DIAMINOPYRIMIDINES AS P2X3 AND P2X2/3 MODULATORS

Methods for treating respiratory and gastrointestinal diseases mediated by a P2X3 receptor antagonist, the methods comprising administering to a subject in need thereof an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof, wherein D, X, Y, R1, R2, R3, R4, R5, R6, R7, and R8 are as defined herein.

(57) Abstract

(54) Title
This invention pertains to compounds and methods for treatment of diseases associated with P2X purinergic receptors, and more particularly to methods of using P2X₃ and/or P2X₂/₃ antagonists for treatment of genitourinary, gastrointestinal, respiratory, and pain-related diseases, conditions and disorders.

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.

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 homomorphic receptors, P2X₁; P2X₂; P2X₃; P2X₄; P2X₅; and P2X₇; and three heteromeric receptors P2X₂/₃, P2X₄/₆, P2X₁/₅ (See, e.g., Chen et al. (1995) Nature 377:428-431; Lewis et al. (1995) Nature 377:432-435; and Burnstock (1997) Neuropharmacol. 36:1127-1139). The structure and chromosomal mapping of mouse genomic P2X₃ receptor subunit has also been described (Souslova et al. (1997) Gene 195:101-111). In vitro, co-expression of P2X₂ and P2X₃ 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).
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.

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)). P2X3 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 P2X3 and/or P2X2/3 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 J 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 P2X2 and P2X3 are involved in nociception, and that modulators of P2X receptors are potentially useful as analgesics.

There is accordingly a need for methods of treating diseases, conditions and disorders mediated by P2X3 and/or P2X2/3 receptors, as well as a need for compounds that act as modulators of P2X receptors, including antagonists of P2X3 and P2X2/3 receptors. The present invention satisfies these needs as well as others.

Other researchers have shown that P2X3 receptors are expressed in human colon, and are expressed at higher levels in inflamed colon than in normal colon (Yiangou et al, Neurogastroenterol Mot (2001) 13:365-69). Other researchers have implicated the P2X3 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).

Inge Brouns et al. (Am J Respir Cell Mol Biol (2000) 23:52-61) found that P2X3 receptors are expressed in pulmonary neuroepithelial bodies (NEBs), implicating the receptor in pain transmission in the lung. More recently, others have implicated P2X2 and P2X3 receptors in P0 detection in pulmonary NEBs (Rong et al., J Neurosci (2003) 23(36):11315-21).

The invention provides methods for treating a respiratory disease mediated by a P2X3 or P2X2/3 receptor antagonist, said method comprising administering to a subject in need thereof an effective amount of a compound of formula (I):

\[
\text{I}
\]

or a pharmaceutically acceptable salt thereof, wherein:

- X is \(-\text{CH}_2-; -\text{O}; -\text{C(O)}-; -\text{CHOH}-; -\text{S(O)}_n^m-\) or \(-\text{NR}^\text{c}-\) wherein n is from 0 to 2 and c is hydrogen or alkyl;
- Y is hydrogen; or \(-\text{NR}^d\text{R}^e\) wherein one of \text{R}^d and \text{R}^e is hydrogen, and the other is hydrogen; alkyl; cycloalkyl; cycloalkylalkyl; haloalkyl; haloalkoxy; hydroxyalkyl; alkoxyalkyl; acetyl; alkylsulfonyl; alkylsulfonylalkyl; aminocarboxyloxyalkyl; hydroxycarboxylalkyl; hydroxyalkyloxycarbonylalkyl; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl;
- D is an optional oxygen;
- \text{R}^1 is alkyl; alkenyl; cycloalkyl; cycloalkenyl; halo; haloalkyl; hydroxyalkyl; or alkoxy;
- \text{R}^2, \text{R}^3, \text{R}^4 and \text{R}^5 each independently is hydrogen; alkyl; alkenyl; amino; halo; amidino; haloalkyl; alkyl; hydroxy; haloalkoxy; nitro; hydroxyalkyl; alkoxyalkyl; hydroxyalkoxy; alkynylalkoxy; alkyloxoyl; alkylsulfonyl; arylsulfonyl; cyano; aryl; heteroaryl; heterocyclyl; heterocyclylalkoxy; arylhexoy; heteroaryloxy; aralkyloxy; heteroaralkyloxy; optionally substituted phenoxy; \(-\text{CH}_2\)\(_m\)\(\text{Z}^n\)-\(\text{CO}\)-\(\text{R}^f\) or \(-\text{CH}_2\)\(_m\)\(\text{Z}^n\)-\(\text{SO}_2\)-\(\text{NR}^g\)\(_n\)-\(\text{R}^f\) where m and n each independently is 0 or 1, Z is O or NR\(^g\); \text{R}^f is hydrogen, alkyl, hydroxy, alkoxy, amino, hydroxyalkyl or alkoxyalkyl, and each \text{R}^g is independently hydrogen or alkyl; or \text{R}^2 and \text{R}^4 may together form an alkylene dioxy; or \text{R}^2 and \text{R}^4 together with the atoms to which they are attached may form a five or six-membered ring that
optionally includes one or two heteroatoms selected from O, S and N; or R² and R³ may together form an alkylene dioxy; or R² and R³ together with the atoms to which they are attached may form a five or six-membered ring that optionally includes one or two heteroatoms selected from O, S and N;

R⁶ is hydrogen; alkyl; halo; haloalkyl; amino; or alkoxy; and

one of R⁷ and R⁸ 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.

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

Exemplary gastrointestinal diseases include Irritable Bowel Syndrome (IBS), Inflammatory Bowel Disease (IBD), biliary colic and other biliary disorders, renal colic, diarrhea-dominant IBS, pain associated with GI distension, and the like.

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.

“Agonist” refers to a compound that enhances the activity of another compound or receptor site.

“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. C₁-C₆alkyl. Examples of alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, isobutyl, sec-butyl, tert-butyl, pentyl, n-hexyl, octyl, dodecyl, and the like.

“Alkenyl” means a linear monovalent hydrocarbon radical of two to six carbon atoms or a branched monovalent hydrocarbon radical of three to six carbon atoms, containing at least one double bond, e.g., ethenyl, propenyl, and the like.
"Alkynyl" means a linear monovalent hydrocarbon radical of two to six carbon atoms or a branched monovalent hydrocarbon radical of three to six carbon atoms, containing at least one triple bond, e.g., ethynyl, propynyl, and the like.

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

“Alkoxy” means a moiety of the formula –OR, wherein R is an alkyl moiety as defined herein. Examples of alkoxy moieties include, but are not limited to, methoxy, ethoxy, isopropoxy, and the like.

“Alkoxyalkyl” means a moiety of the formula Ra-O-Rb-, where R is alkyl and Rb is alkylene as defined herein. Exemplary alkoxyalkyl groups include, by way of example, 2-methoxyethyl, 3-methoxypropyl, 1-methyl-2-methoxyethyl, 1-(2-methoxyethyl)-3-methoxypropyl, and 1-(2-methoxyethyl)-3-methoxypropyl.

"Alkylcarbonyl" means a moiety of the formula –R’-R”, where R’ is oxo and R” is alkyl as defined herein.

"Alkylsulfonyl" means a moiety of the formula –R’-R”, where R’ is -SO2- and R” is alkyl as defined herein.

"Alkylsulfonylalkyl means a moiety of the formula -R'-R"-R’’, where where R’ is alkylene, R’ is -SO2- and R’’ is alkyl as defined herein.

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

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

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

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

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

5 "Alkylsulfonylamido" means a moiety of the formula -NR'SO₂-R wherein R is alkyl and R' is hydrogen or alkyl.

"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.

10 "Alkynylalkoxy" means a group of the formula -O-R-R' wherein R is alkylene and R' is alkynyl as defined herein.

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

“Aryl” means a monovalent cyclic aromatic hydrocarbon moiety consisting of a mono-, bi- or tricyclic aromatic ring. The aryl group can be optionally substituted as defined herein. Examples of aryl moieties include, but are not limited to, optionally substituted phenyl, naphthyl, phenanthryl, fluorenyl, indenyl, pentalenyl, azulenyl, oxydiphenyl, biphenyl, methylenediphenyl, aminodiphenyl, diphenylsulfidyl, diphenylsulfonyl, diphenylisopropylidenyl, benzodioxanly, benzofuranyl, benzodioxylyl, benzopyranyl, benzomorpholiny, methylenedioxyphenyl, ethylenedioxyphenyl, and the like, including partially hydrogenated derivatives thereof.

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

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

"Arylsulfonyl means a group of the formula -SO₂-R wherein R is aryl as defined herein.

"Aryloxy" means a group of the formula -O-R wherein R is aryl as defined herein.
"Aralkyloxy" means a group of the formula \(-\text{O-R-R}'\) wherein R is alkylene and R' is aryl as defined herein.

"Cyanoalkyl" means a moiety of the formula \(-\text{R'-R''}\), where R' is alkylene as defined herein and R'' is cyano or nitrile.

"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, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and the like, including partially unsaturated derivatives thereof.

"Cycloalkylalkyl" means a moiety of the formula \(-\text{R'-R''}\), where R' is alkylene and R'' is cycloalkyl as defined herein.

"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 \(-\text{OR}^a\), \(-\text{NR}^b\text{R}^c\), and \(-\text{S(O)}_n\text{R}^d\) (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, but are not limited to, 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, aminosulfonylethyl, aminosulfonylethyl, aminosulfonylpropyl, methylaminosulfonylethyl, methylaminosulfonylethyl, and the like.

"Heteroaryl" means a monocyclic or bicyclic radical of 5 to 12 ring atoms having at least one aromatic ring containing one, two, or three ring heteroatoms selected from N, O, or S, the remaining ring atoms being C, with the understanding that the attachment point of the heteroaryl radical will be on an aromatic ring. The heteroaryl ring may be optionally substituted as defined herein. Examples of heteroaryl moieties include, but are not limited to, optionally substituted imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, pyrazinyl, thienyl, benzothienyl, thiophenyl, furanyl, pyranyl, pyridyl, pyrrol-

"Heteroaryl" means a group of the formula \(-\text{O-R-R}'\) wherein R is alkylene and R' is aryl as defined herein.

"Cyanoalkyl" means a moiety of the formula \(-\text{R'-R''}\), where R' is alkylene as defined herein and R'' is cyano or nitrile.

"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, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and the like, including partially unsaturated derivatives thereof.

"Cycloalkylalkyl" means a moiety of the formula \(-\text{R'-R''}\), where R' is alkylene and R'' is cycloalkyl as defined herein.

"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 \(-\text{OR}^a\), \(-\text{NR}^b\text{R}^c\), and \(-\text{S(O)}_n\text{R}^d\) (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, cyclo-

"Heteroaryl" means a monocyclic or bicyclic radical of 5 to 12 ring atoms having at least one aromatic ring containing one, two, or three ring heteroatoms selected from N, O, or S, the remaining ring atoms being C, with the understanding that the attachment point of the heteroaryl radical will be on an aromatic ring. The heteroaryl ring may be optionally substituted as defined herein. Examples of heteroaryl moieties include, but are not limited to, optionally substituted imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, pyrazinyl, thienyl, benzothienyl, thiophenyl, furanyl, pyranyl, pyridyl, pyrrol-

"Heteroaryl" means a group of the formula \(-\text{O-R-R}'\) wherein R is alkylene and R' is aryl as defined herein.
tiopyranyl, benzimidazolyl, benzooxazolyl, benzooxadiazolyl, benzothiazolyl, benzothia-
diazolyl, benzopyranyl, indolyl, isoindolyl, triazolyl, triazinyl, quinoxaliny, purinyl, quin-
azoliny, quinoliziny, naphthyridiny, pteridiny, carbazoliny, azepiny, diazepiny, acridiny
and the like, including partially hydrogenated derivatives thereof.

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

"Heteroarylsulfonyl means a group of the formula -SO2-R wherein R is heteroaryl as
defined herein.

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

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

The terms “halo”, “halogen” and "halide", which may be used interchangeably, refer to a
substituent fluoro, chlora, broma, or iodo.

15 “Haloalkyl” means alkyl as defined herein in which one or more hydrogen has been re-
placed with same or different halogen. Exemplary haloalkyls include –CH2Cl, –CH2CF3,
-CH2CCl3, perfluoroalkyl (e.g., –CF3), and the like.

“Haloalkoxy” means a moiety of the formula –OR, wherein R is a haloalkyl moiety as
defined herein. An exemplary haloalkoxy is difluoromethoxy.

20 “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.

“Heterocycyl” means a monovalent saturated moiety, consisting of one to three rings, in-
corporating one, two, or three or four heteroatoms (chosen from nitrogen, oxygen or
sulfur). The heterocycyl ring may be optionally substituted as defined herein. Examples
of heterocycyl moieties include, but are not limited to, optionally substituted piperidiny,
piperaziny, homopiperaziny, azepiny, pyrroldiny, pyrazoliny, imidazoliny, imidazol-
idiny, pyridiny, pyridaziny, pyridiminy, oxazolidiny, isoxazolidiny, morpholiny,
thiazolidiny, isothiazolidiny, quinclidiny, quinoliny, isoquinoliny, benzimidazolyn,
thiadiazolidiny, benzothiazolidiny, benzazolylidency, dihydrofurly, tetrahydrofurly,
dihydropyrany, tetrahydropyrany, thiamorpholiny, thiamorpholinylsulfoxide, thiamor-
pholinylsulfone, dihydroquinolinyl, dihydriosoquinolinyl, tetrahydroquinolinyl, tetra-
hydriosoquinolinyl, and the like.

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

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

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

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

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

"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.

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

"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.

"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, but are not limited
to, hydroxymethyl, 2-hydroxyethyl, 2-hydroxypropyl, 3-hydroxypropyl, 1-(hydroxy-
methyl)-2-methylpropyl, 2-hydroxybutyl, 3-hydroxybutyl, 4-hydroxybutyl, 2,3-dihydroxy-
propyl, 2-hydroxy-1-hydroxymethylethyl, 2,3-dihydroxybutyl, 3,4-dihydroxybutyl and

20 2-(hydroxymethyl)-3-hydroxypropyl

"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 substitu-
ten. Representative examples include, but are not limited to, 2-, 3-, or 4-hydroxycyclo-
heptyl, and the like.
"Urea" or "ureido" means a group of the formula \(-\text{NR}'-\text{C(O)}-\text{NR}''\text{R}''\) wherein \(\text{R}'\), \(\text{R}''\) and \(\text{R}''\) each independently is hydrogen or alkyl.

"Carbamate" means a group of the formula \(-\text{O-C(O)}-\text{NR}'\text{R}''\) wherein \(\text{R}'\) and \(\text{R}''\) each independently is hydrogen or alkyl.

"Carboxy" means a group of the formula \(-\text{O-C(O)}-\text{OH}\).

"Sulfonamido" means a group of the formula \(-\text{SO}_2-\text{NR}'\text{R}''\) wherein \(\text{R}', \text{R}''\) and \(\text{R}''\) each independently is hydrogen or alkyl.

"Optionally substituted", when used in association with "aryl", phenyl", "heteroaryl" "cycloalkyl" or "heterocycl"cyl", 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, \(-\text{COR}\) (where \(\text{R}\) is hydrogen, alkyl, phenyl or phenylalkyl), \(-(\text{CR}'\text{R}'')\text{COOR}\) (where \(n\) is an integer from 0 to 5, \(\text{R}'\) and \(\text{R}''\) are independently hydrogen or alkyl, and \(\text{R}\) is hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, phenyl or phenylalkyl), or \(-(\text{CR}'\text{R}'')\text{CONR}\) (where \(n\) is an integer from 0 to 5, \(\text{R}'\) and \(\text{R}''\) are independently hydrogen or alkyl, and \(\text{R}^a\) and \(\text{R}^b\) are, independently of each other, hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, phenyl or phenylalkyl).

“Leaving group” means the group with the meaning conventionally associated with it in synthetic organic chemistry, i.e., an atom or group displaceable under substitution reaction conditions. Examples of leaving groups include, but are not limited to, halogen, alkane- or arylene sulfonyloxy, such as methanesulfonyloxy, ethanesulfonyloxy, thiomethyl, benzene-sulfonyloxy, tosloxy, and thienyloxy, dihalophosphinoxyloxy, optionally substituted benzylxoy, isopropylxoy, acyloxy, and the like.

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

“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.

"Disease" and “Disease state” means any disease, condition, symptom, disorder or indication.
“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, 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, pyridine, and the like. Unless specified to the contrary, the solvents used in the reactions of the present invention are inert solvents.

“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.

“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, phosphoric acid, and the like; 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, trimethylacetic acid, and the like;
- 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, tromethamine, and the like. Acceptable inorganic bases include aluminum hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate and sodium hydroxide.

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.

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

“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$_2$O, such combination being able to form one or more hydrate.

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

“Disorders of the urinary tract” or “uropathy” used interchangeably with “symptoms of the urinary tract” means the pathologic changes in the urinary tract. Examples of urinary tract disorders include, but are not limited to, incontinence, benign prostatic hypertrophy (BPH), prostatitis, detrusor hyperreflexia, outlet obstruction, urinary frequency, nocturia, urinary urgency, overactive bladder, pelvic hypersensitivity, urge incontinence, urethritis, prostatodynia, cystitis, idiopathic bladder hypersensitivity, and the like.
"Disease states associated with the urinary tract" or "urinary tract disease states" or "uro-pathy" used interchangeably with "symptoms of the urinary tract" mean the pathologic changes in the urinary tract, or dysfunction of urinary bladder smooth muscle or its innervation causing disordered urinary storage or voiding. Symptoms of the urinary tract include, but are not limited to, overactive bladder (also known as detrusor hyperactivity), outlet obstruction, outlet insufficiency, and pelvic hypersensitivity.

"Overactive bladder" or "detrusor hyperactivity" includes, but is not limited to, the changes symptomatically manifested as urgency, frequency, altered bladder capacity, incontinence, micturition threshold, unstable bladder contractions, sphincteric spasticity, detrusor hyperreflexia (neurogenic bladder), detrusor instability, and the like.

"Outlet obstruction" includes, but is not limited to, benign prostatic hypertrophy (BPH), urethral stricture disease, tumors, low flow rates, difficulty in initiating urination, urgency, suprapubic pain, and the like.

"Outlet insufficiency" includes, but is not limited to, urethral hypermobility, intrinsic sphincteric deficiency, mixed incontinence, stress incontinence, and the like.

"Pelvic Hypersensitivity" includes, but is not limited to, pelvic pain, interstitial (cell) cystitis, prostatodynia, prostatitis, vulvodynia, urethritis, orchialgia, overactive bladder, and the like.

"Respiratory disorder" or "respiratory disease" refers to, without limitation, chronic obstructive pulmonary disease (COPD), asthma, bronchospasm, and the like.

"Gastrointestinal disorder" ("GI disorder") or disease refers to, without limitation, Irritable Bowel Syndrome (IBS), Inflammatory Bowel Disease (IBD), biliary colic and other biliary disorders, renal colic, diarrhea-dominant IBS, pain associated with GI distension, and the like.

"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.
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.

“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.

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.

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.

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

In certain embodiments of the invention the respiratory disease may be chronic obstructive pulmonary disease (COPD), asthma, or bronchospasm.

In certain embodiments of the invention the gastrointestinal disease may be Irritable Bowel Syndrome (IBS), Inflammatory Bowel Disease (IBD), biliary colic and other biliary disorders, renal colic, diarrhea-dominant IBS, or pain associated with GI distension.

In many embodiments of the invention the disease is a respiratory disease selected from chronic obstructive pulmonary disease (COPD), asthma, and bronchospasm.
In many embodiments of the invention the disease is a gastrointestinal disease selected from Irritable Bowel Syndrome (IBS), Inflammatory Bowel Disease (IBD), biliary colic, renal colic, diarrhea-dominant IBS, and pain associated with GI distension.

In many embodiments of formula I Y is –NR³R⁴.

5 In certain embodiments of formula I R⁵ and R⁶ are hydrogen.

In certain embodiments of formula I R² is hydrogen.

In certain embodiments of formula I X is –CH₂- or -O-. Preferably X is O.

In certain embodiments of formula I D is absent.

In certain embodiments of formula I R¹ is alkyl, alkenyl or cycloalkyl. Preferably, R¹ is ethyl, cyclopropyl, isopropenyl or isopropyl. More preferably R¹ is isopropyl.

In certain embodiments formula I one of R⁷ and R⁸ is hydrogen, and the other is: alkyl, cycloalkyl; cycloalkylalkyl; haloalkyl; hydroxyalky; alkoxyalkyl; alkylsulfonylalkyl; acetyl; alkylsulfonyl; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl.

15 In certain embodiments of formula I one of R⁷ and R⁸ is hydrogen and the other is alkyl, hydroxyalkyl or haloalkyl.

In certain embodiments formula I one of R⁹ and R¹⁰ is hydrogen, and the other is: alkyl, cycloalkyl; cycloalkylalkyl; haloalkyl; hydroxyalky; alkoxyalkyl; alkylsulfonylalkyl; acetyl; alkylsulfonyl; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl.

20 In certain embodiments of formula I one of R⁹ and R¹⁰ is hydrogen and the other is alkyl, hydroxyalkyl or haloalkyl.

In certain embodiments of formula I R³ and R⁴ each independently is halo, alkoxy, haloalkoxy or alkylsulfonyl.

25 In certain embodiments of formula I R³ is halo, alkoxy, haloalkoxy or hydroxy. Preferably R³ is methoxy, fluoro, or chloro. More preferably R³ is methoxy. In certain embodiments R³ is hydroxy.
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.

In certain embodiments of formula I $R^7$, $R^8$, $R^4$ and $R^3$ are hydrogen.

In certain embodiments of formula I $R^4$ is heteroaryl. The heteroaryl may be, in certain embodiments, tetrazolyl, pyrazolyl, oxazolyl, imidazolyl, thiazolyl, 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-thioly-imidazol-1-yl, pyridin-2-yl, or 2,5-dimethyl-pyrrol-1-yl.

In certain embodiments of formula I $R^3$ and $R^4$ together with the atoms to which they are attached may form a five or six-membered ring that optionally includes one or two heteroatoms selected from O, S and N. In many such embodiments $R^3$ and $R^4$ together with the atoms to which they are attached may form: a five membered aromatic with one nitrogen, i.e. a pyrrol ring; a five membered aromatic with two nitrogens, i.e., a pyrazol or imidazol ring; a five membered aromatic with one nitrogen and one oxygen, i.e., an oxazole or isoxazole ring; a five membered aromatic with one nitrogen and one sulfur, i.e., a thiazole or isothiazole ring; a five membered aromatic ring with one oxygen, i.e., a furanyl ring; or a five membered aromatic with one sulfur, i.e., a thiophenyl ring.

In certain embodiments of formula I $R^2$ and $R^3$ together with the atoms to which they are attached may form a five or six-membered ring that optionally includes one or two heteroatoms selected from O, S and N. In many such embodiments $R^3$ and $R^4$ together with the atoms to which they are attached may form: a five membered aromatic with one nitrogen, i.e. a pyrrol ring; a five membered aromatic with two nitrogens, i.e., a pyrazol or imidazol ring; a five membered aromatic with one nitrogen and one oxygen, i.e., an oxazole or isoxazole ring; a five membered aromatic with one nitrogen and one sulfur, i.e., a thiazole or isothiazole ring; a five membered aromatic ring with one oxygen, i.e., a furanyl ring; or a five membered aromatic with one sulfur, i.e., a thiophenyl ring.
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, benzo thiophenyl, pyridinyl and pyrrolyl, and \( R^5 \) and \( R^6 \) are hydrogen.

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.

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, benzo thiophenyl, pyridinyl and pyrrolyl, and \( R^5 \) and \( R^6 \) are hydrogen.

In another preferred embodiment of formula \( I \) \( X \) is -O- or \(-\text{CH}_2\)-, \( R^1 \) 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.

In another preferred embodiment of formula \( I \) \( X \) is -O- or \(-\text{CH}_2\)-, \( R^1 \) 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 \( R^9 \) and \( R^9 \) is hydrogen and the other is hydrogen, alkyl, acetyl, hydroxy alkyl or halo alkyl.

In another preferred embodiment of formula \( I \) \( X \) is -O- or \(-\text{CH}_2\)-, \( R^1 \) is isopropyl, isopropenyl, cyclopropyl 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.
In another preferred embodiment of formula I X is -O- or -CH₂-, R¹ is isopropyl or iodo, R² is hydrogen, R³ is methoxy, hydroxy, chloro, bromo or iodo, R⁴ methoxy, chloro, bromo or iodo, R⁵ and R⁶ are hydrogen, R⁷ and R⁸ are hydrogen, and one of R⁹ and R¹⁰ is hydrogen and the other is hydrogen, alkyl, hydroxyalkyl or haloalkyl.

In another preferred embodiment of formula I X is -O- or -CH₂-, R¹ is isopropyl, R² is hydrogen, R³ is methoxy, hydroxy, chloro, bromo or iodo, R⁴ is methoxy, chloro, bromo or iodo, and R⁵ and R⁶ are hydrogen.

In another preferred embodiment of formula I X is -O- or -CH₂-, R¹ is isopropyl, R² is hydrogen, R³ is methoxy, hydroxy, chloro, bromo or iodo, R⁴ is methoxy, chloro, bromo or iodo, and R⁵ and R⁶ are hydrogen and the other is hydrogen, alkyl, hydroxyalkyl or haloalkyl.

In certain embodiments the invention provides methods for treating a respiratory disease or a gastrointestinal disease mediated by a P2X₃ or P2X₂/₃ receptor antagonist, said method comprising administering to a subject in need thereof an effective amount of a compound of formula II

![Chemical Structure](image)

wherein:
X is -CH₂- or -O-;
R¹ is alkyl; alkenyl; cycloalkyl; cycloalkenyl; or halo;
R³ and R⁴ each independently is alkyl; alkenyl; amino; halo; amido; haloalkyl; alkoxy; hydroxy; haloalkoxy; nitro; hydroxyalkyl; alkoxyalkyl; hydroxyalkoxy; alkynylalkoxy; alkylsulfonyl; arylsulfonyl; cyano; aryl; heteroaryl; heterocyclyl; heterocyclylalkoxy; arylalkyl; heteroaryalkyl; optionally substituted phenoxy - (CH₂)ₘ-(Z)ₙ-(CO)-R⁴ or -(CH₂)ₘ-(Z)ₙ-SO₂-(NR⁸)ₙ-R¹ where m and n each independently is 0 or 1, Z is O or NR⁸, R¹ is hydrogen, alkyl, hydroxy, alkoxy, amino, hydroxyalkyl or alkoxyalkyl, and each R⁸ is independently hydrogen or alkyl; or R³ and R⁴ may together form an alkylene dioxy; or R³ and R⁴ together with the atoms to which they are attached may form a five or six-membered ring that optionally includes one or two heteroatoms selected from O, S and N;
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; heteroaryalkyl; 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; alkylsulfonylalkyl; aminocarbonyloxyalkyl; hydroxycarbonylalkyl; hydroxyalkyloxycarbonylalkyl; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroaryalkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl.

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.

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; heteroaryalkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl.

In certain embodiments of formula II one of \( R^7 \) and \( R^8 \) is hydrogen and the other is alkyl, hydroxyalkyl or haloalkyl.

In certain embodiments formula II 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; heteroaryalkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl.

In certain embodiments of formula II one of \( R^d \) and \( R^e \) is hydrogen and the other is alkyl, hydroxyalkyl or haloalkyl.

In certain embodiments of formula II \( R^3 \) and \( R^4 \) each independently is halo, alkoxy, haloalkoxy or alkylsulfonyl.

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.

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 meth-
oxy, bromo, chloro or iodo. In specific embodiments R₄ may be methoxy, while in other embodiments R₄ may be iodo.

In certain embodiments of formula II R⁷, R⁸, R⁹ and R⁰ are hydrogen.

In certain embodiments of formula II R⁴ is heteroaryl. The heteroaryl may be, in certain embodiments, tetrazolyl, pyrazolyl, oxazolyl, imidazolyl, thiazolyl, thiophenyl, triazolyl, furanyl, isoxazolyl, oxadiazolyl, 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, 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-thioly-imidazol-1-yl, pyridin-2-yl, or 2,5-dimethyl-pyrrol-1-yl).

In certain embodiments of formula II R³ and R⁴ together with the atoms to which they are attached may form a five or six-membered ring that optionally includes one or two heteroatoms selected from O, S and N. In many such embodiments R³ and R⁴ together with the atoms to which they are attached may form: a five membered aromatic with one nitrogen, i.e. a pyrrol ring; a five membered aromatic with two nitrogens, i.e., a pyrazol or imidazol ring; a five membered aromatic with one nitrogen and one oxygen, i.e., an oxazole or isoxazole ring; a five membered aromatic with one nitrogen and one sulfur, i.e., a thiazole or isothiazole ring; a five membered aromatic with one oxygen, i.e., a furanyl ring; or a five membered aromatic with one sulfur, i.e., a thiophenyl ring.

In one preferred embodiment of formula II X is -O-, R¹ is alkyl, alkenyl, cycloalkyl, or halo, R³ is alkoxy, hydroxy or halo, and R⁴ is alkoxy, halo, alkenyl, or heteroaryl selected from tetrazolyl, pyrazolyl, oxazolyl, imidazolyl, thiazolyl, thiophenyl, triazolyl, furanyl, isoxazolyl, oxadiazolyl, benzothiophenyl, pyridinyl and pyrrolyl.

In another preferred embodiment of formula II X is -O-, R¹ is alkyl, alkenyl, cycloalkyl, or halo, R³ is alkoxy, hydroxy or halo, and R⁴ is alkoxy, halo, or alkenyl.

In another preferred embodiment of formula II X is -O-, R¹ is alkyl, alkenyl, cycloalkyl, or halo, R³ is alkoxy, hydroxy or halo, and R⁴ is heteroaryl selected from tetrazolyl, pyrazolyl, oxazolyl, imidazolyl, thiazolyl, thiophenyl, triazolyl, furanyl, isoxazolyl, oxadiazolyl, benzothiophenyl, pyridinyl and pyrrolyl.
In another preferred embodiment of formula II X is -O-, R³ is alkyl, alkenyl, cycloalkyl, or halo, R³ is alkoxy, hydroxy or halo, R⁴ is alkoxy, halo, or alkenyl, R⁷ and R⁸ are hydrogen, and one of R⁰ and R⁰ is hydrogen and the other is hydrogen, alkyl, hydroxyalkyl or haloalkyl.

In another preferred embodiment of formula II X is -O- or -CH₂-, R¹ is isopropyl, isopropenyl, cyclopropyl or iodo, R³ is methoxy, hydroxy, chloro, bromo or iodo, and R⁴ is methoxy, chloro, bromo or iodo.

In another preferred embodiment of formula II X is -O- or -CH₂-, R¹ is isopropyl, isopropenyl, cyclopropyl or iodo, R³ is methoxy, hydroxy, chloro, bromo or iodo, R⁴ methoxy, chloro, bromo or iodo, R⁷ and R⁸ are hydrogen, and one of R⁰ and R⁰ is hydrogen and the other is hydrogen, alkyl, hydroxyalkyl or haloalkyl.

In another preferred embodiment of formula II X is -O- or -CH₂-, R¹ is isopropyl, R³ is methoxy, hydroxy, chloro, bromo or iodo, and R⁴ is methoxy, chloro, bromo or iodo.

In another preferred embodiment of formula II X is -O- or -CH₂-, R¹ is isopropyl, R³ is methoxy, hydroxy, chloro, bromo or iodo, R⁴ methoxy, chloro, bromo or iodo, R⁷ and R⁸ are hydrogen, and one of R⁰ and R⁰ is hydrogen and the other is hydrogen, alkyl, hydroxyalkyl or haloalkyl.

In certain embodiments the invention provides methods for treating a respiratory disease or a gastrointestinal disease mediated by a P2X₃ or P2X₂/₃ receptor antagonist, said method comprising administering to a subject in need thereof an effective amount of a compound of formula 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; alkylnylalkoxy;
alkylsulfonyl; arylsulfonyl; cyano; aryl; heteroaryl; heterocyclyl; heterocyclylalkoxy;
aryloxy; heteroaryloxy; aralkyloxy; heteroaralkyloxy; optionally substituted phenoxy;

$(\text{CH}_2)_m-(Z)_n-(\text{CO})-R^f$ or $(\text{CH}_2)_m-(Z)_n-\text{SO}_2-(\text{NR}_g)^n-R^f$ 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; or $R^3$ and $R^4$ may together form an alkylene dioxy; or $R^3$ and $R^4$ together with the atoms to which they are attached may form a five or six-membered ring that optionally includes one or two heteroatoms selected from O, S and N;

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; hydroxyalkoxyalkyl; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroaryalkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl; and

one of $R^3$ and $R^4$ is hydrogen, and the other is hydrogen; alkyl; cycloalkyl; cycloalkylalkyl;
haloalkyl; haloalkoxy; hydroxyalkyl; alkoxyalkyl; acetyl; alkylsulfonyl; alkylsulfonylalkyl;
aminocarbonyloxyalkyl; hydroxycarbonylalkyl; hydroxyalkoxyalkyl; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroaryalkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl.

In other embodiments the invention provides methods for treating a respiratory or gastrointestinal disease mediated by a P2X$_3$ or P2X$_{2/3}$ receptor antagonist, said method comprising administering to a subject in need thereof an effective amount of a compound of formula IV

![Diagram](IV)
wherein:

R\textsuperscript{1} is alkyl; alkenyl; cycloalkyl; cycloalkenyl or halo;

R\textsuperscript{3} and R\textsuperscript{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; heteroaryloxyalkoxy; optionally substituted phenoxy;
-(CH\textsubscript{2})\textsuperscript{m}(Z)\textsuperscript{n}-(CO)\textsuperscript{f} or -(CH\textsubscript{2})\textsuperscript{m}(Z)\textsuperscript{n}SO\textsuperscript{2}-(NR\textsuperscript{g})\textsuperscript{n}R\textsuperscript{f} where m and n each independently is 0 or 1, Z is O or NR\textsuperscript{g}, R\textsuperscript{f} is hydrogen, alkyl, hydroxy, alkoxy, amino, hydroxy-
alkyl or alkoxyalkyl, and each R\textsuperscript{g} is independently hydrogen or alkyl; or R\textsuperscript{3} and R\textsuperscript{4} may
together form an alkylene dioxy; or R\textsuperscript{3} and R\textsuperscript{4} together with the atoms to which they
are attached may form a five or six-membered ring that optionally includes one or
two heteroatoms selected from O, S and N;

one of R\textsuperscript{2} and R\textsuperscript{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; heteroaryloxyalkyl; heteroarylsulfonyl; heterocyclyl;
or heterocyclylalkyl; and

one of R\textsuperscript{3} and R\textsuperscript{6} 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; heteroaryloxyalkyl; heteroarylsulfonyl; heterocyclyl;
or heterocyclylalkyl.

In certain embodiments of formula IV R\textsuperscript{1} is alkyl, alkenyl, cycloalkyl or halo. Preferably, R\textsuperscript{1}
is ethyl, cyclopropyl, isopropenyl, isopropyl or iodo. More preferably R\textsuperscript{1} is isopropyl or
iodo.

In certain embodiments formula III or formula IV one of R\textsuperscript{2} and R\textsuperscript{8} is hydrogen, and the
other is: alkyl, cycloalkyl; cycloalkylalkyl; haloalkyl; hydroxyalkyl; alkoxyalkyl; alkylsulfonyl-
alkyl; acetyl; alkylsulfonyl; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroaryloxyalkyl; hetero-
arylsulfonyl; heterocyclyl; or heterocyclylalkyl.

In certain embodiments of formula III or formula IV one of R\textsuperscript{2} and R\textsuperscript{8} is hydrogen and the
other is alkyl, hydroxyalkyl or haloalkyl.

In certain embodiments formula III or formula IV one of R\textsuperscript{4} and R\textsuperscript{6} 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.

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.

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

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.

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 methoxy, while in other embodiments $R^4$ may be iodo.

In certain embodiments of formula III or formula IV $R^3$, $R^8$, $R^d$ and $R^e$ are hydrogen.

In certain embodiments of formula III or formula IV $R^1$ is heteroaryl. The heteroaryl may be, in certain embodiments, tetrazolyl, pyrazolyl, oxazolyl, imidazolyl, thiazolyl, thienophenyl, 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-thioly-imidazol-1-yl, pyridin-2-yl, or 2,5-dimethyl-pyrrol-1-yl).

In certain embodiments of formula III or formula IV $R^3$ and $R^4$ together with the atoms to which they are attached may form a five or six-membered ring that optionally includes one or two heteroatoms selected from O, S and N. In many such embodiments $R^3$ and $R^4$ together with the atoms to which they are attached may form: a five membered aromatic with one nitrogen, i.e. a pyrrol ring; a five membered aromatic with two nitrogens, i.e., a pyrazol or imidazol ring; a five membered aromatic with one nitrogen and one oxygen, i.e., an oxazole or isoxazole ring; a five membered aromatic with one nitrogen and one sulfur,
i.e., a thiazole or isothiazole ring; a five membered aromatic with one oxygen, i.e., a furanyl ring; or a five membered aromatic with one sulfur, i.e., a thiophenyl ring.

In still other embodiments the invention provides methods for treating a respiratory or gastrointestinal disease mediated by a P2X3 or P2X2/3 receptor antagonist, said method comprising administering to a subject in need thereof an effective amount of a compound of formula V

\[
\begin{align*}
H_2C & -CH_3 \\
& \text{NR}^7R^8 \\
& \text{R}^3 \quad \text{R}^4 \\
& \text{N}('V) \quad \text{NR} \quad \text{R}^9 \quad \text{R}^8
\end{align*}
\]

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^i or -(CH_2)_m-(Z)_n-SO_2-(NR^8)_a-R^i where \( m \) and \( n \) each independently is 0 or 1, \( Z \) is O or NR^g, \( R^i \) is hydrogen, alkyl, hydroxy, alkoxy, amino, hydroxyalkyl or alkoxyalkyl, and each \( R^8 \) is independently hydrogen or alkyl; or \( R^3 \) and \( R^4 \) may together form an alkylene dioxy; or \( R^3 \) and \( R^4 \) together with the atoms to which they are attached may form a five or six-membered ring that optionally includes one or two heteroatoms selected from O, S and N;
- 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; heteroaryalkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl; and
- one of \( R^i \) and \( R^g \) is hydrogen, and the other is hydrogen; alkyl; cycloalkyl; cycloalkylalkyl;

In other embodiments the subject methods may utilize compounds of the formula VI.
wherein:

R³ and R⁴ each independently is alkyl; alkenyl; amino; halo; amido; haloalkyl; alkoxy; hydroxy; haloalkoxy; nitro; hydroxyalkyl; alkoxyalkyl; hydroxyalkoxy; alkynylalkoxy; alkylsulfonyl; arylsulfonyl; cyano; aryl; heteroaryl; heterocyclyl; heterocyclylalkoxy; arylalkyloxy; heteroarylalkyloxy; optionally substituted phenoxy; -(CH₂)ₘ-(Z)ₙ-(CO)-R⁵ or -(CH₂)ₘ-(Z)ₙ-SO₂-(NR₆)ₙ-R⁶ where m and n each independently is 0 or 1, Z is O or NR₆, R⁵ is hydrogen, alkyl, hydroxy, alkoxy, amino, hydroxyalkyl or alkoxyalkyl, and each R₆ is independently hydrogen or alkyl; or R³ and R⁴ may together form an alkylene dioxy; or R³ and R⁴ together with the atoms to which they are attached may form a five or six-membered ring that optionally includes one or two heteroatoms selected from O, S and N;

one of R⁷ and R⁸ is hydrogen, and the other is: hydrogen; alkyl; cycloalkyl; cycloalkylalkyl; haloalkyl; haloalkoxy; hydroxyalkyl; alkoxyalkyl; acetyl; alkylsulfonyl; alkylsulfonylalkyl; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl; and

one of R¹ and R² is hydrogen, and the other is hydrogen; alkyl; cycloalkyl; cycloalkylalkyl; haloalkyl; haloalkoxy; hydroxyalkyl; alkoxyalkyl; acetyl; alkylsulfonyl; alkylsulfonylalkyl; aminocarboxyloxyalkyl; hydroxycarboxyalkyl; hydroxyalkyloxyalkylalkyl; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl.

In certain embodiments formula (V) or formula (VI), one of R⁷ and R⁸ is hydrogen, and the other is alkyl, cycloalkyl; cycloalkylalkyl; haloalkyl; hydroxyalkyl; alkoxyalkyl; alkylsulfonylalkyl; acetyl; alkylsulfonyl; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl.

In certain embodiments of formula (V) or formula (VI), one of R³ and R⁴ is hydrogen, and the other is alkyl, hydroxyalkyl or haloalkyl.

In certain embodiments formula (V) or formula (VI), one of R¹ and R² is hydrogen, and the other is: alkyl, cycloalkyl; cycloalkylalkyl; haloalkyl; hydroxyalkyl; alkoxyalkyl; alkylsulfonylalkyl; acetyl; alkylsulfonyl; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl.
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.

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

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.

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 embodiments \( R^4 \) may be iodo.

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

In certain embodiments of formula (V) or formula (VI), \( R^d \) 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-thioly-imidazol-1-yl, pyridin-2-yl, or 2,5-dimethyl-pyrrol-1-yl).
i.e., a thiazole or isothiazole ring; a five membered aromatic with one oxygen, i.e., a furanyl ring; or a five membered aromatic with one sulfur, i.e., a thiophenyl ring.

In certain embodiments, the methods of the invention may use administration of a compound or compounds of the formula (VII)

$$\begin{align*}
&\text{R}_1\text{NR}_7\text{R}_8 \\
&\text{A'}\text{N}\text{NR}\text{R}_7\text{R}_8 \quad \text{E}
\end{align*}$$

wherein:

- **X** is -CH$_2$- or -O-;
- **R$_1$** is alkyl; alkenyl; cycloalkyl; cycloalkenyl; or halo;
- **R$_2$** is hydrogen; alkyl; alkenyl; amino; halo; amido; haloalkyl; alkoxy; hydroxy; haloalkoxy; nitro; hydroxyalkyl; alkoxyalkyl; hydroxyalkoxy; alkylnalkoxy; alkylsulfonyl; arylsulfonyl; cyano; aryl; heteroaryl; heterocyclyl; heterocyclylalkoxy; aralkyl; heteroaralkyl; optionally substituted phenoxy; or -(CH$_2$)$_m$-(Z)$_n$-(CO)-R$^f$ or -(CH$_2$)$_m$-(Z)$_n$-SO$_2$-(NR$_g$)$_n$-R$^g$ 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; alkylnalkoxy; alkylnalkoxyalkyl; alkylnalkoxyalkyl; aminocarbonyloxyalkyl; hydroxycarbonylalkyl; hydroxyalkylcarbonylalkyl; aryl; aralkyl; arylsulfonyl; cyano; aryl; heteroaryl; heteroaralkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl;
- one of R$_d$ and R$_c$ is hydrogen, and the other is hydrogen; alkyl; cycloalkyl; cycloalkylalkyl; haloalkyl; haloalkoxy; hydroxyalkyl; alkoxyalkyl; acetyl; alkylnalkoxy; alkylnalkoxyalkyl; aminocarbonyloxyalkyl; hydroxycarbonylalkyl; hydroxyalkylcarbonylalkyl; aryl; aralkyl; arylsulfonyl; cyano; aryl; heteroaryl; heteroaralkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl;
- Q is CR$^9$, one of A and E is O, S or NR$^{10}$ and the other is CR$^9$ or N; or
- Q is N, one of A and E is NR$^{10}$ and the other is CR$^9$;
- each R$^g$ is independently hydrogen, alkyl, halo or alkoxy; and
- R$^{10}$ is hydrogen, alkyl, hydroxyalkyl, alkoxyalkyl, -(CH$_2$)$_m$-(Z)$_n$-(CO)-R$^f$, or -(CH$_2$)$_m$-(Z)$_n$-SO$_2$-(NR$_g$)$_n$-R$^g$.

In certain embodiments of formula VII A is NR$^{10}$, and Q and E are CR$^9$. 
In certain embodiments of formula VII E is NR$_{10}$, and A and Q are CR$_9$.

In certain embodiments of formula VII Q is NR$_{10}$, and A and E are CR$_9$.

In certain embodiments of formula VII, A is O, E is N, and Q is CR$_9$.

In certain embodiments of formula VII A is N, E is O, and Q is CR$_9$.

In certain embodiments of formula VII A is S, E is N, and Q is CR$_9$.

In certain embodiments of formula VII A is N, E is S, and Q is CR$_9$.

In certain embodiments of formula VII E is S, and A and Q are CR$_9$.

In certain embodiments of formula VII E is 0, and A and Q are CR$_9$.

In certain embodiments of formula VII A is S, and E and Q are CR$_9$.

In certain embodiments of formula VII A is O, and E and Q are CR$_9$.

In certain embodiments of formula VII A is N, and E is S, and Q is CR$_9$.

In certain embodiments of formula VII A is N, E is S, and Q is CR$_9$.

In certain embodiments of formula VII, A is S, E is N, and Q is CR$_9$.

In certain embodiments of formula VII A is N, E is S, and Q is CR$_9$.

In certain embodiments of formula VII E is S, and A and Q are CR$_9$.

In certain embodiments of formula VII E is 0, and A and Q are CR$_9$.

In certain embodiments of formula VII A is S, and E and Q are CR$_9$.

In certain embodiments of formula VII A is O, and E and Q are CR$_9$.

In certain embodiments of formula VII one of R 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.

In certain embodiments of formula VII 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.

In certain embodiments of formula VII R$_2$ is hydrogen.

In certain embodiments of formula VII X is –CH$_2$- or -O-. Preferably X is O.

In certain embodiments of formula VII one of R$_1$ and R$_2$ is alkyl, alkenyl or cycloalkyl. Preferably, R$_1$ is ethyl, cyclopropyl, isopropenyl or isopropyl. More preferably R$_1$ is isopropyl.

In certain embodiments formula VII 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.
In certain embodiments of formula VII one of $R^d$ and $R^e$ is hydrogen and the other is alkyl, hydroxyalkyl or haloalkyl.

In certain embodiments of formula VII $R^7$, $R^8$, $R^d$ and $R^e$ are hydrogen.

In still other embodiments of the invention, the subject methods may be based on use of compounds of the formula (VIII):

![Chemical Structure](VIII)

wherein:

- $X$ is $-$CH$_2$- or $-$O$-$;
- $R^1$ is alkyl; alkenyl; cycloalkyl; cycloalkenyl; or halo;
- $R^2$ is hydrogen; alkyl; alkenyl; amino; halo; amido; haloalkyl; alkoxy; hydroxy; haloalkoxy; nitro; hydroxyalkyl; alkoxycarbonyl; haloalkoxy; alkylnylalkoxy; alkylsulfonyl; arylsulfonyl; cyano; aryl; heteroaryl; heterocyclyl; heterocyclylalkoxy; aryl; heteroaryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroarylsulfonyl; heterocyclyl;
- one of $R^7$ and $R^8$ is hydrogen, and the other is alkyl; cycloalkyl; cycloalkylalkyl; haloalkyl; haloalkoxy; hydroxyalkyl; alkoxyalkyl; acetyl; alkylnylalkyl; alkylnylalkoxy; haloalkoxyalkyl; hydroxyalkylalkoxyalkyl;
- aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl;
- one of $R^d$ and $R^e$ is hydrogen, and the other is alkyl; cycloalkyl; cycloalkylalkyl; haloalkyl; haloalkoxy; hydroxyalkyl; alkoxyalkyl; acetyl; alkylnylalkyl; alkylnylalkoxy; haloalkoxyalkyl; hydroxyalkylalkoxyalkyl;
- aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl;
- $Q$ is CR$^9$, one of A and E is O, S or NR$^{10}$ and the other is CR$^9$ or N; or
- $Q$ is N, one of A and E is NR$^{10}$ and the other is CR$^9$;
- each $R^9$ is independently hydrogen, alkyl, halo or alkoxy; and
- $R^{10}$ is hydrogen, alkyl, hydroxyalkyl, alkoxyalkyl, -(CH$_2$)$_m$-(Z)$_n$-(CO)-R$^f$, or -(CH$_2$)$_m$-(Z)$_n$-SO$_2$-(NR$^g$)$_n$-R$^f$. 
In certain embodiments of formula VIII A is \( NR^{10} \), and Q and E are \( CR^9 \).

In certain embodiments of formula VIII E is \( NR^{10} \), and A and Q are \( CR^9 \).

In certain embodiments of formula VIII Q is \( NR^{10} \), and A and E are \( CR^9 \).

In certain embodiments of formula VIII A is O, E is N, and Q is \( CR^9 \).

In certain embodiments of formula VIII A is N, E is O, and Q is \( CR^9 \).

In certain embodiments of formula VIII A is S, E is N, and Q is \( CR^9 \).

In certain embodiments of formula VIII A is N, E is S, and Q is \( CR^9 \).

In certain embodiments of formula VIII E is S, and A and Q are \( CR^9 \).

In certain embodiments of formula VIII E is 0, and A and Q are \( CR^9 \).

In certain embodiments of formula VIII A is S, and L and Q are \( CR^9 \).

In certain embodiments of formula VIII A is 0, and E and Q are \( CR^9 \).

In certain embodiments of formula VIII A is \( NR \), Q is N, and E is \( CR^9 \).

In certain embodiments of formula VIII E is \( NR^0 \), Q is N, and A is \( CR^9 \).

In certain embodiments of formula VIII X is \(-CH_2-\) or \(-O-\). Preferably X is O.

In certain embodiments of formula VIII \( R^1 \) is alkyl, alkenyl or cycloalkyl. Preferably, \( R^1 \) is ethyl, cyclopropyl, isopropenyl or isopropyl. More preferably \( R^1 \) is isopropyl.

In certain embodiments formula VIII 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.

In certain embodiments of formula VIII one of \( R^7 \) and \( R^8 \) is hydrogen and the other is alkyl, hydroxyalkyl or haloalkyl.

In certain embodiments formula VIII 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.
In certain embodiments of formula VIII one of $R^d$ and $R^e$ is hydrogen and the other is alkyl, hydroxyalkyl or haloalkyl.

In certain embodiments of formula VIII $R^7$, $R^8$, $R^d$ and $R^e$ are hydrogen.

In certain embodiments of formula VIII $R^d$ is halo, alkoxy, haloalkoxy or alkylsulfonyl.

5 In certain embodiments of formula VIII $R^4$ 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.

In certain embodiments of formula VIII $R^4$ 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-thioly-imidazol-1-yl, pyridin-2-yl, or 2,5-dimethyl-pyrrol-1-yl).

In embodiments of the invention where any of $R$, $R^8$, $R^d$ 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-dioxotetrahydrothiopyranyl. More preferably, such heterocyclyl or heterocyclyl moiety may be piperidin-4-yl, 1-methyl-piperidine-4-yl, 1-methanesulfonfyl-piperidin-4-yl, tetrahydropyran-4-yl, tetrahydrothiopyran-4-yl, or 1,1-dioxotetrahydrothiopyran-4-yl.

Where any of $R^1$, $R^2$, $R^3$, $R^4$, $R^5$, $R^7$, $R^8$, $R^9$, $R^{10}$, $R^c$, $R^d$, $R^e$, $R^f$, $R^g$, or $R^h$ is alkyl or contains an alkyl moiety, such alkyl is preferably lower alkyl, i.e. $C_1$-$C_6$alkyl, and more preferably $C_1$-$C_4$alkyl.

Representative compounds in accordance with the methods of the invention are shown in Table 1.

<table>
<thead>
<tr>
<th>#</th>
<th>Name</th>
</tr>
</thead>
</table>

TABLE 1
<table>
<thead>
<tr>
<th></th>
<th>Chemical Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>N\textsuperscript{<em>2}\textsuperscript{</em>}-Isopropyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-N\textsuperscript{<em>4}\textsuperscript{</em>}-methyl-pyrimidine-2,4-diamine</td>
</tr>
<tr>
<td>2</td>
<td>5-(2-Isopropyl-4,5-dimethoxy-phenoxo)-pyrimidine-2,4-diamine</td>
</tr>
<tr>
<td>3</td>
<td>5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N\textsuperscript{<em>4}\textsuperscript{</em>}-isoxazol-5-ylmethyl-pyrimidine-2,4-diamine</td>
</tr>
<tr>
<td>4</td>
<td>N\textsuperscript{<em>2}\textsuperscript{</em>}-Isopropyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine</td>
</tr>
<tr>
<td>5</td>
<td>5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N\textsuperscript{<em>4}\textsuperscript{</em>}-(2-methoxy-benzyl)-pyrimidine-2,4-diamine</td>
</tr>
<tr>
<td>6</td>
<td>5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N\textsuperscript{<em>4}\textsuperscript{</em>}-(2,2,2-trifluoro-ethyl)-pyrimidine-2,4-diamine</td>
</tr>
<tr>
<td>7</td>
<td>3-[2-Amino-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidin-4-ylamino]-propane-1,2-diol</td>
</tr>
<tr>
<td>8</td>
<td>N-[4-Amino-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidin-2-yl]-acetamide</td>
</tr>
<tr>
<td>9</td>
<td>5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N\textsuperscript{<em>4}\textsuperscript{</em>}-(4-methoxy-benzyl)-pyrimidine-2,4-diamine</td>
</tr>
<tr>
<td>10</td>
<td>5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N\textsuperscript{<em>4}\textsuperscript{</em>}-phenyl-pyrimidine-2,4-diamine</td>
</tr>
<tr>
<td>11</td>
<td>5-(5-Chloro-2-isopropyl-4-methoxy-benzyl)-N\textsuperscript{<em>2}\textsuperscript{</em>}-phenethyl-pyrimidine-2,4-diamine</td>
</tr>
<tr>
<td>12</td>
<td>5-(5-Chloro-2-isopropyl-4-methoxy-benzyl)-pyrimidine-2,4-diamine</td>
</tr>
<tr>
<td>13</td>
<td>N\textsuperscript{<em>4}\textsuperscript{</em>}-Isobutyl-N\textsuperscript{<em>2}\textsuperscript{</em>}-isopropyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine</td>
</tr>
<tr>
<td>14</td>
<td>5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N\textsuperscript{<em>2}\textsuperscript{</em>}-phenyl-pyrimidine-2,4-diamine</td>
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<td>15</td>
<td>N\textsuperscript{<em>2}\textsuperscript{</em>},N\textsuperscript{<em>4}\textsuperscript{</em>}-Diisopropyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine</td>
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<td>16</td>
<td>5-(5-Chloro-2-isopropyl-4-methoxy-benzyl)-N\textsuperscript{<em>2}\textsuperscript{</em>}-isopropyl-pyrimidine-2,4-diamine</td>
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<td>17</td>
<td>2-[2-Amino-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidin-4-ylamino]-ethanol</td>
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<td>5-(2-Isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine</td>
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<td>19</td>
<td>5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N\textsuperscript{<em>4}\textsuperscript{</em>}-(2-(4-methoxy-phenyl)-ethyl]-pyrimidine-2,4-diamine</td>
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<td>N\textsuperscript{<em>2}\textsuperscript{</em>}-Benzyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine</td>
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<td>21</td>
<td>5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N\textsuperscript{<em>4}\textsuperscript{</em>}-(4-methanesulfonyl-cyclohexyl)-pyrimidine-2,4-diamine</td>
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<td>22</td>
<td>N\textsuperscript{<em>2}\textsuperscript{</em>}-Cyclopropyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine</td>
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<td>N<em>4</em>-Isopropyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine</td>
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<td>N<em>2</em>-Ethyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine</td>
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<td>25</td>
<td>5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N<em>4</em>-[2-(3-methoxy-phenyl)-ethyl]-pyrimidine-2,4-diamine</td>
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<td>26</td>
<td>2-[4-Amino-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidin-2-ylamino]-ethanol</td>
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<td>27</td>
<td>5-(2-sec-Butyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine</td>
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<td>28</td>
<td>N<em>2</em>-tert-Butyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine</td>
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<td>N<em>2</em>-Isobutyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine</td>
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<td>5-(5-Chloro-2-isopropyl-4-methoxy-benzyl)-N<em>2</em>-cyclopropyl-pyrimidine-2,4-diamine</td>
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<td>5-(2-Isopropyl-4-methoxy-5-phenoxy-benzyl)-pyrimidine-2,4-diamine</td>
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<td>N<em>4</em>-Isobutyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine</td>
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<td>N<em>4</em>-Ethyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine</td>
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<td>N<em>4</em>-Benzyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine</td>
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<td>35</td>
<td>5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N<em>4</em>-(2,2,2-trifluoro-ethyl)-pyrimidine-2,4-diamine</td>
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<td>5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N<em>2</em>-(4-methoxy-phenyl)-pyrimidine-2,4-diamine</td>
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<td>37</td>
<td>N<em>2</em>-Isopropyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-N<em>4</em>-(phenyl)-pyrimidine-2,4-diamine</td>
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<td>N<em>4</em>-Ethyl-N<em>2</em>-isopropyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine</td>
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<td>39</td>
<td>5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N<em>4</em>-(1-methyl-piperidin-4-yl)-pyrimidine-2,4-diamine</td>
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<td>5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N<em>2</em>-(2-methoxy-phenyl)-pyrimidine-2,4-diamine</td>
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<td>5-(4,5-Dichloro-2-isopropyl-benzyl)-pyrimidine-2,4-diamine</td>
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<td>42</td>
<td>5-(5-Chloro-2-isopropyl-4-methoxy-benzyl)-N<em>2</em>-ethyl-pyrimidine-2,4-diamine</td>
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<td>43</td>
<td>5-(2-Isopropyl-4-methoxy-5-methyl-benzyl)-pyrimidine-2,4-diamine</td>
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<td>5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N<em>2</em>-pyrimidin-2-yl-pyrimidine-2,4-diamine</td>
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<td>5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N<em>2</em>-(2-methoxy-ethyl)-pyrimidine-2,4-diamine</td>
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<td>N<em>4</em>-Benzyl-N<em>2</em>-isopropyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine</td>
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<td>47</td>
<td>1-(4-{2-[4-Amino-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidin-2-ylamino]-}</td>
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<td>48</td>
<td>5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N<em>4</em>-tetrahydro-pyran-4-yl-pyrimidine-2,4-diamine</td>
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<td>N<em>4</em>-Cyclopropyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine</td>
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<td>50</td>
<td>5-(5-Ethoxy-2-isopropyl-4-methoxy-benzyl)-pyrimidine-2,4-diamine</td>
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<td>51</td>
<td>N<em>2</em>- (2,4-Dimethoxy-phenyl)-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine</td>
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<td>N<em>2</em>-Cyclobutyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine</td>
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<td>53</td>
<td>N<em>2</em>-(2-Chloro-phenyl)-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine</td>
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<td>54</td>
<td>5-(4-Chloro-2-isopropyl-5-methoxy-benzyl)-pyrimidine-2,4-diamine</td>
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<td>55</td>
<td>5-(5-Bromo-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine</td>
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<td>56</td>
<td>5-(5-Chloro-2-isopropyl-4-methoxy-benzyl)-N<em>2</em>- (3-methoxy-phenyl)-pyrimidine-2,4-diamine</td>
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<td>57</td>
<td>5-(5-Chloro-2-isopropyl-4-methoxy-benzyl)-N<em>2</em>-isobutyl-pyrimidine-2,4-diamine</td>
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<td>58</td>
<td>5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N<em>2</em>,N<em>4</em>-diphenyl-pyrimidine-2,4-diamine</td>
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<td>59</td>
<td>5-(6-Isopropyl-1,3-dimethyl-1H-indol-5-yloxy)-pyrimidine-2,4-diamine</td>
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<td>60</td>
<td>5-(5-Chloro-2-isopropyl-4-methoxy-benzyl)-N<em>2</em>-isobutyl-pyrimidine-2,4-diamine</td>
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<td>61</td>
<td>5-(6-Isopropyl-1-methyl-1H-indol-5-yloxy)-pyrimidine-2,4-diamine</td>
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<td>62</td>
<td>5-(5-Chloro-2-isopropyl-4-methoxy-benzyl)-N<em>2</em>-phenyl-pyrimidine-2,4-diamine</td>
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<td>63</td>
<td>5-(2-Isopropyl-4-methoxy-5-methyl-phenoxy)-pyrimidine-2,4-diamine</td>
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<td>64</td>
<td>5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N<em>2</em>-methyl-pyrimidine-2,4-diamine</td>
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<td>5-(2-Isopropyl-5-methyl-phenoxy)-pyrimidine-2,4-diamine</td>
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<td>5-(5-Chloro-2-isopropyl-4-methoxy-benzyl)-N<em>2</em>-methyl-pyrimidine-2,4-diamine</td>
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<td>N<em>2</em>-Benzyl-5-(5-chloro-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine</td>
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<td>68</td>
<td>2-[2-Isopropylamino-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidin-4-ylamino]-ethanol</td>
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<td>69</td>
<td>5-(5-Chloro-2-isopropyl-4-methoxy-phenoxy)-N<em>2</em>-(tetrahydro-pyran-4-yl)-pyrimidine-2,4-diamine</td>
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<td>N<em>2</em>-(4-Chloro-phenyl)-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine</td>
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<td>71</td>
<td>5-(2-Isopropyl-phenoxy)-pyrimidine-2,4-diamine</td>
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<td>72</td>
<td>5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N<em>4</em>-methyl-pyrimidine-2,4-diamine</td>
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<td>73</td>
<td>5-(5-Chloro-2-isopropyl-4-methoxy-phenoxy)-N*-2*-isopropyl-pyrimidine-2,4-diamine</td>
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<td>74</td>
<td>5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N*-4*-isopropyl-pyridine-2,4-diamine</td>
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<td>75</td>
<td>N*-2*-Isopropyl-5-(2-isopropyl-4,5-dimethoxy-phenoxy)-pyrimidine-2,4-diamine</td>
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<td>76</td>
<td>5-(2-Ethyl-4,5-dimethoxy-benzyl)-pyridine-2,4-diamine</td>
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<td>77</td>
<td>5-(2-Isopropyl-4,5-dimethoxy-phenoxy)-N*-2*-phenyl-pyridine-2,4-diamine</td>
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<td>78</td>
<td>N*-2*-tert-Butyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyridine-2,4-diamine</td>
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<td>79</td>
<td>N*-2*-Benzyl-5-(2-isopropyl-4,5-dimethoxy-phenoxy)-pyridine-2,4-diamine</td>
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<td>80</td>
<td>5-(2-Cyclopropyl-4,5-dimethoxy-benzyl)-pyridine-2,4-diamine</td>
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<td>81</td>
<td>N-[4-Amino-5-(2-isopropyl-4,5-dimethoxy-phenoxy)-pyrimidin-2-yl]-acetamide</td>
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<td>82</td>
<td>N*-2*-Benzyl-5-(5-chloro-2-isopropyl-4-methoxy-benzyl)-pyridine-2,4-diamine</td>
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<td>83</td>
<td>5-(2-Isopropyl-4,5-dimethoxy-phenoxy)-N*-2*-(2,2,2-trifluoro-ethyl)-pyridine-2,4-diamine</td>
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<td>5-(2-Isopropyl-4,5-dimethoxy-phenoxy)-N*-2*-(2-methoxy-ethyl)-pyridine-2,4-diamine</td>
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<td>85</td>
<td>5-(2-Isopropyl-4,5-dimethoxy-benzyl)-pyridin-4-ylamine</td>
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<td>3-[4-Amino-5-(5-chloro-2-isopropyl-4-methoxy-phenoxy)-pyrimidin-2-ylamino]-pentane-1,5-diol</td>
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<td>5-(5-Chloro-2-isopropyl-4-methoxy-benzyl)-N*-2*-cyclohexyl-pyridine-2,4-diamine</td>
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<td>88</td>
<td>2-[4-Amino-5-(5-chloro-2-isopropyl-4-methoxy-phenoxy)-pyrimidin-2-ylamino]-butan-1-ol</td>
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<td>89</td>
<td>1-[5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-ethanone</td>
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<td>5-[5-(1H-Imidazol-2-yl)-2-isopropyl-4-methoxy-phenoxy]-pyridine-2,4-diamine</td>
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<td>91</td>
<td>(2,4-Diamino-pyrimidin-5-yl)-(2-isopropyl-4,5-dimethoxy-phenyl)-methanol</td>
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<td>5-[5-Chloro-2-(2-fluoro-1-methyl-ethyl)-4-methoxy-phenoxy]-pyridine-2,4-diamine</td>
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<td>93</td>
<td>(5-Chloro-2-isopropyl-4-methoxy-phenyl)-(2,4-diamino-pyrimidin-5-yl)-methanol</td>
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<td>94</td>
<td>2-[4-Amino-5-(5-chloro-2-ethyl-4-methoxy-phenoxy)-pyrimidin-2-ylamino]-butan-1-ol</td>
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<td>94</td>
<td>5-(5-Chloro-2-isopropyl-4-methoxy-phenoxy)-N*-2*-(3-ethanesulfonyl-1-methylpropyl)-pyridin-2,4-diamine</td>
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<td>5-(5-Bromo-2-ethyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine</td>
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<td>96</td>
<td>5-(5-Chloro-2-ethyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine</td>
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<td>5-(5-Chloro-2-cyclopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine</td>
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<td>5-(2-Ethyl-5-methanesulfonyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine</td>
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<td>5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-benzenamide</td>
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<td>5-(4,5-Dimethoxy-2-vinyl-phenoxy)-pyrimidine-2,4-diamine</td>
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<td>101</td>
<td>5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-benzoic acid</td>
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<td>5-(2-Cyclopropyl-4,5-dimethoxy-phenoxy)-pyrimidine-2,4-diamine</td>
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<td>5-[2-Isopropyl-4-methoxy-5-(1H-tetrazol-5-yl)-phenoxy]-pyrimidine-2,4-diamine</td>
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<td>104</td>
<td>5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-benzoic acid</td>
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<td>105</td>
<td>4-[4-Amino-5-(5-chloro-2-isopropyl-4-methoxy-phenoxy)-pyrimidin-2-ylamino]-piperidine-1-carboxylic acid ethyl ester</td>
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<td>[5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-urea</td>
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<td>5-(5-Chloro-2-isopropyl-4-methoxy-phenoxy)-N<em>2</em>-Isopropyl-4,5-dimethoxy-benzyl-N<em>2</em>-methyl-pyrimidine-2,4-diamine</td>
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<td>5-(5-Chloro-4-difluoromethoxy-2-isopropyl-phenoxy)-pyrimidine-2,4-diamine</td>
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<td>109</td>
<td>5-(5-Amino-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine</td>
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<td>5-(2-Isopropyl-4-methoxy-5-tetrazol-1-yl-phenoxy)-pyrimidine-2,4-diamine</td>
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<td>5-(2-Isopropyl-4-methoxy-5-methyl-phenoxy)-N<em>4</em>-Isopropyl-5-methyl-pyrimidine-2,4-diamine</td>
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<td>N-[5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-acetamide</td>
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<td>5-(2-Isopropyl-4-methoxy-5-tetrazol-1-yl-phenoxy)-pyrimidine-2,4-diamine</td>
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<td>114</td>
<td>5-(2-Isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine</td>
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<td>5-(2-Isopropyl-4-methoxy-5-methyl-phenoxy)-N<em>4</em>-phenyl-pyrimidine-2,4-diamine</td>
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<td>Methyl-carbamic acid 2-[4-amino-5-(5-chloro-2-isopropyl-4-methoxy-phenoxy)-pyrimidin-2-ylamino]-propyl ester</td>
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<td>5-(4-Chloro-2-isopropyl-5-methyl-phenoxy)-pyrimidine-2,4-diamine</td>
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<td>118</td>
<td>5-(2-Isopropyl-4,5-dimethoxy-phenoxy)-6-methyl-pyrimidine-2,4-diamine</td>
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<td>1-(4-[4-Amino-5-(5-chloro-2-isopropyl-4-methoxy-phenoxy)-pyrimidin-2-ylamino]-propyl]-piperazin-1-yl)-ethanone</td>
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<td>5-(5-Chloro-2-isopropyl-4-methoxy-phenoxy)-N<em>2</em>-Isopropyl-4,5-dimethoxy-pyrimidine-4-yl-pyrimidine-2,4-diamine</td>
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<td>2-[4-Amino-5-(5-chloro-2-isopropyl-4-methoxy-phenoxy)-pyrimidin-2-ylamino]-</td>
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<td>(R)-propan-1-ol</td>
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<td>121</td>
<td>5-(2-Ethyl-4,5-dimethoxy-phenoxy)-pyrimidine-2,4-diamin</td>
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<td>122</td>
<td>5-(2-Isopropyl-5-methanesulfonyl-4-methoxy-phenoxy)-N^2-(tetrahydro-thiopyran-4-yl)-pyrimidine-2,4-diamine</td>
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<td>5-(5-Chloro-2-isopropyl-4-methoxy-phenoxy)-N^2-(1,1-dioxo-hexahydro-1,6-thiopyran-4-yl)-pyrimidine-2,4-diamine</td>
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<td>1-[5-(2,4-Diamino-pyrimidin-5-yloxy)-2-hydroxy-4-isopropyl-phenyl]-ethanone</td>
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<td>5-(5-Iodo-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine</td>
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<td>126</td>
<td>5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-benzenesulfonamide</td>
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<td>4-(2,4-Diamino-pyrimidin-5-yloxy)-2-iodo-5-isopropyl-phenol</td>
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<td>5-(2,5-Diiodo-4-methoxy-phenoxy)-pyrimidine-2,4-diamine</td>
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<td>3-[4-Amino-5-(5-bromo-2-isopropyl-4-methoxy-phenoxy)-pyrimidin-2-ylamino]-</td>
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<td>pentane-1,5-diol</td>
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<td>5-(2-Ethyl-5-iodo-4-methoxy-phenoxy)-pyrimidine-2,4-diamine</td>
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<td>131</td>
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<td>$5\text{-}(6\text{-Isopropyl-4-methyl-3,4\text{-dihydro-2H-benzo[1,4]oxazin-7-yloxy})\text{-pyrimidine\text{-2,4-diamine}}$</td>
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<td>252</td>
<td>5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-benzonitrile</td>
</tr>
<tr>
<td>253</td>
<td>5-[2-Isopropyl-4-methoxy-5-(2-methyl-thiazol-5-yl)-oxy]-pyrimidine-2,4-diamine</td>
</tr>
<tr>
<td>254</td>
<td>5-(2-Isopropyl-4-methoxy-6-methyl-phenoxo)-pyrimidine-2,4-diamine</td>
</tr>
<tr>
<td>255</td>
<td>5-(5-Ethanesulfonyl-2-isopropyl-4-methoxy-phenoxo)-pyrimidine-2,4-diamine</td>
</tr>
<tr>
<td>256</td>
<td>5-(2-Isopropyl-4-methoxy-5-thiazol-5-yl-benzyl)-pyrimidine-2,4-diamine</td>
</tr>
<tr>
<td>257</td>
<td>1-[5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-1H-imidazole-2-thiol</td>
</tr>
<tr>
<td>258</td>
<td>5-[2-Isopropyl-4-methoxy-5-(1-methyl-1H-imidazol-4-yl)-oxy]-pyrimidine-2,4-diamine</td>
</tr>
<tr>
<td>259</td>
<td>5-[5-Iodo-2-isopropyl-4-(pyridin-4-ylmethyl)-oxy]-pyrimidine-2,4-diamine</td>
</tr>
<tr>
<td>260</td>
<td>5-(4-Iodo-2-isopropyl-phenoxo)-pyrimidine-2,4-diamine</td>
</tr>
<tr>
<td>261</td>
<td>5-(5-Iodo-4-isopropyl-2-methoxy-benzyl)-pyrimidine-2,4-diamine</td>
</tr>
<tr>
<td>262</td>
<td>5-(5-Fluoro-2-isopropyl-4-methoxy-phenoxo)-pyrimidine-2,4-diamine</td>
</tr>
<tr>
<td>263</td>
<td>5-(4'-Fluoro-5-isopropyl-2-methoxy-biphenyl-4-yloxy)-pyrimidine-2,4-diamine</td>
</tr>
<tr>
<td>264</td>
<td>5-[4-(3-Fluoro-benzyl)-oxy]-5-iodo-2-isopropyl-phenoxo]-pyrimidine-2,4-diamine</td>
</tr>
<tr>
<td>265</td>
<td>5-(4-Bromo-2-isopropyl-phenoxo)-pyrimidine-2,4-diamine</td>
</tr>
<tr>
<td>266</td>
<td>5-(4'-Furan-2-yl-2-isopropyl-5-methoxy-phenoxo)-pyrimidine-2,4-diamine</td>
</tr>
<tr>
<td>267</td>
<td>2-[[5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-propan-2-ol</td>
</tr>
<tr>
<td>268</td>
<td>5-(2,4-Diamino-pyrimidin-5-yloxy)-6-isopropyl-1-methyl-1H-indole-3-carboxylic acid</td>
</tr>
<tr>
<td>269</td>
<td>5-[[4-(2,6-Difluoro-benzyloxy)-5-iodo-2-isopropyl-phenoxy]-pyrimidine-2,4-diamine</td>
</tr>
<tr>
<td>270</td>
<td>5-(5-Iodo-2-isopropyl-4-phenethyloxy-phenoxy)-pyrimidine-2,4-diamine</td>
</tr>
<tr>
<td>271</td>
<td>5-(2-Isopropyl-4-methoxy-5-pyridin-4-yl-phenoxy)-pyrimidine-2,4-diamine</td>
</tr>
<tr>
<td>272</td>
<td>5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N²-(1-methyl-piperidin-4-yl)-pyrimidine-2,4-diamine</td>
</tr>
<tr>
<td>273</td>
<td>5-(2,4-Diamino-pyrimidin-5-yloxy)-N-ethyl-4-isopropyl-2-methoxy-benzenesulfonamide</td>
</tr>
<tr>
<td>274</td>
<td>5-[[2-Isopropyl-5-(4-methanesulfonyl-piperazin-1-yl)-4-methoxy-phenoxy]-pyrimidine-2,4-diamine</td>
</tr>
<tr>
<td>275</td>
<td>5-(2-Isopropyl-4-methoxy-5-pyridin-3-yl-phenoxy)-pyrimidine-2,4-diamine</td>
</tr>
<tr>
<td>276</td>
<td>5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-N,N-dimethyl-benzenamide</td>
</tr>
<tr>
<td>277</td>
<td>5-[[5-(2,5-Dimethyl-pyrrol-1-yl)-2-isopropyl-4-methoxy-phenoxy]-pyrimidine-2,4-diamine</td>
</tr>
<tr>
<td>278</td>
<td>5-(2-Ethyl-3-methoxy-benzy1)-pyrimidine-2,4-diamine</td>
</tr>
<tr>
<td>279</td>
<td>5-(2-Bromo-4,5-dimethoxy-phenoxy)-pyrimidine-2,4-diamine</td>
</tr>
<tr>
<td>280</td>
<td>6-(2,4-Diamino-pyrimidin-5-yloxy)-5-isopropyl-3-methyl-1H-indole-2-carboxylic acid ethyl ester</td>
</tr>
</tbody>
</table>

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

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.

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

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.

Scheme A below illustrates one synthetic procedure usable to prepare specific compounds of formula (I) wherein X is methylene, Y is -NR₄R', and R, R', R, R, R, R, R, R are as defined herein.

**SCHEME A**

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 \( \text{a} \), after which the masked aldehyde is de-
protected to provide the free aldehyde group. Aldehyde protection schemes of this sort are
shown in the experimental examples below.

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

In step 2, alpha-hydroxy benzyl pyrimidine \( \text{c} \) is reduced to provide benzyl pyrimidine \( \text{d} \).
The reduction of step 2 may be achieved using triethylsilane and trifluoroacetic acid under
polar solvent conditions.

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

In step 4, an oxidation of the methylsulfanyl group of benzyl aminopyrimidine \( \text{f} \) is carried
out to afford amino methanesulfonyl benzylpyrimidine \( \text{g} \). The oxidation of step 4 may be
carried out using metachloroperbenzoic acid (mCPBA), OXONE\textsuperscript{\textregistered}, or like oxidizing agent
under mild, polar solvent conditions.

A second amination occurs in step 6 in which amino methanesulfonyl benzylpyrimidine \( \text{g} \)
is treated with amine \( \text{h} \) to displace the methanesulfonyl group and provide diamino
benzylpyrimidine \( \text{i} \). The diamino benzylpyrimidine \( \text{i} \) 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 \( \text{g} \) in the presence of excess amine \( \text{h} \)
under mild pressure and polar solvent conditions.

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 \( \text{b} \) in step 1. In such variation, described
in the experimental examples below, benzaldehyde \( \text{a} \) 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\textsubscript{2}. The resultant
ketone can then be aminated to displace the methoxy groups to yield a diamino benzylpyrimidine in accordance with the invention.

Scheme B below illustrates another synthetic procedure usable to prepare specific compounds of formula (I) above, wherein X is O, Y is -NR\textsuperscript{4}R\textsuperscript{5}, R\textsuperscript{6} and R\textsuperscript{8} are hydrogen, and R\textsuperscript{1}, R\textsuperscript{2}, R\textsuperscript{3}, R\textsuperscript{4}, R\textsuperscript{5}, and R\textsuperscript{6} are as defined herein.

**SCHEME B**

In step 1 of Scheme B, an O- alkylation is carried out by reaction of phenol j with a haloacetonitrile such as iodoacetonitrile k, to afford cyano ether l. 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.

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.

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.

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 -NH₂ group of diamino pyrimidine using reductive amination or like technique, may be used to introduce R² and R₈ functionalities in accordance with formula (I).

Yet another procedure usable for preparation of the subject compounds is shown in Scheme C, wherein R¹, R², R³, R⁴ and R⁵ 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.

In the procedure of Scheme C, benzaldehyde is treated with acrylonitrile in the presence of sodium methoxide in step 1 to afford a phenyl methoxymethyl cinnamonitrile compound, which in turn is reacted with guanidine in step 2 to yield the diaminopyrimidine. Diamino pyrimidine is a compound of formula (I) in which X is -CH₂-, Y is -NH₂ and R, R and R₈ are hydrogen.

The procedure of Scheme C is effective for use with benzaldehydes in which groups R¹ and R⁵ 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 R¹ 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>
<thead>
<tr>
<th></th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>R⁴</th>
<th>R⁵</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>-H</td>
<td>-OMe</td>
<td>-OMe</td>
<td>-H</td>
<td>67%</td>
</tr>
<tr>
<td>2</td>
<td>-OMe</td>
<td>-H</td>
<td>-OMe</td>
<td>-OMe</td>
<td>-H</td>
<td>37%</td>
</tr>
<tr>
<td>3</td>
<td>-CH₃</td>
<td>-H</td>
<td>-OMe</td>
<td>-OMe</td>
<td>-H</td>
<td>34%</td>
</tr>
<tr>
<td>4</td>
<td>-Et</td>
<td>-H</td>
<td>-OMe</td>
<td>-OMe</td>
<td>-H</td>
<td>18%</td>
</tr>
<tr>
<td>5</td>
<td>-Isopropyl</td>
<td>-H</td>
<td>-OMe</td>
<td>-OMe</td>
<td>-H</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>
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.

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

The compounds of the invention are usable for the treatment of a wide range of genito-urinary diseases, conditions and disorders, including urinary tract disease states associated with bladder outlet obstruction and urinary incontinence conditions such as reduced bladder capacity, frequency of micturition, urge incontinence, stress incontinence, bladder hyperreactivity, benign prostatic hypertrophy (BPH), prostatitis, detrusor hyperreflexia, urinary frequency, nocturia, urinary urgency, overactive bladder, pelvic hypersensitivity, urethritis, prostatitis, pelvic pain syndrome, prostatodynia, cystitis, and idiopathic bladder hypersensitivity, and other symptoms related to overactive bladder.

The compounds of the invention are expected to find utility as analgesics in the treatment of diseases and conditions associated with pain from a wide variety of causes, including, but not limited to, inflammatory pain, surgical pain, visceral pain, dental pain, premenstrual pain, central pain, pain due to burns, migraine or cluster headaches, nerve injury, neuritis, neuralgias, poisoning, ischemic injury, interstitial cystitis, cancer pain, viral, parasitic or bacterial infection, post-traumatic injuries (including fractures and sports injuries), and pain associated with functional bowel disorders such as irritable bowel syndrome.

Further, compounds of the invention are useful for treating respiratory disorders, including chronic obstructive pulmonary disorder (COPD), asthma, bronchospasm, and the like.

Additionally, compounds of the invention are useful for treating gastrointestinal disorders, including Irritable Bowel Syndrome (IBS), Inflammatory Bowel Disease (IBD), biliary colic and other biliary disorders, renal colic, diarrhea-dominant IBS, pain associated with GI distension, and the like.

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.
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.

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

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.

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 but are not limited to magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatine, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term “preparation” is intended to include the formulation of the active compound with encapsulating 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. Tables, powders, capsules, pills, cachets, and lozenges may be as solid forms suitable for oral administration.

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, solubilizing agents, and the like.

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.

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.

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.

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.

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.

The compounds of the invention may be formulated for aerosol administration, particularly to the respiratory tract and including intranasal administration. The compound will generally have a small particle size 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 polyvinylpyrrolidone (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.

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

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.

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

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

\[
\begin{align*}
\text{HO} & \quad \text{OH} \\
\text{H} & \quad \text{H} \\
\text{N} & \quad \text{H} \\
\text{O} & \quad \text{H} \\
\text{cbz} & \quad \text{cbz} \\
\end{align*}
\]

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

To a solution of R-(-)-2-amino-1-propanol (0.59 g, 8.0 mmol) in 50 mL THF was added pyrazole 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/CH₂Cl₂) 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

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 H₂. 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%).

Using the appropriate amines with the above procedure, the following guanidine compounds were also prepared:

N-(3-Ethanesulfonyl-1-methyl-propyl)-guanidine;
4-Guanidino-piperidine-1-carboxylic acid ethyl ester;
N-(1-Hydroxymethyl-propyl)-guanidine
N-(1-Methanesulfonfyl-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

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

![Scheme D diagram]

**Scheme D**

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

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.
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-dimethyl-2-(2,4,5-trimethoxy-phenyl)-4,5-dihydro-oxazoloxide 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% NH₄Cl. 500 mL H₂O was added and the mixture was extracted with ethyl acetate, washed with H₂O, and washed with brine. The combined organics were dried over Na₂SO₄, 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-oxazoloxide 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**

To a solution of 2-[4,5-dimethoxy-2-(1-methyl-2-phenyl-ethyl)-phenyl]-4,4-dimethyl-4,5-dihydro-oxazoloxide (7.515 g, 21.3 mmol) in 50 mL NO₂CH₃ 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 methyl ester**

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 H₂O and washed with brine. The combined organics were dried over Na₂SO₄, 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**

Diisobutyl aluminum hydride (22.9 mL, 1.0 M in THF) was added to a solution of 4,5-dimethoxy-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. H₂O was added and the slurry was extracted with ethyl acetate, washed with H₂O and washed with brine. The combined organics were dried over Na₂SO₄, filtered and concentrated in vacuo to give a crude oil. Purification via flash chromatography (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
A solution of pyridinium chlorochromate (1.253 g, 5.8 mmol) in 40 mL CH₂Cl₂ 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 CH₂Cl₂ was added drop-wise and allowed to stir for 45 min. The mixture was diluted in 200 mL Et₂O, 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
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% NH₄Cl. After 100 mL of H₂O was added the mixture was extracted with ethyl acetate, washed with H₂O and washed with brine. The combined organics were dried over Na₂SO₄, 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
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 MnO₂ (0.335 g, 4.7 mmol). The mixture was warmed to reflux and H₂O 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)-
phenyl]-methanone

A solution of [4,5-dimethoxy-2-(1-methyl-2-phenyl-ethyl)-phenyl]-(2,4-dimethoxy-
pyrimidin-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 CH₂Cl₂/MeOH) afforded (2,4-diamino-pyrimidin-5-yl)-[4,5-di-
methoxy-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

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 LiAlH₄ (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 CH₂Cl₂ 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%
K₂CO₃ was as added and the mixture was extracted with ethyl acetate and washed with
brine. The combined organics were dried over Na₂SO₄, filtered and concentrated in vacuo.
Purification via flash chromatography (95:5 CH₂Cl₂) 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.

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

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

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

A solution of 3-isopropyl phenol (4.975 g, 36.5 mmol) in 37 mL of CCl₄ was cooled to -20°C. Bromine (1.9 mL, 38.4 mmol) was dissolved in 5.0 mL CCl₄ 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 CH₂Cl₂, washed with H₂O and then with brine. The combined organics were dried over Na₂SO₄, 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**

To a mixture of 2-bromo-5-isopropyl-phenol and 4-bromo-5-isopropyl phenol from step 1 (8.663 g, 40.3 mmol), K₂CO₃ (16.710 g, 120.9 mmol) in 50 mL DMF, was added iodo-methane (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 H₂O was added and the solution was extracted with diethyl ether (Et₂O), washed with H₂O and washed with brine. The combined organics were dried over MgSO₄, 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

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 TiCl₄ (6.3 mL, 57.8 mmol) at 0°C. After 10 min, dichloromethoxymethane (Cl₂CHOME) (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 CH₂Cl₂, and washed with brine. The combined organics were dried over MgSO₄, 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

To a solution of 5-bromo-2-isopropyl-4-methoxy-benzaldehyde and 5-bromo-4-isopropyl-2-methoxy-benzaldehyde from step 3 (2.87 g, 11.2 mmol) in 25 mL CH₂Cl₂ was added mCPBA (2.31 g, 13.4 mmol). After 16 hours the mixture was taken up in 150 ml CH₂Cl₂ and washed with sat NaHCO₃, and then with brine. The combined organic layers were dried over Na₂SO₄, 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 Na₂SO₄, 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/CH₂Cl₂) 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

To a mixture of 5-bromo-2-isopropyl-4-methoxy-phenol from step 4 (0.831 g, 3.4 mmol) and K₂CO₃ (0.562 g, 4.1 mmol) in 17 mL dimethyl formamide (DMF) was added iodo-acetonitrile (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 H₂O and extracted with 1:1 toluene/ethyl acetate, washed with H₂O and then with brine. The com-
bined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo to give a crude solid. Purification via flash chromatography (1:1 hexane/CH₂Cl₂) afforded (5-bromo-2-isopropyl-4-methoxy-phenoxy)-acetonitrile (0.611 g, 63%) as a white solid.

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

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 iodo-methane was added in one portion. After 16 hours the solution was quenched with H₂O, concentrated in vacuo, extracted with ethyl acetate, washed with H₂O and then washed with brine. The combined organic layers were dried over Na₂SO₄, 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**

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.OM 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 CH₂Cl₂/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**

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

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 H₂O was removed with a Dean-Stark trap. After 3 h, the solution was cooled, washed with 50 mL saturated NaHCO₃, dried over Na₂SO₄ and filtered. The solution was concentrated in vacuo to give a yellow syrup. Purification via Kügel-Rhôr 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

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 isopropylithium (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% NH₄Cl and concentrated in vacuo. 100 mL of H₂O was added and the mixture was extracted with ethyl acetate, washed with H₂O and then brine. The combined organic layers were dried over Na₂SO₄, 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

(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 H₂O was added and the mixture was extracted with ethyl acetate, washed with H₂O and then with brine. The combined organic layers were dried over Na₂SO₄, 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 (0.331 g, 43%) as a clear oil.
Step 4. (4-Chloro-2-methylsulfanyl-pyrimidin-5-yl)-(2-isopropyl-4,5-dimethoxy-phenyl)-methanol

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 CH₂Cl₂. The combined organic layers were dried over Na₂SO₄, 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

To a solution of (4-chloro-2-methylsulfanyl-pyrimidin-5-yl)-(2-isopropyl-4,5-dimethoxy-phenyl)-methanol (6.5 g, 17.6 mmol) in 200 mL CH₂Cl₂ 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% K₂CO₃ was added and extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried over Na₂SO₄, 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

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 H₂O. The mixture was extracted with ethyl acetate, washed with H₂O and then washed with brine. The combined organic layers were dried over Na₂SO₄, filtered and evaporated in vacuo. Purification via flash chromatography (4:1 hexane/ethyl acetate) afforded ethyl-[5-(2-isopropyl-4,5-dimethoxy-benzyl)-2-methylsulfanyl-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

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 H₂O/THF was added OXONE® (0.461 g,
0.8 mmol) in 4.0 mL H₂O. After 2 hours, 50 mL H₂O was added and the mixture was extracted with ethyl acetate, washed with H₂O and washed with brine. The combined organic layers were dried over Na₂SO₄, 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
To ethyl-[5-(2-isopropyl-4,5-dimethoxy-benzyl)-2-methanesulfonyl-pyrimidin-4-yl]-amine (0.078 g, 0.2 mmol) in microwave reactor vial was added 2.0 mL dimethoxy ethane and 0.5 mL concentrated NH₄OH. 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 NH₄OH 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 CH₂Cl₂/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 alkyl lithium 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

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

**Step 1. 2-Chloro-5-isopropyl-phenol**
A solution of 3-isopropyl phenol (10.0 g, 73.4 mmol) in 350 mL 9:1 benzene/CHCl₃ 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**
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 K₂CO₃. Iodomethane (3.5 mL, 56.5 mmol) was added and the mixture was warmed to 50°C. After 4 hours H₂O was added. The mixture was extracted with ethyl acetate, washed with H₂O, washed and washed with brine. The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo to give 1-chloro-4-isopropyl-2-methoxy-benzene and 1-chloro-2-isopropyl-4-methoxy-benzene (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**
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 TiCl₄ followed by Cl₂CHOMe 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/CH₂Cl₂) 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**
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 a clear oil.
Step 5.  (5-Chloro-2-isopropyl-4-methoxy-phenoxy)-acetonitrile
To a solution of 5-chloro-2-isopropyl-4-methoxy-phenol (10.36 g, 51.6 mmol) in 40 mL DMF was added K$_2$CO$_3$ (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$_2$O mixture and extracted with 1:1 toluene/hexane. The combined organics were washed with brine, dried over Na$_2$SO$_4$, 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
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 iodo-methane 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$_2$SO$_4$, 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
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$_2$O, and extracted with ethyl acetate. The combined organic layers were washed with H$_2$O, dried over Na$_2$SO$_4$, filtered and concentrated in vacuo. Purification via flash chromatography (95:5 CH$_2$Cl$_2$/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-ylamino]-butan-1-ol
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 MgSO₄, 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 of 2-[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.

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: N*2*-(1,1-Dioxo-hexahydro-1 lambda*6*-thiopyran-4-yl)-5-(2-isopropyl-4,5-dimethoxy-phenoxy)-pyrimidine-2,4-diamine

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.

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 MgSO₄. 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

\[
\begin{align*}
\text{H}_2\text{C} & \quad \text{CH}\_3 \\
\text{O} & \quad \text{H}_2\text{N} \\
\text{CH}\_3 & \quad \text{H}_2\text{O} \\
\text{N} & \quad \text{O} \\
\end{align*}
\]

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 MgSO₄. 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

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

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.

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.

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

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

5 Step 1. 5-Benzylxoy-6-isopropyl-3-methyl-1H-indole
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-Benzylxoy-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 (MgSO₄), 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-Benzylxoy-6-isopropyl-1,3-dimethyl-1H-indole
5-Benzylxoy-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 (MgSO₄), 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
5-Benzylxoy-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-ylxoy)-acetonitrile
(6-Isopropyl-1,3-dimethyl-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-yloxy)-4-methoxy-but-2-enenitrile**

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**

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 1N 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**

The synthetic procedure used in this Example is outlined in Scheme J.
Step 1. (2-Isopropyl-4-methoxy-5-methyl-phenoxy)-acetic acid ethyl ester

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 (5 ml, 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

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

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$_4$OH) 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**

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 overnight. 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**

A suspension of 4-chloro-5-(2-isopropyl-4-methoxy-5-methyl-phenoxy)-pyrimidin-2-ylamine (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**
Step 1. 4-Cyclopropyl-1,2-dimethoxy-benzene
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, 1 M in dichloromethane, 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
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

[Chemical structure image]

Step 1. 1-Chloro-4-cyclopropyl-2-methoxy-benzene
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 added, and the mixture was then cooled to RT and stirred for 30 min. The reaction mixture was partitioned between ethyl acetate and water. The com-
bined 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-methoxy-benzene as yellow oily residue (0.81 g, 67%).

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

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 NaHCO₃ solution and extracted into DCM, which was dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified via flash chromatography on silica gel (3%CH₃OH in CH₂Cl₂ with 0.1%NH₄OH) 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-phenox]-pyrimidine-2,4-diamine
Step 1. 5-(5-Iodo-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine
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 (0.4 g, 2.47 mmol) in glacial acetic acid (4 ml) was added. The reaction mixture was stirred for an additional hour at RT. The acidic mixture was basified with saturated NaHCO₃ solution and extracted into DCM. The organic layer was dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified via flash chromatography (5% CH₃OH in CH₂Cl₂ with 0.1% NH₄OH) 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
A mixture of 5-(5-iodo-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine (0.37 g, 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% CH₃OH in CH₂Cl₂ with 0.1% NH₄OH) to release the product from its copper complex and filtered. The filtrate was concentrated and purified via flash chromatography (3% CH₃OH in CH₂Cl₂ with 0.1% NH₄OH) 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
To a hot solution of 5-(2,4-diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-benzonitrile (0.2 g, 0.67 mmol) 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 CH₂Cl₂ (3 x 5 ml). Purification of the solid by preparative HPLC (15-95% CH₃CN 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

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

To a cooled (0°C) suspension of 5-(2,4-diamino-pyrimidin-5-yl)-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, 0.509 mmol) 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 NH₄OH) 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, (0.053 g, 33%).

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

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 overnight, 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

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 (0.2 M, 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

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

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

Step 1. 5-(5-Amino-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine
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
(92/8/0.1 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**

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**

![Chemical structure](image)

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**

The synthetic procedure used in this Example is outlined in Scheme K
SCHEME K

5 Step 1. 2-(1-Hydroxy-1-methyl-ethyl)-4-methoxy-phenol
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% NH₄Cl, carefully acidified to pH = 1 (slow addition) with concentrated HCl and extracted with Et₂O. The combined organics were washed with H₂O, washed with brine, dried over MgSO₄, 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
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 H₂O). 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 H₂O and extracted with ethyl acetate. The combined organics were washed with H₂O, washed with brine, dried over Na₂SO₄, 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
To a solution of 2-isopropyl-4-methoxy-phenol (56.91 g, 342 mmol) TEA (57.3.0 ml, 411 mmol) in 750 ml CH₂Cl₂ was cooled to 0°C. p-Toluenesulfonyl chloride (68.54 g, 360 mmol) in 250 ml CH₂Cl₂ was added dropwise at a rate that maintained the internal tempe-
The mixture was allowed to warm to RT. After 16 h, H₂O was added and the mixture was extracted with CH₂Cl₂. The combined organics were washed with brine, dried with Na₂SO₄, 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**

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 HNO₃ over 20 min. After 16 h the solution was pouring into a rapidly stirring slurry of 21 of ice/H₂O. After 15 min the precipitate was filtered, washed with H₂O 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**

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 1 L of water. The solution was acidified to pH = 1 with 12 M HCl and extracted with ethyl acetate. The combined organics were washed with H₂O, brine, dried over Na₂SO₄, 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-nitrophenol (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**

A mixture of 3-amino-2-isopropyl-5-nitrophenol (9.94 g, 47 mmol), K₂CO₃ (13.00 g, 94 mmol) and toluenesulfonic 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 H₂O and extracted with toluene/ethyl acetate (1:1). The combined organics were washed with H₂O, 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**

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 H₂O. The mixture was extracted with ethyl acetate, washed with H₂O, washed with brine, dried over Na₂SO₄, 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 2 l of an ice/H₂O mixture. The resulting precipitate was filtered, washed with H₂O and dried under vacuum (50°C). The crude solid was re-crystallized 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

Step 1. 5-(5-Amino-2-Isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine
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 H₂ 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 H₂O 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 H₂O, washed with brine, dried over Na₂SO₄, 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
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$_2$Cl$_2$/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

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

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$_2$O. The solution was converted to pH = 8 with 50% NaOH and extracted with ethyl acetate (3x75 mL). The combined organics were washed with H$_2$O, washed with brine, dried with Na$_2$SO$_4$, filtered and concentrated in vacuo to give a brown solid. Purification
via flash chromatography (CH₂Cl₂/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.

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-di-methyl-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

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 trimethylamine (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 CH₂Cl₂. The combined organics were washed with H₂O, washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo. Purification via flash chromatography (94:6 CH₂Cl₂/MeOH) afforded 5-(2-isopropyl-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

Step 1. 4-Chloro-N-[5-(2,4-diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyll-butyramide
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 and Na₂HPO₄ (0.392 g, 2.8 mmol) was added 4-chlorobutyryl chloride (0.194 g, 1.4 mmol) dropwise. After 4.5 h, H₂O and CH₂Cl₂ were added and the mixture was allowed to stir 15 min. The mixture was neutralized with 2N Na₂CO₃ and extracted with CH₂Cl₂. The combined organics were washed with brine, dried over Na₂SO₄, 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-methoxy-phenyl]-pyrrolidin-2-one

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 H₂O, washed with brine, dried over Na₂SO₄, 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

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

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 H₂O 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 CH₂Cl₂. The combined organics were washed with brine, dried over Na₂SO₄, 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

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. The reaction was neutralized with saturated NaHCO₃ and extracted with CH₂Cl₂. The combined organics were washed with brine, dried over Na₂SO₄, 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

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 Cs₂CO₃ (0.616 g, 1.9 mmol) in 4 ml DMF was heated to 100°C. After 72 hours the mixture was cooled, diluted with H₂O and extracted with ethyl acetate. The combined organics were washed with brine, dried over Na₂SO₄, filtered and concentrated in vacuo. Purification via preparative TLC (94:6 CH₂Cl₂/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
To a solution of methylmagnesium bromide (83.4 mmol, 27.8 ml, 3.0 M in Et₂O) 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% NH₄Cl. H₂O was added and the mixture was extracted with ethyl acetate. The combined organics were washed with H₂O, washed with brine, dried over NaHCO₃, filtered and concentrated in vacuo. The crude solid was taken up in 31 mL DMF. K₂CO₃ (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% NH₄Cl and extracted with ethyl acetate. The combined organics were washed with H₂O, washed with brine, dried with Na₂SO₄, 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, yield) as a white solid. [MH]+ = 333.

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

\[ \text{CH₂Cl₂} \rightarrow \text{CF₃CO₂H} \rightarrow \text{CH₃CO₂H} \rightarrow \text{H₂O} \]

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 CH₂Cl₂ was added trifluoroacetic acid (4.0 ml, 52.6 mmol) and triethylsilane (1.7 ml, 10.5 mmol). After 30 min saturated NaHCO₃ was added and the mixture was extracted with ethyl acetate. The combined organics were washed with brine, dried over Na₂SO₄, filtered and concentrated in vacuo to give a crude oil. Purification via flash chromatography (96:4 CH₂Cl₂/MeOH) gave 5-(2,5-diisopropyl-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

\[ \text{NaBH₄} \rightarrow \text{H₂O} \]

To a solution of 1-[5-(2,4-Diamino-pyrimidine-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-ethanone (0.225 g, 0.711 g, yield) as a white solid. [MH]+ = 333.
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 NaBH₄ (1.566 g, 41.4 mmol) at 0°C. The solution was allowed to warm to RT. After 20 h, the saturated NH₄Cl was added, the mixture was concentrated in vacuo and extracted with ethyl acetate. The combined organics were washed with brine, dried over Na₂SO₄, filtered and concentrated in vacuo. Purification via silica gel column chromatography (9:1 CH₂Cl₂/MeOH) afforded 1-[5-(2,4-diamino-pyrimidin-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

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 CH₂Cl₂ at -78°C was added DAST (0.935 g, 5.8 mmol). After stirring 1.5 h, saturated NaHCO₃ was added and the mixture was extracted by CH₂Cl₂. The combined organics were washed with brine and dried Na₂SO₄, filtered and concentrated in vacuo. Purification via silica gel chromatography (95:5 CH₂Cl₂/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

The synthetic procedure used in this Example is outlined in Scheme M.
Step 1. Cyclohexyl-(3-methoxy-benzylidene)-amine

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

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-methoxy-benzylidene)-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% NH₄Cl, and extracted with Et₂O. The combined organics were washed with H₂O, washed with brine, dried over MgSO₄, 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. H₂O was added and the mixture was extracted with ethyl acetate. The combined organics were washed with H₂O, washed with brine, dried over Na₂SO₄, 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

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)-N²-(2,2,2-triflоро-ethyl)-pyrimidine-2,4-diamine

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-ylamine
To 25 ml of saturated NH₃ 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 CH₂Cl₂. 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-ylamine (0.504 g, 92%) as a white solid.

Step 2. 5-(5-Chloro-2-isopropyl-4-methoxy-benzyl)-2-methylsulfonyl-pyrimidine-4-ylamine
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 H₂O 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 Na₂SO₄, 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)-N²-(2,2,2-trifluoro-ethyl)-pyrimidine-2,4-diamine
To a solution of 5-(5-chloro-2-isopropyl-4-methoxy-benzyl)-2-methylsulfanyl-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)-N²-(2,2,2-trifluoro-ethyl)-pyrimidine-2,4-diamine (0.010 g, 19%) as a white solid; [MH]⁺ = 389.

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)-N²-(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

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**

To a mixture of AlCl₃ (8.89 g, 59 mmol) in CH₂Cl₂ 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 CH₂Cl₂ 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 H₂O/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**

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 Et₂O. After 2 h the reaction was quenched by the addition of 10% NH₄Cl. The mixture
was adjusted to pH = 1 with 2M HCl and extracted with ethyl acetate. The combined organics were washed with H₂O, washed with brine, dried with MgSO₄, 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-phenoxyl-pyrimidine-2,4-diamine**

To a mixture of 5-chloro-2-(1-hydroxy-1-methyl-ethyl)-4-methoxy-phenol (2.00 g, 9 mmol) and K₂CO₃ (2.55 g, 19 mmol) in 50 mL DMF was added toluenesulfonyl cyanoethyl 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 Na₂SO₄, 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-phenoxyl-pyrimidine-2,4-diamine (1.62 g, 69%) as a white solid.

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

To a solution of [5-chloro-2-(1-hydroxy-1-methyl-ethyl)-4-methoxy-phenoxyl-pyrimidine-2,4-diamine (1.432 g, 5.6 mmol) in 50 ml CH₂Cl₂ 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 NaHCO₃ solution and extracted with CH₂Cl₂. The combined organics were washed with brine, dried over Na₂SO₄, filtered and concentrated in vacuo to give an inseparable mixture (9:1) of 5-[5-chloro-2-(1-fluoro-1-methyl-ethyl)-methoxy-phenoxyl-acetonitrile (1.543 g) and (5-Chloro-2-isopropenyl-4-methoxy-phenoxyl)-acetonitrile as a pale brown oil.

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

5-[5-Chloro-2-(1-fluoro-1-methyl-ethyl)-methoxy-phenoxyl-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-phenoxyl-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

The synthetic procedure used in this Example is outlined in Scheme 0.

SCHEME 0

Step 1. 3-Bromo-4,5-dihydroxy-benzaldehyde
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 H₂O. The precipitate was filtered, washed with cold H₂O 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
To a solution of 3-bromo-4,5-dihydroxy-benzaldehyde (20.78 g, 95 mmol) in 480 ml DMF was added K₂CO₃ (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 Na₂SO₄, 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
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.

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

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

10 Step 6. (8-Bromo-5-ethyl-2,3-dihydro-benzo[1,4]dioxin-6-yloxy)-acetonitrile
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%).

15 Step 7. 5-(8-Bromo-5-ethyl-2,3-dihydro-benzo[1,4]dioxin-6-yloxy)-pyrimidine-2,4-diamine
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
The synthetic procedure used in this Example is outlined in Scheme P.
SCHEME P

Step 1. 2,3-Dihydro-benzo[1,4]dioxin-6-ol

To a solution of 2,3-dihydro-benzo[1,4]dioxin-6-carboxaldehyde (30.0 g, 183 mmol) in 500 ml CH₂Cl₂ was added mCPBA (37.85 g, 219 mmol). The suspension was heated to 50°C. After 16 h saturated NaHCO₃ was added and the mixture was extracted with CH₂Cl₂. 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 NaHCO₃, washed with brine, concentrated in vacuo, and taken up in CH₂Cl₂. The solution was filtered to remove the precipitate. The resulting solution was stirred with saturated NaHCO₃ for 1 h, separated, dried over MgSO₄, 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

To a mixture of K₂CO₃ (47.54 g, 344 mmol) and Bu₄NI (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 H₂O and extracted with ethyl acetate. The combined organics were washed with brine, dried over MgSO₄, 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

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 ex-
tracted 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**

To a solution of 2-bromopropene (5.4 ml, 59 mmol) in 200 mL DME was added Pd(Ph$_3$P)$_4$ (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$_2$CO$_3$ (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$_2$O 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**

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**

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$_2$Cl$_2$ 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$_2$O, warmed to RT and extracted with CH$_2$Cl$_2$. 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**

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-yloxy)-pyrimidine-2,4-diamine

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

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 310 ml AcOH and 2 ml H2O. After 20 h the reaction was neutralized with Na2CO3 and extracted with CH2Cl2. The combined organics were washed with washed 10% NaHSO3, washed with brine, dried over Na2SO4, filtered and concentrated in vacuo. Purification via flash chromatography (97:3 CH2Cl2/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

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

![Scheme Q](image-url)
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 CH₂Cl₂. The combined organics were washed with brine, dried over Na₂SO₄, 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
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 CH₂Cl₂. The combined organics were washed with brine, dried over Na₂SO₄ 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
To a mixture of NaBH₄ (0.051 g, 1.3 mmol) in 4 ml DME was added TiCl₄ (0.67 ml, 0.67 mmol, 1.0 M in CH₂Cl₂). 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 H₂O and extracted with ethyl acetate. The combined organics were washed with brine, dried over Na₂SO₄, 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 NaHCO₃ and extracted with ethyl acetate. The combined organics were washed with brine, dried over Na₂SO₄, 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-phenoxy-acetonitrile
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
[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

**Step 1. 5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-benzenesulfonyl chloride**

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 H2O 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-benzenemethylsulfonamide**

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 H2O, 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.

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
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 CH₂Cl₂, the combined organic solution was concentrated in vacuo. The residue was purified via preparative TLC silica plates, eluted with 5% MeOH/CH₂Cl₂/NH₄OH 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

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.
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

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 BBr₃ (0.26g, 1.05mmol). The reaction mixture was stirred at RT for 16 hrs., quenched with water and basified with sat. NaHCO₃. The insoluble solid was collected by filtration. The filtrate was washed with water, dried over Na₂SO₄, 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% NH₄OH) 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

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

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

The synthetic procedure used in this Example is outlined in 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

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

The N’-[5-[5-(3-Dimethylamino-acryloyl)-2-isopropyl-4-methoxy-phenoxy]-4-(dimethylamino-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

To 1-[5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-3-dimethylamino-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)-pyrimidine-2,4-diamine

\[
\begin{align*}
\text{To 5-(5-Iodo-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine (600 mg, 1.5 mmol, from Example 14, Step 1) dissolved in N,N-dimethylacetamide (4.8 mL) was added}
\end{align*}
\]
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

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**

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**

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-phen oxy)-pyrimidine-2,4-diamine**

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-phen oxy)-pyrimidine-2,4-diamine was prepared. MS (M+H) = 275.

Similarly prepared was 5-(2-Isopropyl-4-methoxy-phen oxy)-pyrimidine-2,4-diamine. MS (M+H) = 275.

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

![Chemical structure of 5-(5-Ethanesulfonyl-2-isopropyl-4-methoxy-phen oxy)-pyrimidine-2,4-diamine]

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 (400 mg, 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-phen oxy)-pyrimidine-2,4-diamine (77 mg, 20%) as white solid, MS (M+H) = 367.

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

The synthetic procedure used in this Example is outlined in Scheme S.
SCHEMES

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

To a solution of 2-Isopropyl-4-methoxy-1-(toluene-4-sulfonyl)-benzene (10 g, 31.25 mmol) in HOAc (10 ml) was added a solution of ICl (9.6 g, 59.26 mmol) in HOAc (10 ml) and H₂O (5 ml). The reaction mixture was stirred at RT for 16 hrs and basified by saturated NaHCO₃ solution. The aqueous solution was extracted into EtOAc which was washed with water, brine, dried over Na₂SO₄, filtered and concentrated in vacuo to give 1-Iodo-4-isopropyl-2-methoxy-5-(toluene-4-sulfonyl)-benzene (12.35 g, 89%).

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

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 (0.64 g, 4.48 mmol) in portions over 30 min. The reaction mixture was heated for 4 hrs and poured into H₂O (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**

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 (5 ml) and H₂O (5 ml) 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 Na₂SO₄, 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-phenoxo)-pyrimidine-2,4-diamine

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-phenoxo)-pyrimidine-2,4-diamine. (M+H) = 343

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

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

![Scheme T](image)

10 SCHEME T

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

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 AlCl₃ (3.3 g, 24.84 mmol) at RT. The reaction mixture was stirred at RT for 16 hrs and quenched by H₂O (10 ml). Ten min after quenching, the aqueous solution was extracted into CH₂Cl₂. The combined extract was washed with H₂O, dried over Na₂SO₄, filtered and concentrated. Flash chromatography on silica gel (0 to 30% EtOAc in Hex) gave 1-[4-isopropyl-2-methoxy-5-(toluene-4-sulfonyl)-phenyl]-ethanone (4.7 g, 79%) as white solid.

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

To a hot mixture of CuBr₂ (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 CHCl₃ (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

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$_2$CO$_3$ (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$_2$O and methylene chloride. The combined organic extracts was dried over Na$_2$SO$_4$, 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

A mixture of 4-[4-Isopropyl-2-methoxy-5-(toluene-4-sulfonyl)-phenyl]-thiazole (1.0 g, 2.27 mmol) and K$_2$CO$_3$ (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$_2$SO$_4$, 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

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$_2$CO$_3$ (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$_2$SO$_4$, 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

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$_2$SO$_4$, 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$_2$SO$_4$, filtered and concentrated. Flash chromatography on silica (3% MeOH in methylene chloride with 0.1%H$_2$O) 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

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

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

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 K₂CO₃ (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 Na₂SO₄, filtered and concentrated. Flash chromatography on silica(3%MeOH in methylene chloride with 0.1%
NH₄OH) 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
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/H₂O 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 Na₂SO₄, filtered and concentrated. Flash chromatography on silica (5% MeOH in methylene chloride with 0.1% NH₄OH) 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

Step 1.  5-(4-Amino-2-ethylamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-benzonitrile
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% NH₄OH solution (100 ml) and filtered again. The filtrate was concentrated and flash chromatographed on silica (3% MeOH in methylene chloride with 0.1%NH₄OH) 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
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/H₂O (1:1,10 ml) was added a solution of NaOH
(0.37 g, 9.17 mmol) in H₂O (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 Na₂SO₄, 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 (0.086 g, 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

\[
\begin{align*}
\text{HN} & \quad \text{NH} \\
\text{O} & \quad \text{O} \\
\text{N} & \quad \text{N} \\
\text{O} & \quad \text{O} \\
\text{H} & \quad \text{H}
\end{align*}
\]

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 trifluoromethanesulfonic 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. NaHCO₃ solution. The aqueous solution was then extracted into methylene chloride. The combined organic extract was washed with H₂O, dried over Na₂SO₄, filtered and concentrated. Flash chromatography on silica (1% MeOH in methylene chloride with 1% NH₄OH) 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

\[
\begin{align*}
\text{CH(CH₃)₂} & \quad \text{CH(CH₃)₂} \\
\text{C(O)CH₂Br} & \quad \text{C(O)CH₂CHO} \\
\text{H₂CO} & \quad \text{H₂CO} \\
\text{OTs} & \quad \text{OTs} \\
\end{align*}
\]

Step 1. Toluene-4-sulfonic acid 5-(2-formyloxy-acetyl)-2-isopropyl-4-methoxy-phenyl ester
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$_2$O and extracted into EtOAc. The combined organic extract was dried over Na$_2$SO$_4$, 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**

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$_2$SO$_4$, 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-phenoxy)-pyrimidine-2,4-diamine**

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**

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$_3$OH in methylene chloride with 1% NH$_4$OH) 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

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. NaHCO₃ solution. The aqueous solution was extracted into methylene chloride. The combined organic extract was dried over Na₂SO₄, filtered and concentrated. Flash chromatography on silica (5% MeOH in methylene chloride with 1% NH₄OH) 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

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 H₂O. The organic extract was dried over Na₂SO₄, filtered and concentrated. Flash chromatography on silica (3% MeOH in methylene chloride with 1% NH₄OH) 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

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

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 (MgSO₄), 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)-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

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 trimethylorthofromate (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 1½ hours. The resultant mixture was cooled, diluted with DCM (60 ml), then washed with water (20 ml), brine (20 ml) and then dried (MgSO₄) 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-phenoxy)-pyrimidine-2,4-diamine

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

The synthetic procedure used in this Example is outlined in Scheme V.
**SCHEME V**

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

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 (MgSO₄), 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.

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

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 (MgSO₄), 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.

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

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**SCHEME V**

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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
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 (MgSO₄), 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
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
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 (MgSO₄), 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
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 Et₂O, 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 (MgSO₄), 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 (MgSO₄), 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
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 (MgSO₄), 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
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
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(Ph₃)₂Cl₂ (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 (MgSO₄), 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

5-(5-Iodo-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine (400 mg, 1 mmol), potassium acetate ((147 mg), Pd(Ph₃)₂Cl₂ (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 (MgSO₄), 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
The synthetic procedure used in this Example is outlined in Scheme W.

**Scheme W**

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

To a solution of 1-(2-Benzyl-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 (MgSO₄), 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.

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

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 drop-wise, 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 (MgSO₄), 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-Benzylxy-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**
A mixture of 2-[2-Benzylxy-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 under 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**
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 added 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 (MgSO₄), 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**
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 (MgSO₄), 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-methanesulfonyl-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**
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
The synthetic procedure used in this Example is outlined in Scheme X.

**Scheme X**

**Step 1. N-Methoxy-N-methyl-butyramide**

Pyridine (100 mL) was cooled to 0°C, and N,O-dimethylhydroxylamine hydrochloride (20.14 g, 206 mmol) was added with stirring. This solution was stirred for 10 min, and then a solution of butyryl chloride (19.5 ml, 20 g, 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**

3-Bromo thiophene (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

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

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

5-Thiophen-3-yl-heptane-2,4-dione (410 mg, 2 mmol) was dissolved in 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 diethyl 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-yl-oxo)-acetonitrile

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 added, 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

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

3,3-Bis-dimethylamino-2-(4-ethyl-7-methyl-benzo[b]thiophen-5-yloxy)-propionitrile (590 mg, 2 mmol) and aniline HCl (1.1 g, 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%NH₄OH) 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

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, di-
luted 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-benzothiophen-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

The synthetic procedure used in this Example is outlined in Scheme Y.

**SCHEME Y**

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

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**
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 NaNO₂ (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 column 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.**

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**

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

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 addition of 1 N NH₄Cl, 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

5-Methoxy-1,3-dimethyl-6-trifluoromethyl-1H-indole (725 mg, 3 mmol) in methylene chloride (15 ml) was cooled to 0°C, and BBr₃ (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 mL 1 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

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

The synthetic procedure used in this Example is outlined in Scheme Z.
SCHEME Z

Step 1. N-(4-Acetyl-3-methoxy-phenyl)-acetamide
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
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 NH₄Cl and extracted with EtOAc. The combined organic layers were washed with 1 N ammonium chloride, brine, dried over MgSO₄, 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
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 N₂, 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 combined 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
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
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) dissolved 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
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.

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

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

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.

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
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 H₂SO₄ in MeOH (25 μL). The reaction was allowed to warm to RT slowly, stirred overnight, quenched with saturated NaHCO₃, and concentrated. The residue was partitioned between water and methylene chloride. The combined organic phases were dried with Na₂SO₄ 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**

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-diamine. The hydrochloride salt was recrystallized from EtOH/diethyl ether. MS (M+H): 314, MP >300 °C.

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

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 CH₂Cl₂ with 0.1 % NH₄OH) 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

\[
\begin{align*}
\text{OMe} &\quad \text{BBr}_3 \\
\text{MeO} &\quad \text{ClCH}_2\text{CN}
\end{align*}
\]

Step 1. (2,5-Diiodo-4-methoxy-phenoxy)-acetonitrile.
Diiododimethoxybenzene (10 mmol) was dissolved in 75 ml CH₂Cl₂ and cooled to 0°C. BBr₃ (1M in CH₂Cl₂, 1.1 equivalents) was added. After 30 min the reaction was partitioned between CH₂Cl₂ 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 ClCH₂CN and excess K₂CO₃. 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

\[
\begin{align*}
\text{OCH}_2\text{CN} &\quad \text{NH}_2 \\
\text{MeO} &\quad \text{NH}_2
\end{align*}
\]

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

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

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>% wt./wt.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active ingredient</td>
<td>20.0%</td>
</tr>
<tr>
<td>Lactose</td>
<td>79.5%</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>% wt./wt.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active ingredient</td>
<td>20.0%</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>0.5%</td>
</tr>
<tr>
<td>Crosscarmellose sodium</td>
<td>2.0%</td>
</tr>
<tr>
<td>Lactose</td>
<td>76.5%</td>
</tr>
<tr>
<td>PVP (polyvinylpyrrolidin)</td>
<td>1.0%</td>
</tr>
</tbody>
</table>

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

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

The ingredients are mixed to form a suspension for oral administration.
Parenteral Formulation

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>% wt./wt.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active ingredient</td>
<td>0.25 g</td>
</tr>
<tr>
<td>Sodium Chloride</td>
<td>qs to make isotonic</td>
</tr>
<tr>
<td>Water for injection</td>
<td>100 ml</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>% wt./wt.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active ingredient</td>
<td>1.0%</td>
</tr>
<tr>
<td>Polyethylene glycol 1000</td>
<td>74.5%</td>
</tr>
<tr>
<td>Polyethylene glycol 4000</td>
<td>24.5%</td>
</tr>
</tbody>
</table>

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

Topical Formulation

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Grams</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active compound</td>
<td>0.2-2</td>
</tr>
<tr>
<td>Span 60</td>
<td>2</td>
</tr>
<tr>
<td>Tween 60</td>
<td>2</td>
</tr>
<tr>
<td>Mineral oil</td>
<td>5</td>
</tr>
<tr>
<td>Petrolatum</td>
<td>10</td>
</tr>
<tr>
<td>Methyl paraben</td>
<td>0.15</td>
</tr>
<tr>
<td>Propyl paraben</td>
<td>0.05</td>
</tr>
<tr>
<td>BHA (butylated hydroxy anisole)</td>
<td>0.01</td>
</tr>
<tr>
<td>Water</td>
<td>q.s. 100</td>
</tr>
</tbody>
</table>

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

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: P2X3/P2X2/3 FLIPR (Fluorometric Imaging Plate Reader) Assay

CHO-K1 cells were transfected with cloned rat P2X3 or human P2X2/3 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% CO2 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 CaCl2, 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 (P2X3) or 5 μM (P2X2/3). 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 P2X3 receptor. The compound 4-(2,4-Diamino-pyrimidin-5-yloxy)-2-ido-5-isopropyl-phenol, e.g., exhibited a pIC50 of approximately 8.3 using the above assay. As can be seen from
Table 3, compounds of the invention $R^1$ 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

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.

Example 72: Volume Induced Bladder Contraction Assay

Female Sprague-Dawley rats (200-300g) were anesthetized with urethane (1.5 g/kg, sc). The animals were tracheotomized, and a carotid artery and femoral vein were cannulated for blood pressure measurement and drug administration, respectively. A laparotomy was performed and the ureters were ligated and transected proximal to the ligation. The external urethral meatus was ligated with silk suture and the urinary bladder was cannulated via the dome for saline infusion and bladder pressure measurement. Following a 15-30 minute stabilization period the bladder was infused with RT saline at 100 μl/min until continuous volume-induced bladder contractions (VIBCs) were observed. The infusion rate was then lowered to 3-5 μl/min for 30 min before the bladder was drained and allowed to rest for 30 min. All subsequent infusions were performed as indicated except the lower infusion rate was maintained for only 15 min instead of 30 min. Bladder filling and draining cycles were repeated until the threshold volumes (TV; the volume needed to trigger the first micturition bladder contraction) varied by less than 10% for two consecutive baselines and contraction frequency was within 2 contractions for a 10 minute period following the slower infusion rate. Once reproducible TVs and VIBCs were established the bladder was drained and the animal was dosed with drug or vehicle (0.5 ml/kg, i.v.) 3 min prior to the start of the next scheduled infusion.

Example 73: Formalin Pain Assay

Male Sprague Dawley rats (180-220 g) are placed in individual Plexiglas cylinders and allowed to acclimate to the testing environment for 30 min. Vehicle, drug or positive control (morphine 2 mg/kg) is administered subcutaneously at 5 ml/kg, 15 min post dosing.
formalin (5% in 50 µl) is injected into plantar surface of the right hind paw using a 26-gauge needle. Rats are immediately put back to the observation chamber. Mirrors placed around the chamber allow unhindered observation of the formalin-injected paw. The duration of nociphensive behavior of each animal is recorded by a blinded observer using an automated behavioral timer. Hindpaw licking and shaking / lifting are recorded separately in 5 min bin, for a total of 60 min. The sum of time spent licking or shaking in seconds from time 0 to 5 min is considered the early phase, whereas the late phase is taken as the sum of seconds spent licking or shaking from 15 to 40 min. A plasma sample is collected.

Example 74: Colon Pain Assay

Adult male Sprague-Dawley rats (350-425 g; Harlan, Indianapolis, IN) are housed 1-2 per cage in an animal care facility. Rats are deeply anesthetized with pentobarbital sodium (45 mg/kg) administered intraperitoneally. Electrodes are placed and secured into the external oblique musculature for electromyographic (EMG) recording. Electrode leads are tunneled subcutaneously and exteriorized at the nape of the neck for future access. After surgery, rats are housed separately and allowed to recuperate for 4-5 days prior to testing. The descending colon and rectum are distended by pressure-controlled inflation of a 7-8 cm-long flexible latex balloon tied around a flexible tube. The balloon is lubricated, inserted into the colon via the anus, and anchored by taping the balloon catheter to the base of the tail. Colorectal distension (CRD) is achieved by opening a solenoid gate to a constant pressure air reservoir. Intracolonic pressure is controlled and continuously monitored by a pressure control device. Response is quantified as the visceromotor response (VMR), a contraction of the abdominal and hindlimb musculature. EMG activity produced by contraction of the external oblique musculature is quantified using Spike2 software (Cambridge Electronic Design). Each distension trial lasts 60 sec, and EMG activity is quantified for 20 sec before distension (baseline), during 20 sec distension, and 20 sec after distention. The increase in total number of recorded counts during distension above baseline is defined as the response. Stable baseline responses to CRD (10, 20, 40 and 80 mmHg, 20 seconds, 4 min apart) are obtained in conscious, unsedated rats before any treatment.

Compounds are evaluated for effects on responses to colon distension initially in a model of acute visceral nociception and a model of colon hypersensitivity produced by intracolonic treatment with zymosan (1 mL, 25 mg/mL) instilled into the colon with a gavage needle inserted to a depth of about 6 cm. Experimental groups will consist of 8 rats each.
Acute visceral nociception: For testing effects of drug on acute visceral nociception, 1 of 3 doses of drug, vehicle or positive control (morphine, 2.5 mg/kg) are administered after baseline responses are established; responses to distension are followed over the next 60–90 min.

5 Visceral hypersensitivity: For testing effects of drug or vehicle after intracolonic treatment with zymosan, intracolonic treatment is given after baseline responses are established. Prior to drug testing at 4 hours, responses to distension are assessed to establish the presence of hypersensitivity. In zymosan-treated rats, administration of 1 of 3 doses of drug, vehicle or positive control (morphine, 2.5 mg/kg) are given 4 hours after zymosan treatment and responses to distension followed over the next 60–90 min.

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

1. The use of a compound of formula I

\[
\text{(I)}
\]

or a pharmaceutically acceptable salt thereof,

wherein:

- \( X \) is \(-\text{CH}_2-; -\text{O}--; -\text{C(O)}--; -\text{CHOH}--; -\text{S(O)}_n--; \) or \(-\text{NR}^e--; \) wherein \( n \) is from 0 to 2 and \( R^e \) is hydrogen or alkyl;
- \( Y \) is hydrogen; or \(-\text{NR}^d R^e \) wherein one of \( R^d \) and \( R^e \) is hydrogen, and the other is hydrogen; alkyl; cycloalkyl; cycloalkylalkyl; haloalkyl; haloalkoxy; hydroxyalkyl; alkoxyalkyl; acetyl; alkylsulfonly; alkyloxalylalkyl; aminoalkoxyalkyl; hydroxyalkylalkylalkyl; aryl; aralkyl; aminoalkylalkyl; amino; hydroxyalkyl; or alkoxyalkylalkyl;

- \( D \) 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; haloalkyl; alkoxy; hydroxy; haloalkoxy; nitro; hydroxyalkyl; hydroxyalkoxy; alkynylalkoxy; alkyloxalyl; arylsulfonly; cyano; aryl; heteroaryl; heterocyclylalkoxy; aryloxy; heteroaryloxy; heteroaryloxy; optionally substituted phenoxy; \(-(\text{CH}_2)_m-(Z)_n-(\text{CO})-\) or \(-(\text{CH}_2)_m-(Z)_n-\text{SO}_2-(\text{NR}_g)_n-\) \( R^l \) where \( m \) and \( n \) each independently is 0 or 1, \( Z \) is \( \text{O} \) or \( \text{NR}^e \), \( R^l \) is hydrogen, alkyl, hydroxy, alkoxy, amino, hydroxyalkyl or alkoxyalkyl, and each \( R^e \) is independently hydrogen or alkyl; or
- \( R^3 \) and \( R^4 \) may together form an alkylene dioxy; or
- \( R^2 \) and \( R^3 \) together with the atoms to which they are attached form a five or six-membered ring that optionally includes one or two heteroatoms selected from \( \text{O}, \text{S} \) and \( \text{N} \); or
- \( R^2 \) and \( R^3 \) together form an alkylene dioxy; or
- \( R^2 \) and \( R^3 \) together with the atoms to which they are attached form a five or six-membered ring that optionally includes one or two heteroatoms selected from \( \text{O}, \text{S} \) and \( \text{N} \); or
- \( R^5 \) 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; alkyloxalyl; alkyloxalyl;...
alkyl; aminocarbonyloxyalkyl; hydroxycarbonylalkyl; hydroxyalkyloxycarbonylalkyl; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl;

for the preparation of a medicament for the treatment of a respiratory or gastrointestinal disease mediated by a P2X3 or P2X2/3 receptor antagonist.

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

![Chemical Structure](image)

wherein:

- $X$ is $-\text{CH}_2-$ or $-\text{O}-$;
- $R^1$ 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; alkynylalkoxy; alkylsulfanyl; arylsulfanyl; cyano; aryl; heteroaryl; heterocyclyl; heterocyclylalkoxy; aryloxy; heteroaryloxy; aralkyloxy; heteroaralkyloxy; optionally substituted phenoxy;
- $-(\text{CH}_2)_m-(Z)_n-(\text{CO})-R^6$ or $-(\text{CH}_2)_m-(Z)_n-SO_2-(\text{NR}^g)_n-R^6$ where $m$ and $n$ each independently is 0 or 1, $Z$ is O or NR$^g$, $R^6$ is hydrogen, alkyl, hydroxy, alkoxy, amino, hydroxyalkyl or alkoxyalkyl, and each $R^g$ is independently hydrogen or alkyl; or
- $R^3$ and $R^4$ together form an alkylene dioxy; or
- $R^3$ and $R^4$ together with the atoms to which they are attached form a five or six-membered ring that optionally includes one or two heteroatoms selected from O, S and N;
- one of $R^7$ and $R^8$ is hydrogen, and the other is hydrogen; alkyl; cycloalkyl; cycloalkylalkyl; haloalkyl; haloalkoxy; hydroxyalkyl; alkoxyalkyl; acetyl; alkylsulfanyl; alkylsulfonylethyl; aminocarbonylalkyl; hydroxyalkyl; hydroxyalkyloxycarbonylalkyl; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl; and
- one of $R^1$ and $R^5$ is hydrogen, and the other is hydrogen; alkyl; cycloalkyl; cycloalkylalkyl; haloalkyl; haloalkoxy; hydroxyalkyl; alkoxyalkyl; acetyl; alkylsulfanyl; alkylsulfonylalkyl; aminocarbonylalkyl; hydroxyalkyl; hydroxyalkyloxycarbonylalkyl; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl.

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

R\textsubscript{1} is isopropyl, isopropenyl, cyclopropyl or iodo;

R\textsubscript{3} and R\textsubscript{4} each independently is alkyl; alkenyl; amino; halo; amido; haloalkyl; alkoxy;

hydroxy; haloalkoxy; nitro; hydroxyalkyl; alkoxyalkyl; hydroxyalkoxy; alkynylalkoxy; alkylsulfonylethyl; arylsulfonylethyl; cyano; aryl; heteroaryl; heterocyclyl; heterocyclylalkoxy; aryl; heteroaryloxy; aralkyloxy; heteroaralkyloxy; optionally substituted phenoxy;

-(CH\textsubscript{2})\textsuperscript{m}-(Z)\textsuperscript{n}-(CO)-R or -(CH\textsubscript{2})\textsuperscript{m}-(Z)\textsuperscript{n}-SO\textsubscript{2}-(NR\textsubscript{g})\textsuperscript{n}-R where m and n each independently is 0 or 1, Z is O or NR\textsubscript{g}, R\textsubscript{1} is hydrogen, alkyl, hydroxy, alkoxy, amino, hydroxyalkyl or alkoxyalkyl, and each R\textsubscript{8} is independently hydrogen or alkyl; or

R\textsubscript{3} and R\textsubscript{4} together form an alkyene dioxy; or

R\textsubscript{3} and R\textsubscript{4} together with the atoms to which they are attached form a five or six-membered ring that optionally includes one or two heteroatoms selected from O, S and N;

one of R\textsubscript{2} and R\textsubscript{8} is hydrogen, and the other is hydrogen; alkyl; cycloalkyl; cycloalkylalkyl;

haloalkyl; haloalkoxy; hydroxyalkyl; alkoxyalkyl; acetyl; alkylsulfonyl; alkylsulfonylalkyl; aminocarbonyloxyalkyl; hydroxycarbonylalkyl; hydroxyalkyloxyalkyl; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroarylalkylalkyl; heterocyclyl or heterocyclylalkyl; and

one of R\textsubscript{3} and R\textsubscript{4} is hydrogen, and the other is hydrogen; alkyl; cycloalkyl; cycloalkylalkyl;

haloalkyl; haloalkoxy; hydroxyalkyl; alkoxyalkyl; acetyl; alkylsulfonyl; alkylsulfonylalkyl; aminocarbonyloxyalkyl; hydroxycarbonylalkyl; hydroxyalkyloxyalkyl; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroarylalkylalkyl; heterocyclyl or heterocyclylalkyl.

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

![Chemical Structure](image-url) (IV)
R³ and R⁴ each independently is alkyl; alkenyl; amino; halo; amidoo; haloalkyl; alkoxy; hydroxy; haloalkoxy; nitro; hydroxyalkyl; alkoxyalkyl; hydroxalkoxy; alkynyalkoxy; alkylsulfonyl; arylsulfonyl; cyano; aryl; heteroaryl; heterocyclyl; heterocyclalkoxy; aryloxy; heteroaryloxy; aralkyloxy; heteroaralkyloxy; optionally substituted phenoxy; -(CH₂)ₘ-(Z)ₙ-(CO)-R or -(CH₂)ₘ-(Z)ₙ-SO₂-(NR₉)ₙ-R where m and n each independently is 0 or 1, Z is O or NR₉, R¹ is hydrogen, alkyl, hydroxy, alkoxy, amino, hydroxyalkyl or alkoxyalkyl, and each R₉ is independently hydrogen or alkyl; or

R³ and R⁴ together form an alkylene dioxy; or

R³ and R⁴ together with the atoms to which they are attached form a five or six-membered ring that optionally includes one or two heteroatoms selected from O, S and N; one of R³ and R⁴ is hydrogen, and the other is hydrogen; alkyl; cycloalkyl; cycloalkylalkyl; haloalkyl; haloalkoxy; hydroxyalkyl; alkoxyalkyl; acetyl; alkylsulfonyl; alkylsulfonylalkyl; aminocarbonyloxyalkyl; hydroxycarbonylalkyl; hydroxalkylalkoxycarbonylalkyl; aryl; aralkyl; arylosulfonyl; heteroaryl; heteroarylalkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclalkyl; and

one of R⁴ and R⁵ is hydrogen, and the other is hydrogen; alkyl; cycloalkyl; cycloalkylalkyl; haloalkyl; haloalkoxy; hydroxyalkyl; alkoxyalkyl; acetyl; alkylsulfonyl; alkylsulfonylalkyl; aminocarbonyloxyalkyl; hydroxycarbonylalkyl; hydroxalkylalkoxycarbonylalkyl; aryl; aralkyl; arylosulfonyl; heteroaryl; heteroarylalkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclalkyl.

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

\[
\begin{align*}
\text{H}_2\text{C} & \text{CH}_3 \\
R^3 & \text{NR}^7 \text{R}^8 \\
\text{R}^3 & \text{NR}^7 \text{R}^8 \\
\end{align*}
\]

wherein:
R³ and R⁴ each independently is alkyl; alkenyl; amino; halo; amidoo; haloalkyl; alkoxy; hydroxy; haloalkoxy; nitro; hydroxyalkyl; alkoxyalkyl; hydroxalkoxy; alkynyalkoxy; alkylsulfonyl; arylsulfonyl; cyano; aryl; heteroaryl; heterocyclyl; heterocyclalkoxy; aryloxy; heteroaryloxy; aralkyloxy; heteroaralkyloxy; optionally substituted phenoxy; -(CH₂)ₘ-(Z)ₙ-(CO)-R or -(CH₂)ₘ-(Z)ₙ-SO₂-(NR₉)ₙ-R where m and n each independently is 0 or 1, Z is O or NR₉, R¹ is hydrogen, alkyl, hydroxy, alkoxy, amino, hydroxyalkyl or alkoxyalkyl, and each R₉ is independently hydrogen or alkyl; or

R³ and R⁴ together form an alkylene dioxy; or
R³ and R⁴ together with the atoms to which they are attached form a five or six-membered ring that optionally includes one or two heteroatoms selected from O, S and N; one of R⁷ and R⁸ is hydrogen, and the other is hydrogen; alkyl; cycloalkyl; cycloalkylalkyl; haloalkyl; haloalkoxy; hydroxyalkyl; alkoxyalkyl; acetyl; alkylsulfonyl; alkylsulfonylalkyl; aminocarboxyloxyalkyl; hydroxycarboxylalkyl; hydroxyalkylloxycarboxylalkyl; aryl; aralkyl; arylosulfonyl; heteroaryl; heteroaryalkyl; heteroarylsulfonyl; heterocycl; or heterocyclalkyl; and

one of R⁷ and R⁸ is hydrogen, and the other is hydrogen; alkyl; cycloalkyl; cycloalkylalkyl; haloalkyl; haloalkoxy; hydroxyalkyl; alkoxyalkyl; acetyl; alkylsulfonyl; alkylsulfonylalkyl; aminocarboxyloxyalkyl; hydroxycarboxylalkyl; hydroxyalkylloxycarboxylalkyl; aryl; aralkyl; arylosulfonyl; heteroaryl; heteroaryalkyl; heteroarylsulfonyl; heterocycl; or heterocyclalkyl.

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

\[ \text{H}_3\text{C} \text{-CH}_3 \text{NR}_7 \text{R}_8 \]
\[
\text{R}_3 \text{ and } \text{R}_4 \text{ each independently is alkyl; alkenyl; amino; halo; amido; haloalkyl; alkoxy; hydroxy; haloalkoxy; nitro; hydroxyalkyl; alkoxyalkyl; hydroxyalkoxy; alkynylalkoxy; alkylsulfonyl; arylosulfonyl; cyano; aryl; heteroaryl; heterocycl; heterocyclalkoxy; aralkyloxy; heteroaralkyloxy; optionally substituted phenoxy; -(CH}_2\text{)_m-(Z)}\text{_n-(CO)}\text{-R or -(CH}_2\text{)_m-(Z)}\text{_n-SO}_2\text{-}(\text{NR}_5\text{)_n-R}}\text{ where m and n each independently is 0 or 1, Z is O or NR}_6\text{, R}_4\text{ is hydrogen, alkyl, hydroxy, alkoxy, amino, hydroxyalkyl or alkoxalkyl, and each R}_5\text{ is independently hydrogen or alkyl or}
\]
\[
\text{R}_3 \text{ and } \text{R}_4 \text{ together form an alkylene dioxy; or}
\]
\[
\text{R}_3 \text{ and } \text{R}_4 \text{ together with the atoms to which they are attached form a five or six-membered ring that optionally includes one or two heteroatoms selected from O, S and N; one of R}_7\text{ and R}_8\text{ is hydrogen, and the other is hydrogen; alkyl; cycloalkyl; cycloalkylalkyl; haloalkyl; haloalkoxy; hydroxyalkyl; alkoxyalkyl; acetyl; alkylsulfonyl; alkylsulfonylalkyl; aminocarboxyloxyalkyl; hydroxycarboxylalkyl; hydroxyalkylloxycarboxylalkyl; aryl; aralkyl; arylosulfonyl; heteroaryl; heteroaryalkyl; heteroarylsulfonyl; heterocycl; or heterocyclalkyl; and}
\]
one of R¹ and R⁵ is hydrogen, and the other is hydrogen; alkyl; cycloalkyl; cycloalkylalkyl; haloalkyl; haloalkoxy; hydroxyalkyl; alkoxyalkyl; acetyl; alkylsulfonyl; alkylsulfonylalkyl; aminocarboxyloxyalkyl; hydroxycarboxylalkyl; hydroxylalkylalkyloxyalkylalkyl; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroarylalkylalkyl; heterocyclyl; or heterocyclylalkyl.

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

![Chemical structure](image)

(VII)

wherein:

- X is \(-\text{CH}_2−\) or \(-\text{O}-\);
- R¹ is alkyl; alkenyl; cycloalkyl; or cycloalkenyl; or halo;
- R² is hydrogen; alkyl; alkenyl; amino; halo; amido; haloalkyl; alkoxy; hydroxy; haloalcohol; nitro; hydroxyalkyl; alkoxyalkyl; hydroxyalkoxy; alkynylalkoxy; alkylsulfonyl; arylsulfonyl; cyano; aryl; heteroaryl; heterocyclyl; heterocyclylalkoxy; aryloxy; heteroaryloxy; aralkyl; heteroaralkyl; heteroarylsulfonyl; heteroarylsulfonylalkyl; and each R° is independently hydrogen or alkyl;
- one of R⁷ and R⁸ is hydrogen, and the other is hydrogen; alkyl; cycloalkyl; cycloalkylalkyl; haloalkyl; haloalkoxy; hydroxyalkyl; alkoxyalkyl; acetyl; alkylsulfonyl; alkylsulfonylalkyl; aminocarboxyloxyalkyl; hydroxycarboxylalkyl; hydroxylalkylalkyloxyalkylalkyl; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroarylalkylalkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl;
- one of R¹ and R⁵ is hydrogen, and the other is hydrogen; alkyl; cycloalkyl; cycloalkylalkyl; haloalkyl; haloalkoxy; hydroxyalkyl; alkoxyalkyl; acetyl; alkylsulfonyl; alkylsulfonylalkyl; aminocarboxyloxyalkyl; hydroxycarboxylalkyl; hydroxylalkylalkyloxyalkylalkyl; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroarylalkylalkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl;
- Q is CR⁹, one of A and E is O, S or NR¹⁰ and the other is CR⁹ or N; or
- Q is N, one of A and E is NR¹⁰ and the other is CR⁹;
- each R° is independently hydrogen, alkyl, halo or alkoxy; and
8. The use of claim 1, wherein said compound is of the formula (VIII):

\[
\begin{align*}
\text{R}^1 & \text{ is hydrogen, alkyl, hydroxyalkyl, alkoxyalkyl, } -\text{(CH}_2\text{)}_m\text{-(Z)}_n\text{-(CO)-R}, \text{ or } -\text{(CH}_2\text{)}_m\text{-(Z)}_n\text{SO}_2\text{-(NR)}_n\text{R}. \\
\end{align*}
\]

wherein:

- **X** is \(-\text{CH}_2\text{}-\text{ or } -\text{O}-\);
- **R** is alkyl; alkenyl; cycloalkyl; or cycloalkenyl; or halo;
- **R** is hydrogen; alkyl; alkenyl; amino; halo; amido; haloalkyl; alkoxy; hydroxy; haloalkoxy; nitro; hydroxyalkyl; alkoxyalkyl; hydroxycarbonyl; alkynylalkoxy; alkoxyalkyl; cyano; aryl; heteroaryl; heterocyclyl; aryloxy; heteroaryloxy; aralkyl; heteroaralkyl; optionally substituted phenoxy; or
- \(-\text{(CH}_2\text{)}_m\text{-(Z)}_n\text{-(CO)-R}^f\) or \(-\text{(CH}_2\text{)}_m\text{-(Z)}_n\text{SO}_2\text{-(NR)}_n\text{R}^f\) where \(m\) and \(n\) each independently is 0 or 1, \(Z\) is O or \(\text{NR}_9\), \(R\) is hydrogen, alkyl, hydroxy, alkoxy, amino, haloalkyl or alkoxyalkyl, and each \(R\) 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; alkoxyalkyl; alkylsulfonylalkyl; aminocarbonyloxyalkyl; hydroxycarbonylalkyl; hydroxycarbonylalkyl; aryalkyl; aralkyl; aryloxy; heteroaryl; heteroarylsulfonyl; heterocyclyl; heterocyclylalkyl;

one of \(R^6\) and \(R^5\) is hydrogen, and the other is hydrogen; alkyl; cycloalkyl; cycloalkylalkyl; haloalkyl; haloalkoxy; hydroxyalkyl; alkoxyalkyl; acetyl; alkoxyalkyl; alkylsulfonylalkyl; aminocarbonyloxyalkyl; hydroxycarbonylalkyl; hydroxycarbonylalkyl; aryalkyl; aralkyl; aryloxy; heteroaryl; heteroarylsulfonyl; heterocyclyl; heterocyclylalkyl;

one of \(R^9\) is CR, one of \(A\) and \(E\) is O, S or NR, and the other is CR, or N; or

\(Q\) is N, one of \(A\) and \(E\) is \(NR\), and the other is CR, or CR;

each \(R^9\) is independently hydrogen, alkyl, halo or alkoxy, and

\(R^10\) is hydrogen, alkyl, hydroxyalkyl, alkoxyalkyl, -\(\text{(CH}_2\text{)}_m\text{-(Z)}_n\text{-(CO)-R}, \text{ or } -\text{(CH}_2\text{)}_m\text{-(Z)}_n\text{SO}_2\text{-(NR)}_n\text{R}. \\
\)

9. The use of claim 1, wherein said disease is a respiratory disease selected from chronic obstructive pulmonary disease (COPD), asthma and bronchospasm.
10. The use of claim 1, wherein said disease is a gastrointestinal disease selected from Irritable Bowel Syndrome, Inflammatory Bowel Disease, biliary colic, renal colic, diarrhea-dominant irritable bowel syndrome, and pain associated with GI distension.

11. A method for treating a respiratory or gastrointestinal disease mediated by a P2X\textsubscript{3} or P2X\textsubscript{2/3} receptor antagonist, said method comprising administering to a subject in need thereof an effective amount of a compound of formula (I) according to claim 1.