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(71) Applicant *(for all designated States except US)*: **F. HOFFMANN-LA ROCHE AG** [CH/CH]; Grenzacherstrasse 124, CH-4070 Basel (CH).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **DILLON, Michael, Patrick** [GB/US]; 275 Romain Street, San Francisco, California 94131 (US). **JAHANGIR, Alam** [US/US]; 3655 Valley Ridge Lane, San Jose, California 95148 (US). **MOORE, Amy, Geraldine** [US/US]; 2368 Adele Avenue, Mountain View, California 94043 (US). **WAGNER, Paul, J.** [US/US]; 292 Barbara Avenue, Mountain View, California 94040 (US).

(74) Agent: **HEIROTH, Ulrike**; Grenzacherstrasse 124, CH-4070 Basel (CH).

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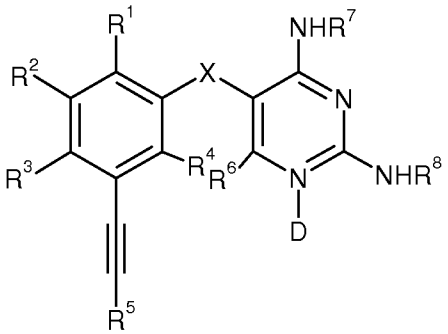
(54) Title: DIAMINOPYRIMIDINES AS P2X3 AND P2X2/3 MODULATORS



(I)

(57) Abstract: Compounds and methods for treating diseases mediated by a $P2X_3$ and/or a $P2X_{2/3}$ receptor antagonist, the methods comprising administering to a subject in need thereof an effective amount of a compound of formula (I), wherein D, X, R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are as defined herein.

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DIAMINOPYRIMIDINES AS P2X3 AND P2X2/3 MODULATORS

This invention pertains to compounds useful for treatment of diseases associated with P2X purinergic receptors, and more particularly to $P2X_3$ and/or $P2X_{2/3}$antagonists usable 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 homomeric receptors, $P2X_1$; $P2X_2$; $P2X_3$; $P2X_4$; $P2X_5$; and $P2X_7$; and three heteromeric receptors $P2X_{2/3}$, $P2X_{4/6}$, $P2X_{1/5}$ (See, e.g., Chen, et al. (1995) Nature 377:428-431; Lewis, et al. (1995) Nature 377:432-435; and Burnstock (1997) Neurophamacol. 36:1127-1139). The structure and chromosomal mapping of mouse genomic $P2X_3$ receptor subunit has also been described (Souslova, et al. (1997) Gene 195:101-111). In vitro, co-expression of $P2X_2$ and $P2X_3$ receptor subunits is necessary to produce ATP-gated currents with the properties seen in some sensory neurons (Lewis, et al. (1995) Nature 377:432-435).

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)). $P2X_3$ receptors have been identified on nociceptive neurons in the tooth pulp (Cook et al., Nature 387:505-508 (1997)). ATP released from damaged cells may thus lead to pain by activating $P2X_3$ and/or $P2X_{2/3}$ containing receptors on nociceptive sensory nerve endings. This is consistent with the induction of pain by intradermally applied ATP in the human blister-base model (Bleehen, Br 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 $P2X_2$ and $P2X_3$ are involved in nociception, and that modulators of P2X receptors are potentially useful as analgesics.

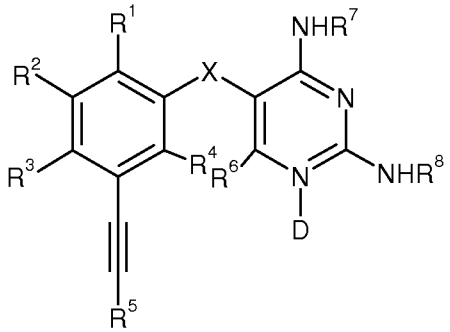
There is accordingly a need for methods of treating diseases, conditions and disorders mediated by $P2X_3$ and/or $P2X_{2/3}$ receptors, as well as a need for compounds that act as modulators of P2X receptors, including antagonists of $P2X_3$ and $P2X_{2/3}$ receptors. The present invention satisfies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

Other researchers have shown that $P2X_3$ receptors are expressed in human colon, and are expressed at higher levels in inflamed colon than in normal colon (Yiangou et al, *Neurogastroenterol Mot* (2001) 13:365-69). Other researchers have implicated the $P2X_3$ receptor in detection of distension or intraluminal pressure in the intestine, and initiation of reflex

contractions (Bian et al., *JPhysiol* (2003) 551.1:309-22), and have linked this to colitis (Wynn et al., *Am JPhysiol Gastrointest Liver Physiol* (2004) 287:G647-57).

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

The invention provides compounds of formula I



(I)

or pharmaceutically acceptable salts thereof,

wherein

X is $-CH_2-$; -O-; $-S(O)_n-$ or $-NR^c-$, wherein n is from 0 to 2 and R^c is hydrogen or alkyl;

D is an optional oxygen;

R^1 is alkyl; alkenyl; cycloalkyl; cycloalkenyl; halo; haloalkyl or hydroxyalkyl;

R^2, R^3, and R^4 each independently is hydrogen; alkyl; alkenyl; amino; halo; amido; haloalkyl; alkoxy; hydroxy; haloalkoxy; nitro; amino; hydroxyalkyl; alkoxyalkyl; hydroxyalkoxy; alkynylalkoxy; alkylsulfonyl; arylsulfonyl; cyano; aryl; heteroaryl; heterocyclyl; heterocyclylalkoxy; aryloxy; heteroaryloxy; aralkyloxy; heteroaralkyloxy; optionally substituted phenoxy; $-C\equiv C-R^a$; $-(CH_2)_m-(Z)_n-(CO)-R^b$; $-(CH_2)_m-(Z)_n-SO_2-(NR^c)_n-R^b$, wherein

m and n each independently is 0 or 1,

Z is O or NR^c,

R^a is hydrogen; alkyl; aryl;aralkyl; heteroaryl; heteroaralkyl; hydroxyalkyl; alkoxyalkyl; alkylsulfonylalkyl; aminoalkyl; cyanoalkyl; alkylsilyl, cycloalkyl, cycloalkylalkyl; heterocyclyl; and heterocyclylalkyl;

R^b is hydrogen, alkyl, hydroxy, alkoxy, amino, hydroxyalkyl or alkoxyalkyl, and each R^c is independently hydrogen or alkyl;

or 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;

R^5 is hydrogen; alkyl; aryl; aralkyl; heteroaryl; heteroaralkyl; hydroxyalkyl; alkoxyalkyl; alkylsulfonylalkyl; aminoalkyl; cyanoalkyl; alkylsilyl, cycloalkyl, cycloalkylalkyl; heterocycl; or heterocyclylalkyl;

R^6 is hydrogen; alkyl; halo; haloalkyl; amino; or alkoxy; and

R^7 and R^8 each independently is hydrogen; alkyl; alkoxyalkyl; aminoalkyl; aminosulfonyl; cycloalkyl; cycloalkylalkyl; haloalkyl; haloalkoxy; hydroxyalky; alkoxyalkyl; alkylsulfonyl; alkylsulfonylalkyl; aminocarbonyloxyalkyl; hydroxycarbonylalkyl; hydroxyalkyloxycarbonylalkyl; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl.

In one aspect the present invention provides compounds of formula I or pharmaceutically acceptable salts thereof, wherein

X is $-CH_2-$; -O-; $-S(O)_n-$ or $-NR^c-$, wherein n is from 0 to 2 and R^c is hydrogen or alkyl;

D is an optional oxygen;

R^1 is alkyl; alkenyl; cycloalkyl; cycloalkenyl; halo; haloalkyl or hydroxyalkyl;

R^2, R^3, and R^4 each independently is hydrogen; alkyl; alkenyl; amino; halo; amido; haloalkyl; alkoxy; hydroxy; haloalkoxy; nitro; amino; hydroxyalkyl; alkoxyalkyl; hydroxyalkoxy; alkynylalkoxy; alkylsulfonyl; arylsulfonyl; cyano; aryl; heteroaryl; heterocyclyl; heterocyclylalkoxy; aryloxy; heteroaryloxy; aralkyloxy; heteroaralkyloxy; optionally substituted phenoxy; $-C\equiv C-R^a$; $-(CH_2)_m-(Z)_n-(CO)-R^b$; $-(CH_2)_m-(Z)_n-SO_2-(NR^c)_n-R^b$, wherein

m and n each independently is 0 or 1,

Z is O or NR^c,

R^a is hydrogen; alkyl; aryl;aralkyl; heteroaryl; heteroaralkyl; hydroxyalkyl; alkoxyalkyl; alkylsulfonylalkyl; aminoalkyl; cyanoalkyl; alkylsilyl, cycloalkyl, cycloalkylalkyl; heterocyclyl; and heterocyclylalkyl;

R^b is hydrogen, alkyl, hydroxy, alkoxy, amino, hydroxyalkyl or alkoxyalkyl, and each R^c is independently hydrogen or alkyl;

or 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;

R^5 is hydrogen; alkyl; aryl; aralkyl; heteroaryl; heteroaralkyl; hydroxyalkyl; alkoxyalkyl; alkylsulfonylalkyl; aminoalkyl; cyanoalkyl; alkylsilyl, cycloalkyl, cycloalkylalkyl; heterocyclyl; or heterocyclylalkyl;

R^6 is hydrogen; alkyl; halo; haloalkyl; amino; or alkoxy; and

R^7 and R^8 each independently is hydrogen; alkyl; cycloalkyl; cycloalkylalkyl; haloalkyl; haloalkoxy; hydroxyalky; alkoxyalkyl; alkylsulfonyl; alkylsulfonylalkyl; aminocarbonyloxyalkyl; hydroxycarbonylalkyl; hydroxyalkyloxycarbonylalkyl; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl.

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

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. C_1-C_6alkyl. Examples of alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, isobutyl, sec-butyl, tert-butyl, pentyl, n-hexyl, octyl, dodecyl, and the like.

"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 R^a–O–R^b–, where R^a is alkyl and R^b is alkylene as defined herein. Exemplary alkoxyalkyl groups include, by way of example, 2-methoxyethyl, 3-methoxypropyl, 1-methyl-2-methoxyethyl, 1-(2-methoxyethyl)-3-methoxypropyl, and 1-(2-methoxyethyl)-3-methoxypropyl.

"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 -SO_2- and R" is alkyl as defined herein.

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

"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.

"Amino" means a group -NR'R" wherein R' and R" each independently is hydrogen or alkyl. "Amino" as used herein thus encompasses "alkylamino" and "dialkylamino".

"Aminoalkyl" means a group -R-NR'R" wherein R is alkylene, and R' and R" each independently is hydrogen or alkyl. "Alkylamino" as used herein thus encompasses "alkylaminoalkyl" and "dialkylaminoalkyl".

"Aminosulfonyl" means a group -SO_2-NR'R" wherein R' and R" each independently is hydrogen or alkyl. "Aminosulfonyl" as used herein thus encompasses "alkylaminosulfonyl" and "dialkylaminosulfonyl".

"Alkylaminoalkyl" means a group -R-NHR' wherein R is alkylene and R' is alkyl. Alkylaminoalkyl includes methylaminomethyl, methylaminoethyl, methylaminopropyl, ethylaminoethyl and the like.

"Dialkylaminoalkyl" means a group -R-NR'R" wherein R is alkylene and R' and R" are alkyl as defined herein. 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.

"Alkylsulfonylamido" means a moiety of the formula -NR'SO_2-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.

"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, benzodioxanyl, benzofuranyl, benzodioxylyl, benzopyranyl, benzoxazinyl, benzoxazinonyl, benzopiperadinyl, benzopiperazinyl, benzopyrrolidinyl, benzomorpholinyl, methylenedioxyphenyl, ethylenedioxyphenyl, and the like, including partially hydrogenated derivatives thereof.

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

"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 -SO_2-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 -O-R-R" wherein R is alkylene and R' is aryl as defined herein.

"Cyanoalkyl" " means a moiety of the formula –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 –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 $-OR^a$, $-NR^bR^c$, and $-S(O)_nR^d$ (where n is an integer from 0 to 2), with the understanding that the point of attachment of the heteroalkyl radical is through a carbon atom, wherein R^a is hydrogen, acyl, alkyl, cycloalkyl, or cycloalkylalkyl; R^b and R^c are independently of each other hydrogen, acyl, alkyl, cycloalkyl, or cycloalkylalkyl; and when n is 0, R^d is hydrogen, alkyl, cycloalkyl, or cycloalkylalkyl, and when n is 1 or 2, R^d is alkyl, cycloalkyl, cycloalkylalkyl, amino, acylamino, monoalkylamino, or dialkylamino. Representative examples include, 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, aminosulfonylmethyl, aminosulfonylethyl, aminosulfonylpropyl, methylaminosulfonylmethyl, methylaminosulfonylethyl, methylaminosulfonylpropyl, 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, pyrrolyl, pyrazolyl, pyrimidyl, quinolinyl, isoquinolinyl, benzofuryl, benzothiophenyl, benzothiopyranyl, benzimidazolyl, benzooxazolyl, benzooxadiazolyl, benzothiazolyl, benzothiadiazolyl, benzopyranyl, indolyl, isoindolyl, triazolyl, triazinyl,

quinoxalinyl, purinyl, quinazolinyl, quinolizinyl, naphthyridinyl, pteridinyl, carbazolyl, azepinyl, diazepinyl, acridinyl and the like, including partially hydrogenated derivatives thereof.

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 -SO_2-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, chloro, bromo, or iodo.

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

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

“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.

“Heterocyclyl” means a monovalent saturated moiety, consisting of one to three rings, incorporating one, two, or three or four heteroatoms (chosen from nitrogen, oxygen or sulfur). The heterocyclyl ring may be optionally substituted as defined herein. Examples of heterocyclyl moieties include, but are not limited to, optionally substituted piperidinyl, piperazinyl, homopiperazinyl, azepinyl, pyrrolidinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, pyridinyl, pyridazinyl, pyrimidinyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, quinuclidinyl, quinolinyl, isoquinolinyl, benzimidazolyl, thiadiazolylidinyl, benzothiazolidinyl, benzoazolylidinyl, dihydrofuryl, tetrahydrofuryl, dihydropyranyl, tetrahydropyranyl, thiamorpholinyl, thiamorpholinylsulfoxide, thiamorpholinylsulfone, dihydroquinolinyl, dihydrisoquinolinyl, tetrahydroquinolinyl, tetrahydrisoquinolinyl, and the like.

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

"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.

"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-(hydroxymethyl)-2-methylpropyl, 2-hydroxybutyl, 3-hydroxybutyl, 4-hydroxybutyl, 2,3-dihydroxypropyl, 2-hydroxy-1-hydroxymethylethyl, 2,3-dihydroxybutyl, 3,4-dihydroxybutyl and 2-(hydroxymethyl)-3-hydroxypropyl

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

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

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

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

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

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

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

"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 dichloromethane, 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; or
salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic or inorganic base. Acceptable organic bases include diethanolamine, ethanolamine, N-methylglucamine, triethanolamine, 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-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, *tert*-butoxycarbonyl (BOC), and the like. The artisan in the art will know how to chose a group for the ease of removal and for the ability to withstand the following reactions.

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

"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, idiophatic bladder hypersensitivity, and the like.

"Disease states associated with the urinary tract" or "urinary tract disease states" or "uropathy" 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, vulvadynia, urethritis, orchidalgia, overactive bladder, and the like.

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

"Gastrointestinal disorder" ("GI disorder") 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. Where a chiral center exists in a structure but no specific stereochemistry is shown for the chiral center, both enantiomers associated with the chiral structure are encompassed by the structure.

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

In certain embodiments of the invention, R^4 and R^6 are hydrogen.

In certain embodiments of the invention, R^2 is hydrogen.

In certain embodiments of the invention, D is absent.

In certain embodiments of formula I, X is -O- or -CH_2-.

In certain embodiments of formula I, X is -O-.

In certain embodiments of formula I, R^1 is isopropyl, iodo or ethynyl. Preferably R^1 is isopropyl.

In certain embodiments of formula I, R^2 and R^4 are hydrogen.

In certain embodiments of formula I, R^3 is hydrogen, alkoxy, hydroxy, or halo. Preferably R^3 is alkoxy.

In certain embodiments of formula I, R^5 is hydrogen, alkyl, phenyl, pyridyl, methoxymethyl, hydroxyethyl, cyanoethyl, thienyl, imidazolyl, hydroxypropyl, methylamino, hydroxymethyl, trimethylsilyl or cyclopropyl. Preferably R^5 is hydrogen.

In certain embodiments of formula I, R^7 and R^8 each independently is hydrogen, alkyl, hydroxyalkyl, aminoalkyl, heterocyclyl or heterocyclylalkyl.

In certain embodiments of formula I, one of R^7 and R^8 is hydrogen and the other is alkyl, hydroxyalkyl, aminoalkyl, heterocyclyl or heterocyclylalkyl.

In certain embodiments of formula I, X is -O-, R^1 is isopropyl or iodo, R^2 and R^4 are hydrogen, R^3 is alkoxy, hydroxy, or halo, R^5 is hydrogen, alkyl, phenyl, pyridyl, methoxymethyl, hydroxyethyl, cyanoethyl, thienyl, imidazolyl, hydroxypropyl, methylamino, hydroxymethyl, trimethylsilyl or cyclopropyl, and one of R^7 and R^8 is hydrogen and the other is alkyl, hydroxyalkyl, aminoalkyl, heterocyclyl or heterocyclylalkyl.

In embodiments of the invention wheren R^7 or R^8 is hydroxyalkyl, preferred hydroxyalkyl include hydroxyethyl, 2-hydroxypropyl, 3-hydroxy-2-methyl-ethyl, 2-hydroxy-1-(hydroxymethyl)-ethyl and 3-hydroxypropyl.

In certain embodiments of formula I, X is -O-, R^1 is isopropyl, R^2 and R^4 are hydrogen, R^3 is hydrogen, alkoxy or halo, R^5 is hydrogen, and R^7 and R^8 each independently is hydrogen, or hydroxyalkyl.

In certain embodiments of formula I, X is -O-, R^1 is isopropyl, iodo or ethynyl, R^2 and R^4 are hydrogen, R^3 is hydrogen, alkoxy, hydroxy, or halo, R^5 is hydrogen, alkyl, phenyl, pyridyl, methoxymethyl, hydroxyethyl, cyanoethyl, thienyl, imidazolyl, hydroxypropyl, methylamino, hydroxymethyl, trimethylsilyl or cyclopropyl, R^7 is hydrogen, and R^8 is hydrogen, alkyl, hydroxyalkyl, aminoalkyl, heterocyclyl or heterocyclylalkyl.

In certain embodiments of formula I, X is -O-, R^1 is isopropyl, iodo or ethynyl, R^2 and R^4 are hydrogen, R^3 is hydrogen, alkoxy, hydroxy, or halo, R^5 is hydrogen, R^7 is hydrogen, and R^8 is hydrogen, alkyl, hydroxyalkyl, aminoalkyl, heterocyclyl or heterocyclylalkyl.

In certain embodiments of formula I, X is -O-, R^1 is isopropyl, iodo or ethynyl, R^2 and R^4 are hydrogen, R^3 is hydrogen, alkoxy, hydroxy, or halo, R^5 is hydrogen, R^8 is hydrogen, and R^7 is hydrogen, alkyl, hydroxyalkyl, aminoalkyl, heterocyclyl or heterocyclylalkyl.

In certain embodiments of formula I, X is -O-, R^1 is isopropyl, R^2 and R^4 are hydrogen, R^3 is alkoxy or halo, R^5 is hydrogen, R^7 is hydrogen, and R^8 is hydrogen or hydroxyalkyl.

In certain embodiments of formula I, X is -O-, R^1 is isopropyl, R^2 and R^4 are hydrogen, R^3 is alkoxy or halo, R^5 is hydrogen, R^8 is hydrogen, and R^7 is hydrogen or hydroxyalkyl.

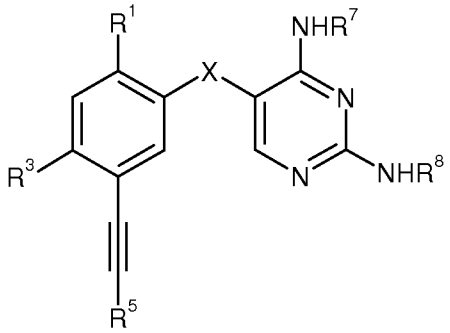
In embodiments of the invention where R^7 or R^8 is hydroxyalkyl, preferred hydroxyalkyl include hydroxyethyl, 2-hydroxypropyl, 2-hydroxy-1-methyl-ethyl, 2-hydroxy-1-(hydroxymethyl)-ethyl and 3-hydroxypropyl.

In embodiments of the invention where R^7 or R^8 is heterocyclyl, preferred heterocyclyl include tetrahydropyranyl and piperidinyl. In certain embodiments the heterocyclyl may be tetrahydropyran-4-yl, or piperidin-4-yl optionally substituted at the one position with methanesulfonyl, alkyl or acetyl.

In embodiments of the invention where R^7 or R^8 is heterocyclylalkyl, preferred heterocyclylalkyl include morpholinylalkyl, piperidinylalkyl and piperazinylalkyl. In certain embodiments the heterocyclylalkyl may be morpholin-4-yl-ethyl, or piperidin-1-yl-ethyl.

In embodiments of the invention where R^5 is heteroaryl, preferred heteroaryl include pyridinyl, thienyl and imidazolyl. In certain embodiments the heteroaryl may be pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, thien-3-yl and 1-methyl-imidazol-2-yl.

In certain embodiments of the invention, the subject compounds are more specifically of formula II:



(II);

wherein X, R^1, R^3, R^5, R^7 and R^8 are as defined herein.

In certain embodiments of either of formula I or II, X is -O- or -CH_2-. More preferably X is -O-.

In certain embodiments of formula II, R^1 is isopropyl, iodo or ethynyl,. Preferably R^1 is isopropyl.

In certain embodiments of formula II, R^3 is hydrogen, alkoxy, hydroxy, or halo.

In certain embodiments of formula II, R^5 is hydrogen, alkyl, phenyl, pyridyl, methoxymethyl, hydroxyethyl, cyanoethyl, thienyl, imidazolyl, hydroxypropyl, methylamino, hydroxymethyl, trimethylsilyl or cyclopropyl. Preferably R^5 is hydrogen.

In certain embodiments of formula I, R^7 and R^8 each independently is hydrogen, alkyl, hydroxyalkyl, aminoalkyl, heterocyclyl or heterocyclylalkyl.

In certain embodiments of formula II, X is -O-, R^1 is isopropyl or iodo, R^3 is hydrogen, alkoxy, hydroxy, or halo, R^5 is hydrogen, alkyl, phenyl, pyridyl, methoxymethyl, hydroxyethyl, cyanoethyl, thienyl, imidazolyl, hydroxypropyl, methylamino, hydroxymethyl, trimethylsilyl or cyclopropyl, and R^7 and R^8 each independently is hydrogen, alkyl, hydroxyalkyl, aminoalkyl, heterocyclyl or heterocyclylalkyl.

In certain embodiments of formula II, X is -O-, R^1 is isopropyl, iodo or ethynyl, R^3 is hydrogen, alkoxy, hydroxy, or halo, R^5 is hydrogen, and R^7 and R^8 each independently is hydrogen, or hydroxyalkyl.

In certain embodiments of formula II, X is -O-, R^1 is isopropyl, iodo or ethynyl, R^3 is hydrogen, alkoxy, hydroxy, or halo, R^5 is hydrogen, alkyl, phenyl, pyridyl, methoxymethyl, hydroxyethyl, cyanoethyl, thienyl, imidazolyl, hydroxypropyl, methylamino, hydroxymethyl, trimethylsilyl or cyclopropyl, R^7 is hydrogen, and R^8 is hydrogen, alkyl, hydroxyalkyl, aminoalkyl, heterocyclyl or heterocyclylalkyl.

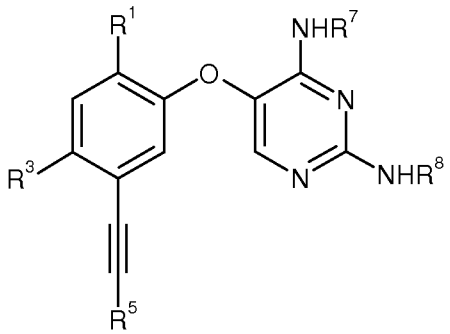
In certain embodiments of formula II, X is -O-, R^1 is isopropyl, iodo or ethynyl, R^3 is hydrogen, alkoxy or halo, R^5 is hydrogen, R^7 is hydrogen, and R^8 is hydrogen, alkyl, hydroxyalkyl, aminoalkyl, heterocyclyl or heterocyclylalkyl.

In certain embodiments of formula II, X is -O-, R^1 is isopropyl, iodo or ethynyl, R^3 is hydrogen, alkoxy or halo, R^5 is hydrogen, R^8 is hydrogen, and R^7 is hydrogen, alkyl, hydroxyalkyl, aminoalkyl, heterocyclyl or heterocyclylalkyl.

In certain embodiments of formula II, X is -O-, R^1 is isopropyl, R^3 is alkoxy or halo, R^5 is hydrogen, R^7 is hydrogen, and R^8 is hydrogen or hydroxyalkyl.

In certain embodiments of formula II, X is -O-, R^1 is isopropyl, R^3 is alkoxy or halo, R^5 is hydrogen, R^8 is hydrogen, and R^7 is hydrogen or hydroxyalkyl.

In certain embodiments of the invention, the subject compounds are more specifically of formula III:



(III);

wherein R^1, R^3, R^5, R^7 and R^8 are as defined herein.

In certain embodiments of any of formulas I, II or III, R^1 may be ethyl, isopropyl, iodo, ethynyl or cyclopropyl. In certain of such embodiments R^1 may be isopropyl, iodo or ethynyl. Preferably R^1 is isopropyl.

In certain embodiments of any of formulas I, II or III, R^7 and R^8 are hydrogen.

In certain embodiments of any of formulas I, II or III, one of R^7 and R^8 is hydrogen and the other is hydrogen, alkyl, hydroxyalkyl or haloalkyl.

In certain embodiments of any of formulas I, II or III, one of R^7 and R^8 is hydrogen and the other is hydrogen or hydroxyalkyl.

In certain embodiments of any of formulas I, II or III, one of R^7 and R^8 is hydrogen and the other is hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, hydroxyalky; or alkoxyalkyl.

In certain embodiments of any of formulas I, II or III, R^3 may be hydrogen, alkyl, alkenyl, halo, haloalkyl, alkoxy, hydroxy, haloalkoxy, alkylsulfonyl, cyano or -C≡C-R^a.

In certain embodiments of any of formulas I, II or III, R^3 may be hydrogen, halo, alkoxy, haloalkoxy, hydroxy, alkylsulfonyl, or -C≡C-R^a.

In certain embodiments of any of formulas I, II or III, R^3 may be hydrogen; halo; alkoxy; haloalkoxy; alkylsulfonyl; or hydroxy.

In certain embodiments of any of formulas I, II or III, R^3 may be hydrogen, halo, alkoxy, haloalkoxy or hydroxy.

In certain embodiments of any of formulas I, II or III, R^3 may be hydrogen, halo, alkoxy or hydroxy.

In certain embodiments of any of formulas I, II or III, R^3 may be hydrogen, alkoxy or hydroxy.

In certain embodiments of any of formulas I, II or III, R^3 may be alkoxy or hydroxy.

In certain embodiments of any of formulas I, II or III, R^5 may be hydrogen, alkyl; optionally substituted phenyl, optionally substituted pyridinyl, optionally substituted thienyl, optionally substituted imidazolyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, cyano-alkyl, alkylsilyl or cycloalkyl.

In certain embodiments of any of formulas I, II or III, R^5 may be hydrogen or alkyl.

In certain embodiments of any of formulas I, II or III, R^5 may be hydrogen or methyl.

In certain embodiments of any of formulas I, II or III, R^5 may be heteroaryl selected from pyridinyl, pyrimdinyl, thienyl, furanyl, imidazolyl, pyrazolyl and pyrrolyl.

In certain embodiments of any of formulas I, II or III, R^5 may be hydrogen, methyl, ethyl, propyl, phenyl, methoxymethyl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, 2-hydroxyethyl, 3-hydroxypropyl, hydroxymenthyl, methylaminomethyl, 2-cyanoethyl, thien-3-yl, 1-methylimidazol-5-yl, trimethylsilyl or cyclopropyl.

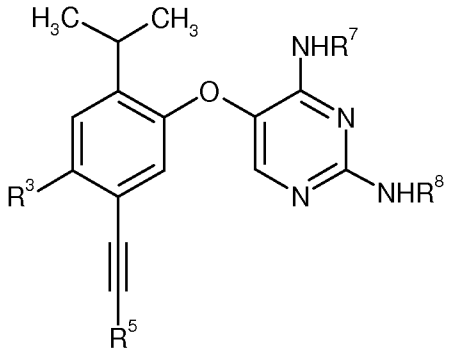
In certain embodiments of any of formulas I, II or III, R^1 is isopropyl, iodo, or ethynyl and R^7 and R^8 are hydrogen.

In certain embodiments of any of formulas I, II or III, R^1 is isopropyl, iodo, or ethynyl, R^7 and R^8 are hydrogen, and R^3 is hydrogen, alkoxy or hydroxy.

In certain embodiments of any of formulas I, II or III, R^1 is isopropyl, iodo, or ethynyl, R^7 and R^8 are hydrogen, R^3 is hydrogen, alkoxy or hydroxy, and R^5 is hydrogen or methyl.

In certain embodiments of any of formulas I, II or III, R^1 is isopropyl, iodo, or ethynyl, one of R^7 and R^8 is hydrogen and the other is hydrogen or hydroxyalkyl, R^3 is hydrogen, alkoxy or hydroxy, and R^5 is hydrogen.

In certain embodiments of the invention, the subject compounds are more specifically of formula IV:



(IV);

wherein R^3, R^5, R^7 and R^8 are as defined herein.

In certain embodiments of formula IV, R^7 and R^8 are hydrogen.

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

In certain embodiments of formula IV, one of R^7 and R^8 is hydrogen and the other is hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, hydroxyalky; or alkoxyalkyl.

In certain embodiments of formula IV, R^3 may be hydrogen, alkyl, alkenyl, halo, haloalkyl, alkoxy, hydroxy, haloalkoxy, alkylsulfonyl, cyano or $-C\equiv C-R^a$.

In certain embodiments of formula IV, R^3 may be hydrogen, halo, alkoxy, haloalkoxy, hydroxy, alkylsulfonyl, or $-C\equiv C-R^a$.

In certain embodiments of formula IV, R^3 may be hydrogen; halo; alkoxy; haloalkoxy; alkylsulfonyl; or hydroxy.

In certain embodiments of formula IV, R^3 may be hydrogen, halo, alkoxy, haloalkoxy or hydroxy.

In certain embodiments of formula IV, R^3 may be hydrogen, halo, alkoxy or hydroxy.

In certain embodiments of formula IV, R^3 may be hydrogen, alkoxy or hydroxy.

In certain embodiments of formula IV, R^3 may be alkoxy or hydroxy.

In certain embodiments of formula IV, R^5 may be hydrogen, alkyl; optionally substituted phenyl, optionally substituted pyridinyl, optionally substituted thienyl, optionally substituted imidazolyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, cyanoalkyl, alkylsilyl or cycloalkyl.

In certain embodiments of formula IV, R^5 may be hydrogen or alkyl.

In certain embodiments of formula IV, R^5 may be hydrogen or methyl.

In certain embodiments of formula IV, R^5 may be heteroaryl selected from pyridinyl, pyrimdinyl, thienyl, furanyl, imidazolyl, pyrazolyl and pyrrolyl.

In certain embodiments of formula IV, R^5 may be hydrogen, methyl, ethyl, propyl, phenyl, methoxymethyl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, 2-hydroxyethyl, 3-hydroxypropyl, hydroxymenthyl, methylaminomethyl, 2-cyanoethyl, thien-3-yl, 1-methylimidazol-5-yl, trimethylsilyl or cyclopropyl.

In certain embodiments of formula IV, R^7 and R^8 are hydrogen and R^3 is hydrogen, alkoxy or hydroxy.

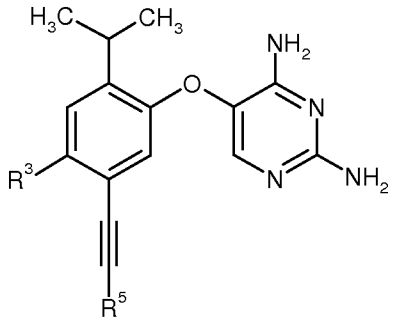
In certain embodiments of formula IV, R^7 and R^8 are hydrogen, R^3 is hydrogen, alkoxy or hydroxy, and R^5 is hydrogen or methyl.

In certain embodiments of formula IV, R^3 is hydrogen, halo, alkoxy or hydroxy, R^5 is hydrogen, one of R^7 and R^8 is hydrogen, and the other is hydrogen or hydroxyalkyl.

In certain embodiments of formula IV, R^3 is hydrogen, halo, alkoxy or hydroxy, R^5 is hydrogen, R^7 is hydrogen, and R^8 is hydrogen or hydroxyalkyl.

In certain embodiments of formula IV, R^3 is hydrogen, halo, alkoxy or hydroxy, R^5 is hydrogen, R^8 is hydrogen, and R^7 is hydrogen or hydroxyalkyl.

In certain embodiments of the invention, the subject compounds are more specifically of formula V:



(V);

wherein R^3 and R^5 are as defined herein.

In certain embodiments of formula V, R^3 may be hydrogen, alkyl, alkenyl, halo, haloalkyl, alkoxy, hydroxy, haloalkoxy, alkylsulfonyl, cyano or -C≡C-R^a.

In certain embodiments of formula IV, R^3 may be hydrogen, halo, alkoxy, haloalkoxy, hydroxy, alkylsulfonyl, or -C≡C-R^a.

In certain embodiments of formula V, R^3 may be hydrogen; halo; alkoxy; haloalkoxy; alkylsulfonyl; or hydroxy.

In certain embodiments of formula V, R^3 may be hydrogen, halo, alkoxy, haloalkoxy or hydroxy.

In certain embodiments of formula V, R^3 may be hydrogen, halo, alkoxy or hydroxy.

In certain embodiments of formula V, R^3 may be hydrogen, alkoxy or hydroxy.

In certain embodiments of formula V, R^3 may be alkoxy or hydroxy.

In certain embodiments of formula V, R^5 may be hydrogen, alkyl; optionally substituted phenyl, optionally substituted pyridinyl, optionally substituted thienyl, optionally substituted imidazolyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, cyanoalkyl, alkylsilyl or cycloalkyl.

In certain embodiments of formula V, R^5 may be hydrogen or alkyl.

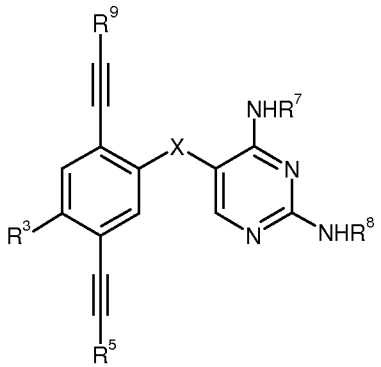
In certain embodiments of formula V, R^5 may be hydrogen or methyl.

In certain embodiments of formula V, R^5 may be heteroaryl selected from pyridinyl, pyrimidinyl, thienyl, furanyl, imidazolyl, pyrazolyl and pyrrolyl.

In certain embodiments of formula V, R^5 may be hydrogen, methyl, ethyl, propyl, phenyl, methoxymethyl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, 2-hydroxyethyl, 3-hydroxypropyl, hydroxymenthyl, methylaminomethyl, 2-cyanoethyl, thien-3-yl, 1-methylimidazol-5-yl, trimethylsilyl or cyclopropyl.

In certain embodiments of formula V, R^3 is hydrogen, alkoxy or hydroxy, and R^5 is hydrogen or methyl.

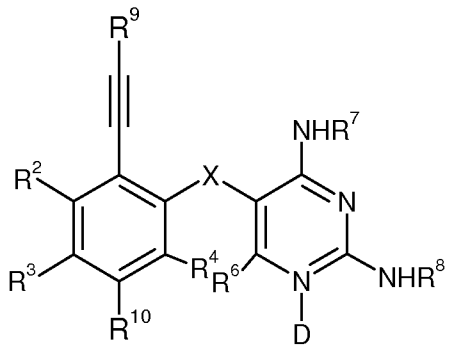
In certain embodiments of the invention, the subject compounds are more specifically of formula VI:



(VI);

wherein R^9 is hydrogen or alkyl, and X, R^3, R^5, R^7 and R^8 are as defined herein.

In another aspect of the invention, there are provided compounds of the formulaVII:



(VII)

or pharmaceutically acceptable salts thereof,

wherein

X is $–CH_2$-; -O-; $-S(O)_n$-; or $-NR^c$- wherein

n is from 0 to 2 and

R^c is hydrogen or alkyl;

D is an optional oxygen;

R^2, R^3, R^4 and R^{10} each independently is hydrogen; alkyl; alkenyl; amino; halo; amido; haloalkyl; alkoxy; hydroxy; haloalkoxy; nitro; amino; hydroxyalkyl; alkoxyalkyl; hydroxyalkoxy; alkynylalkoxy; alkylsulfonyl; arylsulfonyl; cyano; aryl; heteroaryl; heterocyclyl; heterocyclylalkoxy; aryloxy; heteroaryloxy; aralkyloxy; heteroaralkyloxy; optionally substituted phenoxy; $-C\equiv C-R^a$; $-(CH_2)_m-(Z)_n-(CO)-R^b$; $-(CH_2)_m-(Z)_n-SO_2-(NR^c)_n-R^b$, wherein

m and n each independently is 0 or 1,

Z is O or NR^c,

R^a is hydrogen; alkyl; aryl; aralkyl; heteroaryl; heteroaralkyl; hydroxyalkyl; alkoxyalkyl; alkylsulfonylalkyl; aminoalkyl; cyanoalkyl; alkylsilyl, cycloalkyl, cycloalkylalkyl; heterocyclyl; and heterocyclylalkyl;

R^b is hydrogen, alkyl, hydroxy, alkoxy, amino, hydroxyalkyl or alkoxyalkyl, and each R^c is independently hydrogen or alkyl;

or 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;

R^6 is hydrogen; alkyl; halo; haloalkyl; amino; or alkoxy; and

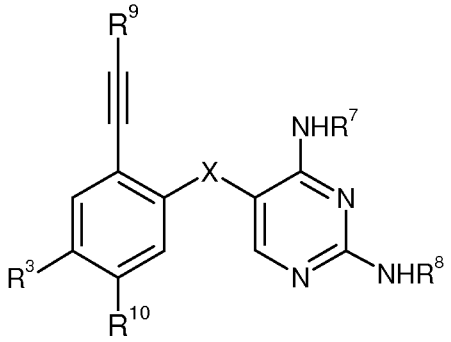
R^7 and R^8 each independently is hydrogen; alkyl; cycloalkyl; cycloalkylalkyl; haloalkyl; haloalkoxy; hydroxyalky; alkoxyalkyl; alkylsulfonyl; alkylsulfonylalkyl; aminocarbonyloxyalkyl; hydroxycarbonylalkyl; hydroxyalkyloxycarbonylalkyl; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl.

In certain embodiments of formula VII, D is absent.

In certain embodiments of formula VII, R^2, R^4 and R^6 are hydrogen.

In certain embodiments of formula VII, X is -O- or $-CH_2-$, R^2, R^4 and R^6 are hydrogen, R^3 is alkoxy or hydroxy, R^{10} is iodo, alkoxy, alkylsulfonyl, or $-C\equiv C-R^a$, and R^7 and R^8 are hydrogen. Preferably X is -O- in such embodiments.

In certain embodiments of formula VII, the subject compounds are more specifically of the formula VIII:

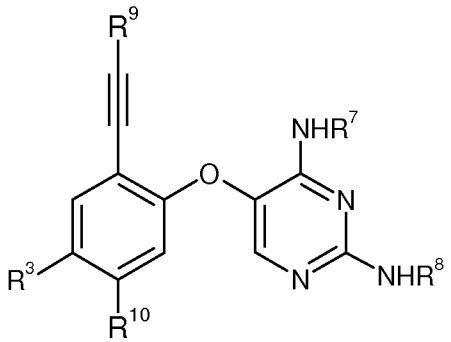


(VIII)

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

In certain embodiments of either of formula VII of VIII, X is -O- or -CH_2-. More preferably X is -O-.

In certain embodiments of formula IX, the subject compounds are more specifically of the formula IX:



(IX)

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

In certain embodiments of any of formulas VII, VIII and IX, R^7 and R^8 may both be hydrogen.

In certain embodiments of any of formulas VII, VIII and IX, one of R^7 and R^8 may is hydrogen and the other is alkyl, hydroxyalkyl or haloalkyl.

In certain embodiments of any of formulas VII, VIII and IX, R^3 and R^{10} each independently may be hydrogen, alkyl, alkenyl, halo, haloalkyl, alkoxy, hydroxy, haloalkoxy, alkylsulfonyl, cyano or -C≡C-R^a.

In certain embodiments of any of formulas VII, VIII and IX, R^3 and R^{10} each independently may be hydrogen, halo, alkoxy, haloalkoxy, hydroxy, alkylsulfonyl, or -C≡C-R^a.

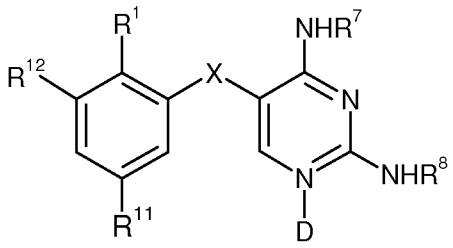
In certain embodiments of any of formulas VII, VIII and IX, R^3 and R^{10} each independently may be halo; alkoxy; haloalkoxy; alkylsulfonyl; hydroxy or -C≡C-R^a.

In certain embodiments of any of formulas VII, VIII and IX, R^3 may be hydrogen, halo, alkoxy, haloalkoxy or hydroxy, and R^{10} may be halo, alkylsulfonyl, or -C≡C-R^a.

In certain embodiments of any of formulas VII, VIII and IX, R^3 may be alkoxy or hydroxy, and R^{10} may be iodo, alkylsulfonyl, or -C≡C-R^a.

In certain embodiments of any of formulas VII, VIII and IX, R^3 is alkoxy or hydroxy, R^{10} is iodo, alkylsulfonyl, or -C≡C-R^a-, and R^7 and R^8 are hydrogen.

In another aspect of the invention compounds of the formula (X) are provided:



(X)

or pharmaceutically acceptable salts thereof,

wherein:

X is $–CH_2$-; -O-; -$S(O)_n$- or -NR^c-, wherein n is from 0 to 2 and R^c is hydrogen or alkyl;

D is an optional oxygen;

R^1 is alkyl; alkenyl; cycloalkyl; cycloalkenyl; halo; haloalkyl; or hydroxyalkyl;

R^{11} is alkyl; alkenyl; amino; halo; amido; haloalkyl; alkoxy; hydroxy; haloalkoxy; nitro; amino; hydroxyalkyl; alkoxyalkyl; hydroxyalkoxy; alkynylalkoxy; alkylsulfonyl; arylsulfonyl; cyano; aryl; heteroaryl; heterocyclyl; heterocyclylalkoxy; aryloxy; heteroaryloxy; aralkyloxy; heteroaralkyloxy; optionally substituted phenoxy; -C≡C-R^a; -$(CH_2)_m$-$(Z)_n$-(CO)-R^b; -$(CH_2)_m$-$(Z)_n$-SO_2-$(NR^c)_n$-R^b, wherein

m and n each independently is 0 or 1,

Z is O or NR^c,

R^a is hydrogen; alkyl; aryl; aralkyl; heteroaryl; heteroaralkyl; hydroxyalkyl; alkoxyalkyl; alkylsulfonylalkyl; aminoalkyl; cyanoalkyl; alkylsilyl, cycloalkyl, cycloalkylalkyl; heterocyclyl; and heterocyclylalkyl;

R^b is hydrogen, alkyl, hydroxy, alkoxy, amino, hydroxyalkyl or alkoxyalkyl, and each R^c is independently hydrogen or alkyl;

or 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;

R^{12} is alkoxy or hydroxy; and

R^7 and R^8 each independently is hydrogen; alkyl; cycloalkyl; cycloalkylalkyl; haloalkyl; haloalkoxy; hydroxyalky; alkoxyalkyl; alkylsulfonyl; alkylsulfonylalkyl; aminocarbonyloxyalkyl; hydroxycarbonylalkyl; hydroxyalkyloxycarbonylalkyl; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl.

In certain embodiments of formula X, D is absent

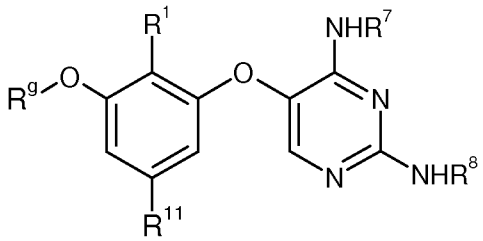
In certain embodiments of formula X, R^1 is ethyl, isopropyl, iodo, ethynyl or cyclopropyl.

In certain embodiments of formula X, X is -O- or $-CH_2-$.

In certain embodiments of formula X, R^{11} is iodo, alkoxy, alkylsulfonyl or $-C\equiv C-R^a$.

In certain embodiments of formula X, R^7 and R^8 are hydrogen.

In certain embodiments of formula X, the compounds may be of formula XI:



(XI)

wherein:

R^1 is ethyl; isopropyl; iodo; ethynyl; or cyclopropyl;

R^{11} is iodo; alkoxy; alkylsulfonyl; or $-C\equiv C-R^a$;

R^g is hydrogen or alkyl; and

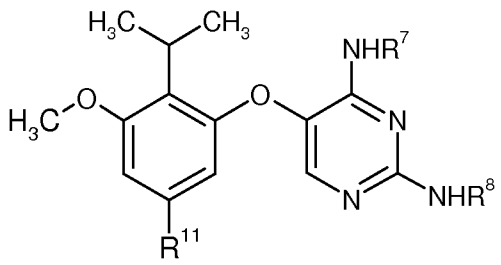
R^7 and R^8 are as defined herein.

In certain embodiments of formula XI, R^1 is isopropyl.

In certain embodiments of formula XI, R^{11} is iodo or $-C\equiv C-R^a$.

In certain embodiments of formula XI, R^7 and R^8 are hydrogen.

In certain embodiments of formula X, the compounds may be of formula XII:



(XII)

wherein R^7, R^8 and R^{11} are as defined herein.

Where any of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^a, R^b, R^c, R^d, R^e R^f or R^g is alkyl or contains an alkyl moiety, such alkyl is preferably lower alkyl, i.e. C_1-C_6alkyl, and more preferably C_1-C_4alkyl.

The invention also provides methods for treating a disease mediated by a $P2X_3$ receptor antagonist, a $P2X_{2/3}$ receptor antagonist, or both, the method comprising administering to a subject in need thereof an effective amount of a compound of any of formulas (I) through (VIII). The disease may be genitorurinary disease or urinary tract disease. In other instances the disease may be a disease is associated with pain. The urinary tract disease may be: reduced bladder capacity; frequenct micturition; urge incontinence; stress incontinence; bladder hyperreactivity; benign prostatic hypertrophy; prostatitis; detrusor hyperreflexia; urinary frequency; nocturia; urinary urgency; overactive bladder; pelvic hypersensitivity; urethritis; prostatitits,; pelvic pain syndrome; prostatodynia; cystitis; or idiophatic bladder hypersensitivity. The disease associated with pain may be: 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 injury; or pain associated with irritable bowel syndrome. The disease may be a respiratory disorder, such as chronic obstructive pulmonary disorder (COPD), asthma, or bronchospasm, or a gastrointestinal (GI) disorder such as Irritable Bowel Syndrome (IBS), Inflammatory Bowel Disease (IBD), biliary colic and other biliary disorders, renal colic, diarrhea-dominant IBS, pain associated with GI distension.

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

TABLE 1

#	Name (Autonom™)	MP/M+H
1	5-(5-Ethynyl-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine	170.0-173.6°C
2	5-(2-Isopropyl-4-methoxy-5-phenylethynyl-phenoxy)-pyrimidine-2,4-diamine	195.1-196.2°C
3	5-(2-Isopropyl-4-methoxy-5-prop-1-ynyl-phenoxy)-pyrimidine-2,4-diamine	218.0-218.9°C
4	5-(5-Ethynyl-4-fluoro-2-isopropyl-phenoxy)-pyrimidine-2,4-diamine	287
5	5-[2-Isopropyl-4-methoxy-5-(3-methoxy-prop-1-ynyl)-phenoxy]-pyrimidine-2,4-diamine	174-175°C
6	5-(2-Isopropyl-4-methoxy-5-pyridin-2-ylethynyl-phenoxy)-pyrimidine-2,4-diamine	222-223°C
7	5-(2-Isopropyl-4-methoxy-5-pyridin-3-ylethynyl-phenoxy)-pyrimidine-2,4-diamine	210-211°C
8	4-[5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-but-3-yn-1-ol	187-189°C
9	5-[5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-pent-4-ynenitrile	190-191°C
10	5-(2-Isopropyl-4-methoxy-5-pent-1-ynyl-phenoxy)-pyrimidine-2,4-diamine	182-183°C
11	5-(2-Isopropyl-4-methoxy-5-pyridin-4-ylethynyl-phenoxy)-pyrimidine-2,4-diamine	227.8-228.3°C
12	5-(2-Isopropyl-4-methoxy-5-thiophen-3-ylethynyl-phenoxy)-pyrimidine-2,4-diamine	206.1-206.5°C
13	5-[2-Isopropyl-4-methoxy-5-(3-methyl-3H-imidazol-4-ylethynyl)-phenoxy]-pyrimidine-2,4-diamine	204.1-205.1°C
14	5-[5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-pent-4-yn-1-ol	169-170°C
15	5-(4-Fluoro-2-isopropyl-5-prop-1-ynyl-phenoxy)-pyrimidine-2,4-diamine	301
16	5-[2-Isopropyl-4-methoxy-5-(3-methylamino-prop-1-ynyl)-phenoxy]-pyrimidine-2,4-diamine	143-145°C
17	3-[5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-	227-229°C

	phenyl]-prop-2-yn-1-ol	
18	5-(2-Isopropyl-4-methoxy-5-trimethylsilanylethynyl-phenoxy)-pyrimidine-2,4-diamine	202.1-203.3°C
19	5-(5-Cyclopropylethynyl-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine	225.5-226.8°C
20	4-(2,4-Diamino-pyrimidin-5-yloxy)-2-ethynyl-5-isopropyl-phenol	230.1-234.4°C
21	5-(5-Ethynyl-2-isopropyl-phenoxy)-pyrimidine-2,4-diamine	150-151°C
22	5-[5-Ethynyl-4-(3-fluoro-benzyloxy)-2-isopropyl-phenoxy]-pyrimidine-2,4-diamine	161.0-163.0°C
23	5-(5-Ethynyl-2-isopropyl-4-methoxy-benzyl)-pyrimidine-2,4-diamine	170.1-171.4°C
24	5-(2-Ethyl-5-ethynyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine	285
25	5-(2,5-Diethynyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine	281
26	5-(2,5-Diethynyl-phenoxy)-pyrimidine-2,4-diamine	251
27	5-(5-Ethynyl-2-iodo-phenoxy)-pyrimidine-2,4-diamine	353
28	5-(2-Ethynyl-5-iodo-4-methoxy-phenoxy)-pyrimidine-2,4-diamine	383
29	5-(5-Iodo-2-isopropyl-3-methoxy-phenoxy)-pyrimidine-2,4-diamine	401
30	2-[4-(2,4-Diamino-pyrimidin-5-yloxy)-2-ethynyl-5-isopropyl-phenoxy]-ethanol	189.3-191.7
31	5-(5-Ethynyl-2-isopropyl-3-methoxy-phenoxy)-pyrimidine-2,4-diamine	299
32	2-[4-Amino-5-(5-ethynyl-2-isopropyl-4-methoxy-phenoxy)-pyrimidin-2-ylamino]-ethanol	343
33	5-(5-Ethynyl-2-isopropyl-4-methoxy-phenoxy)-N*2*-(2-piperidin-1-yl-ethyl)-pyrimidine-2,4-diamine	410
33	N*2*-(2-Dimethylamino-ethyl)-5-(5-ethynyl-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine	370
34	2-[4-Amino-5-(5-ethynyl-2-isopropyl-4-methoxy-phenoxy)-pyrimidin-2-ylamino]-propan-1-ol	357
35	5-(5-Ethynyl-2-isopropyl-4-methoxy-phenoxy)-N*2*-(2-morpholin-4-yl-ethyl)-pyrimidine-2,4-diamine	412
36	1-[4-Amino-5-(5-ethynyl-2-isopropyl-4-methoxy-phenoxy)-pyrimidin-2-ylamino]-propan-2-ol	357

37	5-(5-Ethynyl-2-isopropyl-4-methoxy-phenoxy)-N*2*-(1-methanesulfonyl-piperidin-4-yl)-pyrimidine-2,4-diamine	460
38	5-(5-Ethynyl-2-isopropyl-4-methoxy-phenoxy)-N*2*-(tetrahydro-pyran-4-yl)-pyrimidine-2,4-diamine	
39	2-[4-Amino-5-(5-ethynyl-2-isopropyl-4-methoxy-phenoxy)-pyrimidin-2-ylamino]-propane-1,3-diol	
40	5-(4-Chloro-5-ethynyl-2-isopropyl-phenoxy)-pyrimidine-2,4-diamine	
41	3-[4-Amino-5-(5-ethynyl-2-isopropyl-4-methoxy-phenoxy)-pyrimidin-2-ylamino]-propan-1-ol	

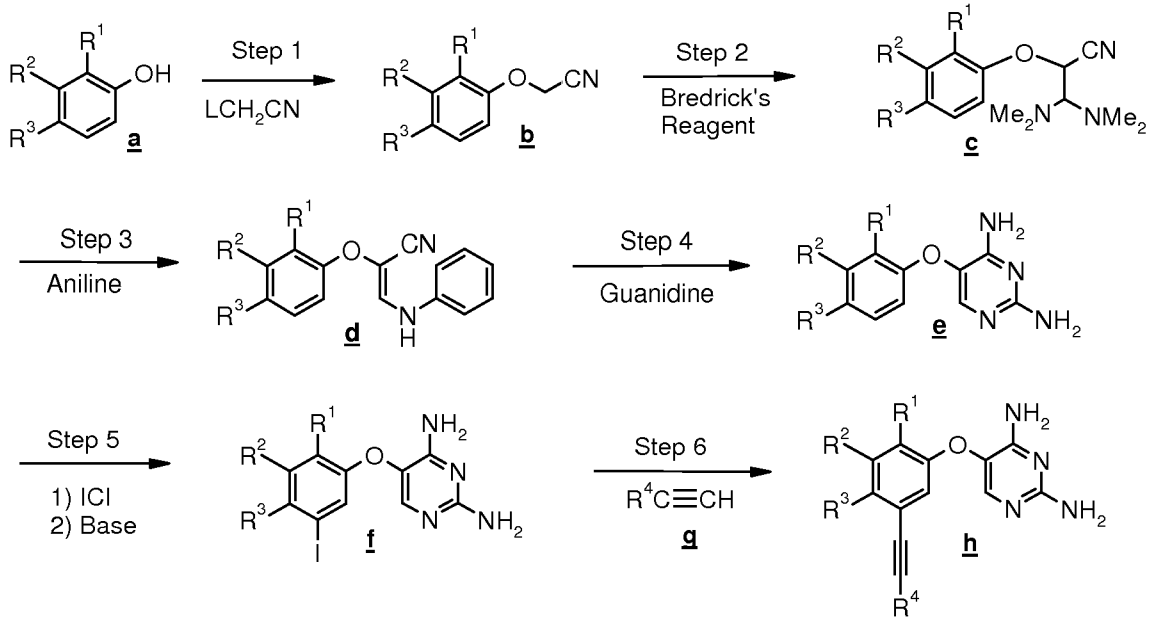
Compounds of the present invention can be made by a variety of methods depicted in the illustrative synthetic reaction schemes shown and described below.

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.

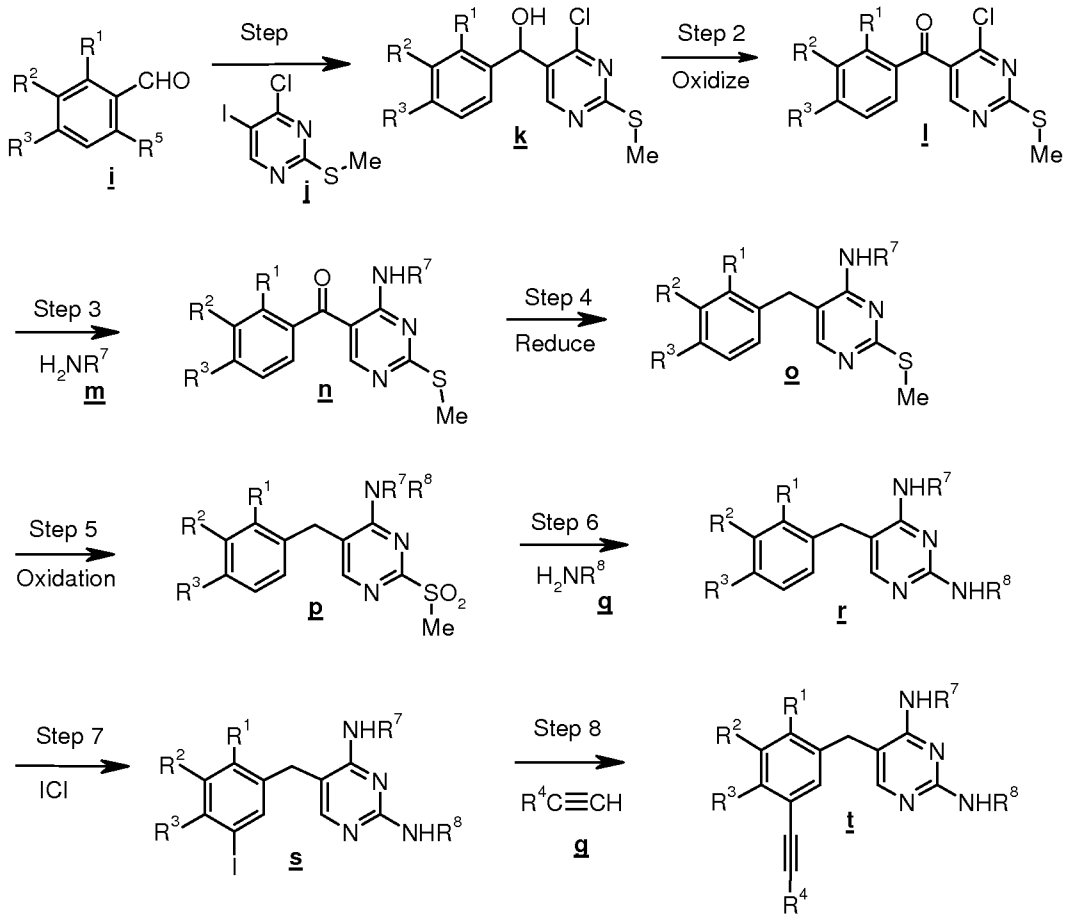
Scheme A below illustrates one synthetic procedure usable to prepare specific compounds of formula (I) wherein L is a leaving group and R^1, R^2, R^3 and R^4 are as defined herein.



SCHEME A

In step 1 of Scheme A, phenol a undergoes an O-alkylation by reaction with an acetonitrile reagent to form cyano ether compound b. Compound b is then treated with Bredrick's reagent (t-butoxybis(dimethylamino)methane) in step 2 to form bisdimethylamino compound c. In step 3 compound c is reacted with aniline to afford the aniline compound d. Compound d then undergoes reaction with guanidine in step 4 to provide phenoxy diamino pyrimidine e. Compound e, in step 5, is subject to iodination to yield iodophenoxy diamino pyrimidine f. In step 6 compound f is treated with acetylene compound g to afford compound h, which is a compound of formula I in accordance with the invention. Where R^4 is H in compound h, a suitable protecting group such as trimethylsilyl may be included on acetylene compound g, which then may be subsequently removed. Alkylation or acylation of the amino groups of compound h to provide desired R^7 and R^8 groups. In certain embodiments guanidine hydrochloride may be used in step 3 together with aniline to form phenoxy diamino pyrimidine e directly, without the need for step 4. In certain embodiments compounds c and/or d need not be isolated as the reaction steps may be carried through in a single reaction vessel.

Scheme B below illustrates another synthetic procedure usable to prepare specific compounds of formula (I) wherein R^1, R^2, R^3, R^4, R^7 and R^8 are as defined herein.



SCHEME B

In Step 1 of Scheme B, benzaldehyde i is alkylated with the Grignard reagent derived from 4-chloro-5-iodo-2-methylsulfanyl-pyrimidine j or like iodopyrimidine to provide an alpha-hydroxy benzyl pyrimidine k. The iodopyrimidine used in this step may be prepared according to the procedure described by Sakamoto et al., Chem. Pharm. Bull., 34 1986, 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 i, after which the masked aldehyde is deprotected to provide the free aldehyde group.

In step 2, alpha-hydroxy benzyl pyrimidine k is oxidized to provide ketone compound l. In step 3, a first amination by reaction of amine m with ketone compound l yields amino-pyrimidine phenone compound n. In step 4 the carbonyl group of compound n is reduced to a methylene group to provide benzyl aminopyridine compound o. In step 5, an oxidation of the methylsulfanyl group of benzyl aminopyrimidine o is carried out to afford amino methanesulfonyl benzylpyrimidine p. A second amination occurs in step 6

in which amino methanesulfonyl benzylpyrimidine p is treated with amine q to displace the methanesulfonyl group and provide diamino benzylpyrimidine r. The diamino benzylpyrimidine r is then subject to iodination in step 7 followed y acetylation in step 8 by reaction with acetylene g, to afford diaminopyrimidine t, which is a compound of formula I in accordance with the invention.

Numerous variations on the above procedure are possible and will suggest themselves to those skilled in the art upon review of this disclosure. 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, prostatitits, pelvic pain syndrome, prostatodynia, cystitis, and idiophatic 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. Tablets, 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 polyvinylpyrrolidine (PVP). The powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form e.g. in capsules or cartridges of e.g., gelatine or blister packs from which the powder may be administered by means of an inhaler.

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

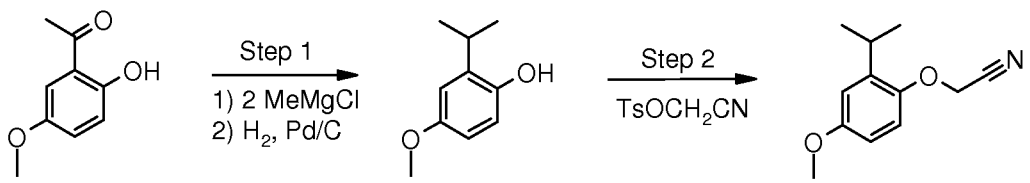
The following preparations and examples are given to enable those skilled in the art to more clearly understand and to practice the present invention. They should not be considered as limiting the scope of the invention, but merely as being illustrative and representative thereof.

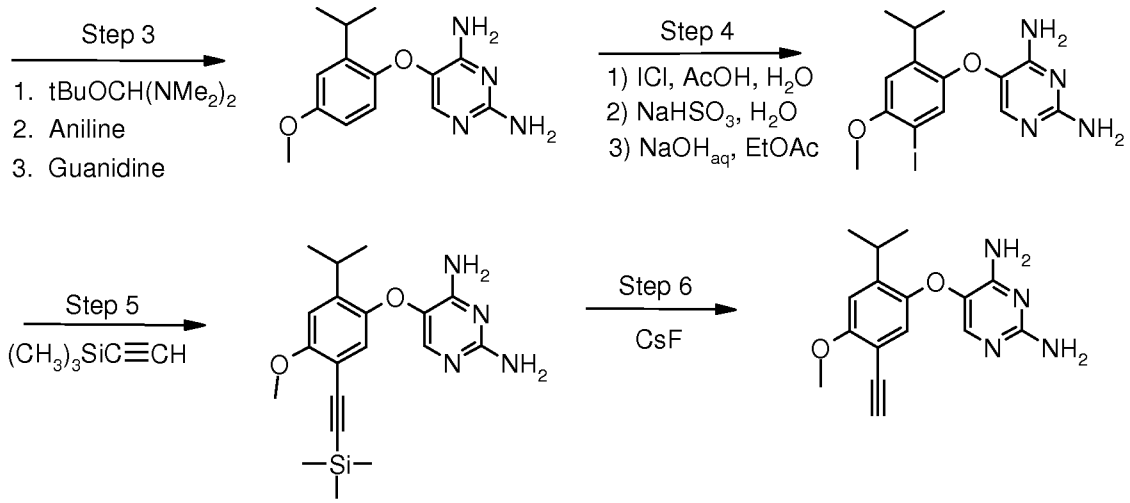
Unless otherwise stated, all temperatures including melting points (i.e., MP) are in degrees celsius (°C). It should be appreciated that the reaction which produces the indicated and/or the desired product may not necessarily result directly from the combination of two reagents which were initially added,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

The following abbreviations may be used in the Examples: DCM: dichloromethane/-methylene chloride; DMF: N,N-dimethylformamide; DMAP: 4-dimethylaminopyridine; EtOAc: ethyl acetate; EtOH: ethanol; gc: gas chromatography; HMPA: hexamethylphosphoramide; hplc: high performance liquid chromatography; mCPBA: *m*-chloroperbenzoic acid; MeCN: acetonitrile; NMP: N-methyl pyrrolidinone; TEA: triethylamine; THF: tetrahydrofuran; LDA: lithium diisopropylamine; TLC: thin layer chromatography; RT: room (ambient) temperature; min: minutes

Example 1: 5-(5-Ethynyl-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine

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





SCHEME C

Step 1 2-Isopropyl-4-methoxy-phenol

To a cooled solution of 1-(2-Hydroxy-5-methoxy-phenyl)-ethanone (10.0 g) in 80 mL of THF was gradually added 46.4 g of 3M solution of MeMgCl in THF at a rate such that the reaction mixture temperature did not exceed 25°C. Following addition of the MeMgCl solution, the reaction mixture was stirred at RT for 18 hours. To the stirred solution was then added 10% palladium on carbon (1.02 g, 50% water wet) suspended in 4 mL of THF. The reaction mixture was placed under a hydrogen atmosphere at 5 psig and cooling was applied to maintain a temperature of approximately 25°C. To the cooled mixture was gradually added concentrated HCl (20 mL) while maintaining the reaction temperature at 25°C. The resultant mixture was stirred at RT for 18 hours, then treated with 45 mL water and filtered through a bed of Celite to remove suspended catalyst. The filter cake was rinsed with EtOAc and the combined filtrate was separated. The organic phase was washed with water, then concentrated under reduced pressure to give 10.4 g of 2-isopropyl-4-methoxy-phenol, MS (M+H) = 167. This product was dissolved in 2-butanone (20.4 g) and the crude solution was employed directly in the next step.

Step 2 (2-Isopropyl-4-methoxy-phenoxy)-acetonitrile

A stirred slurry of toluene-4-sulfonic acid cyanomethyl ester (13.0 g), potassium carbonate (13.0 g) and 2-isopropyl-4-methoxyphenol (9.57 g) in 85 mL of 2-butanone was heated to 55-60°C for 4 days, then heated to relux for 18 hours. The resultant slurry was cooled and filtered to remove solids. The filtrate was concentrated under reduced pressure and the residue was redissolved in toluene. The toluene solution was extracted with 1N KOH, and the organic phase was concentrated under reduced pressure to give 20.6 g of a 1:1 (by weight) solution of (2-isopropyl-4-methoxy-phenoxy)-acetonitrile in toluene, which was used directly in the next step. An aliquot (0.967 g) of this solution

was concentrated to dryness to give 0.509 g of crude (2-isopropyl-4-methoxy-phenoxy)-acetonitrile, MS (M+H) = 206.

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

A 1:1 (by weight) solution of toluene and (2-isopropyl-4-methoxy-phenoxy)-acetonitrile (10.6 g of the nitrile compound) was concentrated under reduced pressure and the residue was treated with 10.8 g of tert-butoxybis(dimethylamino)methane (Bredrick's Reagent). The resulting mixture was dissolved in 22 mL of DMF and the solution was heated to 110°C for 2 hours. The DMF solution was cooled and transferred onto 14.7 g of aniline hydrochloride. The resulting mixture was heated to 120°C for 22 hours, then cooled, diluted with 25 mL toluene, then with 70 mL of water. The organic layer was separated, washed with water, and concentrated under reduced pressure. The residue was transferred into 25 mL DMF, and the DMF solution was transferred onto 6.01 g of guanidine carbonate. The resulting mixture was heated to 120°C for 3 days, then cooled, diluted with 10 mL of EtOAc, then reheated to 60°C. Water (75.1m L) was added and the resultant mixture was allowed to cool to RT. The precipitated solid was collected by filtration, rinsed with isopropanol and dried under vacuum at 50°C to give 9.62 g of 5-(2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine, m.p. 170-171°C, MS (M+H) = 275.

Step 4 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 (6.50 g) in mL glacial acetic acid was added a solution of 9.205 g ICl (iodine monochloride) in 8 mL of acetic acid, with addition carried out at a rate such that the temperature of the resulting mixture did not exceed 24°C. Water (11.0 mL) was added and the resultant mixture was stirred at 25°C for 42 hours. Excess ICl was decomposed by the addition of aqueous solution of sodium bisulfite (3.5 mL) at a rate such that the temperature of the reaction mixture did not exceed 20°C. Water (40 mL) was added, and the precipitate was collected by filtration and air-dried to give 8.86 g of crude 5-(5-iodo-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine. A suspension of the crude product in 90 mL water was made basic by addition of 50% NaOH, and the resulting solution was extracted into warm EtOAc. The combined organic layers were filtered and EtOAc was replaced by isopropanol via distillation. To the hot isopropanol solution was added 3.4 mL of 6N HCl and the resultant mixture was cooled slowly to 15°C. Crystals of the resulting HCl salt were isolated by filtration, rinsed with isopropanol, and dried under vacuum at 70°C to give 6.08 g (58.8%) of 5-(5-iodo-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine hydrochloride salt, m.p. = 262.0-263.0 °C, MS (M+H) = 401.

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

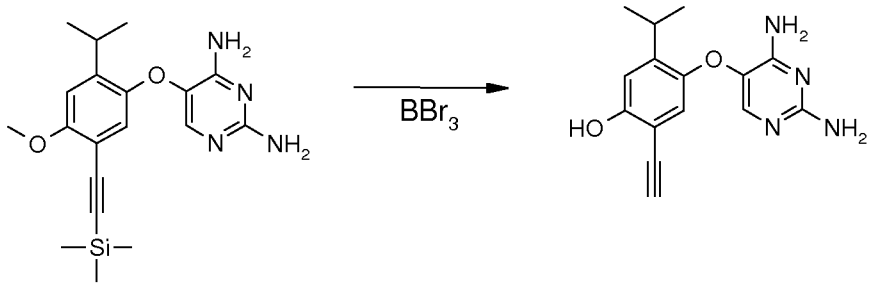
5-(5-Iodo-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine (2.0 g, 5 mmol), bis(triphenylphosphine)-Palladium dichloride (700 mg, 1 mmol) and CuI (100 mg, 0.5 mmol) were added to 14 mL dry THF under nitrogen. Trimethylsilyl acetylene (1.4 mL, 10 mmol) was added, followed by 7 mL diisopropylethylamine. The reaction mixture was stirred at 50°C under nitrogen for 17 hours, then was allowed to cool for two hours with stirring. The reaction mixture was poured into 15 % aqueous NH_4Cl and extracted into EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was chromatographed on 150 g of flash silica (2%-4% MeOH/CH_2Cl_2) to give 1.70 g of 5-(2-Isopropyl-4-methoxy-5-trimethylsilanylethynyl-phenoxy)-pyrimidine-2,4-diamine, MS (M+H) = 371.

Step 6 5-(5-Ethynyl-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine

5-(2-Isopropyl-4-methoxy-5-trimethylsilanylethynyl-phenoxy)-pyrimidine-2,4-diamine (0.75 g, 2 mmol) and Cesium Fluoride (0.46 g, 3 mmol) were added to 10 mL of dry THF under nitrogen, and the reaction mixture was stirred for 6 hours at RT. The reaction mixture was poured into water and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced

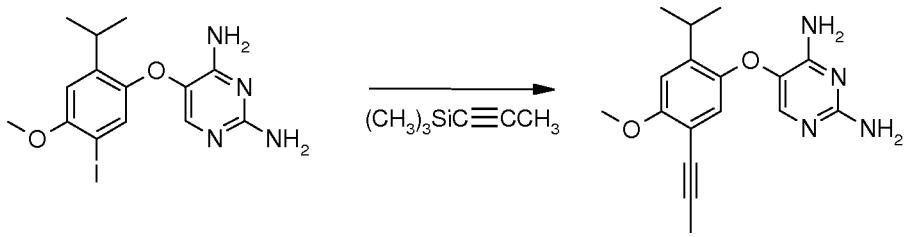
pressure. The residue was chromatographed on 50 g of flash silica (3%-6% MeOH/-CH_2Cl_2) to give 0.54 g of 5-(5-ethynyl-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine, MS (M+H) = 299.

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



5-(2-Isopropyl-4-methoxy-5-trimethylsilanylethynyl-phenoxy)-pyrimidine-2,4-diamine (0.65 g, 1.75 mmol) was added to 40 mL methylene chloride at ice bath temperature and under nitrogen. Boron tribromide (7 mL) was added and the reaction mixture was stirred at ice bath temperature for 1.5 hours, and then for 20 hours at RT. The reaction mixture was added to saturated aqueous $NaHCO_3$, and the resulting mixture was extracted with chloroform. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed on 50 g of flash silica (2%-6% MeOH/CH_2Cl_2) to give 103 mg of 4-(2,4-diamino-pyrimidin-5-yloxy)-2-ethynyl-5-isopropyl-phenol, MS (M+H) = 285.

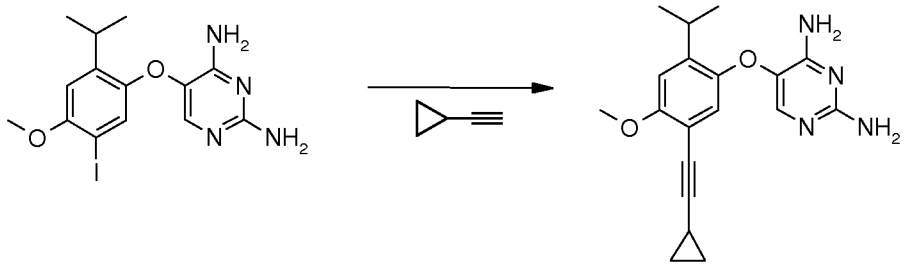
Example 3: 5-(2-Isopropyl-4-methoxy-5-prop-1-ynyl-phenoxy)-pyrimidine-2,4-diamine



5-(5-Iodo-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine (1.0 g, 2.5 mmol), bis(triphenylphosphine)palladium dichloride (290 mg, 0.25 mmol), 1-(trimethylsilyl)-1-propyne (0.44 mL, 3 mmol) and tetrabutyl ammonium fluoride (3 mL, 3 mmol) were added to 20 mL dry THF under nitrogen. The reaction mixture was stirred under nitrogen at 50°C for 22 hours, then 150 mg of bis(triphenylphosphine)-palladium dichloride, 0.22 mL of 1-(trimethylsilyl)-1-propyne and 1. 5 mL tetrabutyl ammonium

fluoride, and 0.1 mL ethanol were added to the reaction mixture. The reaction mixture was stirred under nitrogen for 18 hours at 50°C. The reaction mixture was cooled and poured into saturated aqueous $NaHCO_4$ and extracted into EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed on 125 g of flash silica (2%-4% MeOH/CH_2Cl_2) to give 925 mg of 5-(2-isopropyl-4-methoxy-5-prop-1-ynyl-phenoxy)-pyrimidine-2,4-diamine, MS (M+H) = 313.

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



5-(5-Iodo-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine (873 g, 2 mmol), bis(triphenylphosphine)palladium dichloride (140 mg, 0.2 mmol), and CuI (19 mg, 0.1 mmol) were added to 15 mL of degassed diisopropylamine under nitrogen in a screw cap flask. Ethynylcyclopropane (0.25 mL, 3 mmol) was added, and the flask was sealed and heated to 70°C for 18 hours. The reaction mixture was cooled, poured into water, and extracted into DCM. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed on 100 g of flash silica (2%-3% MeOH/CH_2Cl_2) to give 605 mg of 5-(5-cyclopropylethynyl-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine. MP 225.5-226.8°C; MS (M+H) = 339.

Similarly prepared using the appropriate substituted ethynes, were:

5-(2-Isopropyl-4-methoxy-5-phenylethynyl-phenoxy)-pyrimidine-2,4-diamine; MP 195.1-196.2°C;

5-[2-Isopropyl-4-methoxy-5-(3-methoxy-prop-1-ynyl)-phenoxy]-pyrimidine-2,4-diamine; MP 174-175°C;

5-(2-Isopropyl-4-methoxy-5-pyridin-2-ylethynyl-phenoxy)-pyrimidine-2,4-diamine; MP 222-223°C;

5-(2-Isopropyl-4-methoxy-5-pyridin-3-ylethynyl-phenoxy)-pyrimidine-2,4-diamine; MP 210-211°C;

4-[5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-but-3-yn-1-ol; MP 187-189°C;

5-[5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-pent-4-ynenitrile; MP 190-191°C;

5-(2-Isopropyl-4-methoxy-5-pent-1-ynyl-phenoxy)-pyrimidine-2,4-diamine; MP 182-183°C;

5-(2-Isopropyl-4-methoxy-5-pyridin-4-ylethynyl-phenoxy)-pyrimidine-2,4-diamine; MP 227.8-228.3°C;

5-(2-Isopropyl-4-methoxy-5-thiophen-3-ylethynyl-phenoxy)-pyrimidine-2,4-diamine; MP 206.1-206.5°C;

5-[2-Isopropyl-4-methoxy-5-(3-methyl-3H-imidazol-4-ylethynyl)-phenoxy]-pyrimidine-2,4-diamine; MP 204.1-205.1°C;

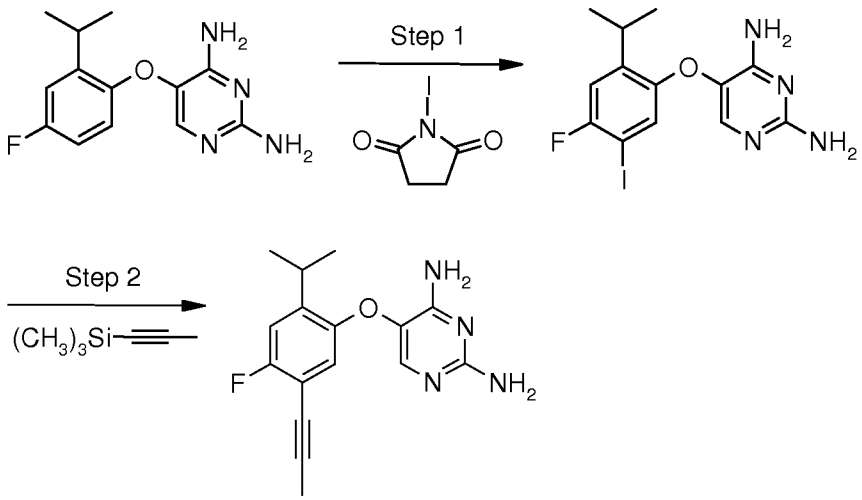
5-[5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-pent-4-yn-1-ol; MP 169-170°C;

5-[2-Isopropyl-4-methoxy-5-(3-methylamino-prop-1-ynyl)-phenoxy]-pyrimidine-2,4-diamine;143-145 °C; and

3-[5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-prop-2-yn-1-ol; MP 227-229°C.

Example 5: 5-(4-Fluoro-2-isopropyl-5-prop-1-ynyl-phenoxy)-pyrimidine-2,4-diamine

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



SCHEME D

Step 1 5-(4-Fluoro-5-iodo-2-isopropyl-phenoxy)-pyrimidine-2,4-diamine

5-(4-Fluoro-2-isopropyl-phenoxy)-pyrimidine-2,4-diamine (400 mg, 1.53 mmol, prepared using the procedure of example 1) was dissolved in dry THF at ice bath temperature, and trifluoromethylsulfonic acid (0.67 mL, 7.63 mmol) was added. After stirring for 10 min, N-iodosuccinimide (378 g, 1.68 mmol) was added in portions. The ice bath was removed and the reaction mixture was stirred for three hours. The reaction mixture was then poured over ice and extracted with DCM. The combined organic layers were washed with 10% aqueous sodium bisulfite solution and water, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed on silica (95%:5%:1% CH_2Cl_2:MeOH:NH_4OH) to give 338 mg of 5-(4-fluoro-5-iodo-2-isopropyl-phenoxy)-pyrimidine-2,4-diamine, MS (M+H) = 389.

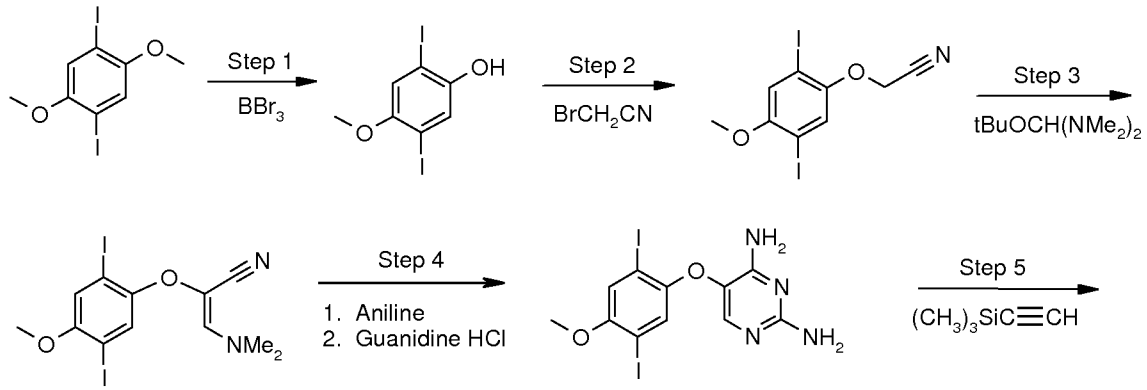
Step 2 5-(4-Fluoro-2-isopropyl-5-prop-1-ynyl-phenoxy)-pyrimidine-2,4-diamine

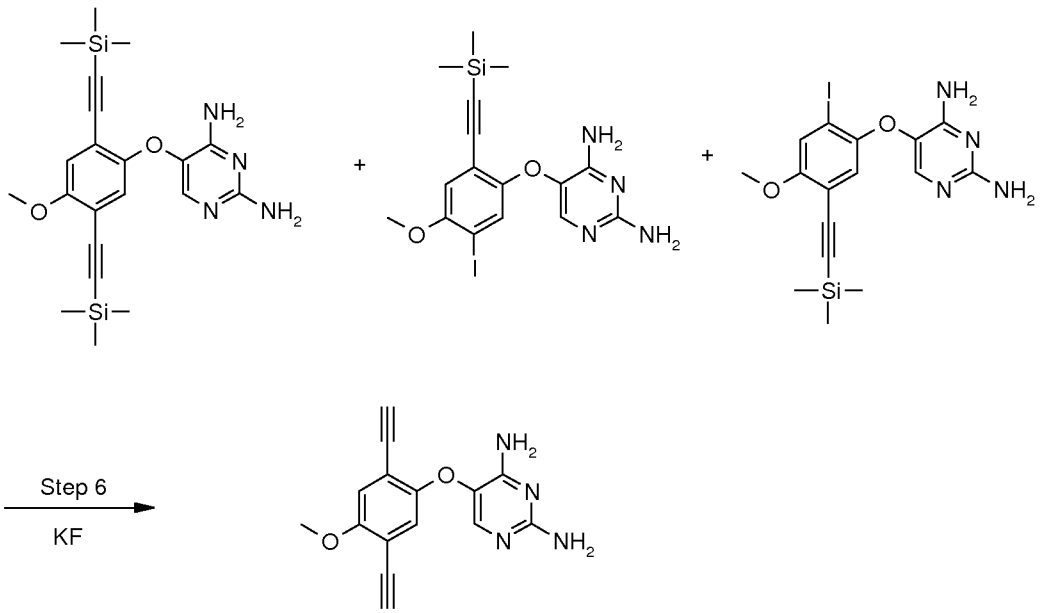
Using the procedure of Example 3, 5-(4-fluoro-5-iodo-2-isopropyl-phenoxy)-pyrimidine-2,4-diamine (MS (M+H) = 301) was prepared from 5-(4-fluoro-5-iodo-2-isopropyl-phenoxy)-pyrimidine-2,4-diamine.

Similarly prepared from 5-(4-fluoro-5-iodo-2-isopropyl-phenoxy)-pyrimidine-2,4-diamine using the procedure of step 8 of example 1 was 5-(5-Ethynyl-4-fluoro-2-isopropyl-phenoxy)-pyrimidine-2,4-diamine, MS (M+H) = 289.

Example 6: 5-(2,5-Diethynyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine

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





SCHEME E

Step 1 2,5-Diiodo-4-methoxy-phenol

1,4-Diiodo-2,5-dimethoxy-benzene (3.65 g, 9.36 mmol) was added to 100 mL of DCM and stirred under nitrogen at ice bath temperature. Boron tribromide (10.3 mL, 10.3 mmol) was added dropwise, and the reaction mixture was stirred at ice bath temperature for 20 hours. The reaction was quenched by dropwise addition of methanol, and the reaction mixture was poured into water and extracted into DCM. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 2.86 g of 2,5-Diiodo-4-methoxy-phenol, MS (M+H) = 377.

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

2,5-Diiodo-4-methoxy-phenol (2.8 g, 7.5 mmol) and potassium carbonate (2.1 g) were added to 30 mL of stirring acetone at RT and under nitrogen. Bromoacetonitrile (0.575 mL, 8.25 mmol) was added, and the reaction mixture was heated to 60°C and stirred under nitrogen for 8 hours, then stirred for 18 hours under nitrogen at RT. The reaction mixture was concentrated under reduced pressure, and the residue was poured into water and extracted into EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed on 150 g of flash silica (5%-20% EtOAc/hexanes) to give 2.86 g of (2,5-Diiodo-4-methoxy-phenoxy)-acetonitrile, MS (M+H) = 416.

Step 3 2-(2,5-Diiodo-4-methoxy-phenoxy)-but-2-enenitrile

(2,5-Diiodo-4-methoxy-phenoxy)-acetonitrile (2.8 g, 6.75 mmol) and tert-butoxybis(dimethylamino)methane (Bredrick's reagent, 7 mL, 33.7 mmol) were combined and heated

to 105°C under nitrogen for 2 hours. The reaction mixture was cooled and concentrated under reduced pressure to yield 3.47 g of crude 2-(2,5-diiodo-4-methoxy-phenoxy)-but-2-enenitrile, which was used directly in the following step.

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

2-(2,5-Diiodo-4-methoxy-phenoxy)-but-2-enenitrile (3.47 g, 6.75 mmol) and aniline hydrochloride (3.5 g, 27 mmol) were dissolved in 27 mL ethanol. The reaction mixture was heated to 85°C and stirred under nitrogen for 18 hours. The reaction mixture was cooled and 25% $NaOCH_3$ in methanol (7.3 mL) was added, followed by guanidine hydrochloride (3.2 g), and ethanol (10 mL). The reaction mixture was heated to 100°C for 21 hours, then cooled and concentrated under reduced pressure. The residue was poured into water and extracted with DCM. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 1.2 g of 5-(2,5-diiodo-4-methoxy-phenoxy)-pyrimidine-2,4-diamine, MS (M+H) = 485.

Step 5 5-(4-Methoxy-2,5-bis-trimethylsilanylethynyl-phenoxy)-pyrimidine-2,4-diamine

5-(2,5-Diiodo-4-methoxy-phenoxy)-pyrimidine-2,4-diamine (1.2 g, 2.5 mmol), bis(triphenylphosphine)palladium dichloride (175 mg, 2.5 mmol), and CuI (25 mg, 0.125 mmol) were added to 7 mL dry THF. Trimethylsilylacetylene ((0.48 mL, 3.3 mmol), and diisopropylethylamine (3.5 mL) were added, and the reaction mixture was heated to 50°C under nitrogen for 27 hours. The reaction mixture was cooled, poured into 15 % aqueous NH_4Cl and extracted into EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give crude 5-(4-methoxy-2,5-bis-trimethylsilanylethynyl-phenoxy)-pyrimidine-2,4-diamine together with monoacetylenes 5-(2-iodo-4-methoxy-5-trimethylsilanylethynyl-phenoxy)-pyrimidine-2,4-diamine and 5-(5-iodo-4-methoxy-2-trimethylsilanylethynyl-phenoxy)-pyrimidine-2,4-diamine. This residue was chromatographed on 125 g of flash silica (6:1:1 CH_2Cl_2:MeOH:NH_4OH) to give 450 mg of 5-(4-Methoxy-2,5-bis-trimethylsilanylethynyl-phenoxy)-pyrimidine-2,4-diamine, MS (M+H) = 425.

Step 6 5-(2,5-Diethynyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine

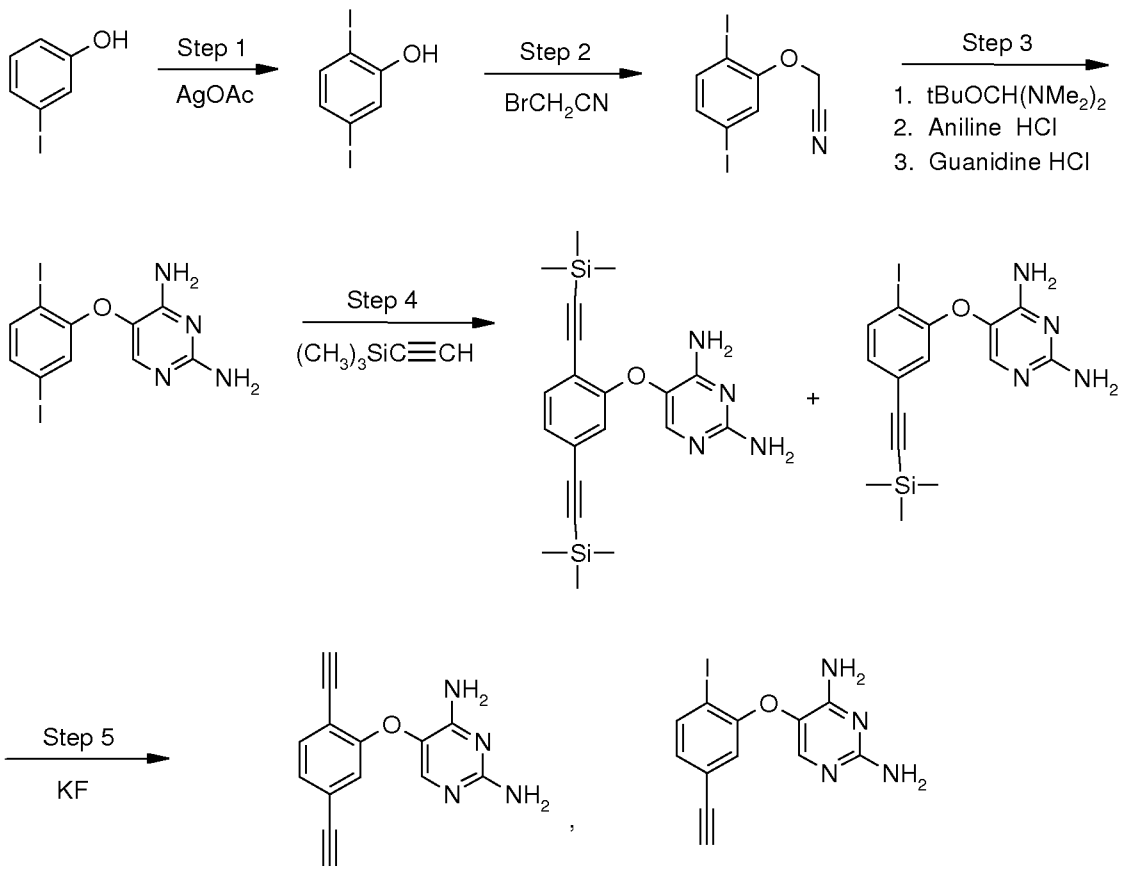
5-(4-Methoxy-2,5-bis-trimethylsilanylethynyl-phenoxy)-pyrimidine-2,4-diamine (450 mg, 1.06 mmol) and potassium fluoride (246 mg, 4.2 mmol) were added to 7 mL dry DMF under nitrogen. Two drops of 48% HBr were added, and the reaction mixture was stirred under nitrogen at RT for four hours. The reaction mixture was poured into water and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was recrystallized from 10%

MeOH in DCM to give 228 g of 5-(2,5-Diethynyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine, MP = 163.2-164.1 °C, MS (M+H) = 281.

The fractions from step 5 containing monoacetylenes 5-(2-iodo-4-methoxy-5-trimethylsilanylethynyl-phenoxy)-pyrimidine-2,4-diamine and 5-(5-iodo-4-methoxy-2-trimethylsilanylethynyl-phenoxy)-pyrimidine-2,4-diamine were deprotected in a similar manner to provide 5-(5-Ethynyl-2-iodo-4-methoxy-phenoxy)-pyrimidine-2,4-diamine (MS (M+H) = 383) and 5-(2-Ethynyl-5-iodo-4-methoxy-phenoxy)-pyrimidine-2,4-diamine (MS (M+H) = 383) respectively.

Example 7: 5-(2,5-Diethynyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine and 5-(5-Ethynyl-2-iodo-4-methoxy-phenoxy)-pyrimidine-2,4-diamine

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



SCHEME F

Step 1 2,5-Diiodo-phenol

A suspension of 3-iodophenyl (11.0 g, 50 mmol) and silver acetate (10.02 g, 60 mmol) in 400 mL DCM was treated dropwise with a solution of iodine (12.7 g, 50 mmol in 250 mL

DCM). The resulting mixture was stirred for 18 hours at RT, then filtered through a Celite pad. The filtrate was concentrated under reduced pressure and the residue was chromatographed on silica (30% DCM in hexanes) to give 7.7 g of 2,5-diiodo-phenol, MS (M+H) = 346.

Step 2 (2,5-Diiodo-phenoxy)-acetonitrile

A mixture of 2,5-diiodo-phenol (3.9 g, 11.28 mmol), bromoacetonitrile (2.03 g, 16.91 mmol) and potassium carbonate (3.11 g, 22.55 mmol) in 7 mL acetonitrile was sealed in a stoppered flask and stirred at RT for 18 hours. The reaction mixture was poured into water and extracted with EtOAc. The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chomatographed on silica gel (30%-70% CH_2Cl_2/hexanes) to give 2.78 g of (2,5-Diiodo-phenoxy)-acetonitrile.

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

A mixture of (2,5-diiodo-phenoxy)-acetonitrile (1.15 g, 2.99 mmol) and tert-butoxybis-(dimethylamino)methane (Bredrick's reagent, 2.08 g, 11.95 mmol) was heated to 100°C under nitrogen for 18 hours. The reaction mixture was cooled and concentrated under reduced pressure. To the residue was added aniline hydrochloride (1.162 g, 8.97 mmol) and EtOH (20 mL). The resulting mixture was heated to reflux for 20 hours under nitrogen atmosphere. The reaction mixture was cooled to RT and concentrated under reduced pressure. A mixture of guanidine hydrochloride (1.43 g, 14.95 mmol) and 25% $NaOCH_3$ in methanol (3.3 mL, 14. 95 mmol) in 7 mL ethanol was added to the residue, and the resulting mixture was heated to reflux under nitrogen for 18 hours. The reaction mixture was cooled, poured into water and extracted with EtOAc. The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chomatographed on silica gel (30% CH_2Cl_2 in hexanes with 0.1% NH_4OH) to give 0.64 g of 5-(2,5-diiodo-4-methoxy-phenoxy)-pyrimidine-2,4-diamine, MP = 136-138 °C. MS (M+H) = 455.

Step 4 5-(2,5-Bis-trimethylsilanylethynyl-phenoxy)-pyrimidine-2,4-diamine and 5-(2-Iodo-5-trimethylsilanylethynyl-phenoxy)-pyrimidine-2,4-diamine

To a mixture of 5-(2,5-diiodo-4-methoxy-phenoxy)-pyrimidine-2,4-diamine (2.043 g, 4.5 mmol), bis(triphenylphosphine)palladium dichloride (0.316 g, 0.45 mmol) and CuI (43 mg, 0.225 mmol) in 14 mL dry THF was added trimethylsilylacetylene (0.441 g, 4.5 mmol), followed by diisopropylethylamine (7 mL). The reaction mixture was heated at 50°C under nitrogen atmosphere for 20 hours. The reaction mixture was cooled, poured into saturated aqueous NH_4Cl and extracted with DCM. The combined organic layers

were washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was chromatographed on silica (4 % MeOH in CH_2Cl_2 with 0.1% NH_4OH) to give 0.350 g of 5-(2,5-Bis-trimethylsilanylethynyl-phenoxy)-pyrimidine-2,4-diamine as a first fraction , and 0.41g of 5-(2-Iodo-5-trimethylsilanylethynyl-phenoxy)-pyrimidine-2,4-diamine as a second fraction.

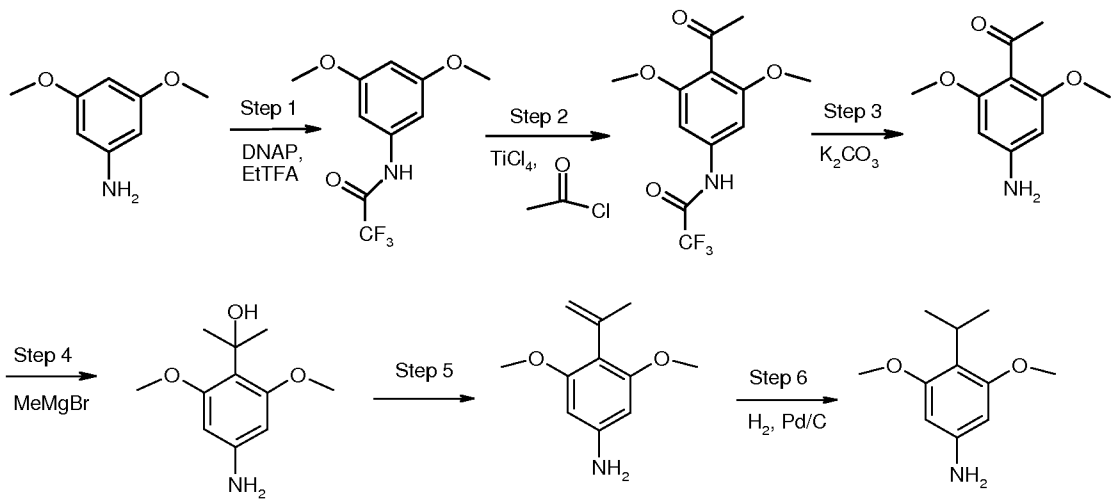
Step 5 5-(2,5-Diethynyl-phenoxy)-pyrimidine-2,4-diamine and 5-(5-Ethynyl-2-iodo-phenoxy)-pyrimidine-2,4-diamine

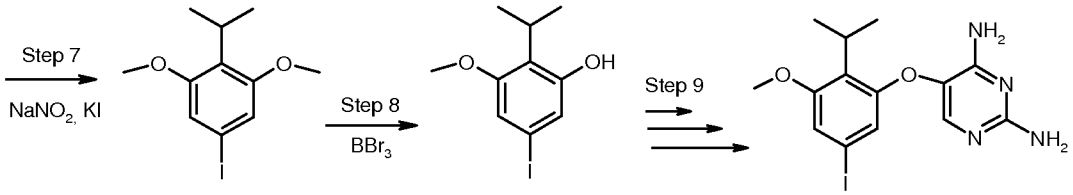
A mixture of 5-(2-Iodo-5-trimethylsilanylethynyl-phenoxy)-pyrimidine-2,4-diamine (0.4 g, 2.36 mmol), potassium fluoride (41 mg, 7.07 mmol) and HBr (2 drops of 48% aqueous solution) in DMF was stirred at RT for 30 min. The reaction mixture was diluted with water and EtOAc and basified with 1 mL NH_4OH. The organic layer was separated, washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was chromatographed on silica (4 % MeOH in CH_2Cl_2 with 0.1% NH_4OH) to give 0.36 g of 5-(5-ethynyl-2-iodo-phenoxy)-pyrimidine-2,4-diamine, MP = 156-159°C, MS (M+H) = 352.

Similarly prepared from 5-(2,5-bis-trimethylsilanylethynyl-phenoxy)-pyrimidine-2,4-diamine was 5-(2,5-diethynyl-phenoxy)-pyrimidine-2,4-diamine, MP = 125=129 °C, MS (M+H) = 251.

Example 8: 5-(5-Iodo-2-isopropyl-3-methoxy-phenoxy)-pyrimidine-2,4-diamine

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





SCHEME G

Step 1 N-(3,5-Dimethoxy-phenyl)-2,2,2-trifluoro-acetamide

To 3,5-dimethoxyaniline (20 g, 131 mmol) dissolved in anhydrous THF (90 mL) was added 4-(dimethylamino)pyridine (1.6 g, 13.1 mmol) and ethyl trifluoroacetate (47 mL, 392 mmol). After refluxing 48 hours, the cooled reaction mixture was concentrated and partitioned between ethyl acetate (300 mL) and 2N hydrochloric acid (100 mL). The ethyl acetate layer was washed with water (100 mL), dried using anhydrous sodium sulfate, and concentrated to yield N-(3,5-Dimethoxy-phenyl)-2,2,2-trifluoro-acetamide (31.8 g, 98%) as pale yellow solid.

Step 2 N-(4-Acetyl-3,5-dimethoxy-phenyl)-2,2,2-trifluoro-acetamide

To a solution of N-(3,5-Dimethoxy-phenyl)-2,2,2-trifluoro-acetamide (31.8 g, 130 mmol) in anhydrous dichloroethane (450 mL), cooled in an ice bath, was added a solution of tin (IV) chloride (29.9 mL, 260 mmol dissolved in 30 mL anhydrous dichloroethane) dropwise over 10 min. Acetyl chloride (9.1 mL, 130 mmol) was added slowly, maintaining the temperature of the reaction below 5°C. After stirring 3 hours at RT, the reaction was cooled in an ice bath. Water (300 mL) was added, maintaining the temperature of the reaction below 25°C, and the reaction was stirred at RT for 18 hours. The reaction mixture was extracted with DCM, and the organic layer was separated, washed wit water, dried over sodium sulfate, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography eluting with 20% to 30% hexanes/ethyl acetate to yield N-(4-acetyl-3,5-dimethoxy-phenyl)-2,2,2-trifluoro-acetamide (4.8 g, 13%) as a white solid.

Step 3 1-(4-Amino-2,6-dimethoxy-phenyl)-ethanone

To N-(4-Acetyl-3,5-dimethoxy-phenyl)-2,2,2-trifluoro-acetamide (4.3 g, 14.8 mmol) dissolved in methanol (90 mL) was added anhydrous potassium carbonate (4.67 g, 33.8 mmol). After refluxing for 18 hours, the reaction mixture was cooled and concentrated under reduced pressure. The concentrate was extracted with ethyl acetate and the organic layer was washed with brine, dried using anhydrous sodium sulfate, filtered and concentrated under reduced pressure to yield 1-(4-amino-2,6-dimethoxy-phenyl)-ethanone (2.5 g, 87%) as a pale yellow solid.

Step 4 2-(4-Amino-2,6-dimethoxy-phenyl)-propan-2-ol

To a solution of methyl magnesium bromide (3M in ether, 16.8 mL, 50.5 mmol) in anhydrous THF (20 mL), cooled in an ice bath, was added 1-(4-amino-2,6-dimethoxy-phenyl)-ethanone (2.19 g, 11.2 mmol- dissolved in 65 mL anhydrous THF), maintaining the reaction temperature below 10°C. After stirring 4 hours at RT, 10% ammonium chloride (20 mL) was added, maintaining the temperature of the reaction below 20°C (with the use of an ice bath) during the addition. The mixture was diluted with water and extracted with ethyl acetate. The ethyl acetate layer was washed with brine, dried using anhydrous sodium sulfate, filtered and concentrated to yield 2-(4-amino-2,6-dimethoxy-phenyl)-propan-2-ol (2.23 g, 94%) as a pale yellow solid.

Step 5 4-Isopropenyl-3,5-dimethoxy-phenylamine

A solution of 2-(4-amino-2,6-dimethoxy-phenyl)-propan-2-ol (2.2 g, 10.4 mmol) in chloroform (100 mL) was refluxed overnight. The cooled reaction mixture was concentrated under reduced pressure to yield 4-isopropenyl-3,5-dimethoxy-phenylamine, which was used directly in the following step.

Step 6 4-Isopropyl-3,5-dimethoxy-phenylamine

A solution of 4-isopropenyl-3,5-dimethoxy-phenylamine (taken directly from step 5) in ethanol (200 mL) was hydrogenated overnight at RT and 1 psig of H_2 gas using 10% palladium on charcoal catalyst (200 mg). The reaction was filtered through Celite and the pad was washed with additional ethanol. Concentration of the filtrate and purification by silica gel column chromatography eluting with 70/30 hexane/ ethyl acetate yielded 4-isopropyl-3,5-dimethoxy-phenylamine (1.4 g, 69%) as a pale pink solid, MS (M+H) = 196.

Step 7 5-Iodo-2-isopropyl-1,3-dimethoxy-benzene

To a suspension of 4-isopropyl-3,5-dimethoxy-phenylamine (1.28 g, 6.56 mmol) in 15% hydrochloric acid (20 mL) at 0°C was added sodium nitrite (0.54 g, 7.87 mmol dissolved in 4 mL water) dropwise. After stirring 20 min, potassium iodide (1.09 g, 6.56 mmol dissolved in 4 mL water) was added slowly at 0°C. After stirring at RT for 18 hours, the reaction mixture was partitioned between ether and 10% aqueous sodium bisulfite solution. The ether layer was washed with water, dried using anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue by silica gel column chromatography eluting with hexane yielded 5-iodo-2-isopropyl-1,3-dimethoxy-benzene (807 mg, 40%) as a white solid, MS (M+H) = 307.

Step 8 5-Iodo-2-isopropyl-3-methoxy-phenol

To a solution of 5-iodo-2-isopropyl-1,3-dimethoxy-benzene (805 mg, 2.63 mmol) in anhydrous DCM (26 mL) at 0°C was added boron tribromide (2.63 mL, 2.63 mmol) 1M in DCM), maintaining the temperature of the reaction at 0°C during the addition. After stirring at RT for 18 hours, water (10 mL) was slowly added to the reaction. After stirring 30 min, the DCM layer was collected, dried using anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue by silica gel column chromatography eluting with 90/10 hexane/ ethyl acetate yielded 5-iodo-2-isopropyl-3-methoxy-phenol (612 mg, 80%) as an oil, MS (M+H) = 293.

Step 9 5-(5-Iodo-2-isopropyl-3-methoxy-phenoxy)-pyrimidine-2,4-diamine

Following the procedure of Steps 2-4 of Example 6, 5-Iodo-2-isopropyl-3-methoxy-phenol was converted to 5-(5-Iodo-2-isopropyl-3-methoxy-phenoxy)-pyrimidine-2,4-diamine, MS (M+H) = 401.

Example 10: 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

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

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

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

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

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

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

Parenteral Formulation

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

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

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

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

Topical Formulation

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

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 carboxymethyl-cellulose, 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 11: $P2X_3/P2X_{2/3}$ FLIPR (Fluorometric Imaging Plate Reader) Assay

CHO-K1 cells were transfected with cloned rat $P2X_3$ or human $P2X_{2/3}$ receptor subunits and passaged in flasks. 18-24 hours before the FLIPR experiment, cells were released from their flasks, centrifuged, and resuspended in nutrient medium at 2.5×10^5 cells/ml. The cells were aliquoted into black-walled 96-well plates at a density of 50,000 cells/well and incubated overnight in 5% CO_2 at 37°C. On the day of the experiment, cells were washed in FLIPR buffer (calcium- and magnesium-free Hank's balanced salt solution, 10 mM HEPES, 2 mM $CaCl_2$, 2.5 mM probenecid; FB). Each well received 100 µl FB and

100 µl of the fluorescent dye Fluo-3 AM [2 µM final conc.]. After a 1 hour dye loading incubation at 37°C, the cells were washed 4 times with FB, and a final 75 µl/well FB was left in each well.

Test compounds (dissolved in DMSO at 10 mM and serially diluted with FB) or vehicle were added to each well (25 µl of a 4X solution) and allowed to equilibrate for 20 min at RT. The plates were then placed in the FLIPR and a baseline fluorescence measurement (excitation at 488 nm and emission at 510-570 nm) was obtained for 10 seconds before a 100 µl/well agonist or vehicle addition. The agonist was a 2X solution of α,β-meATP producing a final concentration of 1 µM ($P2X_3$) or 5 µM ($P2X_{2/3}$). Fluorescence was measured for an additional 2 min at 1 second intervals after agonist addition. A final addition of ionomycin (5 µM, final concentration) was made to each well of the FLIPR test plate to establish cell viability and maximum fluorescence of dye-bound cytosolic calcium. Peak fluorescence in response to the addition of α,β-meATP (in the absence and presence of test compounds) was measured and inhibition curves generated using nonlinear regression. PPADS, a standard P2X antagonist, was used as a positive control. Using the above procedure, compounds of the invention exhibited activity for the $P2X_3$ and $P2X_{2/3}$ receptor. The compound 4-(2,4-Diamino-pyrimidin-5-yloxy)-2-ethynyl-5-isopropyl-phenol, e.g., exhibited a pIC_{50} of approximately 8.24 for the $P2X_3$ receptor, and approximately 7.99 for the $P2X_{2/3}$ receptor, using the above assay.

Example 12: 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 13: 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 14: 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 15: 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.

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.

Example 16: Cold allodynia in Rats with a Chronic Constriction Injury of the Sciatic Nerve

The effects of compounds of this invention on cold allodynia are determined using the chronic constriction injury (CCI) model of neuropathic pain in rats, where cold allodynia is measured in a cold-water bath with a metal-plate floor and water at a depth of 1.5-2.0 cm and a temperature of 3-4°C (Gogas et al., Analgesia, 1997, 3, 1-8).
Specifically, CCI, rats are anesthetized; the trifurcation of the sciatic nerve is located and 4 ligatures (4-0, or 5-0 chromic gut) are placed circumferentially around the sciatic nerve proximal to the trifurcation. The rats are then allowed to recover from the surgery. On days 4-7 after surgery, the rats are initially assessed for cold -induced allodynia by individually placing the animals in the cold-water bath and recording the total lifts of the injured paw during a 1-min period of time: The injured paw is lifted out of the water. Paw lifts associated with locomotion or body repositioning are not recorded. Rats that displayed 5 lifts per min or more on day 4-7 following surgery are considered to exhibit cold allodynia and are used in subsequent studies. In the acute studies, vehicle, reference compound or compounds of this invention are administered subcutaneously (s.c.) 30 min before testing. The effects of repeated administration of the compounds of this invention on cold allodynia are determined 14, 20 or 38 h following the last oral dose of the following regimen: oral (p.o.) administration of vehicle, reference or a compound of this invention at ~12 h intervals (BID) for 7 days.

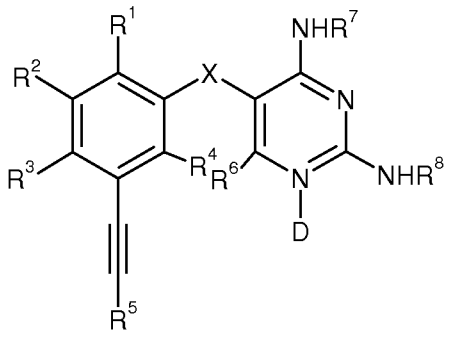
Example 17: Cancer Bone Pain in C3H/HeJ Mice

The effects of compounds of this invention on bone pain are determined between Day 7 to Day 18 following intramedullary injection of 2472 sarcoma cells into the distal femur of C3H/HeJ mice.
Specifically, NCTC 2472 tumor cells (American Type Culture Collection, ATCC), previously shown to form lytic lesions in bone after intramedullary injection, are grown and maintained according to ATCC recommendations. Approximately 10^5 cells are injected directly into the medullary cavity of the distal femur in anesthetized C3H/HeJ mice. Beginning on about Day 7, the mice are assessed for spontaneous nocifensive behaviors (flinching & guarding), palpation-evoked nocifensive behaviors (flinching & guarding), forced ambultory guarding and limb use. The effects of compounds of this invention are determined following a single acute (s.c.) administration on Day 7 – Day 15. In addition, the effects of repeated (BID) administration of compounds of this invention from Day 7 – Day 15 are determined within 1 hour of the first dose on Days 7, 9, 11, 13 and 15.

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.

Claims

1. A compound of formula I



(I)

or pharmaceutically acceptable salts thereof,

wherein

X is $-CH_2-$; -O-; $-S(O)_n-$ or $-NR^c-$, wherein n is from 0 to 2 and R^c is hydrogen or alkyl;

D is an optional oxygen;

R^1 is alkyl; alkenyl; cycloalkyl; cycloalkenyl; halo; haloalkyl or hydroxyalkyl;

R^2, R^3, and R^4 each independently is hydrogen; alkyl; alkenyl; amino; halo; amido; haloalkyl; alkoxy; hydroxy; haloalkoxy; nitro; amino; hydroxyalkyl; alkoxyalkyl; hydroxyalkoxy; alkynylalkoxy; alkylsulfonyl; arylsulfonyl; cyano; aryl; heteroaryl; heterocyclyl; heterocyclylalkoxy; aryloxy; heteroaryloxy; aralkyloxy; heteroaralkyloxy; optionally substituted phenoxy; $-C\equiv C-R^a$; $-(CH_2)_m-(Z)_n-(CO)-R^b$; $-(CH_2)_m-(Z)_n-SO_2-(NR^c)_n-R^b$, wherein

m and n each independently is 0 or 1,

Z is O or NR^c,

R^a is hydrogen; alkyl; aryl;aralkyl; heteroaryl; heteroaralkyl; hydroxyalkyl; alkoxyalkyl; alkylsulfonylalkyl; aminoalkyl; cyanoalkyl; alkylsilyl, cycloalkyl, cycloalkylalkyl; heterocyclyl; and heterocyclylalkyl;

R^b is hydrogen, alkyl, hydroxy, alkoxy, amino, hydroxyalkyl or alkoxyalkyl, and each R^c is independently hydrogen or alkyl;

or 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;

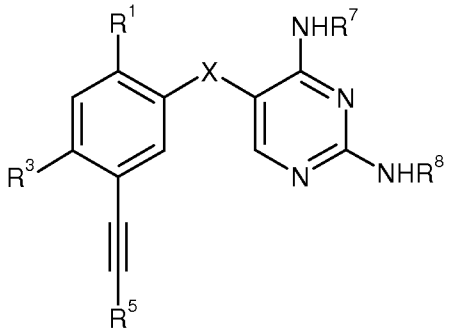
R^5 is hydrogen; alkyl; aryl; aralkyl; heteroaryl; heteroaralkyl; hydroxyalkyl; alkoxyalkyl; alkylsulfonylalkyl; aminoalkyl; cyanoalkyl; alkylsilyl, cycloalkyl, cycloalkylalkyl; heterocycl; or heterocyclylalkyl;

R^6 is hydrogen; alkyl; halo; haloalkyl; amino; or alkoxy; and

R^7 and R^8 each independently is hydrogen; alkyl; alkoxyalkyl; aminoalkyl; aminosulfonyl; cycloalkyl; cycloalkylalkyl; haloalkyl; haloalkoxy; hydroxyalky; alkoxyalkyl; alkylsulfonyl; alkylsulfonylalkyl; aminocarbonyloxyalkyl; hydroxycarbonylalkyl; hydroxyalkyloxycarbonylalkyl; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl.

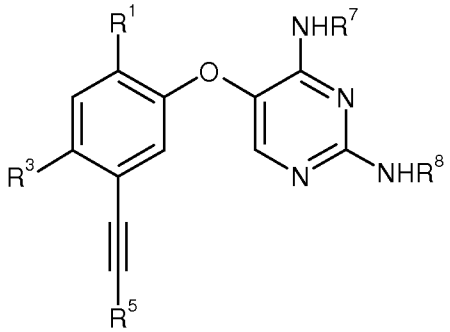
2. The compound of claim 1, wherein X is -O- or $-CH_2-$.

3. The compound of claim 1 wherein said compound is of the formula II



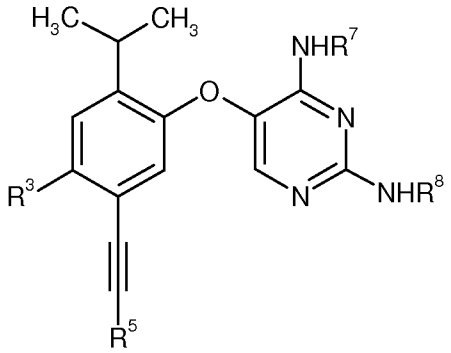
(II);

wherein X, R^1, R^3, R^5, R^7 and R^8 are as defined in claim 1; or
is of formula III



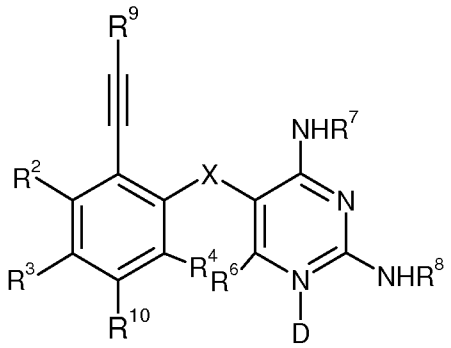
(III);

wherein R^1, R^3, R^5, R^7 and R^8 are as defined in claim 1; or
is of formula IV



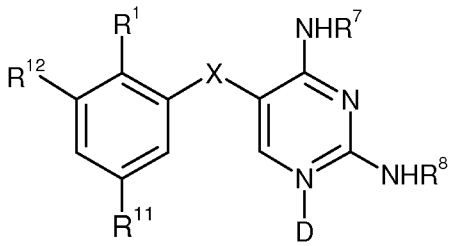
(IV);

wherein R^3, R^5, R^7 and R^8 are as defined in claim 1; or
is of the formulaVII:



(VII)

wherein X, D, R^2, R^3, R^4, R^6, R^7 and R^8 are as defined in claim 1; or
is of the formula (X)



(X)

wherein X, D, R^1, R^7, R^8, R^{11} and R^{12} are as defined in claim 1.

4. A pharmaceutical composition comprising a pharmaceutically acceptable excipient; and a compound of Claim 1.

5. A method for treating a $P2X_3$ or $P2X_{2/3}$ receptor antagonist-mediated urinary tract disease selected from reduced bladder capacity, frequent micturition, urge incontinence, stress incontinence, bladder hyperreactivity, benign prostatic hypertrophy, prostatitis, detrusor hyperreflexia, urinary frequency, nocturia, urinary urgency, overactive bladder, pelvic hypersensitivity, urethritis, prostatitits, pelvic pain syndrome, prostatodynia,

cystitis, or idiophatic bladder hypersensitivity, a pain condition, said pain condition selected from 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 injury, or pain associated with irritable bowel syndrome, respiratory disorder selected from chronic obstructive pulmonary disease, asthma, and bronchospasm, or gastrointestinal disorder selected from irritable bowel syndrome, inflammatory bowel disease, biliary colic, renal colic, diarrhea-dominant IBS, and pain associated with gastrointestinal distension, said method comprising administering to a subject in need thereof an effective amount of a compound of claim 1.

6. The use of a compound according to claim 1 for the preparation of a medicament for the treatment of a $P2X_3$ or $P2X_{2/3}$ receptor antagonist-mediated disease.

7. The invention as hereinbefore described.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/065524

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D239/48 C07D403/12 C07D407/12 C07D413/12 A61K31/506
A61P11/00 A61P13/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 02/094767 A2 (ABBOTT LAB [US]) 28 November 2002 (2002-11-28) abstract; claims 1,86-89	1,4-7
A	WO 01/44213 A (ASTRAZENECA AB [SE]; BAXTER ANDREW [GB]; KINDON NICHOLAS [GB]; PAIRAUD) 21 June 2001 (2001-06-21) abstract; claims 1,9-12	1,4-7
A	EP 1 310 493 A1 (PFIZER PROD INC [US]) 14 May 2003 (2003-05-14) claims 1,9-12	1,4-7

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 October 2006	07/11/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	van Laren, Martijn

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2006/065524

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 5 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2006/065524

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 02094767 A2	28-11-2002	AT 304523 T	15-09-2005
		CA 2447671 A1	28-11-2002
		DE 60206164 D1	20-10-2005
		DE 60206164 T2	22-06-2006
		DK 1392643 T3	30-01-2006
		EP 1392643 A2	03-03-2004
		ES 2249589 T3	01-04-2006
		JP 2005508288 T	31-03-2005
		MX PA03010586 A	02-04-2004
WO 0144213 A	21-06-2001	AT 250590 T	15-10-2003
		AU 775741 B2	12-08-2004
		AU 2244301 A	25-06-2001
		BR 0016396 A	20-08-2002
		CA 2392894 A1	21-06-2001
		CN 1434811 A	06-08-2003
		DE 60005560 D1	30-10-2003
		DE 60005560 T2	15-07-2004
		EP 1242396 A1	25-09-2002
		JP 2003516978 T	20-05-2003
		MX PA02005788 A	18-09-2002
		NO 20022857 A	01-08-2002
		US 2003040513 A1	27-02-2003
		ZA 200204429 A	03-09-2003
EP 1310493 A1	14-05-2003	AT 302196 T	15-09-2005
		BR 0204588 A	16-09-2003
		CA 2411544 A1	12-05-2003
		DE 60205564 D1	22-09-2005
		DE 60205564 T2	01-06-2006
		ES 2244733 T3	16-12-2005
		WO 03042190 A1	22-05-2003
		JP 2003183263 A	03-07-2003
		MX PA02009783 A	21-05-2003