C. The reaction mixture was filtered through celite, and the filtrate was evaporated in vacuo to give 8.6 g 4-methoxy-3-trifluoromethyl-phenylamine, 99%, as a solid.

Step 2. 5-Methoxy-3-methyl-6-trifluoromethyl-1H-indole-2-carboxylic acid ethyl ester

[0469] 4-Methoxy-3-trifluoromethyl-phenylamine (5g, 26 mmol) in 12 mL water was cooled to - 5°C (Ice/Methanol bath). Conc. HCl was added dropwise (7 ml), and the reaction mixture was stirred for 5 min. A solution of $NaNO_2$ (2.0 g, 29 mmol) dissolved in 3 ml water was added dropwise over 10 min, and the reaction mixture was stirred for 30 min. Sodium acetate (1.8 g, 22 mmol) was then added, and stirring was continued at -5°C. In a separate flask, ethyl alpha-acetoacetate (4.55 g, 29 mmol) in 20ml absolute ethanol was stirred, and KOH (1.6 g, 29 mmol) dissolved in 3 ml water was added, followed by ice (30g). The resulting diazonium salt was added quickly to the reaction mixture, rinsing in with 5 ml EtOH, and the reaction mixture was stirred at 0°C for 3.5 hours, then stored at -10°C for 16 hours. The reaction mixture was warmed to RT and extracted with ethyl acetate, washed with brine, and dried over magnesium sulfate. Solvent was removed under reduced pressure to leave a liquid residue. In a separate flask 100 ml EtOH and 21 ml acetyl chloride were mixed, with cooling in an ice bath, then heated to 70°C. The liquid residue was added via pipette over 15 min to the acetyl chloride solution. This reaction mixture was heated to reflux for 2.5 hours, cooled, evaporated under reduced pressure. The residue was purified by colunm chromatography (10% ethyl acetate/hexane) to give 3.0 g 5-methoxy-3-methyl-6-trifluoromethyl-1H-indole-2-carboxylic acid ethyl ester, 38% as a white solid.

Step 3. 5-Methoxy-3-methyl-6-trifluoromethyl-1H-indole-2-carboxylic acid.

[0470] 5-Methoxy-3-methyl-6-trifluoromethyl-1H-indole-2-carboxylic acid ethyl ester (3.0 g, 10 mmol) was dissolved in 10 ml absolute ethanol, and a solution of KOH (1.7 g, 30 mmol) in 7 ml water was added. The reaction mixture was heated to reflux for 2.5 hours, then cooled, acidified slowly with 6 N HCl to pH = 2, and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced

pressure to give 2.0 g, (73 %) 5-Methoxy-3-methyl-6-trifluoromethyl-1H-indole-2-carboxylic acid.

Step 4. 5-Methoxy-3-methyl-6-trifluoromethyl-1H-indole

[0471] To a solution of 5-Methoxy-3-methyl-6-trifluoromethyl-1H-indole-2-carboxylic acid (2.0 g, 7 mmol) in 5 ml quinoline was added copper powder (50 mg), and the reaction mixture was heated to reflux for 1.5 hours. Copper powder (50 mg) was added, and the reaction mixture was refluxed for 1 hour. The reaction mixture was cooled, diluted with EtOAc, poured into 50 ml 6 N HCl, and extracted with EtOAc. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was chromatographed (10% EtOAc/Hexanes) to give 5-Methoxy-3-methyl-6-trifluoromethyl-1H-indole (850 mg, 51%) as a solid.

Step 5. 5-Methoxy-1,3-dimethyl-6-trifluoromethyl-1H-indole

[0472] A solution of 5-methoxy-3-methyl-6-trifluoromethyl-1H-indole (900 mg, 4 mmol) in 7 ml DMF was cooled to 0°C, and sodium hydride (104 mg, 4 mmol, 95% powder) was added. The reaction mixture was stirred 15 min at 0°C, and then iodomethane (270 ul, 4 mmol) was added. The reaction mixture was stirred for 1 hour and allowed to warm to RT. The reaction mixture was then cooled to 0°C, quenched by adddition of 1 N NH_4Cl, diluted with water, and extracted with EtOAc. The combined organic layers were washed with water, brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give 5-methoxy-1,3-dimethyl-6-trifluoromethyl-1H-indole (725 mg, 75%) as a solid.

Step 6. 1,3-Dimethyl-6-trifluoromethyl-1H-indol-5-ol

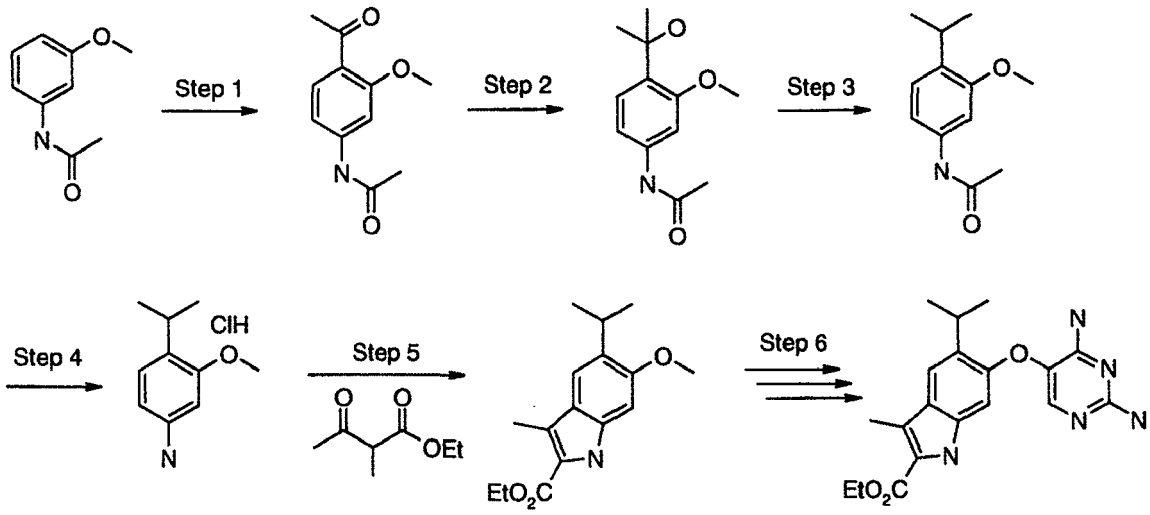
[0473] 5-Methoxy-1,3-dimethyl-6-trifluoromethyl-1H-indole (725 mg, 3 mmol) in methylene chloride (15 ml) was cooled to 0°C, and BBr_3 (14.9 ml of a 1 N solution in methylene chloride) was slowly added via syringe. The reaction mixture was stirred 15 min at 0°C, then allowed to warm to RT with stirring for one hour. The reaction mixture was quenched slowly with 75 mL1 N NaOH. The mixture was acidified to pH 5 with 1 N HCl, extracted with methylene chloride, and the combined organic layers were washed with water, brine, and dried over magnesium sulfate. Solvent was removed under reduced pressure, and the residue was chromatographed (20% EtOAc/Hexanes) to give 235 mg (75%) 1,3-Dimethyl-6-trifluoromethyl-1H-indol-5-ol.

Step 7. 1,3-Dimethyl-6-trifluoromethyl-1H-indol-5-ol

[0474] 1,3-Dimethyl-6-trifluoromethyl-1H-indol-5-ol was converted to 5-(1,3-dimethyl-6-trifluoromethyl-1H-indol-5-yloxy)-pyrimidine-2,4-diamine using the procedure of steps 6-9 of Example 62 (70 mg). The corresponding hydrochloride salt was recrystallized from MeOH/diethyl ether. (M+H) = 338, M.P. 256°C.

Example 64: 6-(2,4-Diamino-pyrimidin-5-yloxy)-5-isopropyl-3-methyl-1H-indole-2-carboxylic acid

[0475] This compound is not covered by the claims. The synthetic procedure used in this Example is outlined in Scheme Z.



SCHEME Z

Step 1. N-(4-Acetyl-3-methoxy-phenyl)-acetamide

[0476] N-(3-Methoxy-phenyl)-acetamide (17.7 g, 107 mmol) in methylene chloride was cooled to 0°C, and acetyl chloride (19.0 ml, 268 mmol) was slowly added, followed by aluminum chloride (35.7 g, 268 mmol) in small portions over 15 min. The reaction mixture was stirred 15 min at 0°C, then allowed to warm to RT with stirring. The reaction mixture was poured into ice, stirred 35 min, and filtered. The solid was washed with water. The filtrate was extracted with EtOAc and solvent was removed under reduced pressure. The combined solids gave N-(4-Acetyl-3-methoxy-phenyl)-acetamide (16.5 g., 74%) as a solid.

Step 2. N-[4-(1-Hydroxy-1-methyl-ethyl)-3-methoxy-phenyl]-acetamide

[0477] Methyl magnesium chloride (49.9 ml, 150 mmol, 3 M solution in THF) in 100 ml THF was cooled to 0°C, and N-(4-Acetyl-3-methoxy-phenyl)-acetamide (14.1 g, 68 mmol) in 200 ml THF was added via cannula to over 25 min. The reaction mixture was stirred and allowed to warm to RT over 2.5 hours. The reaction was quenched by addition of 1 N NH_4Cl and extracted with EtOAc. The combined organic layers were washed with 1 N ammonium chloride, brine, dried over $MgSO_4$, and concentrated under reduced pressure to afford N-[4-(1-Hydroxy-1-methyl-ethyl)-3-methoxy-phenyl]-acetamide (16.4 g, 100%).

Step 3 N-(4-Isopropyl-3-methoxy-phenyl)-acetamide

[0478] N-[4-(1-Hydroxy-1-methyl-ethyl)-3-methoxy-phenyl]-acetamide (16.4 g) in 100 ml glacial acetic acid was stirred at RT under N_2, and palladium on activated carbon (3 g 10 Wt %) was added, followed by 5 g of ammonium formate. The reaction mixture was heated to reflux. After 30 min 5 g ammonium formate was added, and after 45 min another 8.5 g ammonium formate was added. Reflux was continued for another hour, then the reaction mixture was cooled, and filtered through Celite. The filtrate was diluted with water, extracted with EtOAc, and the combinded organic layers were washed with brine and dried over magnesium sulfate. Evaporation under reduced pressure gave N-(4-Isopropyl-3-methoxy-phenyl)-acetamide (15.1 g, 99%).

Step 4. 4-Isopropyl-3-methoxy-phenylamine

[0479] N-(4-Isopropyl-3-methoxy-phenyl)-acetamide (14.5g, 69.9 mmol) in 200 ml 6 N HCl was heated to 95°C for 3.0 hours. The reaction mixture was cooled to RT, and allowed to sit for 72 hours at RT, during which time crystals formed. The reaction mixture was filtered, and the crystals were washed 1 N HCl and dried under vacuum to give 4-Isopropyl-3-methoxy-phenylamine as an HCl salt (7.6 g, 60%).

Step 5. 5-Isopropyl-6-methoxy-3-methyl-1H-indole-2-carboxylic acid ethyl ester

[0480] 4-Isopropyl-3-methoxy-phenylamine HCl salt (3.1g, 19 mmol) was cooled to -5°C (Ice/Methanol bath), and a

mixture of 8 ml water and 5 ml concentrated. HCl was added dropwise. The reaction mixture was stirred for 5 min, and sodium nitrite (1.42 g, 21 mmol) disolved in 3 ml water was added dropwise over 10 min. The reaction mixture was stirred for 45 min, then sodium acetate (1.3 g, 16 mmol) was added. In a separate flask, to a stirring mixture of ethyl alpha-acetoacetate (3.26g, 21 mmol) in 15 ml absolute ethanol was added KOH (1.2 g, 21 mmol) dissolved in 3 ml water and then added ice (10 g). This mixture was added to the diazonium salt, and the reaction mixture was stirred at 0°C for 3.5 hours. The reaction mixture was stored at -10°C for 16 hours, then extracted with EtOAC. The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure to a liquid residue. In a separate flask, mixed 100 ml EtOH was mixed slowly with 22 ml acetyl chloride, with cooling in an ice bath. The EtOH/acetyl chloride solution was heated to 70°C, and added the residue was added via pipette over 10 min. The reaction mixture was heated to reflux for 2.5 hours, cooled, evaporated under reduced pressure to give a slurry; diluted with water (100 ml) and filtered. The solid was washed with water. The solid was triturated with hexanes to give 5-Isopropyl-6-methoxy-3-methyl-1H-indole-2-carboxylic acid ethyl ester (1.7 g, 34%) as a solid.

Step 6. 6-(2,4-Diamino-pyrimidin-5-yloxy)-5-isopropyl-3-methyl-1H-indole-2-carboxylic acid ethyl ester

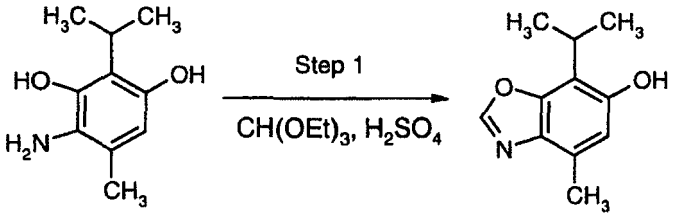
[0481] 5-Isopropyl-6-methoxy-3-methyl-1H-indole-2-carboxylic acid ethyl ester was converted to 6-(2,4-Diamino-pyrimidin-5-yloxy)-5-isopropyl-3-methyl-1H-indole-2-carboxylic acid ethyl ester using the procedure of steps 5-9 of Example 62. Mass Spec M+H = 370, M.P. 188.2°C.

[0482] 6-(2,4-Diamino-pyrimidin-5-yloxy)-5-isopropyl-3-methyl-1H-indole-2-carboxylic acid ethyl ester was converted to 6-(2,4-diamino-pyrimidin5-yloxy)-5-isopropyl-3-methyl-1H-indole-2-carboxylic acid by treatment with ethanolic potassium hydroxide. (91 mg, 76%). Mass Spec M+ H= 342 M.P. >300 C

Example 65: 5-(7-Isopropyl-4-methyl-benzooxazol-6-yloxy)-pyrimidine-2,4-diamine

Step 1. 7-Isopropyl-4-methyl-benzooxazol-6-ol

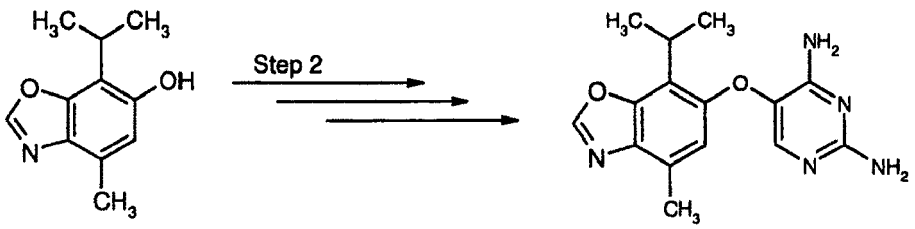
[0483]



[0484] To a flask charged with 4-amino-2-isopropyl-5-methyl-benzene-1,3-diol (450 mg, 2.5 mmol) (Treibs and Albrecht, Journal fuer Praktische Chemie (1961), 13, 291-305), purged with argon, and cooled to 0°C was sequentially added triethylorthoformate (0.7 mL, 4.2 mmol), EtOH (4 mL), and a 10% v/v solution of H_2SO_4 in EtOH (40 μL). The reaction was allowed to warm to RT slowly, stirred overnight, quenched with saturated $NaHCO_3$, and concentrated. The residue was partitioned between water and methylene chloride. The combined organic phases were dried with Na_2SO_4 and concentrated to provide 510 mg of 7-isopropyl-4-methyl-benzooxazol-6-ol.

Step 2. 5-(7-Isopropyl-4-methyl-benzooxazol-6-yloxy)-pyrimidine-2.4-diamine

[0485]



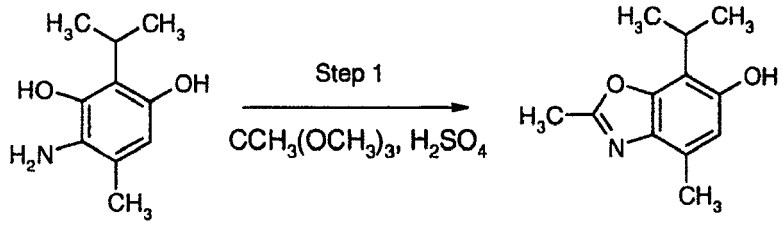
[0486] Using the procedure of steps 5-7 of Example 2, 7-isopropyl-4-methyl-benzooxazol-6-ol was converted to 5-(7-isopropyl-4-methyl-benzooxazol-6-yloxy)-pyrimidine-2,4-diamine. The hydrochloride salt was recrystallized from EtOH/

diethyl ether. MS (M+H): 300. This compound is not covered by the claims.

Example 66: 5-(7-Isopropyl-2,4-dimethyl-benzooxazol-6-yloxy)-pyrimidine-2,4-diamine

Step 1. 7-Isopropyl-2,4-dimethyl-benzooxazol-6-ol

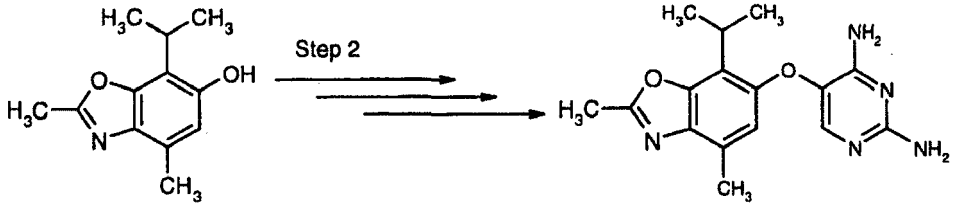
[0487]



[0488] To a flask charged with 4-amino-2-isopropyl-5-methyl-benzene-1,3-diol (250 mg, 1.4 mmol) (Treibs and Albrecht, Journal fuer Praktische Chemie (1961), 13, 291-305), purged with argon, and cooled to 0°C, was sequentially added triethylorthoformate (0.53 mL, 4.2 mmol), MeOH (2.5 mL), and a 10% v/v solution of H_2SO_4 in MeOH (25 μL). The reaction was allowed to warm to RT slowly, stirred overnight, quenched with saturated $NaHCO_3$, and concentrated. The residue was partitioned between water and methylene chloride. The combined organic phases were dried with Na_2SO_4 and concentrated. Purification via flash chromatography afforded 175 mg of 7-isopropyl-2,4-dimethyl-benzooxazol-6-ol.

Step 2. 5-(7-Isopropyl-2,4-dimethyl-benzooxazol-6-yloxy)-pyrimidine-2,4-diamine

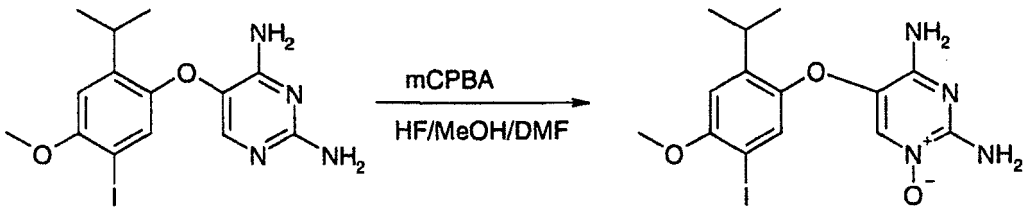
[0489]



[0490] Using the procedure of steps 5-7 of Example 2, 7-isopropyl-2,4-dimethyl-benzooxazol-6-ol was converted to 5-(7-Isopropyl-2,4-dimethyl-benzooxazol-6-yloxy)-pyrimidine-2,4-di-amine. The hydrochloride salt was recrystallized from EtOH/diethyl ether. MS (M+H): 314, MP >300 °C. This compound is not covered by the claims.

Example 67: 5-(5-Iodo-2-isopropyl-4-methoxy-phenoxy)-1-oxy-pyrimidine-2,4-diamine

[0491]

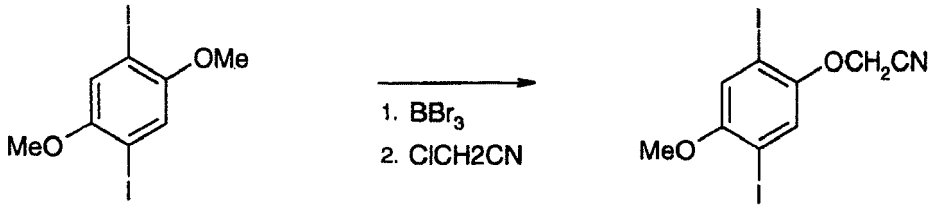


[0492] To a solution of compound 5-(5-Iodo-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine (1.6g, 4.0 mmol) in DMF/MeOH(30 ml/10 ml) was added HF (48% aqueous solution, 0.3 ml, 8.3 mmol). After 3 min, m-chloroperoxybenzoic acid (80%, 2.16 g, 10.0 mmol) was added, the mixture was stirred at RT for one hour. Cold 1N NaOH aqueous solution was added, and the reaction mixture was partitioned between ethyl acetate and water. The organic phase was washed with brine, dried over anhydrous sodium sulfate, filtered, concentrated in vacuo. The residue was purified by silica gel chromatography (gradient: 2%, 5%, 6%, 8% MeOH in CH_2Cl_2 with 0.1 % NH_4OH) to give 5-(5-Iodo-2-isopropyl-4-

methoxy-phenoxy)-1-oxy-pyrimidine-2,4-diamine (0.2g, 12%) as a yellow solid. (M+H) = 417.

Example 68: 5-(2,5-Diiodo-4-methoxy-phenoxy)-pyrimidine-2,4-diamine

[0493]

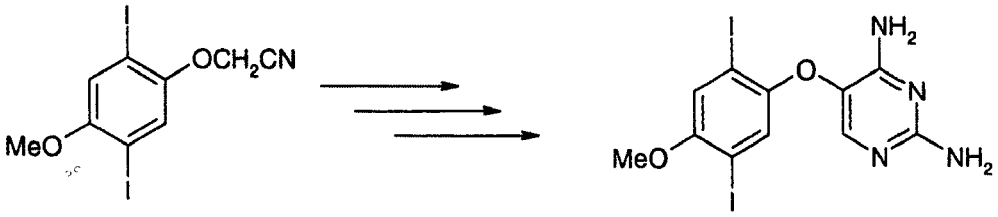


Step 1. (2,5-Diiodo-4-methoxy-phenoxy)-acetonitrile.

[0494] Diiododimethoxybenzene (10 mmol) was dissolved in 75 ml CH_2Cl_2 and cooled to 0°C. BBr3 (1M in CH_2Cl_2, 1.1 equivalents) was added. After 30 min the reaction was partitioned between CH_2Cl_2 and water. The organic layer was dried and evaporated. The resulting crude phenol was dissolved in 60 ml acetone and treated with 1.1 equivalents of $ClCH_2CN$ and excess K_2CO_3. After refluxing overnight the reaction mixture was partitioned between ether and water. Purification by preparative thin layer chromatography (1:5 EtOAc/hexane) gave (2,5-Diiodo-4-methoxy-phenoxy)-acetonitrile, MS (M+H) = 416.

Step 2. 5-(2,5-Diiodo-4-methoxy-phenoxy)-pyrimidine-2,4-diamine

[0495]



[0496] Using the procedure of step 7 of Example 21, (2,5-Diiodo-4-methoxy-phenoxy)-acetonitrile was converted to 240 mg of 5-(2,5-Diiodo-4-methoxy-phenoxy)-pyrimidine-2,4-diamine. MS (m+H) = 484.9.

Example 69: Formulations

[0497] Pharmaceutical preparations for delivery by various routes are formulated as shown in the following Tables. "Active ingredient" or "Active compound" as used in the Tables means one or more of the Compounds of Formula I.

Composition for Oral Administration

[0498]

Ingredient	% wt./wt.
Active ingredient	20.0%
Lactose	79.5%
Magnesium stearate	0.5%

[0499] The ingredients are mixed and dispensed into capsules containing about 100 mg each; one capsule would approximate a total daily dosage.

Composition for Oral Administration

[0500]

Ingredient	% wt./wt.
Active ingredient	20.0%
Magnesium stearate	0.5%
Crosscarmellose sodium	2.0%
Lactose	76.5%
PVP (polyvinylpyrrolidine)	1.0%

[0501] The ingredients are combined and granulated using a solvent such as methanol. The formulation is then dried and formed into tablets (containing about 20 mg of active compound) with an appropriate tablet machine.

Composition for Oral Administration

[0502]

Ingredient	Amount
Active compound	1.0 g
Fumaric acid	0.5 g
Sodium chloride	2.0 g
Methyl paraben	0.15 g
Propyl paraben	0.05 g
Granulated sugar	25.5 g
Sorbitol (70% solution)	12.85 g
Veegum K (Vanderbilt Co.)	1.0 g
Flavoring	0.035 ml
Colorings	0.5 mg
Distilled water	q.s. to 100 ml

[0503] The ingredients are mixed to form a suspension for oral administration.

Parenteral Formulation

[0504]

Ingredient	% wt./wt.
Active ingredient	0.25 g
Sodium Chloride	qs to make isotonic
Water for injection	100 ml

[0505] The active ingredient is dissolved in a portion of the water for injection. A sufficient quantity of sodium chloride is then added with stirring to make the solution isotonic. The solution is made up to weight with the remainder of the water for injection, filtered through a 0.2 micron membrane filter and packaged under sterile conditions.

Suppository Formulation

[0506]

Ingredient	% wt./wt.
Active ingredient	1.0%
Polyethylene glycol 1000	74.5%
Polyethylene glycol 4000	24.5%

[0507] The ingredients are melted together and mixed on a steam bath, and poured into molds containing 2.5 g total weight.

Topical Formulation

[0508]

Ingredients	Grams
Active compound	0.2-2
Span 60	2
Tween 60	2
Mineral oil	5
Petrolatum	10
Methyl paraben	0.15
Propyl paraben	0.05
BHA (butylated hydroxy anisole)	0.01
Water	q.s. 100

[0509] All of the ingredients, except water, are combined and heated to about 60°C with stirring. A sufficient quantity of water at about 60°C is then added with vigorous stirring to emulsify the ingredients, and water then added q.s. about 100 g.

Nasal Spray Formulations

[0510] Several aqueous suspensions containing from about 0.025-0.5 percent active compound are prepared as nasal spray formulations. The formulations optionally contain inactive ingredients such as, for example, microcrystalline cellulose, sodium carboxymethylcellulose, dextrose, and the like. Hydrochloric acid may be added to adjust pH. The nasal spray formulations may be delivered via a nasal spray metered pump typically delivering about 50-100 microliters of formulation per actuation. A typical dosing schedule is 2-4 sprays every 4-12 hours.

Example 70: $P2X_3/P2X_{2/3}$ FLIPR (Fluorometric Imaging Plate Reader) Assay

[0511] CHO-K1 cells were transfected with cloned rat $P2X_3$ or human $P2X_{2/3}$ receptor subunits and passaged in flasks. 18-24 hours before the FLIPR experiment, cells were released from their flasks, centrifuged, and resuspended in nutrient medium at 2.5 x 10^5 cells/ml. The cells were aliquoted into black-walled 96-well plates at a density of 50,000 cells/well and incubated overnight in 5% CO_2 at 37°C. On the day of the experiment, cells were washed in FLIPR buffer (calcium- and magnesium-free Hank's balanced salt solution, 10 mM HEPES, 2 mM $CaCl_2$, 2.5 mM probenecid; FB). Each well received 100 μl FB and 100 μl of the fluorescent dye Fluo-3 AM [2 μM final conc.]. After a 1 hour dye loading incubation at 37°C, the cells were washed 4 times with FB, and a final 75 μl/well FB was left in each well. Test compounds (dissolved in DMSO at 10 mM and serially diluted with FB) or vehicle were added to each well (25 μl of a 4X solution) and allowed to equilibrate for 20 min at RT. The plates were then placed in the FLIPR and a baseline fluorescence measurement (excitation at 488 nm and emission at 510-570 nm) was obtained for 10 seconds before a 100 μl/well agonist or vehicle

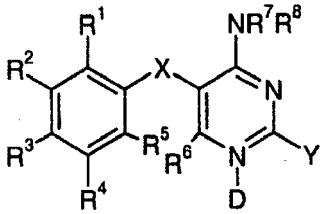
addition. The agonist was a 2X solution of α,β-meATP producing a final concentration of 1 μM ($P2X_3$) or 5 μM ($P2X_{2/3}$). Fluorescence was measured for an additional 2 min at 1 second intervals after agonist addition. A final addition of ionomycin (5 μM, final concentration) was made to each well of the FLIPR test plate to establish cell viability and maximum fluorescence of dye-bound cytosolic calcium. Peak fluorescence in response to the addition of α,β-meATP (in the absence and presence of test compounds) was measured and inhibition curves generated using nonlinear regression. PPADS, a standard P2X antagonist, was used as a positive control. Using the above procedure, compounds of the invention exhibited activity for the $P2X_3$ receptor. The compound 4-(2,4-Diamino-pyrimidin-5-yloxy)-2-iodo-5-isopropyl-phenol, e.g., exhibited a pIC_{50} of approximately 8.3 using the above assay.Compounds of the invention wherein R^1 is isopropyl exhibit better affinity for the $P2X_3$ receptor than analogous compounds having other alkyl substituents as R^1.

Example 71: In vivo Assay for Asthma and Lung Function

[0512] BALb/cJ mice are immunized with a standard immunization protocol. Briefly, mice (N=8/group) are immunized i.p. with ovalbumin (OVA; 10 μg) in alum on days 0 and 14. Mice are then challenged with aerosolized OVA (5%) on day 21 and 22. Animals receive vehicle (p.o.) or a compound of the invention (100 mg/kg p.o.) all starting on day 20. Lung function is evaluated on day 23 using the Buxco system to measure PenH in response to an aerosol methacholine challenge. Mice are then euthanized and plasma samples collected at the end of the study.

Claims

1. The use of a compound of formula I



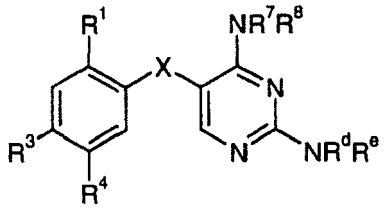
(I)

or a pharmaceutically acceptable salt thereof,
wherein:

X is $-CH_2-$; -O-; or -CHOH-;
Y is hydrogen; or $-NR^dR^e$ wherein one of R^d and R^e is hydrogen, and the other is hydrogen; alkyl; cycloalkyl; cycloalkylalkyl; haloalkyl; haloalkoxy; hydroxyalkyl; alkoxyalkyl; acetyl; alkylsulfonyl; alkylsulfonylalkyl; amino-carbonyloxyalkyl; hydroxycarbonyl-alkyl; hydroxyalkyloxycarbonylalkyl; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl;
D is an optional oxygen;
R^1 is alkyl; alkenyl; cycloalkyl; cycloalkenyl; halo; haloalkyl; hydroxyalkyl; or alkoxy;
R^2, R^3, R^4 and R^5 each independently is hydrogen; alkyl; alkenyl; amino; halo; amido; halo-alkyl; alkoxy; hydroxy; haloalkoxy; nitro; hydroxyalkyl; alkoxyalkyl; hydroxyalkoxy; alkynylalkoxy; alkylsulfonyl; arylsulfonyl; cyano; aryl; heteroaryl; heterocyclyl; hetero-cyclylalkoxy; aryloxy; heteroaryloxy; aralkyloxy; heteroaralkyloxy; optionally substituted phenoxy; $-(CH_2)_m-(Z)_n-(CO)-R^f$ or $-(CH_2)_m-(Z)_n-SO_2-(NR^g)_n-R^f$ where m and n each independently is 0 or 1, Z is O or NR^g, R^f is hydrogen, alkyl, hydroxy, alkoxy, amino, hydroxyalkyl or alkoxyalkyl, and each R^g is independently hydrogen or alkyl;
R^6 is hydrogen; alkyl; halo; haloalkyl; amino; or alkoxy; and
one of R^7 and R^8 is hydrogen, and the other is hydrogen; alkyl; cycloalkyl; cycloalkylalkyl; haloalkyl; haloalkoxy; hydroxyalkyl; alkoxyalkyl; acetyl; alkylsulfonyl; alkylsulfonylalkyl; aminocarbonyloxyalkyl; hydroxycarbonylalkyl; hydroxyalkyloxycarbonylalkyl; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl;

for the preparation of a medicament for the treatment of a respiratory disease mediated by a $P2X_3$ or $P2X_{2/3}$ receptor antagonist, wherein said disease is a respiratory disease selected from chronic obstructive pulmonary disease (COPD), asthma and bronchospasm.

2. The use of claim 1 wherein said compound is of the formula (II):

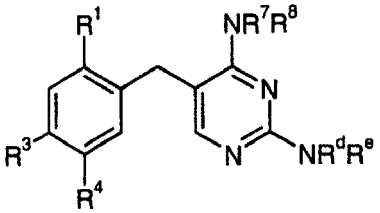


(II)

wherein:

X is $-CH_2-$ or -O-;
R^1 is alkyl; alkenyl; cycloalkyl; cycloalkenyl; or halo;
R^3 and R^4 each independently is alkyl; alkenyl; amino; halo; amido; haloalkyl; alkoxy; hydroxy; haloalkoxy; nitro; hydroxyalkyl; alkoxyalkyl,; hydroxyalkoxy; alkynylalkoxy; alkylsulfonyl; arylsulfonyl; cyano; aryl; heteroaryl; heterocyclyl; heterocyclylalkoxy; aryloxy; heteroaryloxy; aralkyloxy; heteroaralkyloxy; optionally substituted phenoxy; $-(CH_2)_m-(Z)_n-(CO)-R^f$ or $-(CH_2)_m-(Z)_n-SO_2-(NR^g)_n-R^f$ where m and n each independently is 0 or 1, Z is O or NR^g, R^f is hydrogen, alkyl, hydroxy, alkoxy, amino, hydroxyalkyl or alkoxyalkyl, and each R^g is independently hydrogen or alkyl;
one of R^7 and R^8 is hydrogen, and the other is hydrogen; alkyl; cycloalkyl; cycloalkylalkyl; haloalkyl; haloalkoxy; hydroxyalkyl; alkoxyalkyl; acetyl; alkylsulfonyl; alkylsulfonylalkyl; aminocarbonyloxyalkyl; hydroxycarbonylalkyl; hydroxyalkyloxycarbonylalkyl; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl; and
one of R^d and R^e is hydrogen, and the other is hydrogen; alkyl; cycloalkyl; cycloalkylalkyl; haloalkyl; haloalkoxy; hydroxyalkyl; alkoxyalkyl; acetyl; alkylsulfonyl; alkylsulfonylalkyl; aminocarbonyloxyalkyl; hydroxycarbonylalkyl; hydroxyalkyloxycarbonylalkyl; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl.

3. The use of claim 1 wherein said compound is of the formula (III):

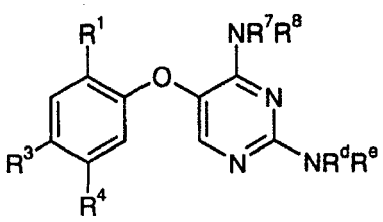


(III)

wherein:

R^1 is isopropyl, isopropenyl, cyclopropyl or iodo;
R^3 and R^4 each independently is alkyl; alkenyl; amino; halo; amido; haloalkyl; alkoxy; hydroxy; haloalkoxy; nitro; hydroxyalkyl; alkoxyalkyl; hydroxyalkoxy; alkynylalkoxy; alkylsulfonyl; arylsulfonyl; cyano; aryl; heteroaryl; heterocyclyl; heterocyclylalkoxy; aryloxy; heteroaryloxy; aralkyloxy; heteroaralkyloxy; optionally substituted phenoxy; $-(CH_2)_m-(Z)_n-(CO)-R^f$ or $-(CH_2)_m-(Z)_n-SO_2-(NR^g)_n-R^f$ where m and n each independently is 0 or 1, Z is O or NR^g, R^f is hydrogen, alkyl, hydroxy, alkoxy, amino, hydroxy-alkyl or alkoxyalkyl, and each R^g is independently hydrogen or alkyl;
one of R^7 and R^8 is hydrogen, and the other is hydrogen; alkyl; cycloalkyl; cycloalkylalkyl; haloalkyl; haloalkoxy; hydroxyalkyl; alkoxyalkyl; acetyl; alkylsulfonyl; alkylsulfonylalkyl; aminocarbonyloxyalkyl; hydroxycarbonylalkyl; hydroxyalkyloxycarbonylalkyl; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl; and
one of R^d and R^e is hydrogen, and the other is hydrogen; alkyl; cycloalkyl; cycloalkylalkyl; haloalkyl; haloalkoxy; hydroxyalkyl; allcoxyalkyl; acetyl; alkylsulfonyl; alkylsulfonylalkyl; aminocarbonyloxyalkyl; hydroxycarbonylalkyl; hydroxyalkyloxycarbonylalkyl; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl.

4. The use of claim 1, wherein said compound is of the formula (IV):

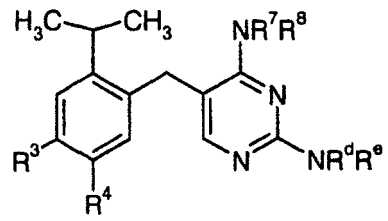


(IV)

wherein:

R^1 is alkyl; alkenyl; cycloalkyl; cycloalkenyl; or halo;
R^3 and R^4 each independently is alkyl; alkenyl; amino; halo; amido; haloalkyl; alkoxy; hydroxy; haloalkoxy; nitro; hydroxyalkyl; alkoxyalkyl; hydroxyalkoxy; alkynylalkoxy; alkylsulfonyl; arylsulfonyl; cyano; aryl; heteroaryl; heterocyclyl; heterocyclylalkoxy; aryloxy; heteroaryloxy; aralkyloxy; heteroaralkyloxy; optionally substituted phenoxy; $-(CH_2)_m-(Z)_n-(CO)-R^f$ or $-(CH_2)_m-(Z)_n-SO_2-(NR^g)_n-R^f$ where m and n each independently is 0 or 1, Z is O or NR^g, R^f is hydrogen, alkyl, hydroxy, alkoxy, amino, hydroxyalkyl or alkoxyalkyl, and each R^g is independently hydrogen or alkyl;
one of R^7 and R^8 is hydrogen, and the other is hydrogen; alkyl; cycloalkyl; cycloalkylalkyl; haloalkyl; haloalkoxy; hydroxyalkyl; alkoxyalkyl; acetyl; alkylsulfonyl; alkylsulfonyl-alkyl; aminocarbonyloxyalkyl; hydroxycarbonylalkyl; hydroxyalkyloxycarbonylalkyl; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl; and
one of R^d and R^e is hydrogen, and the other is hydrogen; alkyl; cycloalkyl; cycloalkylalkyl; haloalkyl; haloalkoxy; hydroxyalkyl; alkoxyalkyl; acetyl; alkylsulfonyl; alkylsulfonylalkyl; aminocarbonyloxyalkyl; hydroxycarbonylalkyl; hydroxyalkyloxycarbonylalkyl; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl.

5. The use of claim 1, wherein said compound is of the formula (V):

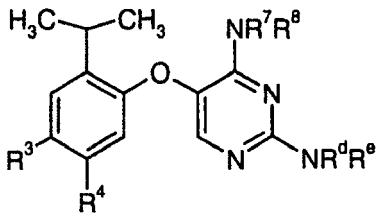


(V)

wherein:

R^3 and R^4 each independently is alkyl; alkenyl; amino; halo; amido; haloalkyl; alkoxy; hydroxy; haloalkoxy; nitro; hydroxyalkyl; alkoxyalkyl; hydroxyalkoxy; alkynylalkoxy; alkylsulfonyl; arylsulfonyl; cyano; aryl; heteroaryl; heterocyclyl; heterocyclylalkoxy; aryloxy; heteroaryloxy; aralkyloxy; heteroaralkyloxy; optionally substituted phenoxy; $-(CH_2)_m-(Z)_n-(CO)-R^f$ or $-(CH_2)_m-(Z)_n-SO_2-(NR^g)_n-R^f$ where m and n each independently is 0 or 1, Z is O or NR^g, R^f is hydrogen, alkyl, hydroxy, alkoxy, amino, hydroxyalkyl or alkoxyalkyl, and each R^g is independently hydrogen or alkyl;
one of R^7 and R^8 is hydrogen, and the other is hydrogen; alkyl; cycloalkyl; cycloalkylalkyl; haloalkyl; haloalkoxy; hydroxyalkyl; alkoxyalkyl; acetyl; alkylsulfonyl; alkylsulfonylalkyl; aminocarbonyloxyalkyl; hydroxycarbonylalkyl; hydroxyalkyloxycarbonylalkyl; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl; and
one of R^d and R^e is hydrogen, and the other is hydrogen; alkyl; cycloalkyl; cycloalkylalkyl; haloalkyl; haloalkoxy; hydroxyalkyl; alkoxyalkyl; acetyl; alkylsulfonyl; alkylsulfonylalkyl; aminocarbonyloxyalkyl; hydroxycarbonylalkyl; hydroxyalkyloxycarbonylalkyl; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl.

6. The use of claim 1, wherein said compound is of the formula (VI):



(VI)

wherein:

R^3 and R^4 each independently is alkyl; alkenyl; amino; halo; amido; haloalkyl; alkoxy; hydroxy; haloalkoxy; nitro; hydroxyalkyl; alkoxyalkyl; hydroxyalkoxy; alkynylalkoxy; alkylsulfonyl; arylsulfonyl; cyano; aryl; heteroaryl; heterocyclyl; heterocyclylalkoxy; aryloxy; heteroaryloxy; aralkyloxy; heteroaralkyloxy; optionally substituted phenoxy; $-(CH_2)_m-(Z)_n-(CO)-R^f$ or $-(CH_2)_m-(Z)_n-SO_2-(NR^g)_n-R^f$ where m and n each independently is 0 or 1, Z is O or NR^g, R^f is hydrogen, alkyl, hydroxy, alkoxy, amino, hydroxyalkyl or alkoxyalkyl, and each R^g is independently hydrogen or alkyl;
one of R^7 and R^8 is hydrogen, and the other is hydrogen; alkyl; cycloalkyl; cycloalkylalkyl; haloalkyl; haloalkoxy; hydroxyalkyl; alkoxyalkyl; acetyl; alkylsulfonyl; alkylsulfonylalkyl; aminocarbonyloxyalkyl; hydroxycarbonylalkyl; hydroxyalkyloxycarbonylalkyl; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl; and
one of R^d and R^e is hydrogen, and the other is hydrogen; alkyl; cycloalkyl; cycloalkylalkyl; haloalkyl; haloalkoxy; hydroxyalkyl; alkoxyalkyl; acetyl; alkylsulfonyl; alkylsulfonylalkyl; aminocarbonyloxyalkyl; hydroxycarbonylalkyl; hydroxyalkyloxycarbonylalkyl; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl.

7. The use according to claim 1, wherein such compound of formula I is selected from the group consisting of:

N^2-Isopropyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-N^4-methyl-pyrimidine-2,4-diamine,
5-(2-Isopropyl-4,5-dimethoxy-phenoxy)-pyrimidine-2,4-diamine,
5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N^4-isoxazol-5-ylmethyl-pyrimidine-2,4-diamine,
N^2-Isopropyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine,
5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N^4-(2-methoxy-benzyl)-pyrimidine-2,4-diamine,
5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N^2-(2,2,2-trifluoro-ethyl)-pyrimidine-2,4-diamine,
3-[2-Amino-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidin-4-ylamino]-propane-1,2-diol,
N-[4-Amino-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidin-2-yl]-acetamide,
5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N^4-(4-methoxy-benzyl)-pyrimidine-2,4-diamine,
5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N^4-phenyl-pyrimidine-2,4-diamine,
5-(5-Chloro-2-isopropyl-4-methoxy-benzyl)-N^2-phenethyl-pyrimidine-2,4-diamine,
5-(5-Chloro-2-isopropyl-4-methoxy-benzyl)-pyrimidine-2,4-diamine,
N^4-Isobutyl-N^2-isopropyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine,
5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N^2-phenyl-pyrimidine-2,4-diamine,
N^2,N^4-Diisopropyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine,
5-(5-Chloro-2-isopropyl-4-methoxy-benzyl)-N^2-isopropyl-pyrimidine-2,4-diamine,
2-[2-Amino-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidin-4-ylamino]-ethanol,
5-(2-Isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine,
5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N^4-[2-(4-methoxy-phenyl)-ethyl]-pyrimidine-2,4-diamine,
N^2-Benzyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine,
5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N^4-(4-methanesulfonyl-cyclohexyl)-pyrimidine-2,4-diamine,
N^2-Cyclopropyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine,
N^4-Isopropyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine,
N^2-Ethyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine,
5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N^4-[2-(3-methoxy-phenyl)-ethyl]-pyrimidine-2,4-diamine,
2-[4-Amino-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidin-2-ylamino]-ethanol,
5-(2-sec-Butyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine,
N^2-tert-Butyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine,
N^2-Isobutyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine,
5-(5-Chloro-2-isopropyl-4-methoxy-benzyl)-N^2-cyclopropyl-pyrimidine-2,4-diamine,

5-(2-Isopropyl-4-methoxy-5-phenoxy-benzyl)-pyrimidine-2,4-diamine,
N^4-Isobutyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine,
N^4-Ethyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine,
N^4-Benzyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine,
5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N^4-(2,2,2-trifluoro-ethyl)-pyrimidine-2,4-diamine,
5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N^2-(4-methoxy-phenyl)-pyrimidine-2,4-diamine,
N^2-Isopropyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-N^4-phenyl-pyrimidine-2,4-diamine,
N^4-Ethyl-N^2-isopropyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine,
5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N^4-(1-methyl-piperidin-4-yl)-pyrimidine-2,4-diamine,
5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N^2-(2-methoxy-phenyl)-pyrimidine-2,4-diamine,
5-(4,5-Dichloro-2-isopropyl-benzyl)-pyrimidine-2,4-diamine,
5-(5-Chloro-2-isopropyl-4-methoxy-benzyl)-N^2-ethyl-pyrimidine-2,4-diamine,
5-(2-Isopropyl-4-methoxy-5-methyl-benzyl)-pyrimidine-2,4-diamine,
5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N^2-pyrimidin-2-yl-pyrimidine-2,4-diamine,
5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N^2-(2-methoxy-ethyl)-pyrimidine-2,4-diamine,
N^4-Benzyl-N^2-isopropyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine,
1-(4-{2-[4-Amino-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidin-2-ylamino]-propyl}-piperazin-1-yl)-ethanone,
5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N^4-(tetrahydro-pyran-4-yl)-pyrimidine-2,4-diamine,
N^4-Cyclopropyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine,
5-(5-Ethoxy-2-isopropyl-4-methoxy-benzyl)-pyrimidine-2,4-diamine,
N^2-(2,4-Dimethoxy-phenyl)-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine,
N^2-Cyclobutyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine,
N^2-(2-Chloro-phenyl)-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine,
5-(4-Chloro-2-isopropyl-5-methoxy-benzyl)-pyrimidine-2,4-diamine,
5-(5-Bromo-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine,
5-(5-Chloro-2-isopropyl-4-methoxy-benzyl)-N^2-(3-methoxy-phenyl)-pyrimidine-2,4-diamine,
5-(5-Chloro-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine,
5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N^2,N^4-diphenyl-pyrimidine-2,4-diamine,
5-(5-Chloro-2-isopropyl-4-methoxy-benzyl)-N^2-isobutyl-pyrimidine-2,4-diamine,
5-(5-Chloro-2-isopropyl-4-methoxy-benzyl)-N^2-phenyl-pyrimidine-2,4-diamine,
5-(2-Isopropyl-4-methoxy-5-methyl-phenoxy)-pyrimidine-2,4-diamine,
5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N^2-methyl-pyrimidine-2,4-diamine,
5-(2-Isopropyl-5-methyl-phenoxy)-pyrimidine-2,4-diamine,
5-(5-Chloro-2-isopropyl-4-methoxy-benzyl)-N^2-methyl-pyrimidine-2,4-diamine,
N^2-Benzyl-5-(5-chloro-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine,
2-[2-Isopropylamino-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidin-4-ylamino]-ethanol,
5-(5-Chloro-2-isopropyl-4-methoxy-phenoxy)-N^2-(tetrahydro-pyran-4-yl)-pyrimidine-2,4-diamine,
N^2-(4-Chloro-phenyl)-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine,
5-(2-Isopropyl-phenoxy)-pyrimidine-2,4-diamine,
5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N^4-methyl-pyrimidine-2,4-diamine,
5-(5-Chloro-2-isopropyl-4-methoxy-phenoxy)-N^2-isopropyl-pyrimidine-2,4-diamine,
5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N^4-(2-methoxy-ethyl)-pyrimidine-2,4-diamine,
N^2-Isopropyl-5-(2-isopropyl-4,5-dimethoxy-phenoxy)-pyrimidine-2,4-diamine,
5-(2-Ethyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine,
5-(2-Isopropyl-4,5-dimethoxy-phenoxy)-N^2-phenyl-pyrimidine-2,4-diamine,
N^2-tert-Butyl-5-(5-chloro-2-isopropyl-4-methoxy-benzyl)-pyrimidine-2,4-diamine,
N^2-Benzyl-5-(2-isopropyl-4,5-dimethoxy-phenoxy)-pyrimidine-2,4-diamine,
5-(2-Cyclopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine,
N-[4-Amino-5-(2-isopropyl-4,5-dimethoxy-phenoxy)-pyrimidin-2-yl]-acetamide,
N^2-Benzyl-5-(5-chloro-2-isopropyl-4-methoxy-benzyl)-pyrimidine-2,4-diamine,
5-(2-Isopropyl-4,5-dimethoxy-phenoxy)-N^2-(2,2,2-trifluoro-ethyl)-pyrimidine-2,4-diamine,
5-(2-Isopropyl-4,5-dimethoxy-phenoxy)-N^2-(2-methoxy-ethyl)-pyrimidine-2,4-diamine,
5-(2-Isopropyl-4,5-dimethoxy-benzyl)-pyrimidin-4-ylamine,
3-[4-Amino-5-(5-chloro-2-isopropyl-4-methoxy-phenoxy)-pyrimidin-2-ylamino]-pentane-1,5-diol,
5-(5-Chloro-2-isopropyl-4-methoxy-benzyl)-N^2-cyclohexyl-pyrimidine-2,4-diamine,
2-[4-Amino-5-(5-chloro-2-isopropyl-4-methoxy-phenoxy)-pyrimidin-2-ylamino]-butan-1-ol,
1-[5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-ethanone,
5-[5-(1H-Imidazol-2-yl)-2-isopropyl-4-methoxy-phenoxy]-pyrimidine-2,4-diamine,

(2,4-Diamino-pyrimidin-5-yl)-(2-isopropyl-4,5-dimethoxy-phenyl)-methanol,
5-[5-Chloro-2-(2-fluoro-1-methyl-ethyl)-4-methoxy-phenoxy]-pyrimidine-2,4-diamine,
(5-Chloro-2-isopropyl-4-methoxy-phenyl)-(2,4-diamino-pyrimidin-5-yl)-methanol,
2-[4-Amino-5-(5-chloro-2-ethyl-4-methoxy-phenoxy)-pyrimidin-2-ylamino]-butan-1-ol,
5-(5-Chloro-2-isopropyl-4-methoxy-phenoxy)-N^2-(3-ethanesulfonyl-1-methyl-propyl)-pyrimidine-2,4-diamine,
5-(5-Bromo-2-ethyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine,
5-(5-Chloro-2-ethyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine,
5-(5-Chloro-2-cyclopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine,
5-(2-Ethyl-5-methanesulfonyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine,
5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-benzamide,
5-(4,5-Dimethoxy-2-vinyl-phenoxy)-pyrimidine-2,4-diamine,
5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-benzoic acid,
5-(2-Cyclopropyl-4,5-dimethoxy-phenoxy)-pyrimidine-2,4-diamine,
5-[2-Isopropyl-4-methoxy-5-(1H-tetrazol-5-yl)-phenoxy]-pyrimidine-2,4-diamine,
5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-benzonitrile,
4-[4-Amino-5-(5-chloro-2-isopropyl-4-methoxy-phenoxy)-pyrimidin-2-ylamino]-piperidine-1-carboxylic acid ethyl ester,
[5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-urea,
5-(5-Chloro-2-isopropyl-4-methoxy-phenoxy)-N^2-(1-cyclopropyl-ethyl)-pyrimidine-2,4-diamine,
5-(5-Chloro-4-difluoromethoxy-2-isopropyl-phenoxy)-pyrimidine-2,4-diamine,
5-(5-Amino-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine,
N^4-Isopropyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-N^2-methyl-pyrimidine-2,4-diamine,
N-[5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-acetamide,
5-(2-Isopropyl-4-methoxy-5-tetrazol-1-yl-phenoxy)-pyrimidine-2,4-diamine,
5-(2-Isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine,
5-(2-Isopropyl-5-methanesulfonyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine,
5-(2-Isopropyl-4-methoxy-5-methyl-phenoxy)-N^4-phenyl-pyrimidine-2,4-diamine,
5-(5-Chloro-2-isopropyl-4-methoxy-phenoxy)-N^2-(1,1-dioxo-hexahydro-1λ^6-thiopyran-4-yl)-pyrimidine-2,4-diamine,
Methyl-carbamic acid 2-[4-amino-5-(5-chloro-2-isopropyl-4-methoxy-phenoxy)-pyrimidin-2-ylamino]-propyl ester,
5-(4-Chloro-2-isopropyl-5-methyl-phenoxy)-pyrimidine-2,4-diamine,
5-(2-Isopropyl-4,5-dimethoxy-phenoxy)-6-methyl-pyrimidine-2,4-diamine,
1-(4-{2-[4-Amino-5-(5-chloro-2-isopropyl-4-methoxy-phenoxy)-pyrimidin-2-ylamino]-propyl}-piperazin-1-yl)-ethanone,
5-(5-Chloro-2-isopropyl-4-methoxy-phenoxy)-N^2-(1-methanesulfonyl-piperidin-4-yl)-pyrimidine-2,4-diamine,
2-[4-Amino-5-(5-chloro-2-isopropyl-4-methoxy-phenoxy)-pyrimidin-2-ylamino]-(R)-propan-1-ol,
5-(2-Ethyl-4,5-dimethoxy-phenoxy)-pyrimidine-2,4-diamine,
5-(2-Isopropyl-5-methanesulfonyl-4-methoxy-phenoxy)-*N*^{2}-(tetrahydro-thiopyran-4-yl)-pyrimidine-2,4-diamine,
5-(5-Chloro-2-isopropyl-4-methoxy-phenoxy)-*N*^{2}-(1,1-dioxo-hexahydro-1λ^6-thiopyran-4-yl)-pyrimidine-2,4-diamine,
1-[5-(2,4-Diamino-pyrimidin-5-yloxy)-2-hydroxy-4-isopropyl-phenyl]-ethanone,
5-(5-Iodo-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine,
5-(2-Iodo-4,5-dimethoxy-phenoxy)-pyrimidine-2,4-diamine,
5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-benzenesulfonamide,
4-(2,4-Diamino-pyrimidin-5-yloxy)-2-iodo-5-isopropyl-phenol,
5-(2,5-Diiodo-4-methoxy-phenoxy)-pyrimidine-2,4-diamine,
3-[4-Amino-5-(5-bromo-2-isopropyl-4-methoxy-phenoxy)-pyrimidin-2-ylamino]-pentane-1,5-diol,
5-(2-Ethyl-5-iodo-4-methoxy-phenoxy)-pyrimidine-2,4-diamine,
5-(5-Iodo-2-isopropyl-4-methoxy-phenoxy)-1-oxy-pyrimidine-2,4-diamine,
5-(2-Isopropyl-4methoxy-5-vinyl-phenoxy)-pyrimidine-2,4-diamine,
5-(5-Iodo-2-isopropenyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine,
5-(2-Isopropyl-4-methoxy-5-pyrazol-1-yl-phenoxy)-pyrimidine-2,4-diamine,
5-(5-Iodo-2-isopropyl-phenoxy)-pyrimidine-2,4-diamine,
5-[2-Isopropyl-4-methoxy-5-(3-methyl-pyrazol-1-yl)-phenoxy]-pyrimidine-2,4-diamine,
4-(2,4-Diamino-pyrimidin-5-ylmethyl)-2-iodo-5-isopropyl-phenol,
5-(2-Isopropyl-4-methoxy-5-oxazol-2-yl-phenoxy)-pyrimidine-2,4-diamine,
(S)-2-[4-Amino-5-(5-bromo-2-isopropyl-4-methoxy-phenoxy)-pyrimidin-2-ylamino]-butan-1-ol,

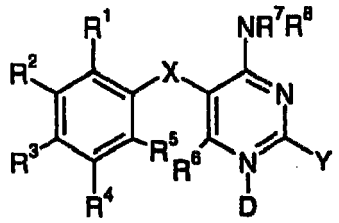
5-(4-Iodo-2-isopropyl-5-methoxy-phenoxy)-pyrimidine-2,4-diamine,
5-(4-Bromo-2-isopropyl-5-methoxy-phenoxy)-pyrimidine-2,4-diamine,
5-(2-Ethyl-5-iodo-phenoxy)-pyrimidine-2,4-diamine,
5-(2-Isopropyl-4-methoxy-5-trifluoromethyl-phenoxy)-pyrimidine-2,4-diamine,
5-(2-Isopropyl-4-methoxy-5-thiazol-4-yl-phenoxy)-pyrimidine-2,4-diamine,
[4-(2,4-Diamino-pyrimidin-5-yloxy)-2-iodo-5-isopropyl-phenoxy]-acetonitrile,
5-(2-Isopropyl-4-methoxy-5-thiophen-3-yl-phenoxy)-pyrimidine-2,4-diamine,
(R)-2-[4-Amino-5-(2-isopropyl-5-methanesulfonyl-4-methoxy-phenoxy)-pyrimidin-2-ylamino]-butan-1-ol,
(S)-2-[4-Amino-5-(5-chloro-2-isopropyl-4-methoxy-phenoxy)-pyrimidin-2-ylamino]-propionic acid,
5-[5-(4,5-Dihydro-oxazol-2-yl)-2-isopropyl-4-methoxy-phenoxy]-pyrimidine-2,4-diamine,
5-(2-Isopropyl-5-methanesulfonyl-4-methoxy-phenoxy)-N^2-(2,2,2-trifluoro-ethyl)-pyrimidine-2,4-diamine,
5-(5-Iodo-2-isopropyl-4-methoxy-benzyl)-pyrimidine-2,4-diamine,
5-(5-Bromo-2-cyclopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine,
(S)-2-[4-Amino-5-(5-chloro-2-isopropyl-4-methoxy-phenoxy)-pyrimidin-2-ylamino]-propionic acid 3-hydroxy-2-hydroxymethyl-2-methyl-propyl ester,
5-[5-(5-Chloro-thiophen-2-yl)-2-isopropyl-4-methoxy-phenoxy]-pyrimidine-2,4-diamine,
5-(2-Ethyl-4-methoxy-5-trifluoromethyl-phenoxy)-pyrimidine-2,4-diamine,
5-[2-Isopropyl-4-methoxy-5-(1-methyl-1H-imidazol-2-yl)-phenoxy]-pyrimidine-2,4-diamine,
5-[2-Isopropyl-4-methoxy-5-(2H-pyrazol-3-yl)-phenoxy]-pyrimidine-2,4-diamine,
5-(5-Imidazol-1-yl-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine,
N^2-Isopropyl-5-(2-isopropyl-5-methanesulfonyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine,
2-[4-(2,4-Diamino-pyrimidin-5-yloxy)-2-iodo-5-isopropyl-phenoxy]-ethanol,
5-(2-Isopropyl-5-methanesulfonyl-4-methoxy-phenoxy)-N^2-phenyl-pyrimidine-2,4-diamine,
5-(4-Amino-2-ethylamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-benzamide,
2-[4-Amino-5-(2-isopropyl-5-methanesulfonyl-4-methoxy-phenoxy)-pyrimidin-2-ylamino]-ethanol,
5-[2-Isopropyl-4-methoxy-5-(2-methyl-thiazol-4-yl)-phenoxy]-pyrimidine-2,4-diamine,
5-[5-Iodo-2-isopropyl-4-(pyrazin-2-ylmethoxy)-phenoxy]-pyrimidine-2,4-diamine,
5-(2-Isopropyl-5-methanesulfonyl-4-methoxy-phenoxy)-N^2-(2-methoxy-ethyl)-pyrimidine-2,4-diamine,
5-(2-Isopropyl-4-methoxy-5-[1,2,3]triazol-1-yl-phenoxy)-pyrimidine-2,4-diamine,
5-(5-Furan-2-yl-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine,
1-[5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-3-ethyl-urea,
N^2-Cyclopropyl-5-(2-isopropyl-5-methanesulfonyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine,
2-[4-(2,4-Diamino-pyrimidin-5-yloxy)-2-iodo-5-isopropyl-phenoxy]-acetamide,
5-[5-(3,5-Dimethyl-pyrazol-1-yl)-2-isopropyl-4-methoxy-phenoxy]-pyrimidine-2,4-diamine,
N^2-Benzyl-5-(2-isopropyl-5-methanesulfonyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine,
N^2-Ethyl-5-(2-isopropyl-5-methanesulfonyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine,
5-(2-Isopropyl-5-methanesulfonyl-4-methoxy-phenoxy)-N^2-(1-methanesulfonyl-piperidin-4-yl)-pyrimidine-2,4-diamine,
1-[4-Amino-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidin-2-ylamino]-2-methyl-propan-2-ol,
N^2-Isobutyl-5-(2-isopropyl-5-methanesulfonyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine,
5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-N-methyl-benzamide,
5-(2-Isopropyl-5-isoxazol-5-yl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine,
N^2-(4-Fluoro-phenyl)-5-(2-isopropyl-5-methanesulfonyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine,
5-(5-Chloro-2-isopropyl-4-methoxy-benzyl)-N^2-(2,2,2-trifluoro-ethyl)-pyrimidine-2,4-diamine,
5-(2-Isopropyl-4-methoxy-5-[1,2,4]oxadiazol-3-yl-phenoxy)-pyrimidine-2,4-diamine,
5-(2-Isopropyl-5-methanesulfonyl-4-methoxy-phenoxy)-N^2-(tetrahydro-pyran-4-yl)-pyrimidine-2,4-diamine,
1-[5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-ethanol,
5-(2,5-Diisopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine,
5-(5-Benzo[*b*]thiophen-3-yl-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine,
5-[2-Isopropyl-4-methoxy-5-(1-methoxy-ethyl)-phenoxy]-pyrimidine-2,4-diamine,
5-(2-Isopropyl-4-methoxy-5-oxazol-4-yl-phenoxy)-pyrimidine-2,4-diamine,
5-[5-(5-Chloro-thiophen-2-yl)-2-isopropyl-4-methoxy-benzyl]-pyrimidine-2,4-diamine,
5-(2-Isopropyl-4-methoxy-5-thiazol-2-yl-phenoxy)-pyrimidine-2,4-diamine,
5-(2-Isopropyl-4-methoxy-5-thiophen-3-yl-benzyl)-pyrimidine-2,4-diamine,
5-(5-Furan-3-yl-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine,
5-(2-Isopropyl-5-methoxy-phenoxy)-pyrimidine-2,4-diamine,
5-[5-Iodo-2-isopropyl-4-(pyrimidin-2-ylmethoxy)-phenoxy]-pyrimidine-2,4-diamine,
5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N^2-pyridin-2-yl-pyrimidine-2,4-diamine,

5-(2-Isopropyl-4-methoxy-5-thiophen-2-yl-phenoxy)-pyrimidine-2,4-diamine,
1-[5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-3-phenyl-urea,
5-(5-Chloro-2-isopropyl-4-methoxy-benzyl)-N^2-(2-methoxy-ethyl)-pyrimidine-2,4-diamine,
5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-N-methyl-benzenesulfonamide,
5-(2-Isopropyl-5-methanesulfonyl-4-methoxy-phenoxy)-N^2-methyl-pyrimidine-2,4-diamine,
5-[5-Iodo-2-isopropyl-4-(pyridin-2-ylmethoxy)-phenoxy]-pyrimidine-2,4-diamine,
N-[2-Acetylamino-5-(2-isopropyl-4-methoxy-5-methyl-benzyl)-pyrimidin-4-yl]-acetamide,
5-[4-(2-Fluoro-benzyloxy)-5-iodo-2-isopropyl-phenoxy]-pyrimidine-2,4-diamine,
5-(2-Isopropyl-4-methoxy-5-pyrrol-1-yl-phenoxy)-pyrimidine-2,4-diamine,
5-(2-Isopropyl-4-methoxy-5-trifluoromethoxy-phenoxy)-pyrimidine-2,4-diamine,
2-[4-(2,4-Diamino-pyrimidin-5-ylmethyl)-2-iodo-5-isopropyl-phenoxy]-ethanol,
5-[5-(4,5-Dihydro-oxazol-2-yl)-2-isopropyl-4-methoxy-benzyl]-pyrimidine-2,4-diamine,
5'-(2,4-Diamino-pyrimidin-5-yloxy)-4'-isopropyl-2'-methoxy-biphenyl-3-carbonitrile,
5-[2-Isopropyl-4-methoxy-5-(4-methyl-thiophen-2-yl)-phenoxy]-pyrimidine-2,4-diamine,
5-(5-Chloro-2-isopropyl-4-methoxy-phenoxy)-N^2-[(*S*)-1-(4-methyl-2,6,7-trioxa-bicyclo[2.2.2]oct-1-yl)-ethyl]-pyrimidine-2,4-diamine,
5-(5-Iodo-2-isopropyl-4-prop-2-ynyloxy-phenoxy)-pyrimidine-2,4-diamine,
5-(2-Isopropyl-4-methoxy-5-nitro-phenoxy)-pyrimidine-2,4-diamine,
5-(4-Ethoxy-5-iodo-2-isopropyl-phenoxy)-pyrimidine-2,4-diamine,
5-[5-Iodo-2-isopropyl-4-(pyridin-3-ylmethoxy)-phenoxy]-pyrimidine-2,4-diamine,
5-(4-Benzyloxy-5-iodo-2-isopropyl-phenoxy)-pyrimidine-2,4-diamine,
5-(4-Isopropyl-6-methoxy-biphenyl-3-yloxy)-pyrimidine-2,4-diamine,
5-(5-Furan-2-yl-2-isopropyl-4-methoxy-benzyl)-pyrimidine-2,4-diamine,
5-(2-Isopropyl-4-methoxy-5-thiazol-5-yl-phenoxy)-pyrimidine-2,4-diamine,
1-[5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-pyrrolidin-2-one,
5-(2-Isopropyl-5-methanesulfonyl-4-methoxy-benzyl)-pyrimidine-2,4-diamine,
5-[5-Chloro-2-(1-fluoro-1-methyl-ethyl)-4-methoxy-phenoxy]-pyrimidine-2,4-diamine,
5-[5-Iodo-2-isopropyl-4-(2-methoxy-ethoxy)-phenoxy]-pyrimidine-2,4-diamine,
5-(2-Isopropyl-4-methoxy-5-oxazol-5-yl-phenoxy)-pyrimidine-2,4-diamine,
1-[4-Chloro-2-(2,4-diamino-pyrimidin-5-yloxy)-5-methoxy-phenyl]-ethanol,
1-[4-Chloro-2-(2,4-diamino-pyrimidin-5-yloxy)-5-methoxy-phenyl]-ethanol,
2-[2-(2,4-Diamino-pyrimidin-5-yloxy)-4-iodo-5-methoxy-phenyl]-propan-1-ol,
5-[5-Iodo-2-isopropyl-4-(2-methoxy-benzyloxy)-phenoxy]-pyrimidine-2,4-diamine,
5-[5-Iodo-2-isopropyl-4-(2,2,2-trifluoro-ethoxy)-phenoxy]-pyrimidine-2,4-diamine,
5-[5-Iodo-2-isopropyl-4-(3,4,5-trimethoxy-benzyloxy)-phenoxy]-pyrimidine-2,4-diamine,
2-[2-(2,4-Diamino-pyrimidin-5-yloxy)-4-iodo-5-methoxy-phenyl]-propan-2-ol,
5-[2-Isopropyl-4-methoxy-5-(4-methyl-thiophen-3-yl)-phenoxy]-pyrimidine-2,4-diamine,
5-(2-Isopropyl-4-methoxy-5-nitro-phenoxy)-pyrimidine-2,4-diamine,
5-[5-Iodo-2-isopropyl-4-(1-methyl-piperidin-2-ylmethoxy)-phenoxy]-pyrimidine-2,4-diamine,
5-[5-Iodo-2-isopropyl-4-(tetrahydro-pyran-2-ylmethoxy)-phenoxy]-pyrimidine-2,4-diamine,
5-(2-Isopropyl-4-methoxy-5-[1,2,4]triazol-1-yl-phenoxy)-pyrimidine-2,4-diamine,
5-(2-Isopropyl-4,5-dimethoxy-phenoxy)-N^2-(2-methoxy-ethyl)-pyrimidine-2,4-diamine,
5-(4'-Fluoro-4-isopropyl-6-methoxy-biphenyl-3-yloxy)-pyrimidine-2,4-diamine,
5-(5-Chloro-2-isopropyl-4-methoxy-phenoxy)-N^2-(2,2,2-trifluoro-ethyl)-pyrimidine-2,4-diamine,
5-(2,4-Diamino-pyrimidin-5-ylmethyl)-4-isopropyl-2-methoxy-benzonitrile,
5-[2-Isopropyl-4-methoxy-5-(2-methyl-thiazol-5-yl)-phenoxy]-pyrimidine-2,4-diamine,
5-(2-Isopropyl-4-methoxy-6-methyl-phenoxy)-pyrimidine-2,4-diamine,
5-(5-Ethanesulfonyl-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine,
5-(2-Isopropyl-4-methoxy-5-thiazol-5-yl-benzyl)-pyrimidine-2,4-diamine,
1-[5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-1*H*-imidazole-2-thiol,
5-[2-Isopropyl-4-methoxy-5-(1-methyl-1*H*-pyrazol-4-yl)-phenoxy]-pyrimidine-2,4-diamine,
5-[5-Iodo-2-isopropyl-4-(pyridin-4-ylmethoxy)-phenoxy]-pyrimidine-2,4-diamine,
5-(4-Iodo-2-isopropyl-phenoxy)-pyrimidine-2,4-diamine,
5-(5-Iodo-4-isopropyl-2-methoxy-benzyl)-pyrimidine-2,4-diamine,
5-(5-Fluoro-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine,
5-(4'-Fluoro-5-isopropyl-2-methoxy-biphenyl-4-yloxy)-pyrimidine-2,4-diamine,
5-[4-(3-Fluoro-benzyloxy)-5-iodo-2-isopropyl-phenoxy]-pyrimidine-2,4-diamine,
5-(4-Bromo-2-isopropyl-phenoxy)-pyrimidine-2,4-diamine,

5-(4-Furan-2-yl-2-isopropyl-5-methoxy-phenoxy)-pyrimidine-2,4-diamine,
2-[5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-propan-2-ol,
5-[4-(2,6-Difluoro-benzyloxy)-5-iodo-2-isopropyl-phenoxy]-pyrimidine-2,4-diamine,
5-(5-Iodo-2-isopropyl-4-phenethyloxy-phenoxy)-pyrimidine-2,4-diamine,
5-(2-Isopropyl-4-methoxy-5-pyridin-4-yl-phenoxy)-pyrimidine-2,4-diamine,
5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N^2-(1-methyl-piperidin-4-yl)-pyrimidine-2,4-diamine,
5-(2,4-Diamino-pyrimidin-5-yloxy)-N-ethyl-4-isopropyl-2-methoxy-benzenesulfonamide,
5-[2-Isopropyl-5-(4-methanesulfonyl-piperazin-1-yl)-4-methoxy-phenoxy]-pyrimidine-2,4-diamine,
5-(2-Isopropyl-4-methoxy-5-pyridin-3-yl-phenoxy)-pyrimidine-2,4-diamine,
5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-N,N-dimethyl-benzamide,
5-[5-(2,5-Dimethyl-pyrrol-1-yl)-2-isopropyl-4-methoxy-phenoxy]-pyrimidine-2,4-diamine,
5-(2-Ethyl-3-methoxy-benzyl)-pyrimidine-2,4-diamine,
5-(2-Bromo-4,5-dimethoxy-phenoxy)-pyrimidine-2,4-diamine,
5-(2-Isopropyl-5-methanesulfonyl-4-methoxy-phenoxy)-N^2-(2,2,2-trifluoro-ethyl)-pyrimidine-2,4-diamine ; and
5'-(2,4-Diamino-pyrimidin-5-yloxy)-4'-isopropyl-2'-methoxy-biphenyl-3-carbonitrile.

Patentansprüche

1. Verwendung einer Verbindung der Formel I

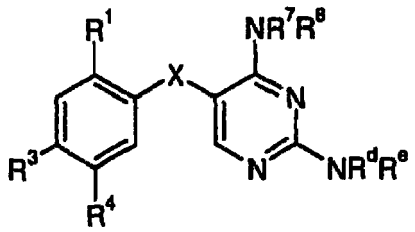


(I)

oder eines pharmazeutisch verträglichen Salzes davon,
wobei:

X $-CH_2-$; -O-; oder -CHOH- ist;
Y Wasserstoff; oder $-NR^dR^e$ ist, wobei einer der Reste R^d und R^e Wasserstoff ist, und der andere Wasserstoff; Alkyl; Cycloalkyl; Cycloalkylalkyl; Halogenalkyl; Halogenalkoxy; Hydroxyalkyl; Alkoxyalkyl; Acetyl; Alkylsulfonyl; Alkylsulfonylalkyl; Aminocarbonyloxyalkyl; Hydroxycarbonylalkyl; Hydroxyalkyloxycarbonylalkyl; Aryl; Aralkyl; Arylsulfonyl; Heteroaryl; Heteroarylalkyl; Heteroarylsulfonyl; Heterocyclyl; oder Heterocyclylalkyl ist;
D ein gegebenenfalls vorhandener Sauerstoff ist;
R^1 Alkyl; Alkenyl; Cycloalkyl; Cycloalkenyl; Halogen; Halogenalkyl; Hydroxyalkyl; oder Alkoxy ist;
R^2, R^3, R^4 und R^5 jeweils unabhängig Wasserstoff; Alkyl; Alkenyl; Amino; Halogen; Amido; Halogenalkyl; Alkoxy; Hydroxy; Halogenalkoxy; Nitro; Hydroxyalkyl; Alkoxyalkyl; Hydroxyalkoxy; Alkinylalkoxy; Alkylsulfonyl; Arylsulfonyl; Cyano; Aryl; Heteroaryl; Heterocyclyl; Heterocyclylalkoxy; Aryloxy; Heteroaryloxy; Aralkyloxy; Heteroaralkyloxy; gegebenenfalls substituiertes Phenoxy; $-(CH_2)_m-(Z)_n-(CO)-R^f$ oder $-(CH_2)_m-(Z)_n-SO_2-(NR^g)_n-R^f$ sind, wobei m und n jeweils unabhängig 0 oder 1 sind, Z O oder NR^g ist, R^f Wasserstoff, Alkyl, Hydroxy, Alkoxy, Amino, Hydroxyalkyl oder Alkoxyalkyl ist, und jedes R^g unabhängig Wasserstoff oder Alkyl ist;
R^6 Wasserstoff; Alkyl; Halogen; Halogenalkyl; Amino; oder Alkoxy ist; und
einer der Reste R^7 und R^8 Wasserstoff ist, und der andere Wasserstoff; Alkyl; Cycloalkyl; Cycloalkylalkyl; Halogenalkyl; Halogenalkoxy; Hydroxyalkyl; Alkoxyalkyl; Acetyl; Alkylsulfonyl; Alkylsulfonylalkyl; Aminocarbonyloxyalkyl; Hydroxycarbonylalkyl; Hydroxyalkyloxycarbonylalkyl; Aryl; Aralkyl; Arylsulfonyl; Heteroaryl; Heteroarylalkyl; Heteroarylsulfonyl; Heterocyclyl; oder Heterocyclylalkyl ist;
für die Herstellung eines Medikaments zur Behandlung einer Atemwegserkrankung, die durch einen $P2X_3$- oder $P2X_{2/3}$-Rezeptor-Antagonisten vermittelt wird, wobei die Erkrankung eine Atemwegserkrankung ausgewählt aus chronisch obstruktiver Lungenerkrankung (COPD), Asthma und Bronchospasmus ist.

2. Verwendung gemäß Anspruch 1, wobei die Verbindung die Formel (II) hat:

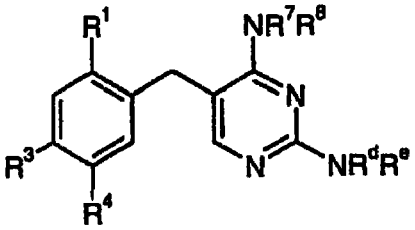


(II)

wobei:

X $-CH_2-$ oder -O- ist;
R^1 Alkyl; Alkenyl; Cycloalkyl; Cycloalkenyl; oder Halogen ist;
R^3 und R^4 jeweils unabhängig Alkyl; Alkenyl; Amino; Halogen; Amido; Halogenalkyl; Alkoxy; Hydroxy; Halogenalkoxy; Nitro; Hydroxyalkyl; Alkoxyalkyl; Hydroxyalkoxy; Alkinylalkoxy; Alkylsulfonyl; Arylsulfonyl; Cyano; Aryl; Heteroaryl; Heterocyclyl; Heterocyclylalkoxy; Aryloxy; Heteroaryloxy; Aralkyloxy; Heteroaralkyloxy; gegebenenfalls substituiertes Phenoxy; $-(CH_2)_m(Z)_n-(CO)-R^f$ oder $-(CH_2)_m(Z)_n-SO_2-(NR^g)_n-R^f$ sind, wobei m und n jeweils unabhängig 0 oder 1 sind, Z O oder NR^g ist, R^f Wasserstoff, Alkyl, Hydroxy, Alkoxy, Amino, Hydroxyalkyl oder Alkoxyalkyl ist, und jedes R^g unabhängig Wasserstoff oder Alkyl ist;
einer der Reste R^7 und R^8 Wasserstoff ist, und der andere Wasserstoff; Alkyl; Cycloalkyl; Cycloalkylalkyl; Halogenalkyl; Halogenalkoxy; Hydroxyalkyl; Alkoxyalkyl; Acetyl; Alkylsulfonyl; Alkylsulfonylalkyl; Aminocarbonyloxyalkyl; Hydroxycarbonylalkyl; Hydroxyalkyloxycarbonylalkyl; Aryl; Aralkyl; Arylsulfonyl; Heteroaryl; Heteroarylalkyl; Heteroarylsulfonyl; Heterocyclyl; oder Heterocyclylalkyl ist; und einer der Reste R^d und R^e Wasserstoff ist, und der andere Wasserstoff; Alkyl; Cycloalkyl; Cycloalkylalkyl; Halogenalkyl; Halogenalkoxy; Hydroxyalkyl; Alkoxyalkyl; Acetyl; Alkylsulfonyl; Alkylsulfonylalkyl; Aminocarbonyloxyalkyl; Hydroxycarbonylalkyl; Hydroxyalkyloxycarbonylalkyl; Aryl; Aralkyl; Arylsulfonyl; Heteroaryl; Heteroarylalkyl; Heteroarylsulfonyl; Heterocyclyl; oder Heterocyclylalkyl ist.

3. Verwendung gemäß Anspruch 1, wobei die Verbindung die Formel (III) hat:

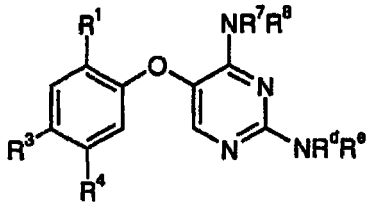


(III)

wobei:

R^1 Isopropyl, Isopropenyl, Cyclopropyl oder Iod ist;
R^3 und R^4 jeweils unabhängig Alkyl; Alkenyl; Amino; Halogen; Amido; Halogenalkyl; Alkoxy, Hydroxy; Halogenalkoxy; Nitro; Hydroxyalkyl; Alkoxyalkyl; Hydroxyalkoxy; Alkinylalkoxy; Alkylsulfonyl; Arylsulfonyl; Cyano; Aryl; Heteroaryl; Heterocyclyl; Heterocyclylalkoxy; Aryloxy; Heteroaryloxy; Aralkyloxy; Heteroaralkyloxy; gegebenenfalls substituiertes Phenoxy; $-(CH_2)_m-(Z)_n-(CO)-R^f$ oder $-(CH_2)_m-(Z)_n-SO_2-(NR^g)_n-R^f$ sind, wobei m und n jeweils unabhängig 0 oder 1 sind, Z O oder NR^g ist, R^f Wasserstoff, Alkyl, Hydroxy, Alkoxy, Amino, Hydroxyalkyl oder Alkoxyalkyl ist, und jedes R^g unabhängig Wasserstoff oder Alkyl ist;
einer der Reste R^7 und R^8 Wasserstoff ist, und der andere Wasserstoff; Alkyl; Cycloalkyl; Cycloalkylalkyl; Halogenalkyl; Halogenalkoxy; Hydroxyalkyl; Alkoxyalkyl; Acetyl; Alkylsulfonyl; Alkylsulfonylalkyl; Aminocarbonyloxyalkyl; Hydroxycarbonylalkyl; Hydroxyalkyloxycarbonylalkyl; Aryl; Aralkyl; Arylsulfonyl; Heteroaryl; Heteroarylalkyl; Heteroarylsulfonyl; Heterocyclyl; oder Heterocyclylalkyl ist; und
einer der Reste R^d und R^e Wasserstoff ist, und der andere Wasserstoff; Alkyl; Cycloalkyl; Cycloalkylalkyl; Halogenalkyl; Halogenalkoxy; Hydroxyalkyl; Alkoxyalkyl; Acetyl; Alkylsulfonyl; Alkylsulfonylalkyl; Aminocarbonyloxyalkyl; Hydroxycarbonylalkyl; Hydroxyalkyloxycarbonylalkyl; Aryl; Aralkyl; Arylsulfonyl; Heteroaryl; Heteroarylalkyl; Heteroarylsulfonyl; Heterocyclyl; oder Heterocyclylalkyl ist.

4. Verwendung gemäß Anspruch 1, wobei die Verbindung die Formel (IV) hat:

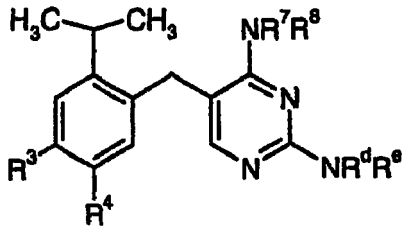


(IV)

wobei:

R^1 Alkyl; Alkenyl; Cycloalkyl; Cycloalkenyl; oder Halogen ist;
R^3 und R^4 jeweils unabhängig Alkyl; Alkenyl; Amino; Halogen; Amido; Halogenalkyl; Alkoxy; Hydroxy; Halogenalkoxy; Nitro; Hydroxyalkyl; Alkoxyalkyl; Hydroxyalkoxy; Alkinylalkoxy; Alkylsulfonyl; Arylsulfonyl; Cyano; Aryl; Heteroaryl; Heterocyclyl; Heterocyclylalkoxy; Aryloxy; Heteroaryloxy; Aralkyloxy; Heteroaralkyloxy; gegebenenfalls substituiertes Phenoxy; $-(CH_2)_m-(Z)_n-(CO)-R^f$ oder $-(CH_2)_m-(Z)_n-SO_2-(NR^g)_n-R^f$ sind, wobei m und n jeweils unabhängig 0 oder 1 sind, Z O oder NR^g ist, R^f Wasserstoff, Alkyl, Hydroxy, Alkoxy, Amino, Hydroxyalkyl oder Alkoxyalkyl ist, und jedes R^8 unabhängig Wasserstoff oder Alkyl ist;
einer der Reste R^7 und R^8 Wasserstoff ist, und der andere Wasserstoff; Alkyl; Cycloalkyl; Cycloalkylalkyl; Halogenalkyl; Halogenalkoxy; Hydroxyalkyl; Alkoxyalkyl; Acetyl; Alkylsulfonyl; Alkylsulfonylalkyl; Aminocarbonyloxyalkyl; Hydroxycarbonylalkyl; Hydroxyalkyloxycarbonylalkyl; Aryl; Aralkyl; Arylsulfonyl; Heteroaryl; Heteroarylalkyl; Heteroarylsulfonyl; Heterocyclyl; oder Heterocyclylalkyl ist; und
einer der Reste R^d und R^e Wasserstoff ist, und der andere Wasserstoff; Alkyl; Cycloalkyl; Cycloalkylalkyl; Halogenalkyl; Halogenalkoxy; Hydroxyalkyl; Alkoxyalkyl; Acetyl; Alkylsulfonyl; Alkylsulfonylalkyl; Aminocarbonyloxyalkyl; Hydroxycarbonylalkyl; Hydroxyalkyloxycarbonylalkyl; Aryl; Aralkyl; Arylsulfonyl; Heteroaryl; Heteroarylalkyl; Heteroarylsulfonyl; Heterocyclyl; oder Heterocyclylalkyl ist.

5. Verwendung gemäß Anspruch 1, wobei die Verbindung die Formel (V) hat:

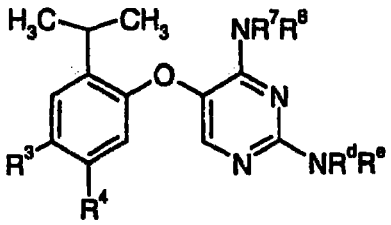


(V)

wobei:

R^3 und R^4 jeweils unabhängig Alkyl; Alkenyl; Amino; Halogen; Amido; Halogenalkyl; Alkoxy; Hydroxy; Halogenalkoxy; Nitro; Hydroxyalkyl; Alkoxyalkyl; Hydroxyalkoxy; Alkinylalkoxy; Alkylsulfonyl; Arylsulfonyl; Cyano; Aryl; Heteroaryl; Heterocyclyl; Heterocyclylalkoxy; Aryloxy; Heteroaryloxy; Aralkyloxy; Heteroaralkyloxy; gegebenenfalls substituiertes Phenoxy; $-(CH_2)_m-(Z)_n-(CO)-R^f$ oder $-(CH_2)_m-(Z)_n-SO_2-(NR^g)_n-R^f$ sind, wobei m und n jeweils unabhängig 0 oder 1 sind, Z O oder NR^g ist, R^f Wasserstoff, Alkyl, Hydroxy, Alkoxy, Amino, Hydroxyalkyl oder Alkoxyalkyl ist, und jedes R^g unabhängig Wasserstoff oder Alkyl ist;
einer der Reste R^7 und R^8 Wasserstoff ist, und der andere Wasserstoff; Alkyl; Cycloalkyl; Cycloalkylalkyl; Halogenalkyl; Halogenalkoxy; Hydroxyalkyl; Alkoxyalkyl; Acetyl; Alkylsulfonyl; Alkylsulfonylalkyl; Aminocarbonyloxyalkyl; Hydroxycarbonylalkyl; Hydroxyalkyloxycarbonylalkyl; Aryl; Aralkyl; Arylsulfonyl; Heteroaryl; Heteroarylalkyl; Heteroarylsulfonyl; Heterocyclyl; oder Heterocyclylalkyl ist; und
einer der Reste R^d und R^e Wasserstoff ist, und der andere Wasserstoff; Alkyl; Cycloalkyl; Cycloalkylalkyl; Halogenalkyl; Halogenalkoxy; Hydroxyalkyl; Alkoxyalkyl; Acetyl; Alkylsulfonyl; Alkylsulfonylalkyl; Aminocarbonyloxyalkyl; Hydroxycarbonylalkyl; Hydroxyalkyloxycarbonylalkyl; Aryl; Aralkyl; Arylsulfonyl; Heteroaryl; Heteroarylalkyl; Heteroarylsulfonyl; Heterocyclyl; oder Heterocyclylalkyl ist.

6. Verwendung gemäß Anspruch 1, wobei die Verbindung die Formel (VI) hat:



(VI)

wobei:

R^3 und R^4 jeweils unabhängig Alkyl; Alkenyl; Amino; Halogen; Amido; Halogenalkyl; Alkoxy; Hydroxy; Halogenalkoxy; Nitro; Hydroxyalkyl; Alkoxyalkyl; Hydroxyalkoxy; Alkinylalkoxy; Alkylsulfonyl; Arylsulfonyl; Cyano; Aryl; Heteroaryl; Heterocyclyl; Heterocyclylalkoxy; Aryloxy; Heteroaryloxy; Aralkyloxy; Heteroaralkyloxy; gegebenenfalls substituiertes Phenoxy; $-(CH_2)_m-(Z)_n-(CO)-R^f$ oder $-(CH_2)_m-(Z)_n-SO_2-(NR^g)_n-R^f$ sind, wobei m und n jeweils unabhängig 0 oder 1 sind, Z O oder NR^g ist, R^f Wasserstoff, Alkyl, Hydroxy, Alkoxy, Amino, Hydroxyalkyl oder Alkoxyalkyl ist, und jedes R^g unabhängig Wasserstoff oder Alkyl ist;
einer der Reste R^7 und R^8 Wasserstoff ist, und der andere Wasserstoff; Alkyl; Cycloalkyl; Cycloalkylalkyl; Halogenalkyl; Halogenalkoxy; Hydroxyalkyl; Alkoxyalkyl; Acetyl; Alkylsulfonyl; Alkylsulfonylalkyl; Aminocarbonyloxyalkyl; Hydroxycarbonylalkyl; Hydroxyalkyloxycarbonylalkyl; Aryl; Aralkyl; Arylsulfonyl; Heteroaryl; Heteroarylalkyl; Heteroarylsulfonyl; Heterocyclyl; oder Heterocyclylalkyl ist; und
einer der Reste R^d und R^e Wasserstoff ist, und der andere Wasserstoff; Alkyl; Cycloalkyl; Cycloalkylalkyl; Halogenalkyl; Halogenalkoxy; Hydroxyalkyl; Alkoxyalkyl; Acetyl; Alkylsulfonyl; Alkylsulfonylalkyl; Aminocarbonyloxyalkyl; Hydroxycarbonylalkyl; Hydroxyalkyloxycarbonylalkyl; Aryl; Aralkyl; Arylsulfonyl; Heteroaryl; Heteroarylalkyl; Heteroarylsulfonyl; Heterocyclyl; oder Heterocyclylalkyl ist.

7. Verwendung gemäß Anspruch 1, wobei die Verbindung der Formel I ausgewählt ist aus der Gruppe bestehend aus:

N^2-Isopropyl-5-(2-isopropyl-4,5-dimethoxybenzyl)-N^4-methylpyrimidin-2,4-diamin,
5-(2-Isopropyl-4,5-dimethoxyphenoxy)pyrimidin-2,4-diamin,
5-(2-Isopropyl-4,5-dimethoxybenzyl)-N^4-isoxazol-5-ylmethylpyrimidin-2,4-diamin,
N^2-Isopropyl-5-(2-isopropyl-4,5-dimethoxybenzyl)pyrimidin-2,4-diamin,
5-(2-Isopropyl-4,5-dimethoxybenzyl)-N^4-(2-methoxybenzyl)pyrimidin-2,4-diamin,
5-(2-Isopropyl-4,5-dimethoxybenzyl)-N^2-(2,2,2-trifluorethyl)pyrimidin-2,4-diamin,
3-[2-Amino-5-(2-isopropyl-4,5-dimethoxybenzyl)pyrimidin-4-ylamino]propan-1,2-diol,
N-[4-Amino-5-(2-isopropyl-4,5-dimethoxybenzyl)pyrimidin-2-yl]acetamid,
5-(2-Isopropyl-4,5-dimethoxybenzyl)-N^4-(4-methoxybenzyl)pyrimidin-2,4-diamin,
5-(2-Isopropyl-4,5-dimethoxybenzyl)-N^4-phenylpyrimidin-2,4-diamin,
5-(5-Chlor-2-isopropyl-4-methoxybenzyl)-N^2-phenethylpyrimidin-2,4-diamin,
5-(5-Chlor-2-isopropyl-4-methoxybenzyl)pyrimidin-2,4-diamin,
N^4-Isobutyl-N^2-isopropyl-5-(2-isopropyl-4,5-dimethoxybenzyl)pyrimidin-2,4-diamin,
5-(2-Isopropyl-4,5-dimethoxybenzyl)-N^2-phenylpyrimidin-2,4-diamin,
N^2,N^4-Diisopropyl-5-(2-isopropyl-4,5-dimethoxybenzyl)pyrimidin-2,4-diamin,
5-(5-Chlor-2-isopropyl-4-methoxybenzyl)-N^2-isopropylpyrimidin-2,4-diamin,
2-[2-Amino-5-(2-isopropyl-4,5-dimethoxybenzyl)pyrimidin-4-ylamino]ethanol,
5-(2-Isopropyl-4,5-dimethoxybenzyl)pyrimidin-2,4-diamin,
5-(2-Isopropyl-4,5-dimethoxybenzyl)-N^4-[2-(4-methoxyphenyl)ethyl]pyrimidin-2,4-diamin,
N^2-Benzyl-5-(2-isopropyl-4,5-dimethoxybenzyl)pyrimidin-2,4-diamin,
5-(2-Isopropyl-4,5-dimethoxybenzyl)-N^4-(4-methansulfonylcyclohexyl)pyrimidin-2,4-diamin,
N^2-Cyclopropyl-5-(2-isopropyl-4,5-dimethoxybenzyl)pyrimidin-2,4-diamin,
N^4-Isopropyl-5-(2-isopropyl-4,5-dimethoxybenzyl)pyrimidin-2,4-diamin,
N^2-Ethyl-5-(2-isopropyl-4,5-dimethoxybenzyl)pyrimidin-2,4-diamin,
5-(2-Isopropyl-4,5-dimethoxybenzyl)-N^4-[2-(3-methoxyphenyl)ethyl]pyrimidin-2,4-diamin,
2-[4-Amino-5-(2-isopropyl-4,5-dimethoxybenzyl)pyrimidin-2-ylamino]ethanol,
5-(2-sek-Butyl-4,5-dimethoxybenzyl)pyrimidin-2,4-diamin,
N^2-tert-Butyl-5-(2-isopropyl-4,5-dimethoxybenzyl)pyrimidin-2,4-diamin,
N^2-Isobutyl-5-(2-isopropyl-4,5-dimethoxybenzyl)pyrimidin-2,4-diamin,
5-(5-Chlor-2-isopropyl-4-methoxybenzyl)-N^2-cyclopropylpyrimidin-2,4-diamin,

5-(2-Isopropyl-4-methoxy-5-phenoxybenzyl)pyrimidin-2,4-diamin,
N^4-Isobutyl-5-(2-isopropyl-4,5-dimethoxybenzyl)pyrimidin-2,4-diamin,
N^4-Ethyl-5-(2-isopropyl-4,5-dimethoxybenzyl)pyrimidin-2,4-diamin,
N^4-Benzyl-5-(2-isopropyl-4,5-dimethoxybenzyl)pyrimidin-2,4-diamin,
5-(2-Isopropyl-4,5-dimethoxybenzyl)-N^4-(2,2,2-trifluorethyl)pyrimidin-2,4-diamin,
5-(2-Isopropyl-4,5-dimethoxybenzyl)-N^2-(4-methoxyphenyl)pyrimidin-2,4-diamin,
N^2-Isopropyl-5-(2-isopropyl-4,5-dimethoxybenzyl)-N^4-phenylpyrimidin- 2,4-diamin,
N^4-Ethyl-N^2-isopropyl-5-(2-isopropyl-4,5-dimethoxybenzyl)pyrimidin-2,4-diamin,
5-(2-Isopropyl-4,5-dimethoxybenzyl)-N^4-(1-methylpiperidin-4-yl)pyrimidin-2,4-diamin,
5-(2-Isopropyl-4,5-dimethoxybenzyl)-N^2-(2-methoxyphenyl)pyrimidin-2,4-diamin,
5-(4,5-Dichlor-2-isopropylbenzyl)pyrimidin-2,4-diamin,
5-(5-Chlor-2-isopropyl-4-methoxybenzyl)-N^2-ethylpyrimidin-2,4-diamin,
5-(2-Isopropyl-4-methoxy-5-methylbenzyl)pyrimidin-2,4-diamin,
5-(2-Isopropyl-4,5-dimethoxybenzyl)-N^2-pyrimidin-2-ylpyrimidin-2,4-diamin,
5-(2-Isopropyl-4,5-dimethoxybenzyl)-N^2-(2-methoxyethyl)pyrimidin-2,4-diamin,
N^4-Benzyl-N^2-isopropyl-5-(2-isopropyl-4,5-dimethoxybenzyl)pyrimidin-2,4-diamin,
1-(4-{2-[4-Amino-5-(2-isopropyl-4,5-dimethoxybenzyl)pyrimidin-2-ylamino]-propyl}piperazin-1-yl)ethanon,
5-(2-Isopropyl-4,5-dimethoxybenzyl)-N^4-(tetrahydropyran-4-yl)pyrimidin-2,4-diamin,
N^4-Cyclopropyl-5-(2-isopropyl-4,5-dimethoxybenzyl)pyrimidin-2,4-diamin,
5-(5-Ethoxy-2-isopropyl-4-methoxybenzyl)pyrimidin-2,4-diamin,
N^2-(2,4-Dimethoxyphenyl)-5-(2-isopropyl-4,5-dimethoxybenzyl)pyrimidin-2,4-diamin,
N^2-Cyclobutyl-5-(2-isopropyl-4,5-dimethoxybenzyl)pyrimidin-2,4-diamin,
N^2-(2-Chlorphenyl)-5-(2-isopropyl-4,5-dimethoxybenzyl)pyrimidin-2,4-diamin,
5-(4-Chlor-2-isopropyl-5-methoxybenzyl)pyrimidin-2,4-diamin,
5-(5-Brom-2-isopropyl-4-methoxyphenoxy)pyrimidin-2,4-diamin,
5-(5-Chlor-2-isopropyl-4-methoxybenzyl)-N^2-(3-methoxyphenyl)pyrimidin-2,4-diamin,
5-(5-Chlor-2-isopropyl-4-methoxyphenoxy)pyrimidin-2,4-diamin,
5-(2-Isopropyl-4,5-dimethoxybenzyl)-N^2,N^4-diphenylpyrimidin-2,4-diamin,
5-(5-Chlor-2-isopropyl-4-methoxybenzyl)-N^2-isobutylpyrimidin-2,4-diamin,
5-(5-Chlor-2-isopropyl-4-methoxybenzyl)-N^2-phenylpyrimidin-2,4-diamin,
5-(2-Isopropyl-4-methoxy-5-methylphenoxy)pyrimidin-2,4-diamin,
5-(2-Isopropyl-4,5-dimethoxybenzyl)-N^2-methylpyrimidin-2,4-diamin,
5-(2-Isopropyl-5-methylphenoxy)pyrimidin-2,4-diamin,
5-(5-Chlor-2-isopropyl-4-methoxybenzyl)-N^2-methylpyrimidin-2,4-diamin,
N^2-Benzyl-5-(5-chlor-2-isopropyl-4-methoxyphenoxy)pyrimidin-2,4-diamin,
2-[2-Isopropylamino-5-(2-isopropyl-4,5-dimethoxybenzyl)pyrimidin-4-ylamino]ethanol,
5-(5-Chlor-2-isopropyl-4-methoxyphenoxy)-N^2-(tetrahydropyran-4-yl)pyrimidin-2,4-diamin,
N^2-(4-Chlorphenyl)-5-(2-isopropyl-4,5-dimethoxybenzyl)pyrimidin-2,4-diamin,
5-(2-Isopropylphenoxy)pyrimidin-2,4-diamin,
5-(2-Isopropyl-4,5-dimethoxybenzyl)-N^4-methylpyrimidin-2,4-diamin,
5-(5-Chlor-2-isopropyl-4-methoxyphenoxy)-N^2-isopropylpyrimidin-2,4-diamin,
5-(2-Isopropyl-4,5-dimethoxybenzyl)-N^4-(2-methoxyethyl)pyrimidin-2,4-diamin,
N^2-Isopropyl-5-(2-isopropyl-4,5-dimethoxyphenoxy)pyrimidin-2,4-diamin,
5-(2-Ethyl-4,5-dimethoxybenzyl)pyrimidin-2,4-diamin,
5-(2-Isopropyl-4, 5-dimethoxyphenoxy)-N^2-phenylpyrimidin-2,4-diamin,
N^2-tert-Butyl-5-(5-chlor-2-isopropyl-4-methoxybenzyl)pyrimidin-2,4-diamin,
N^2-Benzyl-5-(2-isopropyl-4,5-dimethoxyphenoxy)pyrimidin-2,4-diamin,
5-(2-Cyclopropyl-4,5-dimethoxybenzyl)pyrimidin-2,4-diamin,
N-[4-Amino-5-(2-isopropyl-4,5-dimethoxyphenoxy)pyrimidin-2-yl]acetamid,
N^2-Benzyl-5-(5-chlor-2-isopropyl-4-methoxybenzyl)pyrimidin-2,4-diamin,
5-(2-Isopropyl-4,5-dimethoxyphenoxy)-N^2-(2,2,2-trifluorethyl)pyrimidin-2,4-diamin,
5-(2-Isopropyl-4,5-dimethoxyphenoxy)-N^2-(2-methoxyethyl)pyrimidin-2,4-diamin,
5-(2-Isopropyl-4,5-dimethoxybenzyl)pyrimidin-4-ylamin,
3-[4-Amino-5-(5-chlor-2-isopropyl-4-methoxyphenoxy)pyrimidin-2-ylamino]pentan-1,5-diol,
5-(5-Chlor-2-isopropyl-4-methoxybenzyl)-N^2-cyclohexylpyrimidin-2,4-diamin,
2-[4-Amino-5-(5-chlor-2-isopropyl-4-methoxyphenoxy)pyrimidin-2-ylamino]butan-1-ol,
1-[5-(2,4-Diaminopyrimidin-5-yloxy)-4-isopropyl-2-methoxyphenyl]ethanon,
5-[5-(1H-Imidazal-2-yl)-2-isopropyl-4-methoxyphenoxy]pyrimidin-2,4-diamin,

(2,4-Diaminopyrimidin-5-yl)-(2-isopropyl-4,5-dimethoxyphenyl)methanol,
5-[5-Chlor-2-(2-fluor-1-methylethyl)-4-methoxyphenoxy]pyrimidin-2,4-diamin,
(5-Chlor-2-isopropyl-4-methoxyphenyl)-(2,4-diaminopyrimidin-5-yl)-methanol,
2-[4-Amino-5-(5-chlor-2-ethyl-4-methoxyphenoxy)pyrimidin-2-ylamino]butan-1-ol,
5-(5-Chlor-2-isopropyl-4-methoxyphenoxy)-N^2-(3-ethansulfonyl-1-methylpropyl)pyrimidin-2,4-diamin,
5-(5-Brom-2-ethyl-4-methoxyphenoxy)pyrimidin-2,4-diamin,
5-(5-Chlor-2-ethyl-4-methoxyphenoxy)pyrimidin-2,4-diamin,
5-(5-Chlor-2-cyclopropyl-4-methoxyphenoxy)pyrimidin-2,4-diamin,
5-(2-Ethyl-5-methansulfonyl-4-methoxyphenoxy)pyrimidin-2,4-diamin,
5-(2,4-Diaminopyrimidin-5-yloxy)-4-isopropyl-2-methoxybenzamid,
5-(4,5-Dimethoxy-2-vinylphenoxy)pyrimidin-2,4-diamin,
5-(2,4-Diaminopyrimidin-5-yloxy)-4-isopropyl-2-methoxybenzoesäure,
5-(2-Cyclopropyl-4,5-dimethoxyphenoxy)pyrimidin-2,4-diamin,
5-[2-Isopropyl-4-methoxy-5-(1H-tetrazol-5-yl)phenoxy]pyrimidin-2,4-diamin,
5-(2,4-Diaminopyrimidin-5-yloxy)-4-isopropyl-2-methoxybenzonitril,
4-[4-Amino-5-(5-chlor-2-isopropyl-4-methoxyphenoxy)pyrimidin-2-ylamino]piperidin-1-carbonsäureethylester,
[5-(2,4-Diaminopyrimidin-5-yloxy)-4-isopropyl-2-methoxyphenyl]harnstoff,
5-(5-Chlor-2-isopropyl-4-methoxyphenoxy)-N^2-(1-cyclopropylethyl)pyrimidin-2,4-diamin,
5-(5-Chlor-4-difluormethoxy-2-isopropylphenoxy)pyrimidin-2,4-diamin,
5-(5-Amino-2-isopropyl-4-methoxyphenoxy)pyrimidin-2,4-diamin,
N^4-Isopropyl-5-(2-isopropyl-4,5-dimethoxybenzyl)-N^2-methylpyrimidin-2,4-diamin,
N-[5-(2,4-Diaminopyrimidin-5-yloxy)-4-isopropyl-2-methoxyphenyl]acetamid,
5-(2-Isopropyl-4-methoxy-5-tetrazol-1-ylphenoxy)pyrimidin-2,4-diamin,
5-(2-Isopropyl-4-methoxyphenoxy)pyrimidin-2,4-diamin,
5-(2-Isopropyl-5-methansulfonyl-4-methoxyphenoxy)pyrimidin-2,4-diamin,
5-(2-Isopropyl-4-methoxy-5-methylphenoxy)-N^4-phenylpyrimidin-2,4-diamin,
5-(5-Chlor-2-isopropyl-4-methoxyphenoxy)-N^2-(1,1-dioxohexahydro-1λ^6-thiopyran-4-yl)pyrimidin-2,4-diamin,
Methylcarbaminsäure-2-[4-amino-5-(5-chlor-2-isopropyl-4-methoxyphenoxy)pyrimidin-2-ylamino]propylester,
5-(4-Chlor-2-isopropyl-5-methylphenoxy)pyrimidin-2,4-diamin,
5-(2-Isopropyl-4,5-dimethoxyphenoxy)-6-methylpyrimidin-2,4-diamin,
1-(4-{2-[4-Amino-5-(5-chlor-2-isopropyl-4-methoxyphenoxy)pyrimidin-2-ylamino]propyl}piperazin-1-yl)ethanon,
5-(5-Chlor-2-isopropyl-4-methoxyphenoxy)-N^2-(1-methansulfonylpiperidin-4-yl)pyrimidin-2,4-diamin,
2-[4-Amino-5-(5-chlor-2-isopropyl-4-methoxyphenoxy)pyrimidin-2-ylamino]-(R)-propan-1-ol,
5-(2-Ethyl-4,5-dimethoxyphenoxy)pyrimidin-2,4-diamin,
5-(2-Isopropyl-5-methansulfonyl-4-methoxyphenoxy)-*N*^{2}-(tetrahydrothiopyran-4-yl)pyrimidin-2,4-diamin,
5-(5-Chlor-2-isopropyl-4-methoxyphenoxy)-*N*^{2}-(1,1-dioxohexahydro-1λ^6-thiopyran-4-yl)pyrimidin-2,4-diamin,
1-[5-(2,4-Diaminopyrimidin-5-yloxy)-2-hydroxy-4-isopropylphenyl]ethanon,
5-(5-Iod-2-isopropyl-4-methoxyphenoxy)pyrimidin-2,4-diamin,
5-(2-Iod-4,5-dimethoxyphenoxy)pyrimidin-2,4-diamin,
5-(2,4-Diaminopyrimidin-5-yloxy)-4-isopropyl-2-methoxybenzolsulfonamid,
4-(2,4-Diaminopyrimidin-5-yloxy)-2-iod-5-isopropylphenol,
5-(2,5-Diiod-4-methoxyphenoxy)pyrimidin-2,4-diamin,
3-[4-Amino-5-(5-brom-2-isopropyl-4-methoxyphenoxy)pyrimidin-2-ylamino]pentan-1,5-diol,
5-(2-Ethyl-5-iod-4-methoxyphenoxy)pyrimidin-2,4-diamin,
5-(5-Iod-2-isopropyl-4-methoxyphenoxy)-1-oxypyrimidin-2,4-diamin,
5-(2-Isopropyl-4-methoxy-5-vinylphenoxy)pyrimidin-2,4-diamin,
5-(5-Iod-2-isopropenyl-4-methoxyphenoxy)pyrimidin-2,4-diamin,
5-(2-Isopropyl-4-methoxy-5-pyrazol-1-ylphenoxy)pyrimidin-2,4-diamin,
5-(5-Iod-2-isopropylphenoxy)pyrimidin-2,4-diamin,
5-[2-Isopropyl-4-methoxy-5-(3-methylpyrazol-1-yl)phenoxy]pyrimidin-2,4-diamin,
4-(2,4-Diaminopyrimidin-5-ylmethyl)-2-iod-5-isopropylphenol,
5-(2-Isopropyl-4-methoxy-5-oxazol-2-ylphenoxy)pyrimidin-2,4-diamin,
(S)-2-[4-Amino-5-(5-brom-2-isopropyl-4-methoxyphenoxy)pyrimidin-2-ylamino]butan-1-ol,
5-(4-Iod-2-isopropyl-5-methoxyphenoxy)pyrimidin-2,4-diamin,
5-(4-Brom-2-isopropyl-5-methoxyphenoxy)pyrimidin-2,4-diamin,
5-(2-Ethyl-5-iodphenoxy)pyrimidin-2,4-diamin,
5-(2-Isopropyl-4-methoxy-5-trifluormethylphenoxy)pyrimidin-2,4-diamin,

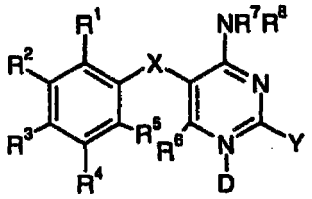
5-(2-Isopropyl-4-methoxy-5-thiazol-4-ylphenoxy)pyrimidin-2,4-diamin,
[4-(2,4-Diaminopyrimidin-5-yloxy)-2-iod-5-isopropylphenoxy]acetonitril,
5-(2-Isopropyl-4-methoxy-5-thiophen-3-ylphenoxy)pyrimidin-2,4-diamin,
(R)-2-[4-Amino-5-(2-isopropyl-5-methansulfonyl-4-methoxyphenoxy)pyrimidin-2-ylamino]-butan-1-ol,
(S)-2-[4-Amino-5-(5-chlor-2-isopropyl-4-methoxyphenoxy)pyrimidin-2-ylamino]propionsäure,
5-[5-(4,5-Dihydrooxazo 1-2-yl)-2-isopropyl-4-methoxyphenoxy]pyrimidin-2,4-diamin,
5-(2-Isopropyl-5-methansulfonyl-4-methoxyphenoxy)-N^2-(2,2,2-trifluorethyl)pyrimidin-2,4-diamin,
5-(5-Iod-2-isopropyl-4-methoxybenzyl)pyrimidin-2,4-diamin,
5-(5-Brom-2-cyclopropyl-4-methoxyphenoxy)pyrimidin-2,4-diamin,
(S)-2-[4-Amino-5-(5-chlor-2-isopropyl-4-methoxyphenoxy)pyrimidin-2-ylamino]propionsäure-3-hydroxy-2-hydroxymethyl-2-methylpropylester,
5-[5-(5-Chlorthiophen-2-yl)-2-isopropyl-4-methoxyphenoxy]pyrimidin-2,4-diamin,
5-(2-Ethyl-4-methoxy-5-trifluormethylphenoxy)pyrimidin-2,4-diamin,
5-[2-Isopropyl-4-methoxy-5-(1-methyl-1H-imidazol-2-yl)phenoxy]pyrimidin-2,4-diamin,
5-[2-Isopropyl-4-methoxy-5-(2H-pyrazol-3-yl)phenoxy]pyrimidin-2,4-diamin,
5-(5-Imidazol-1-yl-2-isopropyl-4-methoxyphenoxy)pyrimidin-2,4-diamin,
N^2-Isopropyl-5-(2-isopropyl-5-methansulfonyl-4-methoxyphenoxy)pyrimidin-2,4-diamin,
2-[4-(2,4-Diaminopyrimidin-5-yloxy)-2-iod-5-isopropylphenoxy]ethanol,
5-(2-Isopropyl-5-methansulfonyl-4-methoxyphenoxy)-N^2-phenylpyrimidin-2,4-diamin,
5-(4-Amino-2-ethylaminopyrimidin-5-yloxy)-4-isopropyl-2-methoxybenzamid,
2-[4-Amino-5-(2-isopropyl-5-methansulfonyl-4-methoxyphenoxy)pyrimidin-2-ylamino]ethanol,
5-[2-Isopropyl-4-methoxy-5-(2-methylthiazol-4-yl)phenoxy]pyrimidin-2,4-diamin,
5-[5-Iod-2-isopropyl-4-(pyrazin-2-ylmethoxy)phenoxy]pyrimidin-2,4-diamin,
5-(2-Isopropyl-5-methansulfonyl-4-methoxyphenoxy)-N^2-(2-methoxyethyl)pyrimidin-2,4-diamin,
5-(2-Isopropyl-4-methoxy-5-[1,2,3]-triazol-1-ylphenoxy)pyrimidin-2,4-diamin,
5-(5-Furan-2-yl-2-isopropyl-4-methoxyphenoxy)pyrimidin-2,4-diamin,
1-[5-(2,4-Diaminopyrimidin-5-yloxy)-4-isopropyl-2-methoxyphenyl]-3-ethylharnstoff,
N^2-Cyclopropyl-5-(2-isopropyl-5-methansulfonyl-4-methoxyphenoxy)pyrimidin-2,4-diamin,
2-[4-(2,4-Diaminopyrimidin-5-yloxy)-2-iod-5-isopropylphenoxy]acetamid,
5-[5-(3,5-Dimethylpyrazol-1-yl)-2-isopropyl-4-methoxyphenoxy] pyrimidin-2,4-diamin,
N^2-Benzyl-5-(2-isopropyl-5-methansulfonyl-4-methoxyphenoxy)pyrimidin-2,4-diamin,
N^2-Ethyl-5-(2-isopropyl-5-methansulfonyl-4-methoxyphenoxy)pyrimidin-2,4-diamin,
5-(2-Isopropyl-5-methansulfonyl-4-methoxyphenoxy)-N^2-(1-methansulfonylpiperidin-4-yl)pyrimidin-2,4-diamin,
1-[4-Amino-5-(2-isopropyl-4,5-dimethoxybenzyl)pyrimidin-2-ylamino]-2-methylpropan-2-ol,
N^2-Isobutyl-5-(2-isopropyl-5-methansulfonyl-4-methoxyphenoxy)pyrimidin-2,4-diamin,
5-(2,4-Diaminopyrimidin-5-yloxy)-4-isopropyl-2-methoxy-N-methylbenzamid,
5-(2-Isopropyl-5-isoxazol-5-yl-4-methoxyphenoxy)pyrimidin-2,4-diamin,
N^2-(4-Fluorphenyl)-5-(2-isopropyl-5-methansulfonyl-4-methoxyphenoxy)pyrimidin-2,4-diamin,
5-(5-Chlor-2-isopropyl-4-methoxybenzyl)-N^2-(2,2,2-trifluorethyl)pyrimidin-2,4-diamin,
5-(2-Isopropyl-4-methoxy-5-[1,2,4]oxadiazol-3-ylphenoxy)pyrimidin-2,4-diamin,
5-(2-Isopropyl-5-methansulfonyl-4-methoxyphenoxy)-N^2-(tetrahydropyran-4-yl)pyrimidin-2,4-diamin,
1-[5-(2,4-Diaminopyrimidin-5-yloxy)-4-isopropyl-2-methoxyphenyl]ethanol,
5-(2,5-Diisopropyl-4-methoxyphenoxy)pyrimidin-2,4-diamin,
5-(5-Benzo[b]thiophen-3-yl-2-isopropyl-4-methoxyphenoxy)pyrimidin-2,4-diamin,
5-[2-Isopropyl-4-methoxy-5-(1-methoxyethyl)phenoxy]pyrimidin-2,4-diamin,
5-(2-Isopropyl-4-methoxy-5-oxazol-4-ylphenoxy)pyrimidin-2,4-diamin,
5-[5-(5-Chlorthiophen-2-yl)-2-isopropyl-4-methoxybenzyl]pyrimidin-2,4-diamin,
5-(2-Isopropyl-4-methoxy-5-thiazol-2-ylphenoxy)pyrimidin-2,4-diamin,
5-(2-Isopropyl-4-methoxy-5-thiophen-3-yl-benzyl)pyrimidin-2,4-diamin,
5-(5-Furan-3-yl-2-isopropyl-4-methoxyphenoxy)pyrimidin-2,4-diamin,
5-(2-Isopropyl-5-methoxyphenoxy)pyrimidin-2,4-diamin,
5-[5-Iod-2-isopropyl-4-(pyrimidin-2-ylmethoxy)phenoxy]pyrimidin-2,4-diamin,
5-(2-Isopropyl-4,5-dimethoxybenzyl)-N^2-pyridin-2-ylpyrimidin-2,4-diamin,
5-(2-Isopropyl-4-methoxy-5-thiophen-2-ylphenoxy)pyrimidin-2,4-diamin,
1-[5-(2,4-Diaminopyrimidin-5-yloxy)-4-isopropyl-2-methoxyphenyl]-3-phenylharnstoff,
5-(5-Chlor-2-isopropyl-4-methoxybenzyl)-*N*^{2}-(2-methoxyethyl)pyrimidin-2,4-diamin,
5-(2,4-Diaminopyrimidin-5-yloxy)-4-isopropyl-2-methoxy-N-methylbenzolsulfonamid,

5-(2-Isopropyl-5-methansulfonyl-4-methoxyphenoxy)-N^2-methylpyrimidin-2,4-diamin,
5-[5-Iod-2-isopropyl-4-(pyridin-2-ylmethoxy)phenoxy]pyrimidin-2,4-diamin,
N-[2-Acetylamino-5-(2-isopropyl-4-methoxy-5-methylbenzyl)pyrimidin-4-yl]acetamid,
5-[4-(2-Fluorbenzyloxy)-5-iod-2-isopropylphenoxy]pyrimidin-2,4-diamin,
5-(2-Isopropyl-4-methoxy-5-pyrrol-1-ylphenoxy)pyrimidin-2,4-diamin,
5-(2-Isopropyl-4-methoxy-5-trifluormethoxyphenoxy)pyrimidin-2,4-diamin,
2-[4-(2,4-Diaminopyrimidin-5-ylmethyl)-2-iod-5-isopropylphenoxy]ethanol,
5-[5-(4,5-Dihydrooxazol-2-yl)-2-isopropyl-4-methoxybenzyl]pyrimidin-2,4-diamin,
5'-(2,4-Diaminopyrimidin-5-yloxy)-4'-isopropyl-2'-methoxybiphenyl-3-carbonitril,
5-[2-Isopropyl-4-methoxy-5-(4-methylthiophen-2-yl)phenoxy]pyrimidin-2,4-diamin,
5-(5-Chlor-2-isopropyl-4-methoxyphenoxy)-N^2-[(S)-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]oct-1-yl)ethyl]pyrimidin-2,4-diamin,
5-(5-Iod-2-isopropyl-4-prop-2-ynyloxyphenoxy)pyrimidin-2,4-diamin,
5-(2-Isopropyl-4-methoxy-5-nitrophenoxy)pyrimidin-2,4-diamin,
5-(4-Ethoxy-5-iod-2-isopropylphenoxy)pyrimidin-2,4-diamin,
5-[5-Iod-2-isopropyl-4-(pyridin-3- ylmethoxy)phenoxy]pyrimidin-2,4-diamin,
5-(4-Benzyloxy-5-iod-2-isopropylphenoxy)pyrimidin-2,4-diamin,
5-(4-Isopropyl-6-methoxybiphenyl-3-yloxy)pyrimidin-2,4-diamin,
5-(5-Furan-2-yl-2-isopropyl-4-methoxybenzyl)pyrimidin-2,4-diamin,
5-(2-Isopropyl-4-methoxy-5-thiazol-5-ylphenoxy)pyrimidin-2,4-diamin,
1-[5-(2,4-Diaminopyrimidin-5-yloxy)-4-isopropyl-2-methoxyphenyl]pyrrolidin-2-on,
5-(2-Isopropyl-5-methansulfonyl-4-methoxybenzyl)pyrimidin-2,4-diamin,
5-[5-Chlor-2-(1-Fluor-1-methylethyl)-4-methoxyphenoxy]pyrimidin-2,4-diamin,
5-[5-Iod-2-isopropyl-4-(2-methoxyethoxy)phenoxy]pyrimidin-2,4-diamin,
5-(2-Isopropyl-4-methoxy-5-oxazol-5-ylphenoxy)pyrimidin-2,4-diamin,
1-[4-Chlor-2-(2,4-diaminopyrimidin-5-yloxy)-5-methoxyphenyl]ethanol,
1-[4-Chlor-2-(2,4-diaminopyrimidin-5-yloxy)-5-methoxyphenyl]ethanol,
2-[2-(2,4-Diaminopyrimidin-5-yloxy)-4-iod-5-methoxyphenyl]propan-1-ol,
5-[5-Iod-2-isopropyl-4-(2-methoxybenzyloxy)phenoxy]pyrimidin-2,4-diamin,
5-[5-Iod-2-isopropyl-4-(2,2,2-trifluorethoxy)phenoxy]pyrimidin-2,4-diamin,
5-[5-Iod-2-isopropyl-4-(3,4,5-trimethoxybenzyloxy)phenoxy]pyrimidin-2,4-diamin,
2-[2-(2,4-Diaminopyrimidin-5-yloxy)-4-iod-5-methoxyphenyl]propan-2-ol,
5-[2-Isopropyl-4-methoxy-5-(4-methylthiophen-3-yl)phenoxy]pyrimidin-2,4-diamin,
5-(2-Isopropyl-4-methoxy-5-nitrophenoxy)pyrimidin-2,4-diamin,
5-[5-Iod-2-isopropyl-4-(1-methylpiperidin-2-ylmethoxy)phenoxy]pyrimidin-2,4-diamin,
5-[5-Iod-2-isopropyl-4-(tetrahydropyran-2-ylmethoxy)phenoxy]pyrimidin-2,4-diamin,
5-(2-Isopropyl-4-methoxy-5-[1,2,4]triazol-1-ylphenoxy)pyrimidin-2,4-diamin,
5-(2-Isopropyl-4,5-dimethoxyphenoxy)-N^2-(2-methoxyethyl)pyrimidin-2,4-diamin,
5-(4'-Fluor-4-isopropyl-6-methoxybiphenyl-3-yloxy)pyrimidin-2,4-diamin,
5-(5-Chlor-2-isopropyl-4-methoxyphenoxy)-N^2-(2,2,2-trifluorethyl)pyrimidin-2,4-diamin,
5-(2,4-Diaminopyrimidin-5-ylmethyl)-4-isopropyl-2-methoxybenzonitril,
5-[2-Isopropyl-4-methoxy-5-(2-methylthiazol-5-yl)phenoxy]pyrimidin-2,4-diamin,
5-(2-Isopropyl-4-methoxy-6-methylphenoxy)pyrimidin-2,4-diamin,
5-(5-Ethansulfonyl-2-isopropyl-4-methoxyphenoxy)pyrimidin-2,4-diamin,
5-(2-Isopropyl-4-methoxy-5-thiazol-5-ylbenzyl)pyrimidin-2,4-diamin,
1-[5-(2,4-Diaminopyrimidin-5-yloxy)-4-isopropyl-2-methoxyphenyl]-1*H*-imidazol-2-thiol,
5-[2-Isopropyl-4-methoxy-5-(1-methyl-1*H*-pyrazol-4-yl)phenoxy]pyrimidin-2,4-diamin,
5-[5-Iod-2-isopropyl-4-(pyridin-4-ylmethoxy)phenoxy]pyrimidin-2,4-diamin,
5-(4-Iod-2-isopropylphenoxy)pyrimidin-2,4-diamin,
5-(5-Iod-4-isopropyl-2-methoxybenzyl)pyrimidin-2,4-diamin,
5-(5-Fluor-2-isopropyl-4-methoxyphenoxy)pyrimidin-2,4-diamin,
5-(4'-Fluor-5-isopropyl-2-methoxybiphenyl-4-yloxy)pyrimidin-2,4-diamin,
5-[4-(3-Fluorbenzyloxy)-5-iod-2-isopropylphenoxy]pyrimidin-2,4-diamin,
5-(4-Brom-2-isopropylphenoxy)pyrimidin-2,4-diamin,
5-(4-Furan-2-yl-2-isopropyl-5-methoxyphenoxy)pyrimidin-2,4-diamin,
2-[5-(2,4-Diaminopyrimidin-5-yloxy)-4-isopropyl-2-methoxyphenyl]propan-2-ol,
5-[4-(2,6-Difluorbenzyloxy)-5-iod-2-isopropylphenoxy]pyrimidin-2,4-diamin,
5-(5-Iod-2-isopropyl-4-phenethyloxyphenoxy)pyrimidin-2,4-diamin,

5-(2-Isopropyl-4-methoxy-5-pyridin-4-ylphenoxy)pyrimidin-2,4-diamin,
5-(2-Isopropyl-4,5-dimethoxybenzyl)-N^2-(1-methylpiperidin-4-yl)pyrimidin-2,4-diamin,
5-(2,4-Diaminopyrimidin-5-yloxy)-N-ethyl-4-isopropyl-2-methoxybenzolsulfonamid,
5-[2-Isopropyl-5-(4-methansulfonylpiperazin-1-yl)-4-methoxyphenoxy]pyrimidin-2,4-diamin,
5-(2-Isopropyl-4-methoxy-5-pyridin-3-ylphenoxy)pyrimidin-2,4-diamin,
5-(2,4-Diaminopyrimidin-5-yloxy)-4-isopropyl-2-methoxy-N,N-dimethylbenzamid,
5-[5-(2,5-Dimethylpyrrol-1-yl)-2-isopropyl-4-methoxyphenoxy]pyrimidin-2,4-diamin,
5-(2-Ethyl-3-methoxybenzyl)pyrimidin-2,4-diamin,
5-(2-Brom-4,5-dimethoxyphenoxy)pyrimidin-2,4-diamin,
5-(2-Isopropyl-5-methansulfonyl-4-methoxyphenoxy)-N^2-(2,2,2-trifluorethyl)pyrimidin-2,4-diamin; und
5'-(2,4-Diaminopyrimidin-5-yloxy)-4'-isopropyl-2'-methoxybiphenyl-3-carbonitril.

Revendications

1. Utilisation d'un composé de formule I



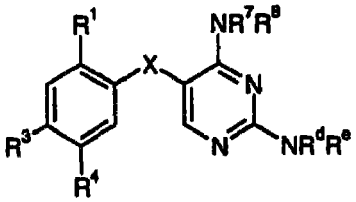
(I)

ou d'un de ses sels pharmaceutiquement acceptables,
formule dans laquelle :

X représente un groupe $-CH_2-$; -O- : ou -CHOH- ;
Y représente un atome d'hydrogène ; ou un groupe $-NR^dR^e$, dans lequel un de R^d et R^e représente un atome d'hydrogène, et l'autre représente un atome d'hydrogène ; un groupe alkyle ; cycloalkyle ; cycloalkylalkyle ; halogénoalkyle ; halogénoalkoxy ; hydroxyalkyle ; alkoxyalkyle ; acétyle ; alkyl-sulfonyle ; alkylsulfonylalkyle ; aminocarbonyloxy-alkyle ; hydroxycarbonylalkyle ; hydroxyalkyloxy-carbonylalkyle ; aryle ; aralkyle ; arylsulfonyle ; hétéroaryle ; hétéroarylalkyle ; hétéroarylsulfonyle ; hétérocyclyle ; ou hétérocyclylalkyle ;
D représente un atome d'oxygène facultatif ;
R^1 représente un groupe alkyle ; alcényle ; cycloalkyle ; cycloalcényle ; halogéno ; halogénoalkyle ; hydroxyalkyle ; ou alkoxy ;
R^2, R^3, R^4 et R^5 représentent chacun indépendamment un atome d'hydrogène ; un groupe alkyle ; alcényle ; amino ; halogéno ; amido ; halogénoalkyle ; alkoxy ; hydroxy ; halogénoalkoxy ; nitro ; hydroxyalkyle ; alkoxyalkyle ; hydroxyalkoxy ; alcynylalkoxy ; alkylsulfonyle ; arylsulfonyle ; cyano ; aryle ; hétéroaryle ; hétérocyclyle ; hétérocyclylalkoxy ; aryloxy ; hétéroaryloxy ; aralkyloxy ; hétéroaralkyloxy ; phénoxy facultativement substitué; $-(CH_2)_m-(Z)_n-(CO)-R^f$ ou $-(CH_2)_m-(Z)_n-SO_2-(NR^g)_n-R^f$, dans lequel m et n sont chacun égaux indépendamment à 0 ou 1, Z représente O ou un groupe NR^g, R^f représente un atome d'hydrogène, un groupe alkyle, hydroxy, alkoxy, amino, hydroxyalkyle ou alkoxyalkyle, et chaque groupe R^g représente indépendamment un atome d'hydrogène ou un groupe alkyle ;
R^6 représente un atome d'hydrogène ; un groupe alkyle ; halogéno ; halogénoalkyle ; amino ; ou alkoxy ; et
un de R^7 et R^8 représente un atome d'hydrogène, et l'autre représente un atome d'hydrogène ; un groupe alkyle ; cycloalkyle ; cycloalkylalkyle ; halogénoalkyle ; halogénoalkoxy ; hydroxyalkyle ; alkoxyalkyle ; acétyle ; alkylsulfonyle ; alkylsulfonylalkyle ; amino-carbonyloxyalkyle ; hydroxycarbonylalkyle ; hydroxy-alkyloxycarbonylalkyle ; aryle ; aralkyle ; aryl-sulfonyle ; hétéroaryle ; hétéroarylalkyle ; hétéroaryl-sulfonyle ; hétérocyclyle ; ou hétérocyclylalkyle ;

pour la préparation d'un médicament pour le traitement d'une maladie respiratoire à médiation par un antagoniste du récepteur $P2X_3$ ou $P2X_{2/3}$, ladite maladie étant une maladie respiratoire choisie entre la maladie pulmonaire obstructive chronique (COPD), l'asthme et le bronchospasme.

2. Utilisation suivant la revendication 1, dans laquelle ledit composé répond à la formule (II) :

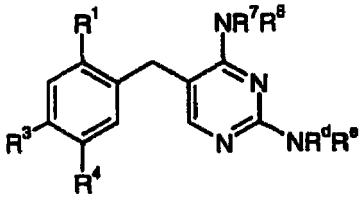


(II)

dans laquelle :

X représente un groupe $-CH_2-$ ou -O- ;
R^1 représente un groupe alkyle ; alcényle ; cycloalkyle ; cycloalcényle ; ou halogéno ;
R^3 et R^4 représentent chacun indépendamment un groupe alkyle ; alcényle ; amino ; halogéno ; amido ; halogénoalkyle ; alkoxy ; hydroxy ; halogénoalkoxy ; nitro ; hydroxyalkyle ; alkoxyalkyle ; hydroxyalkoxy ; alcynylalkoxy ; alkylsulfonyle ; arylsulfonyle ; cyano ; aryle ; hétéroaryle ; hétérocyclyle ; hétérocyclyl-alkoxy ; aryloxy ; hétéroaryloxy ; aralkyloxy ; hétéroaralkyloxy ; phénoxy facultativement substitué ; $-(CH_2)_m-(Z)_n-(CO)-R^f$ ou $-(CH_2)_m(Z)_n-SO_2-(NR^g)_n-R^f$, dans lequel m et n sont chacun égaux indépendamment à 0 ou 1, Z représente O ou un groupe NR^g, R^f représente un atome d'hydrogène, un groupe alkyle, hydroxy, alkoxy, amino, hydroxyalkyle ou alkoxyalkyle, et chaque groupe R^g représente indépendamment un atome d'hydrogène ou un groupe alkyle ;
un de R^7 et R^8 représente un atome d'hydrogène, et l'autre représente un atome d'hydrogène ; un groupe alkyle ; cycloalkyle ; cycloalkylalkyle ; halogénoalkyle ; halogénoalkoxy ; hydroxyalkyle ; alkoxyalkyle ; acétyle ; alkylsulfonyle ; alkylsulfonylalkyle ; amino-carbonyloxyalkyle ; hydroxycarbonylalkyle ; hydroxy-alkyloxycarbonylalkyle ; aryle ; aralkyle ; aryl-sulfonyle ; hétéroaryle ; hétéroarylalkyle ; hétéroaryl-sulfonyle ; hétérocyclyle ; ou hétérocyclylalkyle ; et un
de R^d et R^e représente un atome d'hydrogène, et l'autre représente un atome d'hydrogène ; un groupe alkyle ; cycloalkyle ; cycloalkylalkyle ; halogénoalkyle ; halogénoalkoxy ; hydroxyalkyl alkoxyalkyle ; acétyle ; alkylsulfonyle ; alkylsulfonylalkyle ; amino-carbonyloxyalkyle ; hydroxycarbonylalkyle ; hydroxy-alkyloxycarbonylalkyle ; aryle ; aralkyle ; arylsulfonyle ; hétéroaryle ; hétéroarylalkyle ; hétéroarylsulfonyle ; hétérocyclyle ou hétérocyclylalkyle.

3. Utilisation suivant la revendication 1, dans laquelle ledit composé répond à la formule (III) :



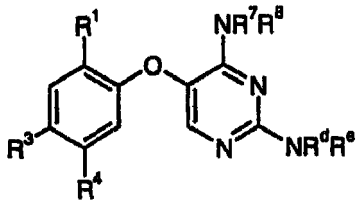
(III)

dans laquelle :

R^1 représente un groupe isopropyle, isopropényle, cyclopropyle ou iodo ;
R^3 et R^4 représentent chacun indépendamment un groupe alkyle ; alcényle ; amino ; halogéno ; amido ; halogénoalkyle ; alkoxy ; hydroxy ; halogénoalkoxy ; nitro ; hydroxyalkyle ; alkoxyalkyle ; hydroxyalkoxy ; alcynylalkoxy ; alkylsulfonyle ; arylsulfonyle ; cyano ; aryle ; hétéroaryle ; hétérocyclyle ; hétérocyclyl-alkoxy ; aryloxy ; hétéroaryloxy ; aralkyloxy ; hétéroaralkyloxy ; phénoxy facultativement substitué ; $-(CH_2)_m-(Z)_n-(CO)-R^f$ ou $-(CH_2)_m-(Z)_n-SO_2-(NR^g)_n-R^f$, dans lequel m et n sont chacun égaux indépendamment à 0 ou 1, Z représente 0 ou un groupe NR^g, R^f représente un atome d'hydrogène, un groupe alkyle, hydroxy, alkoxy, amino, hydroxyalkyle ou alkoxyalkyle, et chaque groupe R^g représente indépendamment un atome d'hydrogène ou un groupe alkyle ;
un de R^7 et R^8 représente un atome d'hydrogène, et l'autre représente un atome d'hydrogène ; un groupe alkyle ; cycloalkyle ; cycloalkylalkyle ; halogénoalkyle ; halogénoalkoxy ; hydroxyalkyle ; alkoxyalkyle ; acétyle ; alkylsulfonyle ; alkylsulfonylalkyle ; amino-carbonyloxyalkyle ; hydroxycarbonylalkyle ; hydroxy-alkyloxycarbonylalkyle ; aryle ; aralkyle ; aryl-sulfonyle ; hétéroaryle ; hétéroarylalkyle ; hétéroaryl-sulfonyle ; hétérocyclyle ; ou hétérocyclylalkyle ; et un
de R^d et R^e représente un atome d'hydrogène, et l'autre représente un atome d'hydrogène ; un groupe alkyle ;

cycloalkyle ; cycloalkylalkyle ; halogénoalkyle ; halogénoalkoxy ; hydroxyalkyle ; alkoxyalkyle ; acétyle ; alkylsulfonyle ; alkylsulfonylalkyle ; amino-carbonyloxyalkyle ; hydroxycarbonylalkyle ; hydroxy-alkyloxycarbonylalkyle ; aryle ; aralkyle ; aryl-sulfonyle ; hétéroaryle ; hétéroarylalkyle ; hétéro-arylsulfonyle ; hétérocyclyle ou hétérocyclylalkyle.

4. Utilisation suivant la revendication 1, dans laquelle ledit composé répond à la formule (IV) :

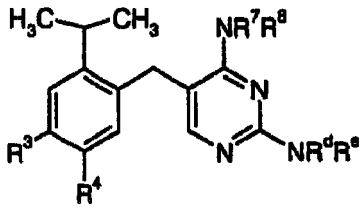


(IV)

dans laquelle :

R^1 représente un groupe alkyle ; alcényle ; cycloalkyle ; cycloalcényle ; ou halogéno ;
R^3 et R^4 représentent chacun indépendamment un groupe alkyle ; alcényle ; amino ; halogéno ; amido ; halogénoalkyle ; alkoxy ; hydroxy ; halogénoalkoxy ; nitro ; hydroxyalkyle ; alkoxyalkyle ; hydroxyalkoxy ; alcynylalkoxy ; alkylsulfonyle ; arylsulfonyle ; cyano ; aryle ; hétéroaryle ; hétérocyclyle ; hétérocyclyl-alkoxy ; aryloxy ; hétéroaryloxy ; aralkyloxy ; hétéroaralkyloxy ; phénoxy facultativement substitué ; $-(CH_2)_m-(Z)_n-(CO)-R^f$ ou $-(CH_2)_m(Z)_n-SO_2-(NR^g)_n-R^f$, dans lequel m et n sont chacun égaux indépendamment à 0 ou 1, Z représente O ou un groupe NR^g, R^f représente un atome d'hydrogène, un groupe alkyle, hydroxy, alkoxy, amino, hydroxyalkyle ou alkoxyalkyle, et chaque groupe R^g représente indépendamment un atome d'hydrogène ou un groupe alkyle ;
un de R^7 et R^8 représente un atome d'hydrogène, et l'autre représente un atome d'hydrogène ; un groupe alkyle ; cycloalkyle ; cycloalkylalkyle ; halogénoalkyle ; halogénoalkoxy ; hydraxyalkyle : alkoxyalkyle ; acétyle ; alkylsulfonyle ; alkylsulfonylalkyle ; amino-carbonyloxyalkyle ; hydroxycarbonylalkyle ; hydroxy-alkyloxycarbonylalkyle ; aryle ; aralkyle ; aryl-sulfonyle ; hétéroaryle ; hétéroarylalkyle ; hétéroaryl-sulfonyle ; hétérocyclyle ; ou hétérocyclylalkyle ; et
un de R^d et R^e représente un atome d'hydrogène, et l'autre représente un atome d'hydrogène ; un groupe alkyle ; cycloalkyle ; cycloalkylalkyle ; halogénoalkyle ; halogénoalkoxy ; hydroxyalkyle ; alkoxyalkyle ; acétyle ; alkylsulfonyle ; alkylsulfonylalkyle ; amino-carbonyloxyalkyle ; hydroxycarbonylalkyle ; hydroxy-alkyloxycarbonylalkyle ; aryle ; aralkyle ; arylsulfonyle ; hétéroaryle ; hétéroarylalkyle ; hétéroarylsulfonyle ; hétérocyclyle ou hétérocyclylalkyle.

5. Utilisation suivant la revendication 1, dans laquelle ledit composé répond à la formule (V) :



(V)

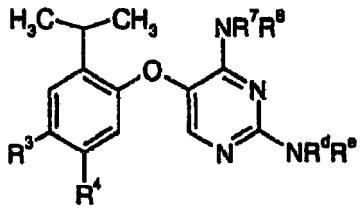
dans laquelle :

R^3 et R^4 représentent chacun indépendamment un groupe alkyle ; alcényle ; amino ; halogéno ; amido ; halogénoalkyle ; alkoxy ; hydroxy ; halogénoalkoxy ; nitro ; hydroxyalkyle ; alkoxyalkyle ; hydroxyalkoxy ; alcynylalkoxy ; alkylsulfonyle ; arylsulfonyle ; cyano ; aryle ; hétéroaryle ; hétérocyclyle ; hétérocyclyl-alkoxy ; aryloxy ; hétéroaryloxy ; aralkyloxy ; hétéroaralkyloxy ; phénoxy facultativement substitué ; $-(CH_2)_n-(Z)_n-(CO)-R^f$ ou $-(CH_2)_m-(Z)_n-SO_2-(NR^g)_n-R^f$, dans lequel m et n sont chacun égaux indépendamment à 0 ou 1, Z représente O ou un groupe NR^g, R^f représente un atome d'hydrogène, un groupe alkyle, hydroxy, alkoxy, amino, hydroxyalkyle ou alkoxyalkyle, et chaque groupe R^g représente indépendamment un atome d'hydrogène ou un groupe alkyle ;
un de R^7 et R^8 représente un atome d'hydrogène, et l'autre représente un atome d'hydrogène ; un groupe

alkyle ; cycloalkyle ; cycloalkylalkyle ; halogénoalkyle ; halogénoalkoxy ; hydroxyalkyle ; alkoxyalkyle ; acétyle ; alkylsulfonyle ; alkylsulfonylalkyle ; amino-carbonyloxyalkyle ; hydroxycarbonylalkyle ; hydroxy-alkyloxycarbonylalkyle ; aryle ; aralkyle ; aryl-sulfonyle ; hétéroaryle ; hétéroarylalkyle ; hétéroaryl-sulfonyle ; hétérocyclyle ; ou hétérocyclylalkyle ; et

un de R^d et R^e représente un atome d'hydrogène, et l'autre représente un atome d'hydrogène : un groupe alkyle ; cycloalkyle ; cycloalkylalkyle ; halogénoalkyle ; halogénoalkoxy ; hydroxyalkyle ; alkoxyalkyle ; acétyle ; alkylsulfonyle ; alkylsulfonylalkyle ; amino-carbonyloxyalkyle ; hydroxycarbonylalkyle ; hydroxy-alkyloxycarbonylalkyle ; aryle ; aralkyle ; arylsulfonyle ; hétéroaryle ; hétéroarylalkyle ; hétéroarylsulfonyle ; hétérocyclyle ou hétérocyclylalkyle.

6. Utilisation suivant la revendication 1, dans laquelle ledit composé répond à la formule (VI) :



(VI)

dans laquelle :

R^3 et R^4 représentent chacun indépendamment un groupe alkyle ; alcényle ; amino ; halogéno ; amido ; halogénoalkyle ; alkoxy ; hydroxy ; halogénoalkoxy ; nitro ; hydroxyalkyle ; alkoxyalkyle ; hydroxyalkoxy ; alcynylalkoxy ; alkylsulfonyle ; arylsulfonyle ; cyano ; aryle ; hétéroaryle ; hétérocyclyle ; hétérocyclyl-alkoxy ; aryloxy ; hétéroaryloxy ; aralkyloxy ; hétéroaralkyloxy ; phénoxy facultativement substitué ; $-(CH_2)_m-(Z)_n-(CO)-R^f$ ou $-(CH_2)_m-(Z)_n-SO_2-(NR^g)_n-R^f$, dans lequel m et n sont chacun égaux indépendamment à 0 ou 1, Z représente O ou un groupe NR^g, R^f représente un atome d'hydrogène, un groupe alkyle, hydroxy, alkoxy, amino, hydroxyalkyle ou alkoxyalkyle, et chaque groupe R^g représente indépendamment un atome d'hydrogène ou un groupe alkyle ;

un de R^7 et R^8 représente un atome d'hydrogène, et l'autre représente un atome d'hydrogène ; un groupe alkyle ; cycloalkyle ; cycloalkylalkyle ; halogénoalkyle ; halogénoalkoxy ; hydroxyalkyle ; alkoxyalkyle ; acétyle ; alkylsulfonyle ; alkylsulfonylalkyle ; amino-carbonyloxyalkyle ; hydroxycarbonylalkyle ; hydroxy-alkyloxycarbonylalkyle ; aryle ; aralkyle ; aryl-sulfonyle ; hétéroaryle ; hétéroarylalkyle ; hétéroaryl-sulfonyle ; hétérocyclyle ; ou hétérocyclylalkyle ; et

un de R^d et R^e représente un atome d'hydrogène, et l'autre représente un atome d'hydrogène ; un groupe alkyle ; cycloalkyle ; cycloalkylalkyle ; halogénoalkyle ; halogénoalkoxy ; hydroxyalkyle ; alkoxyalkyle ; acétyle ; alkylsulfonyle ; alkylsulfonylalkyle ; amino-carbonyloxyalkyle ; hydroxycarbonylalkyle ; hydroxy-alkyloxycarbonylalkyle ; aryle ; aralkyle ; arylsulfonyle ; hétéroaryle ; hétéroarylalkyle ; hétéroarylsulfonyle ; hétérocyclyle ou hétérocyclylalkyle.

7. Utilisation suivant la revendication 1, dans laquelle ce composé de formule I est choisi dans le groupe consistant en :

la N^2-isopropyl-5-(2-isopropyl-4,5-diméthoxybenzyl)-N^4-méthyl)-pyrimidine-2,4-diamine,
la 5-(2-isopropyl-4,5-diméthoxy-phénoxy)-pyrimidine-2,4-diamine,
la 5-(2-isopropyl-4,5-diméthoxybenzyl)-N^4-isoxazole-5-ylméthyl-pyrimidine-2,4-diamine,
la N^2-isopropyl-5-(2-isopropyl-4,5-diméthoxybenzyl)-pyrimidine-2,4-diamine,
la 5-(2-isopropyl-4,5-diméthoxybenzyl)-N^4-(2-méthoxy-benzyl)-pyrimidine-2,4-diamine,
la 5-(2-isopropyl-4,5-diméthoxybenzyl)-N^2-(2,2,2-trifluoro-éthyl)-pyrimidine-2,4-diamine,
le 3-[2-amino-5-(2-isopropyl-4,5-diméthoxybenzyl)-pyrimididine-4-ylamino]-propane-1,2-diol,
le N-[4-amino-5-(2-isopropyl-4,5-diméthoxybenzyl)-pyrimidine-2-yl]-acétamide,
la 5-(2-isopropyl-4,5-diméthoxybenzyl)-N^4-(4-méthoxy-benzyl)-pyrimidine-2,4-diamine,
la 5-(2-isopropyl-4,5-diméthoxybenzyl)-N^4-phényl-pyrimidine-2,4-diamine,
la 5-(5-chloro-2-isopropyl-4-méthoxybenzyl)-N^2-phénéthyl-pyrimidine-2,4-diamine,
la 5-(5-chloro-2-isopropyl-4-méthoxybenzyl)-pyrimidine-2,4-diamine,
la N^4-isobutyl-N^2-isopropyl-5-(2-isopropyl-4,5-diméthoxy-benzyl)-pyrimidine-2,4-diamine,
la 5-(2-isopropyl-4,5-diméthoxybenzyl)-N^2-phényl-pyrimidine-2,4-diamine,
la N^2,N^4-diisopropyl-5-(2-isopropyl-4,5-diméthoxybenzyl)-pyrimidine-2,4-diamine,

la 5-(5-chloro-2-isopropyl-4-méthoxybenzyl)-N^2-isopropyl-pyrimidine-2,4-diamine,
le 2-[2-amino-5-(2-isopropyl-4,5-diméthoxybenzyl)-pyrimididine-4-ylamino]-éthanol,
la 5-(2-isopropyl-4,5-diméthoxybenzyl)-pyrimidine-2,4-diamine,
la 5-(2-isopropyl-4,5-diméthoxybenzyl)-N^4-[2-(4-méthoxy-phényl)-éthyl]-pyrimidine-2,4-diamine,
la N^2-benzyl-5-(2-isopropyl-4,5-diméthoxybenzyl)-pyrimidine-2,4-diamine,
la 5-(2-isopropyl-4,5-diméthoxybenzyl)-N^4-(4-méthane-sulfonyl-cyclohexyl)-pyrimidine-2,4-diamine,
la N^2-cyclopropyl-5-(2-isopropyl-4,5-diméthoxybenzyl)-pyrimidine-2,4-diamine,
la N^4-isopropyl-5-(2-isopropyl-4,5-diméthoxybenzyl)-pyrimidine-2,4-diamine,
la N^2-éthyl-5-(2-isopropyl-4,5-diméthoxybenzyl)-pyrimidine-2,4-diamine,
la 5-(2-isopropyl-4,5-diméthoxybenzyl)-N^4-[2-(3-méthoxy-phényl)-éthyl]-pyrimidine-2,4-diamine,
le 2-[4-amino-5-(2-isopropyl-4,5-diméthoxybenzyl)-pyrimididine-2-ylamino]-éthanol,
la 5-(2-sec.-butyl-4,5-diméthoxybenzyl)-pyrimidine-2,4-diamine,
la N^2-tertiobutyl-5-(2-isopropyl-4,5-diméthoxybenzyl)-pyrimidine-2,4-diamine,
la N^2-isobutyl-5-(2-isopropyl-4,5-diméthoxybenzyl)-pyrimidine-2,4-diamine,
la 5-(5-chloro-2-isopropyl-4-méthoxybenzyl)-N^2-cyclopropyl-pyrimidine-2,4-diamine,
la 5-(2-isopropyl-4-méthoxy-5-phénoxybenzyl)-pyrimidine-2,4-diamine,
la N^4-isobutyl-5-(2-isopropyl-4,5-diméthoxybenzyl)-pyrimidine-2,4-diamine,
la N^4-éthyl-5-(2-isopropyl-4,5-diméthoxybenzyl)-pyrimidine-2,4-diamine,
la N^4-benzyl-5-(2-isopropyl-4,5-diméthoxybenzyl)-pyrimidine-2,4-diamine,
la 5-(2-isopropyl-4,5-diméthoxybenzyl)-N^4-(2,2,2-trifluoro-éthyl)-pyrimidine-2,4-diamine,
la 5-(2-isopropyl-4,5-diméthoxybenzyl)-N^2-(4-méthoxy-phényl)-pyrimidine-2,4-diamine,
la N^2-isopropyl-5-(2-isopropyl-4,5-diméthoxybenzyl)-N^4-phényl-pyrimidine-2,4-diamine,
la N^4-éthyl-N^2-isopropyl-5-(2-isopropyl-4,5-diméthoxy-benzyl)-pyrimidine-2,4-diamine,
la 5-(2-isopropyl-4,5-diméthoxybenzyl)-N^4-(1-méthyl-pipéridine-4-yl)-pyrimidine-2,4-diamine,
la 5-(2-isopropyl-4,5-diméthoxybenzyl)-N^2-(2-méthoxy-phényl)-pyrimidine-2,4-diamine,
la 5-(4,5-dichloro-2-isopropylbenzyl)-pyrimidine-2,4-diamine,
la 5-(5-chloro-2-isopropyl-4-méthoxybenzyl)-N^2-éthyl-pyrimidine-2,4-diamine,
la 5-(2-isopropyl-4-méthoxy-5-méthylbenzyl)-pyrimidine-2,4-diamine,
la 5-(2-isopropyl-4,5-diméthoxybenzyl)-N^2-pyrimidine-2-yl-pyrimidine-2,4-diamine,
la 5-(2-isopropyl-4,5-diméthoxybenzyl)-N^2-(2-méthoxy-éthyl)-pyrimidine-2,4-diamine,
la N^4-benzyl-N^2-isopropyl-5-(2-isopropyl-4,5-diméthoxy-benzyl)-pyrimidine-2,4-diamine,
la 1-(4-{2-[4-amino-5-(2-isopropyl-4,5-diméthoxybenzyl)-pyrimidine-2-ylamino]-propyl}-pipérazine-1-yl)-éthanone,
la 5-(2-isopropyl-4,5-diméthoxybenzyl)-N^4-(tétrahydro-pyrane-4-yl)-pyrimidine-2,4-diamine,
la N^4-cyclopropyl-5-(2-isopropyl-4,5-diméthoxybenzyl)-pyrimidine-2,4-diamine,
la 5-(5-éthoxy-2-isopropyl-4-méthoxybenzyl)-pyrimidine-2,4-diamine,
la N^2-(2,4-diméthoxyphényl)-5-(2-isopropyl-4,5-diméthoxy-benzyl)-pyrimidine-2,4-diamine,
la N^2-cyclobutyl-5-(2-isopropyl-4,5-diméthoxybenzyl)-pyrimidine-2,4-diamine,
la N^2-(2-chlorophényl)-5-(2-isopropyl-4,5-diméthoxy-benzyl)-pyrimidine-2,4-diamine,
la 5-(4-chloro-2-isopropyl-5-méthoxybenzyl)-pyrimidine-2,4-diamine,
la 5-(5-bromo-2-isopropyl-4-méthoxy-phénoxy)-pyrimidine-2,4-diamine,
la 5-(5-chloro-2-isopropyl-4-méthoxybenzyl)-N^2-(3-méthoxy-phényl)-pyrimidine-2,4-diamine,
la 5-(5-chloro-2-isopropyl-4-méthoxy-phénoxy)-pyrimidine-2,4-diamine,
la 5-(2-isopropyl-4,5-diméthoxybenzyl)-N^2,N^4-diphényl-pyrimidine-2,4-diamine,
la 5-(5-chloro-2-isopropyl-4-méthoxybenzyl)-N^2-isobutyl-pyrimidine-2,4-diamine,
la 5-(5-chloro-2-isopropyl-4-méthoxybenzyl)-N^2-phényl-pyrimidine-2,4-diamine,
la 5-(2-isopropyl-4-méthoxy-5-méthyl-phénoxy)-pyrimidine-2,4-diamine,
la 5-(2-isopropyl-4,5-diméthoxybenzyl)-N^2-méthyl-pyrimidine-2,4-diamine,
la 5-(2-isopropyl-5-méthylphénoxy)-pyrimidine-2,4-diamine,
la 5-(5-chloro-2-isopropyl-4-méthoxybenzyl)-N^2-méthyl-pyrimidine-2,4-diamine,
la N^2-benzyl-5-(5-chloro-2-isopropyl-4-méthoxy-phénoxy)-pyrimidine-2,4-diamine,
le 2-[2-isopropylamino-5-(2-isopropyl-4,5-diméthoxy-benzyl)-pyrimidine-4-ylamino]-éthanol,
la 5-(5-chloro-2-isopropyl-4-méthoxy-phénoxy)-N^2-(tétrahydro-pyrane-4-yl)-pyrimidine-2,4-diamine,
la N^2-(4-chlorophényl)-5-(2-isopropyl-4,5-diméthoxy-benzyl)-pyrimidine-2,4-diamine,
la 5-(2-isopropyl-phénoxy)-pyrimidine-2,4-diamine,
la 5-(2-isopropyl-4,5-diméthoxybenzyl)-N^4-méthyl-pyrimidine-2,4-diamine,
la 5-(5-chloro-2-isopropyl-4-méthoxy-phénoxy)-N^2-isopropyl-pyrimidine-2,4-diamine,
la 5-(2-isopropyl-4,5-diméthoxybenzyl)-N^4-(2-méthoxy-éthyl)-pyrimidine-2,4-diamine,

la N^2-isopropyl-5-(2-isopropyl-4,5-diméthoxy-phénoxy)-pyrimidine-2,4-diamine,
la 5-(2-éthyl-4,5-diméthoxybenzyl)-pyrimidine-2,4-diamine,
la 5-(2-isopropyl-4,5-diméthoxy-phénoxy)-N^2-phényl-pyrimidine-2,4-diamine,
la N^2-tertiobutyl-5-(5-chloro-2-isopropyl-4-méthoxybenzyl)-pyrimidine-2,4-diamine,
la N^2-benzyl-5-(2-isopropyl-4,5-diméthoxy-phénoxy)-pyrimidine-2,4-diamine,
la 5-(2-cyclopropyl-4,5-diméthoxybenzyl)-pyrimidine-2,4-diamine,
le N-[4-amino-5-(2-isopropyl-4,5-diméthoxy-phénoxy)-pyrimidine-2-yl]-acétamide,
la N^2-benzyl-5-(5-chloro-2-isopropyl-4-méthoxybenzyl)-pyrimidine-2,4-diamine,
la 5-(2-isopropyl-4,5-diméthoxy-phénoxy)-N^2-(2,2,2-trifluoro-éthyl)-pyrimidine-2,4-diamine,
la 5-(2-isopropyl-4,5-diméthoxy-phénoxy)-N^2-(2-méthoxy-éthyl)-pyrimidine-2,4-diamine,
la 5-(2-isopropyl-4,5-diméthoxybenzyl)-pyrimidine-4-ylamine,
le 3-[4-amino-5-(5-chloro-2-isopropyl-4-méthoxy-phénoxy)-pyrimidine-2-ylamino]-pentane-1,5-diol,
la 5-(5-chloro-2-isopropyl-4-méthoxybenzyl)-N^2-cyclohexyl-pyrimidine-2,4-diamine,
le 2-[4-amino-5-(5-chloro-2-isopropyl-4-méthoxy-phénoxy)-pyrimidine-2-ylamino]-butane-1-ol,
la 1-[5-(2,4-diamino-pyrimidine-5-yloxy)-4-isopropyl-2-méthoxyphényl]-éthanone,
la 5-[5-(1H-imidazole-2-yl)-2-isopropyl-4-méthoxy-phénoxy]-pyrimidine-2,4-diamine,
le (2,4-diamino-pyrimidine-5-yl)-(2-isopropyl-4,5-diméthoxy-phényl)-méthanol,
la 5-[5-chloro-2-(2-fluoro-1-méthyl-éthyl)-4-méthoxy-phénoxy]-pyrimidine-2,4-diamine,
le (5-chloro-2-isopropyl-4-méthoxyphényl)-(2,4-diamino-pyrimidine-5-yl)-méthanol,
le 2-[4-amino-5-(5-chloro-2-éthyl-4-méthoxy-phénoxy)-pyrimidine-2-ylamino]-butane-1-ol,
la 5-(5-chloro-2-isopropyl-4-méthoxy-phénoxy)-N^2-(3-éthane-sulfonyl-1-méthylpropyl)-pyrimidine-2,4-diamine,
la 5-(5-bromo-2-éthyl-4-méthoxy-phénoxy)-pyrimidine-2,4-diamine,
la 5-(5-chloro-2-éthyl-4-méthoxy-phénoxy)-pyrimidine-2,4-diamine,
la 5-(5-chloro-2-cyclopropyl-4-méthoxy-phénoxy)-pyrimidine-2,4-diamine,
la 5-(2-éthyl-5-méthanesulfonyl-4-méthoxy-phénoxy)-pyrimidine-2,4-diamine,
le 5-(2,4-diaminopyrimidine-5-yloxy)-4-isopropyl-2-méthoxy-benzamide,
la 5-(4,5-diméthoxy-2-vinylphénoxy)-pyrimidine-2,4-diamine,
l'acide 5-(2,4-diaminopyrimidine-5-yloxy)-4-isopropyl-2-méthoxybenzoïque,
la 5-(2-cyclopropyl-4,5-diméthoxy-phénoxy)-pyrimidine-2,4-diamine,
la 5-[2-isopropyl-4-méthoxy-5-(1H-tétrazole-5-yl)-phénoxy]-pyrimidine-2,4-diamine,
le 5-(2,4-diaminopyrimidine-5-yloxy)-4-isopropyl-2-méthoxy-benzonitrile,
l'ester éthylique d'acide 4-[4-amino-5-(5-chloro-2-isopropyl-4-méthoxy-phénoxy)-pyrimidine-2-ylamino]-pipéridine-1-carboxylique,
la [5-(2,4-diamino-pyrimidine-5-yloxy)-4-isopropyl-2-méthoxyphényl]-urée,
la 5-(5-chloro-2-isopropyl-4-méthoxy-phénoxy)-N^2-(1-cyclopropyl-éthyl)-pyrimidine-2,4-diamine,
la 5-(5-chloro-4-difluorométhoxy-2-isopropyl-phénoxy)-pyrimidine-2,4-diamine,
la 5-(5-amino-2-isopropyl-4-méthoxy-phénoxy)-pyrimidine-2,4-diamine,
la N^4-isopropyl-5-(2-isopropyl-4,5-diméthoxybenzyl)-N^2-méthyl-pyrimidine-2,4-diamine,
le N-[5-(2,4-diaminopyrimidine-5-yloxy)-4-isopropyl-2-méthoxyphényl]-acétamide,
la 5-(2-isopropyl-4-méthoxy-5-tétrazole-1-yl-phénoxy)-pyrimidine-2,4-diamine,
la 5-(2-isopropyl-4-méthoxy-phénoxy)-pyrimidine-2,4-diamine,
la 5-(2-isopropyl-5-méthanesulfonyl-4-méthoxy-phénoxy)-pyrimidine-2,4-diamine,
la 5-(2-isopropyl-4-méthoxy-5-méthyl-phénoxy)-N^4-phényl-pyrimidine-2,4-diamine,
la 5-(5-chloro-2-isopropyl-4-méthoxy-phénoxy)-N^2-(1,1-dioxo-hexahydro-1λ^6-thiopyrane-4-yl)-pyrimidine-2,4-diamine,
l'ester 2-[4-amino-5-(5-chloro-2-isopropyl-4-méthoxy-phénoxy)-pyrimidine-2-ylamino]-propylique d'acide méthyl-carbamique,
la 5-(4-chloro-2-isopropyl-5-méthylphénoxy)-pyrimidine-2,4-diamine,
la 5-(2-isopropyl-4,5-diméthoxy-phénoxy)-6-méthyl-pyrimidine-2,4-diamine,
la 1-(4-{2-[4-amino-5-(5-chloro-2-isopropyl-4-méthoxy-phénoxy)-pyrimidine-2-ylamino]-propyl}-pipérazine-1-yl)-éthanone,
la 5-(5-chloro-2-isopropyl-4-méthoxy-phénoxy)-N^2-(1-méthanesulfonyl-pipéridine-4-yl)-pyrimidine-2,4-diamine,
le 2-[4-amino-5-(5-chloro-2-isopropyl-4-méthoxy-phénoxy)-pyrimidine-2-ylamino]-(R)-propane-1-ol,
la 5-(2-éthyl-4,5-diméthoxy-phénoxy)-pyrimidine-2,4-diamine,
la 5-(2-isopropyl-5-méthanesulfonyl-4-méthoxy-phénoxy)-N^2-tétrahydrothiopyrane-4-yl)-pyrimidine-2,4-diamine,
la 5-(5-chloro-2-isopropyl-4-méthoxy-phénoxy)-N^2-(1,1-dioxo-hexahydro-1λ^6-thiopyrane-4-yl)-pyrimidine-2,4-

diamine,
la 1-[5-(2,4-diaminopyrimidine-5-yloxy)-2-hydroxy-4-isopropylphényl]-éthanone,
la 5-(5-iodo-2-isopropyl-4-méthoxy-phénoxy)-pyrimidine-2,4-diamine,
la 5-(2-iodo-4,5-diméthoxy-phénoxy)-pyrimidine-2,4-diamine,
le 5-(2,4-diaminopyrimidine-5-yloxy)-4-isopropyl-2-méthoxy-benzènesulfonamide,
le 4-(2,4-diaminopyrimidine-5-yloxy)-2-iodo-5-isopropyl-phénol,
la 5-(2,5-diiodo-4-méthoxy-phénoxy)-pyrimidine-2,4-diamine,
le 3-[4-amino-5-(5-bromo-2-isopropyl-4-méthoxy-phénoxy)-pyrimidine-2-ylamino)-pentane-1,5-diol,
la 5-(2-éthyl-5-iodo-4-méthoxy-phénoxy)-pyrimidine-2,4-diamine,
la 5-(5-iodo-2-isopropyl-4-méthoxy-phénoxy)-1-oxy-pyrimidine-2,4-diamine,
la 5-(2-isopropyl-4-méthoxy-5-vinyl-phénoxy)-pyrimidine-2,4-diamine,
la 5-(5-iodo-2-isopropényl-4-méthoxy-phénoxy)-pyrimidine-2,4-diamine,
la 5-(2-isopropyl-4-méthoxy-5-pyrazole-1-yl-phénoxy)-pyrimidine-2,4-diamine,
la 5-(5-iodo-2-isopropyl-phénoxy)-pyrimidine-2,4-diamine,
la 5-[2-isopropyl-4-méthoxy-5-(3-méthyl-pyrazole-1-yl)-phénoxy]-pyrimidine-2,4-diamine,
le 4-(2,4-diamino-pyrimidine-5-ylméthyl)-2-iodo-5-isopropyl-phénol,
la 5-(2-isopropyl-4-méthoxy-5-oxazole-2-yl-phénoxy)-pyrimidine-2,4-diamine,
le (S)-2-[4-amino-5-(5-bromo-2-isopropyl-4-méthoxy-phénoxy)-pyrimidine-2-ylamino]-butane-1-ol,
la 5-(4-iodo-2-isopropyl-5-méthoxy-phénoxy)-pyrimidine-2,4-diamine,
la 5-(4-bromo-2-isopropyl-5-méthoxy-phénoxy)-pyrimidine-2,4-diamine,
la 5-(2-éthyl-5-iodo-phénoxy)-pyrimidine-2,4-diamine,
la 5-(2-isopropyl-4-méthoxy-5-trifluorométhyl-phénoxy)-pyrimidine-2,4-diamine,
la 5-(2-isopropyl-4-méthoxy-5-thiazole-4-yl-phénoxy)-pyrimidine-2,4-diamine,
le [4-(2,4-diamino-pyrimidine-5-yloxy)-2-iodo-5-isopropyl-phénoxy]-acétonitrile,
la 5-(2-isopropyl-4-méthoxy-5-thiophène-3-yl-phénoxy)-pyrimidine-2,4-diamine,
le (R)-2-[4-amino-5-(2-isopropyl-5-méthanesulfonyl-4-méthoxy-phénoxy)-pyrimidine-2-ylamino]-butane-1-ol,
l'acide (S)-2-[4-amino-5-(5-chloro-2-isopropyl-4-méthoxy-phénoxy)-pyrimidine-2-ylamino]-propionique,
la 5-[5-(4,5-dihydro-oxazole-2-yl)-2-isopropyl-4-méthoxy-phénoxy]-pyrimidine-2,4-diamine,
la 5-(2-isopropyl-5-méthanesulfonyl-4-méthoxy-phénoxy)-N^2-(2,2,2-trifluoro-éthyl)-pyrimidine-2,4-diamine,
la 5-(5-iodo-2-isopropyl-4-méthoxybenzyl)-pyrimidine-2,4-diamine,
la 5-(5-bromo-2-cyclopropyl-4-méthoxy-phénoxy)-pyrimidine-2,4-diamine,
l'ester 3-hydroxy-2-hydroxyméthyl-2-méthyl-propylique d'acide (S)-2-[4-amino-5-(5-chloro-2-isopropyl-4-méthoxy-phénoxy)-pyrimidine-2-ylamino]-propionique,
la 5-[5-(5-chlorothiophène-2-yl)-2-isopropyl-4-méthoxy-phénoxy]-pyrimidine-2,4-diamine,
la 5-(2-éthyl-4-méthoxy-5-trifluorométhyl-phénoxy)-pyrimidine-2,4-diamine,
la 5-[2-isopropyl-4-méthoxy-5-(1-méthyl-1H-imidazole-2-yl)-phénoxy]-pyrimidine-2,4-diamine,
la 5-[2-isopropyl-4-méthoxy-5-(2H-pyrazole-3-yl)-phénoxy]-pyrimidine-2,4-diamine,
la 5-(5-imidazole-1-yl-2-isopropyl-4-méthoxy-phénoxy)-pyrimidine-2,4-diamine,
la N^2-isopropyl-5-(2-isopropyl-5-méthanesulfonyl-4-méthoxy-phénoxy)-pyrimidine-2,4-diamine,
le 2-[4-(2,4-diamino-pyrimidine-5-yloxy)-2-iodo-5-isopropyl-phénoxy]-éthanol,
la 5-(2-isopropyl-5-méthanesulfonyl-4-méthoxy-phénoxy)-N^2-phényl-pyrimidine-2,4-diamine,
le 5-(4-amino-2-éthylamino-pyrimidine-5-yloxy)-4-isopropyl-2-méthoxy-benzamide,
le 2-[4-amino-5-(2-isopropyl-5-méthanesulfonyl-4-méthoxy-phénoxy)-pyrimidine-2-ylamino)-éthanol,
la 5-[2-isopropyl-4-méthoxy-5-(2-méthyl-thiazole-4-yl)-phénoxy]-pyrimidine-2,4-diamine,
la 5-[5-iodo-2-isopropyl-4-(pyrazine-2-ylméthoxy)-phénoxy]-pyrimidine-2,4-diamine,
la 5-(2-isopropyl-5-méthanesulfonyl-4-méthoxy-phénoxy)-N^2-(2-méthoxy-éthyl)-pyrimidine-2,4-diamine,
la 5-(2-isopropyl-4-méthoxy-5-[1,2,3]triazole-1-yl-phénoxy)-pyrimidine-2,4-diamine,
la 5-(5-furane-2-yl-2-isopropyl-4-méthoxy-phénoxy)-pyrimidine-2,4-diamine,
la 1-[5-(2,4-diamino-pyrimidine-5-yloxy)-4-isopropyl-2-méthoxyphényl]-3-éthyl-urée,
la N^2-cyclopropyl-5-(2-isopropyl-5-méthanesulfonyl-4-méthoxy-phénoxy)-pyrimidine-2,4-diamine,
le 2-[4-(2,4-diamino-pyrimidine-5-yloxy)-2-iodo-5-isopropyl-phénoxy]-acétamide,
la 5-[5-(3,5-diméthylpyrazole-1-yl)-2-isopropyl-4-méthoxy-phénoxy]-pyrimidine-2,4-diamine,
la N^2-benzyl-5-(2-isopropyl-5-méthanesulfonyl-4-méthoxy-phénoxy)-pyrimidine-2,4-diamine,
la N^2-éthyl-5-(2-isopropyl-5-méthanesulfonyl-4-méthoxy-phénoxy)-pyrimidine-2,4-diamine,
la 5-(2-isopropyl-5-méthanesulfonyl-4-méthoxy-phénoxy)-N^2-(1-méthanesulfonyl-pipéridine-4-yl)-pyrimidine-2,4-diamine,
le 1-[4-amino-5-(2-isopropyl-4,5-diméthoxybenzyl)-pyrimidine-2-ylamino]-2-méthylpropane-2-ol,
la N^2-isobutyl-5-(2-isopropyl-5-méthanesulfonyl-4-méthoxy-phénoxy)-pyrimidine-2,4-diamine,

le 5-(2,4-diamino-pyrimidine-5-yloxy)-4-isopropyl-2-méthoxy-N-méthylbenzamide,
la 5-(2-isopropyl-5-isoxazole-5-yl-4-méthoxy-phénoxy)-pyrimidine-2,4-diamine,
la N^2-(4-fluorophényl)-5-(2-isopropyl-5-méthanesulfonyl-4-méthoxy-phénoxy)-pyrimidine-2,4-diamine,
la 5-(5-chloro-2-isopropyl-4-méthoxybenzyl)-N^2-(2,2,2-trifluoro-éthyl)-pyrimidine-2,4-diamine,
la 5-(2-isopropyl-4-méthoxy-5-[1,2,4]oxadiazole-3-yl-phénoxy)-pyrimidine-2,4-diamine,
la 5-(2-isopropyl-5-méthanesulfonyl-4-méthoxy-phénoxy)-N^2-(tétrahydropyrane-4-yl)-pyrimidine-2,4-diamine,
le 1-[5-(2,4-diamino-pyrimidine-5-yloxy)-4-isopropyl-2-méthoxyphényl]-éthanol,
la 5-(2,5-diisopropyl-4-méthoxy-phénoxy)-pyrimidine-2,4-diamine,
la 5-(5-benzo[b]thiophéne-3-yl-2-isopropyl-4-méthoxy-phénoxy)-pyrimidine-2,4-diamine,
la 5-[2-isopropyl-4-méthoxy-5-(1-méthoxy-éthyl)-phénoxy]-pyrimidine-2,4-diamine,
la 5-(2-isopropyl-4-méthoxy-5-oxazole-4-yl-phénoxy)-pyrimidine-2,4-diamine,
la 5-[5-(5-chlorothiophène-2-yl)-2-isopropyl-4-méthoxy-benzyl]-pyrimidine-2,4-diamine,
la 5-(2-isopropyl-4-méthoxy-5-thiazole-2-yl-phénoxy)-pyrimidine-2,4-diamine,
la 5-(2-isopropyl-4-méthoxy-5-thiophène-3-yl-benzyl)-pyrimidine-2,4-diamine,
la 5-(5-furane-3-yl-2-isopropyl-4-méthoxy-phénoxy)-pyrimidine-2,4-diamine,
la 5-(2-isopropyl-5-méthoxy-phénoxy)-pyrimidine-2,4-diamine,
la 5-[5-iodo-2-isopropyl-4-(pyrimidine-2-ylméthoxy)-phénoxy]-pyrimidine-2,4-diamine,
la 5-(2-isopropyl-4,5-diméthoxybenzyl)-N^2-pyridine-2-yl-pyrimidine-2,4-diamine,
la 5-(2-isopropyl-4-méthoxy-5-thiophène-2-yl-phénoxy)-pyrimidine-2,4-diamine,
la 1-[5-(2,4-diamino-pyrimidine-5-yloxy)-4-isopropyl-2-méthoxyphényl]-3-phényl-urée,
la 5-(5-chloro-2-isopropyl-4-méthoxybenzyl)-*N*^{2}-(2-méthoxy-éthyl)-pyrimidine-2,4-diamine,
le 5-(2,4-diamino-pyrimidine-5-yloxy)-4-isopropyl-2-méthoxy-N-méthyl-benzènesulfonamide,
la 5-(2-isopropyl-5-méthanesulfonyl-4-méthoxy-phénoxy)-N^2-méthyl-pyrimidine-2,4-diamine,
la 5-[5-iodo-2-isopropyl-4-(pyridine-2-ylméthoxy)-phénoxy]-pyrimidine-2,4-diamine,
le *N*-[2-acétylamino-5-(2-isopropyl-4-méthoxy-5-méthyl-benzyl)-pyrimidine-4-yl]-acétamide,
la 5-[4-(2-fluorobenzyloxy)-5-iodo-2-isopropyl-phénoxy]-pyrimidine-2,4-diamine,
la 5-(2-isopropyl-4-méthoxy-5-pyrrole-1-yl-phénoxy)-pyrimidine-2,4-diamine,
la 5-(2-isopropyl-4-méthoxy-5-trifluorométhoxy-phénoxy)-pyrimidine-2,4-diamine,
le 2-[4-(2,4-diamino-pyrimidine-5-ylméthyl)-2-iodo-5-isopropyl-phénoxy]-éthanol,
la 5-[5-(4,5-dihydro-oxazole-2-yl)-2-isopropyl-4-méthoxy-benzyl]-pyrimidine-2,4-diamine,
le 5'-(2,4-diamino-pyrimidine-5-yloxy)-4'-isopropyl-2'-méthoxy-biphényl-3-carbonitrile,
la 5-[2-isopropyl-4-méthoxy-5-(4-méthylthiophène-2-yl)-phénoxy]-pyrimidine-2,4-diamine,
la 5-(5-chloro-2-isopropyl-4-méthoxy-phénoxy)-*N*^{2}-[(S)-1-(4-méthyl-2,6,7-trioxabicyclo[2.2.2]oct-1-yl)-éthyl]-pyrimidine-2,4-diamine,
la 5-(5-iodo-2-isopropyl-4-prop-2-ynyloxy-phénoxy)-pyrimidine-2,4-diamine,
la 5-(2-isopropyl-4-méthoxy-5-nitro-phénoxy)-pyrimidine-2,4-diamine,
la 5-(4-éthoxy-5-iodo-2-isopropyl-phénoxy)-pyrimidine-2,4-diamine,
la 5-[5-iodo-2-isopropyl-4-(pyridine-3-ylméthoxy)-phénoxy]-pyrimidine-2,4-diamine,
la 5-(4-benzyloxy-5-iodo-2-isopropyl-phénoxy)-pyrimidine-2,4-diamine,
la 5-(4-isopropyl-6-méthoxy-biphényl-3-yloxy)-pyrimidine-2,4-diamine,
la 5-(5-furane-2-yl-2-isopropyl-4-méthoxybenzyl)-pyrimidine-2,4-diamine,
la 5-(2-isopropyl-4-méthoxy-5-thiazole-5-yl-phénoxy)-pyrimidine-2,4-diamine,
la 1-[5-(2,4-diamino-pyrimidine-5-yloxy)-4-isopropyl-2-méthoxyphényl]-pyrrolidine-2-one,
la 5-(2-isopropyl-5-méthanesulfonyl-4-méthoxybenzyl)-pyrimidine-2,4-diamine,
la 5-[5-chloro-2-(1-fluoro-1-méthyl-éthyl)-4-méthoxy-phénoxy]-pyrimidine-2,4-diamine,
la 5-[5-iodo-2-isopropyl-4-(2-méthoxy-éthoxy)-phénoxy]-pyrimidine-2,4-diamine,
la 5-(2-isopropyl-4-méthoxy-5-oxazole-5-yl-phénoxy)-pyrimidine-2,4-diamine,
le 1-[4-chloro-2-(2,4-diamino-pyrimidine-5-yloxy)-5-méthoxyphényl]-éthanol,
le 1-[4-chloro-2-(2,4-diamino-pyrimidine-5-yloxy)-5-méthoxyphényl]-éthanol,
le 2-[2-(2,4-diamino-pyrimidine-5-yloxy)-4-iodo-5-méthoxy-phényl]-propane-1-ol,
la 5-[5-iodo-2-isopropyl-4-(2-méthoxy-benzyloxy)-phénoxy]-pyrimidine-2,4-diamine,
la 5-[5-iodo-2-isopropyl-4-(2,2,2-trifluoro-éthoxy)-phénoxy]-pyrimidine-2,4-diamine,
la 5-[5-iodo-2-isopropyl-4-(3,4,5-triméthoxy-benzyloxy)-phénoxy]-pyrimidine-2,4-diamine,
le 2-[2-(2,4-diamino-pyrimidine-5-yloxy)-4-iodo-5-méthoxy-phényl]-propane-2-ol,
la 5-[2-isopropyl-4-méthoxy-5-(4-méthylthiophène-3-yl)-phénoxy]-pyrimidine-2,4-diamine,
la 5-(2-isopropyl-4-méthoxy-5-nitrophénoxy)-pyrimidine-2,4-diamine,
la 5-[5-iodo-2-isopropyl-4-(1-méthyl-pipéridine-2-yl-méthoxy)-phénoxy]-pyrimidine-2,4-diamine,
la 5-[5-iodo-2-isopropyl-4-(tétrahydropyrane-2-ylméthoxy)-phénoxy]-pyrimidine-2,4-diamine,

la 5-(2-isopropyl-4-méthoxy-5-[1,2,4]triazole-1-yl-phénoxy)-pyrimidine-2,4-diamine,
la 5-(2-isopropyl-4,5-diméthoxy-phénoxy)-N^2-(2-méthoxy-éthyl)-pyrimidine-2,4-diamine,
la 5-(4'-fluoro-4-isopropyl-6-méthoxy-biphényl-3-yloxy)-pyrimidine-2,4-diamine,
la 5-(5-chloro-2-isopropyl-4-méthoxy-phénoxy)-N^2-(2,2,2-trifluoro-éthyl)-pyrimidine-2,4-diamine,
le 5-(2,4-diamino-pyrimidine-5-ylméthyl)-4-isopropyl-2-méthoxy-benzonitrile,
la 5-[2-isopropyl-4-méthoxy-5-(2-méthyl-thiazole-5-yl)-phénoxy]-pyrimidine-2,4-diamine,
la 5-(2-isopropyl-4-méthoxy-6-méthyl-phénoxy)-pyrimidine-2,4-diamine,
la 5-(5-éthanesulfonyl-2-isopropyl-4-méthoxy-phénoxy)-pyrimidine-2,4-diamine,
la 5-(2-isopropyl-4-méthoxy-5-thiazole-5-yl-benzyl)-pyrimidine-2,4-diamine,
le 1-[5-(2,4-diamino-pyrimidine-5-yloxy)-4-isopropyl-2-méthoxyphényl]-1*H*-imidazole-2-thiol,
la 5-[2-isopropyl-4-méthoxy-5-(1-méthyl-1*H*-pyrazole-4-yl)-phénoxy]-pyrimidine-2,4-diamine,
la 5-[5-iodo-2-isopropyl-4-(pyridine-4-ylméthoxy)-phénoxy]-pyrimidine-2,4-diamine,
la 5-(4-iodo-2-isopropyl-phénoxy)-pyrimidine-2,4-diamine,
la 5-(5-iodo-4-isopropyl-2-méthoxybenzyl)-pyrimidine-2,4-diamine,
la 5-(5-fluoro-2-isopropyl-4-méthoxy-phénoxy)-pyrimidine-2,4-diamine,
la 5-(4'-fluoro-5-isopropyl-2-méthoxy-biphényl-4-yloxy)-pyrimidine-2,4-diamine,
la 5-[4-(3-fluorobenzyloxy)-5-iodo-2-isopropyl-phénoxy]-pyrimidine-2,4-diamine,
la 5-(4-bromo-2-isopropyl-phénoxy)-pyrimidine-2,4-diamine,
la 5-(4-furane-2-yl-2-isopropyl-5-méthoxy-phénoxy)-pyrimidine-2,4-diamine,
le 2-[5-(2,4-diamino-pyrimidine-5-yloxy)-4-isopropyl-2-méthoxyphényl]-propane-2-ol,
la 5-[4-(2,6-difluorobenzyloxy)-5-iodo-2-isopropyl-phénoxy]-pyrimidine-2,4-diamine,
la 5-(5-iodo-2-isopropyl-4-phénéthyloxy-phénoxy)-pyrimidine-2,4-diamine,
la 5-(2-isopropyl-4-méthoxy-5-pyridine-4-yl-phénoxy)-pyrimidine-2,4-diamine,
la 5-(2-isopropyl-4,5-diméthylbenzyl)-N^2-(1-méthyl-pipéridine-4-yl)-pyrimidine-2,4-diamine,
le 5-(2,4-diamino-pyrimidine-5-yloxy)-N-éthyl-4-isopropyl-2-méthoxy-benzènesulfonamide,
la 5-[2-isopropyl-5-(4-méthanesulfonyl-pipérazine-1-yl)-4-méthoxy-phénoxy]-pyrimidine-2,4-diamine,
la 5-(2-isopropyl-4-méthoxy-5-pyridine-3-yl-phénoxy)-pyrimidine-2,4-diamine,
le 5-(2,4-diamino-pyrimidine-5-yloxy)-4-isopropyl-2-méthoxy-N,N-diméthylbenzamide
la 5-[5-(2,5-diméthyl-pyrrole-1-yl)-2-isopropyl-4-méthoxy-phénoxy]-pyrimidine-2,4-diamine,
la 5-(2-éthyl-3-méthoxybenzyl)-pyrimidine-2,4-diamine,
la 5-(2-bromo-4,5-diméthoxy-phénoxy)-pyrimidine-2,4-diamine,
la 5-(2-isopropyl-5-méthanesulfonyl-4-méthoxy-phénoxy)-N^2-(2,2,2-trifluoro-éthyl)-pyrimidine-2,4-diamine ; et
le 5'-(2,4-diamino-pyrimidine-5-yloxy)-4'-isopropyl-2'-méthoxy-biphényl-3-carbonitrile.

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