Diaminopyrimidines as P2X3 and P2X2/3 Antagonists

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 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. 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 $P2X_{2/3}$, $P2X_{4/6}$, $P2X_{1/5}$. The structure and chromosomal mapping of mouse genomic $P2X_3$ receptor subunit has also been described. 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.

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. ATP released in this manner may serve a role in conveying information to sensory neurons located in subepithelial components, e.g., suburothelial lamina propria. The P2X receptors have been studied in a number of neurons, including sensory, sympathetic, parasympathetic, mesenteric, and central neurons. These studies indicate that purinergic receptors play a role in afferent

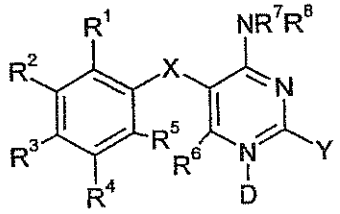
neurotransmission from the bladder, and that modulators of P2X receptors are potentially useful in the treatment of bladder disorders and other genitourinary diseases or conditions.

Recent evidence also suggests a role of endogenous ATP and purinergic receptors in nociceptive responses in mice. 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. $P2X_3$ receptors have been identified on nociceptive neurons in the tooth pulp. 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. P2X antagonists have been shown to be analgesic in animal models. 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.

Many diaminopyrimidine compounds, such as "ormetoprim" (US 2,658,897) and "trimetoprim" (US 2,909,522), have previously been made and identified as antibacterial agents. However, no diaminopyrimidines have heretofore been identified as modulators of P2X receptors.

The invention provides a compound of formula (I)



(I)

or a pharmaceutically acceptable salts thereof,

wherein:

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

Y is hydrogen; or $-NR^dR^e$ wherein one of R^d and R^e is hydrogen, and the other is hydrogen; alkyl; cycloalkyl; cycloalkylalkyl; haloalkyl; haloalkoxy; hydroxyalky; alkoxyalkyl; acetyl; alkylsulfonyl; alkylsulfonylalkyl; aminocarbonyloxyalkyl;

hydroxycarbonylalkyl; hydroxyalkyloxycarbonylalkyl; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl;

D is an optional oxygen;

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

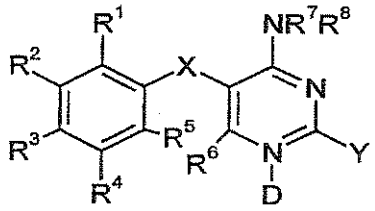
R^2, R^3, R^4 and R^5 each independently is hydrogen; alkyl; alkenyl; amino; halo; amido; haloalkyl; alkoxy; hydroxy; haloalkoxy; nitro; amino; hydroxyalkyl; alkoxyalkyl; hydroxyalkoxy; alkynylalkoxy; alkylsulfonyl; arylsulfonyl; cyano; aryl; heteroaryl; heterocyclyl; heterocyclylalkoxy; aryloxy; heteroaryloxy; aralkyloxy; heteroaralkyloxy; optionally substituted phenoxy; $-(CH_2)_m-(Z)_n-(CO)-R^f$ or $-(CH_2)_m-(Z)_n-SO_2-(NR^g)_n-R^f$ where m and n each independently is 0 or 1, Z is O or NR^g, R^f is hydrogen, alkyl, hydroxy, alkoxy, amino, hydroxyalkyl or alkoxyalkyl, and each R^g is independently hydrogen or alkyl; or R^3 and R^4 may together form an alkylene dioxy; or R^3 and R^4 together with the atoms to which they are attached may form a five or six-membered ring that optionally includes one or two heteroatoms selected from O, S and N; or R^2 and R^3 may together form an alkylene dioxy; 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

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

provided that when X is $-CH_2-$ and R^7, R^8, R^d and R^e are hydrogen, R^1 is isopropyl, isopropenyl, cyclopropyl or iodo.

In a first aspect, there is a compound of formula (I)



(I)

or a pharmaceutically acceptable salt thereof,

wherein:

X is -O-;

Y is hydrogen; or $-NR^dR^e$ wherein one of R^d and R^e is hydrogen, and the other is hydrogen; alkyl; cycloalkyl; cycloalkylalkyl; haloalkyl; haloalkoxy; hydroxyalkyl; alkoxyalkyl; acetyl; alkylsulfonyl; alkylsulfonylalkyl; aminocarbonyloxyalkyl; hydroxy-carbonylalkyl; hydroxyalkyloxycarbonylalkyl; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl;

D is an optional oxygen;

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

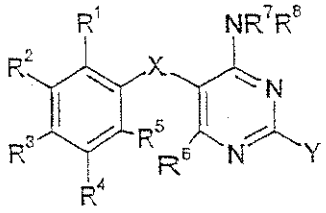
R^2, R^4 and R^5 each independently is hydrogen; alkyl; alkenyl; amino; halo; amido; haloalkyl; alkoxy; hydroxy; haloalkoxy, nitro; amino; hydroxyalkyl; alkoxyalkyl; hydroxyalkoxy; alkynylalkoxy; alkylsulfonyl; arylsulfonyl; cyano; aryl; heteroaryl; heterocyclyl; heterocyclylalkoxy, aryloxy; heteroaryloxy; aralkyloxy; heteroaralkyloxy; optionally substituted phenoxy, $-(CH_2)_m-(Z)_n-(CO)-R^f$ or $-(CH_2)_m-(Z)_n-SO_2-(NR^g)_n-R^f$ where m and n each independently is 0 or 1, Z is O or NR^g, R^f is hydrogen, alkyl, hydroxy, alkoxy, amino, hydroxyalkyl or alkoxyalkyl, and each R^g is independently hydrogen or alkyl;

R^3 is methoxy;

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

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

In another embodiment the disclosure provides a method for treating a disease mediated by a $P2X_3$ receptor antagonist, a $P2X_{2/3}$ receptor antagonist, or both, said method comprising administering to a subject in need thereof an effective amount of a compound of formula (I*):



(I*)

or a pharmaceutically acceptable salt, solvate or prodrug thereof,

wherein:

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

Y is hydrogen; or $-NR^dR^e$ wherein one of R^d and R^e is hydrogen, and the other is hydrogen; alkyl; cycloalkyl; cycloalkylalkyl; haloalkyl; haloalkoxy; hydroxyalky; alkoxyalkyl; acetyl; alkylsulfonyl; alkylsulfonylalkyl; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl;

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

R^2, R^3, R^4 and R^5 each independently is hydrogen; alkyl; amino; amido; haloalkyl; alkoxy; alkylsulfonyl; arylsulfonyl; sulfonamido; cyano; acetyl; heteroaryl; carboxylic acid; carboxylic amide; urea; carbamate; acetamido; or optionally substituted phenoxy; or R^3 and R^4 may together form an alkylene dioxy; or R^3 and R^4 together with the atoms to which they are attached may form a five or six-membered ring that includes one or two heteroatoms selected from O, S and N; or or R^2 and R^3 may together form an alkylene dioxy; or R^2 and R^3 together with the atoms to which they are attached may form a five or six-membered ring that includes one or two heteroatoms selected from O, S and N;

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

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

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

In a second aspect, there is provided a pharmaceutical composition comprising a pharmaceutically acceptable excipient; and a compound as defined above.

In a third aspect, there is provided use of a compound as defined above for the manufacture of a medicament for the treatment of a disease mediated by a $P2X_3$ or $P2X_{2/3}$ receptor antagonist.

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.

"Antagonist" refers to a compound that diminishes or prevents the action 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.

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

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

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

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

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

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

"Aminoalkoxy" means a group -OR-R' wherein R' is amino and R is alkylene as defined herein. "Alkylsulfonylamido" means a moiety of the formula -NR'SO_2-R wherein R is alkyl and R' is hydrogen or alkyl.

"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.

"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.

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, tetrahydroisoquinolinyl, 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.

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

"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.

The terms "pro-drug" and "prodrug", which may be used interchangeably herein, refer to any compound which releases an active parent drug according to formula I *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of a compound of formula I are prepared by modifying one or more functional group(s) present in the compound of formula I in such a way that the modification(s) may be cleaved *in vivo* to release the parent compound. Prodrugs include compounds of formula I wherein a hydroxy, amino, or sulfhydryl group in a compound of Formula I is bonded to any group that may be cleaved *in vivo* to regenerate the free hydroxyl, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, esters (e.g., acetate, formate, and benzoate derivatives), carbamates (e.g., N,N-dimethylaminocarbonyl) of hydroxy functional groups in compounds of formula I, N-acyl derivatives (e.g. N-acetyl) N-Mannich bases, Schiff bases and enaminones of amino functional groups, oximes, acetals, ketals and enol esters of ketone and aldehyde functional groups in compounds of Formula I, and the like, see Bundegaard,"Design of Prodrugs" p1-92, Elsevier, New York-Oxford (1985), and the like.

"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.

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

The terms "those defined above" and "those defined herein" when referring to a variable incorporates by reference the broad definition of the variable as well as preferred, more preferred and most preferred definitions, if any.

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

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

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

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

In certain embodiments of formula (I), R^5 and R^6 are hydrogen.

In certain embodiments of formula (I), R^2 is hydrogen.

In certain embodiments of formula (I), X is $-CH_2-$ or -O-. Preferably X is O.

In certain embodiments of formula (I), D is absent.

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

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

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

In many embodiments of formula (I), Y is $-NR^dR^e$.

In certain embodiments formula (I), Y is $-NR^dR^e$ and one of R^d and R^e is hydrogen, and the other is: alkyl, cycloalkyl; cycloalkylalkyl; haloalkyl; hydroxyalky; alkoxyalkyl; alkylsulfonylalkyl; acetyl; alkylsulfonyl; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl.

In certain embodiments of formula (I), Y is $-NR^dR^e$ and one of R^d and R^e is hydrogen and the other is alkyl, hydroxyalkyl or haloalkyl.

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

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

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

In certain embodiments of formula (I), R^7, R^8, R^d and R^e are hydrogen.

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

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

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

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

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

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

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

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

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

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

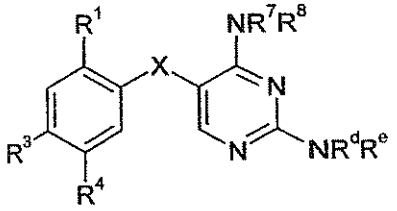
In another preferred embodiment of formula (I), X is -O- or $-CH_2-$, R^1 is isopropyl or iodo, R^2 is hydrogen, R^3 is methoxy, hydroxy, chloro, bromo or iodo, R^4 is methoxy, chloro, bromo or iodo, and R^5 and R^6 are hydrogen.

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

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

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

The compounds of the invention in many embodiments may be of the formula (II)



(II)

wherein:

X is: $-CH_2-$; or -O-;

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

R^3 and R^4 each independently is: hydrogen; alkyl; alkenyl; amino; halo; amido; haloalkyl; alkoxy; hydroxy; haloalkoxy; nitro; hydroxyalkyl; alkoxyalkyl; hydroxyalkoxy; alkynyl-alkoxy; alkylsulfonyl; arylsulfonyl; cyano; aryl; heteroaryl; heterocyclyl; heterocyclyl-alkoxy; aryloxy; heteroaryloxy; aralkyloxy; heteroaralkyloxy; optionally substituted phenoxy; $-(CH_2)_m-(Z)_n-(CO)-R^f$ or $-(CH_2)_m-(Z)_n-SO_2-(NR^g)_n-R^f$ where m and n each independently is 0 or 1, Z is O or NR^g, R^f is hydrogen, alkyl, hydroxy, alkoxy, amino, hydroxyalkyl or alkoxyalkyl, and each R^g is independently hydrogen or alkyl; or R^3 and R^4 may together form an alkylene dioxy; or R^3 and R^4 together with the atoms to which they are attached may form a five or six-membered ring that optionally includes one or two heteroatoms selected from O, S and N;

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

one of R^d and R^e is hydrogen, and the other is: hydrogen; alkyl; cycloalkyl; cycloalkylalkyl; haloalkyl; haloalkoxy; hydroxyalky; alkoxyalkyl; acetyl; alkylsulfonyl; alkylsulfonyl-alkyl; aminocarbonyloxyalkyl; hydroxycarbonylalkyl; hydroxyalkyloxycarbonylalkyl;

aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl.

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

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

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

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

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

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

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

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

In certain embodiments of formula (II), R^7, R^8, R^d and R^e are hydrogen.

In certain embodiments of formula (II), R^4 is heteroaryl. The heteroaryl may be, in certain embodiments, tetrazolyl, pyrazolyl, oxazolyl, imidazolyl, thiazolyl, thiophenyl, triazolyl, furanyl, isoxazolyl, oxadiazolyl, benzothiophenyl, pyridinyl, or pyrrolyl. More specifically, the heteroaryl may be tetrazol-5-yl, pyrazol-1-yl, 3-methylpyrazol-1-yl, oxazol-2-yl, ox-

azol-5-yl, imidazol-2-yl, thiazol-2-yl, thiazol-4-yl, thiophen-3-yl, 5-chloro-thiophen-2-yl, 1-methyl-imidazol-2-yl, imidazol-1-yl, pyrazol-3-yl, 2-methyl-thiazol-4-yl, furan-2-yl, 3,5-dimethyl-pyrazol-1-yl, 4,5-dihydrooxazol-2-yl, isoxazol-5-yl, [1,2,4]-oxadiazol-3-yl, benzo[b]thiophen-3-yl, oxazol-4-yl, furan-3-yl, 4-methyl-thiophen-2-yl, thiazol-5-yl, tetrazol-1-yl, [1,2,4]triazol-1-yl, 2-methyl-thiazol-5-yl, 1-methyl-pyrazol-4-yl, 2-thiolyl-imidazol-1-yl, pyridin-2-yl, or 2,5-dimethyl-pyrrol-1-yl).

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

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

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

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

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

In another preferred embodiment of formula (II), X is -O-, R^1 is alkyl, alkenyl, cycloalkyl, or halo, R^3 is alkoxy, hydroxy or halo, R^4 is heteroaryl selected from tetrazolyl, pyrazolyl, oxazolyl, imidazolyl, thiazolyl, thiophenyl, triazolyl, furanyl, isoxazolyl, oxadiazolyl, benzo-

thiophenyl, pyridinyl and pyrrolyl, R^7 and R^8 are hydrogen, and one of R^a and R^b is hydrogen and the other is hydrogen, alkyl, acetyl, hydroxyalkyl or haloalkyl.

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

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

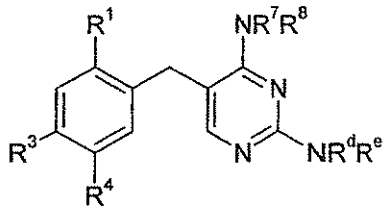
In another preferred embodiment of formula (II), X is -O- or $-CH_2-$, R^1 is isopropyl or iodo, R^3 is methoxy, hydroxy, chloro, bromo or iodo, and R^4 is methoxy, chloro, bromo or iodo.

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

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

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

The compounds of the invention in certain embodiments may be of the formula (III)



(III)

wherein:

R^1 is isopropyl; isopropenyl; cyclopropyl; or iodo;

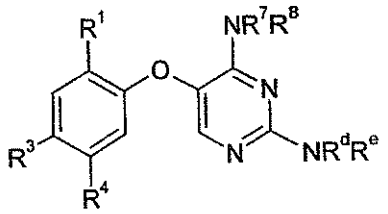
R^3 and R^4 each independently is: hydrogen; alkyl; alkenyl; amino; halo; amido; haloalkyl; alkoxy; hydroxy; haloalkoxy; nitro; hydroxyalkyl; alkoxyalkyl; hydroxyalkoxy; alkynylalkoxy; alkylsulfonyl; arylsulfonyl; cyano; aryl; heteroaryl; heterocyclyl; heterocyclyl-

alkoxy; aryloxy; heteroaryloxy; aralkyloxy; heteroaralkyloxy; optionally substituted phenoxy; $-(CH_2)_m-(Z)_n-(CO)-R^f$ or $-(CH_2)_m-(Z)_n-SO_2-(NR^g)_n-R^f$ where m and n each independently is 0 or 1, Z is O or NR^g, R^f is hydrogen, alkyl, hydroxy, alkoxy, amino, hydroxyalkyl or alkoxyalkyl, and each R^g is independently hydrogen or alkyl; or R^3 and R^4 may together form an alkylene dioxy; or R^3 and R^4 together with the atoms to which they are attached may form a five or six-membered ring that optionally includes one or two heteroatoms selected from O, S and N;

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

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

In other embodiments the subject compounds may be of the formula (IV)



(IV)

wherein:

R^1 is: alkyl; alkenyl; cycloalkyl; or cycloalkenyl;

R^3 and R^4 each independently is: hydrogen; alkyl; alkenyl; amino; halo; amido; haloalkyl; alkoxy; hydroxy; haloalkoxy; nitro; hydroxyalkyl; alkoxyalkyl; hydroxyalkoxy; alkynylalkoxy; alkylsulfonyl; arylsulfonyl; cyano; aryl; heteroaryl; heterocyclyl; heterocyclylalkoxy; aryloxy; heteroaryloxy; aralkyloxy; heteroaralkyloxy; optionally substituted phenoxy; $-(CH_2)_m-(Z)_n-(CO)-R^f$ or $-(CH_2)_m-(Z)_n-SO_2-(NR^g)_n-R^f$ where m and n each independently is 0 or 1, Z is O or NR^g, R^f is hydrogen, alkyl, hydroxy, alkoxy, amino, hydroxyalkyl or alkoxyalkyl, and each R^g is independently hydrogen or alkyl; or R^3 and R^4 may together form an alkylene dioxy; or R^3 and R^4 together with the atoms to which they are attached may form a five or six-membered ring that optionally includes one or two heteroatoms selected from O, S and N;

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

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

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

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

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

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

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

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

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

In certain embodiments of formula (III) or formula (IV), R^4 is halo, alkoxy, alkylsulfonyl or heteroaryl. Preferably R^4 is methoxy, iodo, methanesulfonyl or heteroaryl. More prefer-

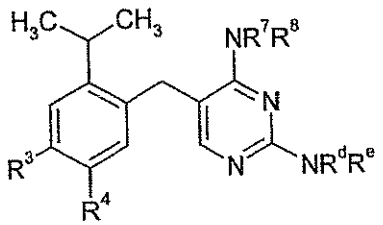
ably R^4 is methoxy, bromo, chloro or iodo. In specific embodiments R^4 may be methoxy, while in other embodimets R^4 may be iodo.

In certain embodiments of formula (III) or formula (IV), R^7, R^8, R^d and R^e are hydrogen.

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

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

The compounds of the invention in certain embodiments may be of the formula (V)



(V)

wherein:

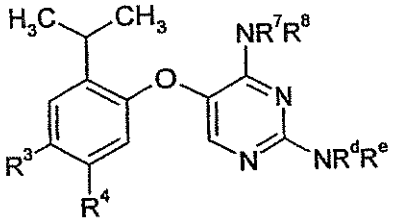
R^3 and R^4 each independently is: hydrogen; alkyl; alkenyl; amino; halo; amido; haloalkyl; alkoxy; hydroxy; haloalkoxy; nitro; hydroxyalkyl; alkoxyalkyl; hydroxyalkoxy; alkynylalkoxy; alkylsulfonyl; arylsulfonyl; cyano; aryl; heteroaryl; heterocyclyl; heterocyclylalkoxy; aryloxy; heteroaryloxy; aralkyloxy; heteroaralkyloxy; optionally substituted

phenoxy; $-(CH_2)_m-(Z)_n-(CO)-R^f$ or $-(CH_2)_m-(Z)_n-SO_2-(NR^g)_n-R^f$ where m and n each independently is 0 or 1, Z is O or NR^g, R^f is hydrogen, alkyl, hydroxy, alkoxy, amino, hydroxyalkyl or alkoxyalkyl, and each R^g is independently hydrogen or alkyl; or R^3 and R^4 may together form an alkylene dioxy; or R^3 and R^4 together with the atoms to which they are attached may form a five or six-membered ring that optionally includes one or two heteroatoms selected from O, S and N;

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

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

In other embodiments the subject compounds may be of the formula (VI)



(VI)

wherein:

R^3 and R^4 each independently is: hydrogen; alkyl; alkenyl; amino; halo; amido; haloalkyl; alkoxy; hydroxy; haloalkoxy; nitro; hydroxyalkyl; alkoxyalkyl; hydroxyalkoxy; alkynylalkoxy; alkylsulfonyl; arylsulfonyl; cyano; aryl; heteroaryl; heterocyclyl; heterocyclylalkoxy; aryloxy; heteroaryloxy; aralkyloxy; heteroaralkyloxy; optionally substituted phenoxy; $-(CH_2)_m-(Z)_n-(CO)-R^f$ or $-(CH_2)_m-(Z)_n-SO_2-(NR^g)_n-R^f$ where m and n each independently is 0 or 1, Z is O or NR^g, R^f is hydrogen, alkyl, hydroxy, alkoxy, amino, hydroxyalkyl or alkoxyalkyl, and each R^g is independently hydrogen or alkyl; or R^3 and R^4 may together form an alkylene dioxy; or R^3 and R^4 together with the atoms to which they are attached may form a five or six-membered ring that optionally includes one or two heteroatoms selected from O, S and N;

one of R^7 and R^8 is hydrogen, and the other is: hydrogen; alkyl; cycloalkyl; cycloalkylalkyl; haloalkyl; haloalkoxy; hydroxyalky; alkoxyalkyl; acetyl; alkylsulfonyl; alkylsulfonyl-

alkyl; aminocarbonyloxyalkyl; hydroxycarbonylalkyl; hydroxyalkyloxycarbonylalkyl; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroarylsulfonyl; heterocyclyl; or heterocyclylalkyl; and

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

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

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

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

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

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

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

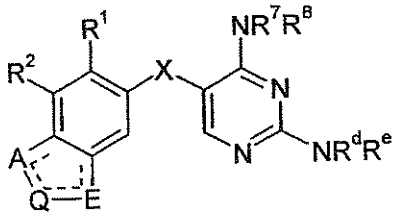
In certain embodiments of formula (V) or formula (V), R^4 is halo, alkoxy, alkylsulfonyl or heteroaryl. Preferably R^4 is methoxy, iodo, methanesulfonyl or heteroaryl. More preferably R^4 is methoxy, bromo, chloro or iodo. In specific embodiments R^4 may be methoxy, while in other embodimets R^4 may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

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

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

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

In certain embodiments, the compounds of the invention may be of the formula (VII)



(VII)

wherein:

X is $-CH_2-$; or -O-;

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

R^2 is hydrogen; alkyl; alkenyl; amino; halo; amido; haloalkyl; alkoxy; hydroxy; haloalkoxy; nitro; hydroxyalkyl; alkoxyalkyl; hydroxyalkoxy; alkynylalkoxy; alkylsulfonyl; arylsulfonyl; cyano; aryl; heteroaryl; heterocyclyl; heterocyclylalkoxy; aryloxy; heteroaryloxy; aralkyloxy; heteroaralkyloxy; optionally substituted phenoxy; or $-(CH_2)_m-(Z)_n-(CO)-R^f$ or $-(CH_2)_m-(Z)_n-SO_2-(NR^g)_n-R^f$ where m and n each independently is 0 or 1, Z is O or NR^g, R^f is hydrogen, alkyl, hydroxy, alkoxy, amino, hydroxyalkyl or alkoxyalkyl, and each R^g is independently hydrogen or alkyl;

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

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

Q is CR^9, one of A and E is O, S or NR^{10} and the other is CR^9 or N; or

Q is N, one of A and E is NR^{10} and the other is CR^9;

each R^9 is independently hydrogen, alkyl, halo or alkoxy; and

R^{10} is hydrogen, alkyl, hydroxyalkyl, alkoxyalkyl, $-(CH_2)_m-(Z)_n-(CO)-R^f$, or $-(CH_2)_m-(Z)_n-SO_2-(NR^8)_n-R^f$.

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

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

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

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

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

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

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

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

In certain embodiments of formula (VII), E is O, and A and Q are CR^9.

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

In certain embodiments of formula (VII), A is O, and E and Q are CR^9.

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

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

In certain embodiments of formula (VII), R^2 is hydrogen.

In certain embodiments of formula (VII), X is $-CH_2-$ or -O-. Preferably X is O.

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

In certain embodiments formula (VII), one of R^7 and R^8 is hydrogen, and the other is: alkyl, cycloalkyl; cycloalkylalkyl; haloalkyl; hydroxyalky; alkoxyalkyl; alkylsulfonylalkyl; acetyl; alkylsulfonyl; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroaryl-sulfonyl; heterocyclyl; or heterocyclylalkyl.

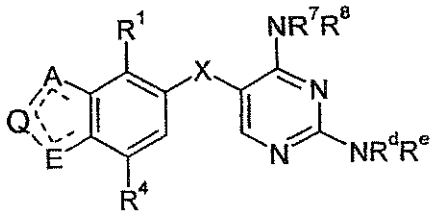
In certain embodiments of formula (VII), one of R^7 and R^8 is hydrogen and the other is alkyl, hydroxyalkyl or haloalkyl.

In certain embodiments formula (VII), one of R^d and R^e is hydrogen, and the other is: alkyl, cycloalkyl; cycloalkylalkyl; haloalkyl; hydroxyalky; alkoxyalkyl; alkylsulfonylalkyl; acetyl; alkylsulfonyl; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroaryl-sulfonyl; heterocyclyl; or heterocyclylalkyl.

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

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

In other embodiments of the invention, the compounds may be of the formula (VIII)



(VIII)

wherein:

X is: $-CH_2-$; or -O-;

R^1 is: alkyl; alkenyl; cycloalkyl; or cycloalkenyl; or halo;

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

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

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

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

Q is CR^9, one of A and E is O, S or NR^{10} and the other is CR^9 or N; or

Q is N, one of A and E is NR^{10} and the other is CR^9;

each R^9 is independently hydrogen, alkyl, halo or alkoxy; and

R^{10} is hydrogen, alkyl, hydroxyalkyl, alkoxyalkyl, $-(CH_2)_m-(Z)_n-(CO)-R^f$, or $-(CH_2)_m-(Z)_n-SO_2-(NR^g)_n-R^f$.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

In certain embodiments formula (VIII), one of R^7 and R^8 is hydrogen, and the other is: alkyl, cycloalkyl; cycloalkylalkyl; haloalkyl; hydroxyalky; alkoxyalkyl; alkylsulfonylalkyl; acetyl; alkylsulfonyl; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroaryl-sulfonyl; heterocyclyl; or heterocyclylalkyl.

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

In certain embodiments formula (VIII), one of R^d and R^e is hydrogen, and the other is: alkyl, cycloalkyl; cycloalkylalkyl; haloalkyl; hydroxyalky; alkoxyalkyl; alkylsulfonylalkyl; acetyl; alkylsulfonyl; aryl; aralkyl; arylsulfonyl; heteroaryl; heteroarylalkyl; heteroaryl-sulfonyl; heterocyclyl; or heterocyclylalkyl.

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

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

In certain embodiments of formula (VIII), R^4 is halo, alkoxy, haloalkoxy or alkylsulfonyl.

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

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

azol-5-yl, tetrazol-1-yl, [1,2,4]triazol-1-yl, 2-methyl-thiazol-5-yl, 1-methyl-pyrazol-4-yl, 2-thiolyl-imidazol-1-yl, pyridin-2-yl, or 2,5-dimethyl-pyrrol-1-yl).

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

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

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.

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

Table 1:

#	Name
1	N*2*-Isopropyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-N*4*-methyl-pyrimidine-2,4-diamine
2	5-(2-Isopropyl-4,5-dimethoxy-phenoxy)-pyrimidine-2,4-diamine
3	5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N*4*-isoxazol-5-ylmethyl-pyrimidine-2,4-

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

28	N*2*-tert-Butyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine
29	N*2*-Isobutyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine
30	5-(5-Chloro-2-isopropyl-4-methoxy-benzyl)-N*2*-cyclopropyl-pyrimidine-2,4-diamine
31	5-(2-Isopropyl-4-methoxy-5-phenoxy-benzyl)-pyrimidine-2,4-diamine
32	N*4*-Isobutyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine
33	N*4*-Ethyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine
34	N*4*-Benzyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine
35	5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N*4*-(2,2,2-trifluoro-ethyl)-pyrimidine-2,4-diamine
36	5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N*2*-(4-methoxy-phenyl)-pyrimidine-2,4-diamine
37	N*2*-Isopropyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-N*4*-phenyl-pyrimidine-2,4-diamine
38	N*4*-Ethyl-N*2*-isopropyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine
39	5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N*4*-(1-methyl-piperidin-4-yl)-pyrimidine-2,4-diamine
40	5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N*2*-(2-methoxy-phenyl)-pyrimidine-2,4-diamine
41	5-(4,5-Dichloro-2-isopropyl-benzyl)-pyrimidine-2,4-diamine
42	5-(5-Chloro-2-isopropyl-4-methoxy-benzyl)-N*2*-ethyl-pyrimidine-2,4-diamine
43	5-(2-Isopropyl-4-methoxy-5-methyl-benzyl)-pyrimidine-2,4-diamine
44	5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N*2*-pyrimidin-2-yl-pyrimidine-2,4-diamine
45	5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N*2*-(2-methoxy-ethyl)-pyrimidine-2,4-diamine
46	N*4*-Benzyl-N*2*-isopropyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine
47	1-(4-{2-[4-Amino-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidin-2-ylamino]-propyl}-piperazin-1-yl)-ethanone
48	5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N*4*-(tetrahydro-pyran-4-yl)-pyrimidine-2,4-diamine
49	N*4*-Cyclopropyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine
50	5-(5-Ethoxy-2-isopropyl-4-methoxy-benzyl)-pyrimidine-2,4-diamine
51	N*2*-(2,4-Dimethoxy-phenyl)-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-

	2,4-diamine
52	N*2*-Cyclobutyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine
53	5-(4,5-Dimethoxy-2-methyl-benzyl)-pyrimidine-2,4-diamine
54	N*2*-(2-Chloro-phenyl)-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine
55	5-(4-Chloro-2-isopropyl-5-methoxy-benzyl)-pyrimidine-2,4-diamine
56	5-(5-Bromo-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine
57	5-(5-Chloro-2-isopropyl-4-methoxy-benzyl)-N*2*-(3-methoxy-phenyl)-pyrimidine-2,4-diamine
58	5-(5-Chloro-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine
59	5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N*2*,N*4*-diphenyl-pyrimidine-2,4-diamine
60	5-(6-Isopropyl-1,3-dimethyl-1H-indol-5-yloxy)-pyrimidine-2,4-diamine
61	5-(5-Chloro-2-isopropyl-4-methoxy-benzyl)-N*2*-isobutyl-pyrimidine-2,4-diamine
62	5-(6-Isopropyl-1-methyl-1H-indol-5-yloxy)-pyrimidine-2,4-diamine
63	5-(5-Chloro-2-isopropyl-4-methoxy-benzyl)-N*2*-phenyl-pyrimidine-2,4-diamine
64	5-(2-Isopropyl-4-methoxy-5-methyl-phenoxy)-pyrimidine-2,4-diamine
65	5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N*2*-methyl-pyrimidine-2,4-diamine
66	5-(2-Isopropyl-5-methyl-phenoxy)-pyrimidine-2,4-diamine
67	5-(5-Chloro-2-isopropyl-4-methoxy-benzyl)-N*2*-methyl-pyrimidine-2,4-diamine
68	N*2*-Benzyl-5-(5-chloro-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine
69	2-[2-Isopropylamino-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidin-4-ylamino]-ethanol
70	5-(5-Chloro-2-isopropyl-4-methoxy-phenoxy)-N*2*-(tetrahydro-pyran-4-yl)-pyrimidine-2,4-diamine
71	N*2*-(4-Chloro-phenyl)-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine
72	5-(2-Isopropyl-phenoxy)-pyrimidine-2,4-diamine
73	5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N*4*-methyl-pyrimidine-2,4-diamine
74	5-(5-Chloro-2-isopropyl-4-methoxy-phenoxy)-N*2*-isopropyl-pyrimidine-2,4-diamine
75	5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N*4*-(2-methoxy-ethyl)-pyrimidine-2,4-diamine
76	N*2*-Isopropyl-5-(2-isopropyl-4,5-dimethoxy-phenoxy)-pyrimidine-2,4-diamine

77	5-(2-Ethyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine
78	5-(2-Isopropyl-4,5-dimethoxy-phenoxy)-N*2*-phenyl-pyrimidine-2,4-diamine
79	N*2*-tert-Butyl-5-(5-chloro-2-isopropyl-4-methoxy-benzyl)-pyrimidine-2,4-diamine
80	N*2*-Benzyl-5-(2-isopropyl-4,5-dimethoxy-phenoxy)-pyrimidine-2,4-diamine
81	5-(2-Cyclopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine
82	N-[4-Amino-5-(2-isopropyl-4,5-dimethoxy-phenoxy)-pyrimidin-2-yl]-acetamide
83	N*2*-Benzyl-5-(5-chloro-2-isopropyl-4-methoxy-benzyl)-pyrimidine-2,4-diamine
84	5-(2-Isopropyl-4,5-dimethoxy-phenoxy)-N*2*-(2,2,2-trifluoro-ethyl)-pyrimidine-2,4-diamine
85	5-(2-Isopropyl-4,5-dimethoxy-phenoxy)-N*2*-(2-methoxy-ethyl)-pyrimidine-2,4-diamine
86	5-(2-Isopropyl-4,5-dimethoxy-benzyl)-pyrimidin-4-ylamine
87	3-[4-Amino-5-(5-chloro-2-isopropyl-4-methoxy-phenoxy)-pyrimidin-2-ylamino]-pentane-1,5-diol
88	5-(5-Chloro-2-isopropyl-4-methoxy-benzyl)-N*2*-cyclohexyl-pyrimidine-2,4-diamine
89	2-[4-Amino-5-(5-chloro-2-isopropyl-4-methoxy-phenoxy)-pyrimidin-2-ylamino]-butan-1-ol
90	5-(2-Cyclobutyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine
91	1-[5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-ethanone
92	(2,4-Diamino-pyrimidin-5-yl)-(2-isopropyl-4,5-dimethoxy-phenyl)-methanone
93	5-[5-(1H-Imidazol-2-yl)-2-isopropyl-4-methoxy-phenoxy]-pyrimidine-2,4-diamine
94	(2,4-Diamino-pyrimidin-5-yl)-(2-isopropyl-4,5-dimethoxy-phenyl)-methanol
95	5-(2-Bromo-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine
96	5-[5-Chloro-2-(2-fluoro-1-methyl-ethyl)-4-methoxy-phenoxy]-pyrimidine-2,4-diamine
97	(5-Chloro-2-isopropyl-4-methoxy-phenyl)-(2,4-diamino-pyrimidin-5-yl)-methanol
98	2-[4-Amino-5-(5-chloro-2-ethyl-4-methoxy-phenoxy)-pyrimidin-2-ylamino]-butan-1-ol
99	5-(5-Chloro-2-isopropyl-4-methoxy-phenoxy)-N*2*-(3-ethanesulfonyl-1-methyl-propyl)-pyrimidine-2,4-diamine
100	5-(5-Bromo-2-ethyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine
101	5-(5-Chloro-2-ethyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine
102	5-(5-Chloro-2-cyclopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine

103	(5-(5-Fluoro-2-isopropyl-4-methoxy-benzyl)-pyrimidine-2,4-diamine
104	5-(2-Ethyl-5-methanesulfonyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine
105	5-(2-Allyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine
106	5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-benzamide
107	5-(4,5-Dimethoxy-2-vinyl-phenoxy)-pyrimidine-2,4-diamine
108	5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-benzoic acid
109	5-(2-Cyclopropyl-4,5-dimethoxy-phenoxy)-pyrimidine-2,4-diamine
110	5-[2-Isopropyl-4-methoxy-5-(1H-tetrazol-5-yl)-phenoxy]-pyrimidine-2,4-diamine
111	5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-benzonitrile
112	4-[4-Amino-5-(5-chloro-2-isopropyl-4-methoxy-phenoxy)-pyrimidin-2-ylamino]-piperidine-1-carboxylic acid ethyl ester
113	[5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-urea
114	5-(5-Chloro-2-isopropyl-4-methoxy-phenoxy)-N*2*-(1-cyclopropyl-ethyl)-pyrimidine-2,4-diamine
115	5-(5-Chloro-4-difluoromethoxy-2-isopropyl-phenoxy)-pyrimidine-2,4-diamine
116	5-(5-Amino-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine
117	N*4*-Isopropyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-N*2*-methyl-pyrimidine-2,4-diamine
118	N-[5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-acetamide
119	5-(2-Isopropyl-4-methoxy-5-tetrazol-1-yl-phenoxy)-pyrimidine-2,4-diamine
120	5-(2-Isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine
121	5-(2-Isopropyl-5-methanesulfonyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine
122	5-(5-Chloro-4-ethoxy-2-isopropyl-benzyl)-pyrimidine-2,4-diamine
123	5-(2-Isopropyl-4-methoxy-5-methyl-phenoxy)-N*4*-phenyl-pyrimidine-2,4-diamine
124	5-(5-Chloro-2-isopropyl-4-methoxy-phenoxy)-N*2*-(1,1-dioxo-hexahydro-1lambda*6*-thiopyran-4-yl)-pyrimidine-2,4-diamine
125	Methyl-carbamic acid 2-[4-amino-5-(5-chloro-2-isopropyl-4-methoxy-phenoxy)-pyrimidin-2-ylamino]-propyl ester
126	5-(4-Chloro-2-isopropyl-5-methyl-phenoxy)-pyrimidine-2,4-diamine
127	5-(2-Isopropyl-4,5-dimethoxy-phenoxy)-6-methyl-pyrimidine-2,4-diamine
128	5-[4,5-Dimethoxy-2-(1-methyl-2-phenyl-ethyl)-benzyl]-pyrimidine-2,4-diamine
129	1-(4-{2-[4-Amino-5-(5-chloro-2-isopropyl-4-methoxy-phenoxy)-pyrimidin-2-ylamino]-propyl}-piperazin-1-yl)-ethanone
130	5-(5-Chloro-2-isopropyl-4-methoxy-phenoxy)-N*2*-(1-methanesulfonyl-piperidin-

	4-yl)-pyrimidine-2,4-diamine
131	2-[4-Amino-5-(5-chloro-2-isopropyl-4-methoxy-phenoxy)-pyrimidin-2-ylamino]-(R)-propan-1-ol
132	5-(2-Ethyl-4,5-dimethoxy-phenoxy)-pyrimidine-2,4-diamine
133	5-(2-Isopropyl-5-methanesulfonyl-4-methoxy-phenoxy)-N^2-(tetrahydro-thiopyran-4-yl)-pyrimidine-2,4-diamine
134	5-(5-Chloro-2-isopropyl-4-methoxy-phenoxy)-N^2-(1,1-dioxo-hexahydro-1λ^6-thiopyran-4-yl)-pyrimidine-2,4-diamine
135	5-[5-(4,5-Dihydro-1H-imidazol-2-yl)-2-isopropyl-4-methoxy-phenoxy]-pyrimidine-2,4-diamine
136	1-[5-(2,4-Diamino-pyrimidin-5-yloxy)-2-hydroxy-4-isopropyl-phenyl]-ethanone
137	5-(5-Iodo-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine
138	5-(2-Iodo-4,5-dimethoxy-phenoxy)-pyrimidine-2,4-diamine
139	5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-benzenesulfonamide
140	4-(2,4-Diamino-pyrimidin-5-yloxy)-2-iodo-5-isopropyl-phenol
141	5-(2,5-Diiodo-4-methoxy-phenoxy)-pyrimidine-2,4-diamine
142	3-[4-Amino-5-(5-bromo-2-isopropyl-4-methoxy-phenoxy)-pyrimidin-2-ylamino]-pentane-1,5-diol
143	5-(2-Ethyl-5-iodo-4-methoxy-phenoxy)-pyrimidine-2,4-diamine
144	5-(5-Iodo-2-isopropyl-4-methoxy-phenoxy)-1-oxy-pyrimidine-2,4-diamine
145	5-(2-Isopropyl-4methoxy-5-vinyl-phenoxy)-pyrimidine-2,4-diamine
146	5-(5-Iodo-2-isopropenyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine
147	5-(2-Isopropyl-4-methoxy-5-pyrazol-1-yl-phenoxy)-pyrimidine-2,4-diamine
148	5-(5-Iodo-2-isopropyl-phenoxy)-pyrimidine-2,4-diamine
149	5-[2-Isopropyl-4-methoxy-5-(3-methyl-pyrazol-1-yl)-phenoxy]-pyrimidine-2,4-diamine
150	4-(2,4-Diamino-pyrimidin-5-ylmethyl)-2-iodo-5-isopropyl-phenol
151	5-(2-Isopropyl-4-methoxy-5-oxazol-2-yl-phenoxy)-pyrimidine-2,4-diamine
152	(S)-2-[4-Amino-5-(5-bromo-2-isopropyl-4-methoxy-phenoxy)-pyrimidin-2-ylamino]-butan-1-ol
153	5-(4-Iodo-2-isopropyl-5-methoxy-phenoxy)-pyrimidine-2,4-diamine
154	5-(4-Bromo-2-isopropyl-5-methoxy-phenoxy)-pyrimidine-2,4-diamine
155	5-(2-Ethyl-5-iodo-phenoxy)-pyrimidine-2,4-diamine
156	5-(2-Isopropyl-4-methoxy-5-trifluoromethyl-phenoxy)-pyrimidine-2,4-diamine
157	5-(2-Isopropyl-4-methoxy-5-thiazol-4-yl-phenoxy)-pyrimidine-2,4-diamine

158	[4-(2,4-Diamino-pyrimidin-5-yloxy)-2-iodo-5-isopropyl-phenoxy]-acetonitrile
159	5-(2-Isopropyl-4-methoxy-5-thiophen-3-yl-phenoxy)-pyrimidine-2,4-diamine
160	(R)-2-[4-Amino-5-(2-isopropyl-5-methanesulfonyl-4-methoxy-phenoxy)-pyrimidin-2-ylamino]-butan-1-ol
161	5-(7-Isopropyl-4-methyl-benzooxazol-6-yloxy)-pyrimidine-2,4-diamine
162	(S)-2-[4-Amino-5-(5-chloro-2-isopropyl-4-methoxy-phenoxy)-pyrimidin-2-ylamino]-propionic acid
163	5-[5-(4,5-Dihydro-oxazol-2-yl)-2-isopropyl-4-methoxy-phenoxy]-pyrimidine-2,4-diamine
164	5-(8-Bromo-5-ethyl-2,3-dihydro-benzo[1,4]dioxin-6-yloxy)-pyrimidine-2,4-diamine
165	5-(2-Iodo-4,5-dimethoxy-phenoxy)-pyrimidine-2,4-diamine
166	5-(2-Isopropyl-5-methanesulfonyl-4-methoxy-phenoxy)-N2-(2,2,2-trifluoro-ethyl)-pyrimidine-2,4-diamine
167	5-(5-Iodo-2-isopropyl-4-methoxy-benzyl)-pyrimidine-2,4-diamine
168	5-(5-Bromo-2-cyclopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine
169	(S)-2-[4-Amino-5-(5-chloro-2-isopropyl-4-methoxy-phenoxy)-pyrimidin-2-ylamino]-propionic acid 3-hydroxy-2-hydroxymethyl-2-methyl-propyl ester
170	5-[5-(5-Chloro-thiophen-2-yl)-2-isopropyl-4-methoxy-phenoxy]-pyrimidine-2,4-diamine
171	5-(2-Ethyl-4-methoxy-5-trifluoromethyl-phenoxy)-pyrimidine-2,4-diamine
172	5-[2-Isopropyl-4-methoxy-5-(1-methyl-1H-imidazol-2-yl)-phenoxy]-pyrimidine-2,4-diamine
173	5-[2-Isopropyl-4-methoxy-5-(2H-pyrazol-3-yl)-phenoxy]-pyrimidine-2,4-diamine
174	5-(5-Imidazol-1-yl-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine
175	N2-Isopropyl-5-(2-isopropyl-5-methanesulfonyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine
176	2-[4-(2,4-Diamino-pyrimidin-5-yloxy)-2-iodo-5-isopropyl-phenoxy]-ethanol
177	5-(2-Isopropyl-5-methanesulfonyl-4-methoxy-phenoxy)-N2-phenyl-pyrimidine-2,4-diamine
178	5-(4-Amino-2-ethylamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-benzamide
179	5-(7-Isopropyl-2,4-dimethyl-benzooxazol-6-yloxy)-pyrimidine-2,4-diamine
180	2-[4-Amino-5-(2-isopropyl-5-methanesulfonyl-4-methoxy-phenoxy)-pyrimidin-2-ylamino]-ethanol
181	5-[2-Isopropyl-4-methoxy-5-(2-methyl-thiazol-4-yl)-phenoxy]-pyrimidine-2,4-diamine

182	5-[5-Iodo-2-isopropyl-4-(pyrazin-2-ylmethoxy)-phenoxy]-pyrimidine-2,4-diamine
183	5-(2-Isopropyl-5-methanesulfonyl-4-methoxy-phenoxy)-N2-(2-methoxy-ethyl)-pyrimidine-2,4-diamine
184	5-(2-Isopropyl-4-methoxy-5-[1,2,3]triazol-1-yl-phenoxy)-pyrimidine-2,4-diamine
185	5-(5-Furan-2-yl-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine
186	1-[5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-3-ethyl-urea
187	N2-Cyclopropyl-5-(2-isopropyl-5-methanesulfonyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine
188	2-[4-(2,4-Diamino-pyrimidin-5-yloxy)-2-iodo-5-isopropyl-phenoxy]-acetamide
189	5-[5-(3,5-Dimethyl-pyrazol-1-yl)-2-isopropyl-4-methoxy-phenoxy]-pyrimidine-2,4-diamine
190	N2-Benzyl-5-(2-isopropyl-5-methanesulfonyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine
191	N2-Ethyl-5-(2-isopropyl-5-methanesulfonyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine
192	5-(2-Isopropyl-5-methanesulfonyl-4-methoxy-phenoxy)-N2-(1-methanesulfonyl-piperidin-4-yl)-pyrimidine-2,4-diamine
193	1-[4-Amino-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidin-2-ylamino]-2-methyl-propan-2-ol
194	N2-Isobutyl-5-(2-isopropyl-5-methanesulfonyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine
195	5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-N-methyl-benzamide
196	5-(2,4-Diamino-pyrimidin-5-yloxy)-6-isopropyl-1-methyl-1*H*-indole-3-carboxylic acid ethyl ester
197	5-(2-Isopropyl-5-isoxazol-5-yl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine
198	5-(4-Ethyl-7-methyl-benzo[b]thiophen-5-yloxy)-pyrimidine-2,4-diamine
199	N2-(4-Fluoro-phenyl)-5-(2-isopropyl-5-methanesulfonyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine
200	5-(5-Chloro-2-isopropyl-4-methoxy-benzyl)-N2-(2,2,2-trifluoro-ethyl)-pyrimidine-2,4-diamine
201	5-(2-Isopropyl-4-methoxy-5-[1,2,4]oxadiazol-3-yl-phenoxy)-pyrimidine-2,4-diamine
202	5-(2-Isopropyl-5-methanesulfonyl-4-methoxy-phenoxy)-N2-(tetrahydro-pyran-4-yl)-pyrimidine-2,4-diamine
203	1-[5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-ethanol

204	5-(6-Isopropyl-4-methyl-3,4-dihydro-2*H*-benzo[1,4]oxazin-7-yloxy)-pyrimidine-2,4-diamine
205	5-(2,5-Diisopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine
206	5-(5-Benzo[*b*]thiophen-3-yl-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine
207	5-[2-Isopropyl-4-methoxy-5-(1-methoxy-ethyl)-phenoxy]-pyrimidine-2,4-diamine
208	5-(2-Isopropyl-4-methoxy-5-oxazol-4-yl-phenoxy)-pyrimidine-2,4-diamine
209	5-(4-Ethyl-7-methyl-benzo[*b*]thiophen-5-yloxy)-pyrimidine-2,4-diamine
210	5-[5-(5-Chloro-thiophen-2-yl)-2-isopropyl-4-methoxy-benzyl]-pyrimidine-2,4-diamine
211	5-(2-Isopropyl-4-methoxy-5-thiazol-2-yl-phenoxy)-pyrimidine-2,4-diamine
212	5-(2-Isopropyl-4-methoxy-5-thiophen-3-yl-benzyl)-pyrimidine-2,4-diamine
213	5-(5-Furan-3-yl-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine
214	5-(2-Isopropyl-5-methoxy-phenoxy)-pyrimidine-2,4-diamine
215	5-[5-Iodo-2-isopropyl-4-(pyrimidin-2-ylmethoxy)-phenoxy]-pyrimidine-2,4-diamine
216	5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N2-pyridin-2-yl-pyrimidine-2,4-diamine
217	5-(1,3-Dimethyl-6-trifluoromethyl-1H-indol-5-yloxy)-pyrimidine-2,4-diamine
218	5-(2-Isopropyl-4-methoxy-5-thiophen-2-yl-phenoxy)-pyrimidine-2,4-diamine
219	1-[5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-3-phenyl-urea
220	5-(5-Chloro-2-isopropyl-4-methoxy-benzyl)-N^2-(2-methoxy-ethyl)-pyrimidine-2,4-diamine
221	5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-N-methyl-benzenesulfonamide
222	5-(2-Isopropyl-5-methanesulfonyl-4-methoxy-phenoxy)-N2-methyl-pyrimidine-2,4-diamine
223	5-[5-Iodo-2-isopropyl-4-(pyridin-2-ylmethoxy)-phenoxy]-pyrimidine-2,4-diamine
224	*N*-[2-Acetylamino-5-(2-isopropyl-4-methoxy-5-methyl-benzyl)-pyrimidin-4-yl]-acetamide
225	5-[4-(2-Fluoro-benzyloxy)-5-iodo-2-isopropyl-phenoxy]-pyrimidine-2,4-diamine
226	5-(2-Isopropyl-4-methoxy-5-pyrrol-1-yl-phenoxy)-pyrimidine-2,4-diamine
227	5-(2-Isopropyl-4-methoxy-5-trifluoromethoxy-phenoxy)-pyrimidine-2,4-diamine
228	2-[4-(2,4-Diamino-pyrimidin-5-ylmethyl)-2-iodo-5-isopropyl-phenoxy]-ethanol
229	5-(6-Isopropyl-1-methyl-1*H*-indazol-5-yloxy)-pyrimidine-2,4-diamine

230	5-[5-(4,5-Dihydro-oxazol-2-yl)-2-isopropyl-4-methoxy-benzyl]-pyrimidine-2,4-diamine
231	5'-(2,4-Diamino-pyrimidin-5-yloxy)-4'-isopropyl-2'-methoxy-biphenyl-3-carbonitrile
232	5-[2-Isopropyl-4-methoxy-5-(4-methyl-thiophen-2-yl)-phenoxy]-pyrimidine-2,4-diamine
233	5-(7,8-Diiodo-5-isopropyl-2,3-dihydro-benzo[1,4]dioxin-6-yloxy)-pyrimidine-2,4-diamine
234	5-(7-Iodo-5-isopropyl-2,3-dihydro-benzo[1,4]dioxin-6-yloxy)-pyrimidine-2,4-diamine
235	5-(5-Chloro-2-isopropyl-4-methoxy-phenoxy)-N^2-[(S)-1-(4-methyl-2,6,7-trioxa-bicyclo[2.2.2]oct-1-yl)-ethyl]-pyrimidine-2,4-diamine
236	5-(5-Iodo-2-isopropyl-4-prop-2-ynyloxy-phenoxy)-pyrimidine-2,4-diamine
237	5-(2-Isopropyl-4-methoxy-5-nitro-phenoxy)-pyrimidine-2,4-diamine
238	5-(4-Ethoxy-5-iodo-2-isopropyl-phenoxy)-pyrimidine-2,4-diamine
239	5-[5-Iodo-2-isopropyl-4-(pyridin-3-ylmethoxy)-phenoxy]-pyrimidine-2,4-diamine
240	5-(4-Benzyloxy-5-iodo-2-isopropyl-phenoxy)-pyrimidine-2,4-diamine
241	5-(4-Isopropyl-6-methoxy-biphenyl-3-yloxy)-pyrimidine-2,4-diamine
242	5-(6-Isopropyl-2-methyl-2*H*-indazol-5-yloxy)-pyrimidine-2,4-diamine
243	5-(5-Furan-2-yl-2-isopropyl-4-methoxy-benzyl)-pyrimidine-2,4-diamine
244	5-(2-Isopropyl-4-methoxy-5-thiazol-5-yl-phenoxy)-pyrimidine-2,4-diamine
245	1-[5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-pyrrolidin-2-one
246	5-(2-Isopropyl-5-methanesulfonyl-4-methoxy-benzyl)-pyrimidine-2,4-diamine
247	5-[5-Chloro-2-(1-fluoro-1-methyl-ethyl)-4-methoxy-phenoxy]-pyrimidine-2,4-diamine
248	5-[5-Iodo-2-isopropyl-4-(2-methoxy-ethoxy)-phenoxy]-pyrimidine-2,4-diamine
249	5-(2-Isopropyl-4-methoxy-5-oxazol-5-yl-phenoxy)-pyrimidine-2,4-diamine
250	1-[4-Chloro-2-(2,4-diamino-pyrimidin-5-yloxy)-5-methoxy-phenyl]-ethanol
251	5-(2-Isopropyl-3-methoxy-phenoxy)-pyrimidine-2,4-diamine
252	2-[2-(2,4-Diamino-pyrimidin-5-yloxy)-4-iodo-5-methoxy-phenyl]-propan-1-ol
253	6-(2,4-Diamino-pyrimidin-5-yloxy)-5-isopropyl-3-methyl-1*H*-indole-2-carboxylic acid
254	5-[5-Iodo-2-isopropyl-4-(2-methoxy-benzyloxy)-phenoxy]-pyrimidine-2,4-diamine
255	5-[5-Iodo-2-isopropyl-4-(2,2,2-trifluoro-ethoxy)-phenoxy]-pyrimidine-2,4-diamine

256	5-[5-Iodo-2-isopropyl-4-(3,4,5-trimethoxy-benzyloxy)-phenoxy]-pyrimidine-2,4-diamine
257	2-[2-(2,4-Diamino-pyrimidin-5-yloxy)-4-iodo-5-methoxy-phenyl]-propan-2-ol
258	5-[2-Isopropyl-4-methoxy-5-(4-methyl-thiophen-3-yl)-phenoxy]-pyrimidine-2,4-diamine
259	5-(2-Isopropyl-4-methoxy-5-nitro-phenoxy)-pyrimidine-2,4-diamine
260	5-[5-Iodo-2-isopropyl-4-(1-methyl-piperidin-2-ylmethoxy)-phenoxy]-pyrimidine-2,4-diamine
261	5-[5-Iodo-2-isopropyl-4-(tetrahydro-pyran-2-ylmethoxy)-phenoxy]-pyrimidine-2,4-diamine
262	5-(2-Isopropyl-4-methoxy-5-[1,2,4]triazol-1-yl-phenoxy)-pyrimidine-2,4-diamine
263	5-(2-Isopropyl-4,5-dimethoxy-phenoxy)-N^2-(2-methoxy-ethyl)-pyrimidine-2,4-diamine
264	5-(4'-Fluoro-4-isopropyl-6-methoxy-biphenyl-3-yloxy)-pyrimidine-2,4-diamine
265	5-(5-Chloro-2-isopropyl-4-methoxy-phenoxy)-N^2-(2,2,2-trifluoro-ethyl)-pyrimidine-2,4-diamine
266	5-(2,4-Diamino-pyrimidin-5-ylmethyl)-4-isopropyl-2-methoxy-benzonitrile
267	5-[2-Isopropyl-4-methoxy-5-(2-methyl-thiazol-5-yl)-phenoxy]-pyrimidine-2,4-diamine
268	5-(2-Isopropyl-4-methoxy-6-methyl-phenoxy)-pyrimidine-2,4-diamine
269	5-(5-Ethanesulfonyl-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine
270	5-(2-Isopropyl-4-methoxy-5-thiazol-5-yl-benzyl)-pyrimidine-2,4-diamine
271	1-[5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-1*H*-imidazole-2-thiol
272	5-[2-Isopropyl-4-methoxy-5-(1-methyl-1*H*-pyrazol-4-yl)-phenoxy]-pyrimidine-2,4-diamine
273	5-[5-Iodo-2-isopropyl-4-(pyridin-4-ylmethoxy)-phenoxy]-pyrimidine-2,4-diamine
274	5-(4-Iodo-2-isopropyl-phenoxy)-pyrimidine-2,4-diamine
275	5-(5-Iodo-4-isopropyl-2-methoxy-benzyl)-pyrimidine-2,4-diamine
276	5-(5-Fluoro-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine
277	5-(4'-Fluoro-5-isopropyl-2-methoxy-biphenyl-4-yloxy)-pyrimidine-2,4-diamine
278	5-[4-(3-Fluoro-benzyloxy)-5-iodo-2-isopropyl-phenoxy]-pyrimidine-2,4-diamine
279	5-(4-Bromo-2-isopropyl-phenoxy)-pyrimidine-2,4-diamine
280	5-(4-Furan-2-yl-2-isopropyl-5-methoxy-phenoxy)-pyrimidine-2,4-diamine
281	2-[5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-propan-2-ol

282	5-(2,4-Diamino-pyrimidin-5-yloxy)-6-isopropyl-1-methyl-1*H*-indole-3-carboxylic acid
283	5-[4-(2,6-Difluoro-benzyloxy)-5-iodo-2-isopropyl-phenoxy]-pyrimidine-2,4-diamine
284	5-(5-Iodo-2-isopropyl-4-phenethyloxy-phenoxy)-pyrimidine-2,4-diamine
285	5-(2-Isopropyl-4-methoxy-5-pyridin-4-yl-phenoxy)-pyrimidine-2,4-diamine
286	5-(2-Isopropyl-4,5-dimethoxy-benzyl)-N^2-(1-methyl-piperidin-4-yl)-pyrimidine-2,4-diamine
287	5-(2,4-Diamino-pyrimidin-5-yloxy)-N-ethyl-4-isopropyl-2-methoxy-benzenesulfonamide
288	5-[2-Isopropyl-5-(4-methanesulfonyl-piperazin-1-yl)-4-methoxy-phenoxy]-pyrimidine-2,4-diamine
289	5-(2-Isopropyl-4-methoxy-5-pyridin-3-yl-phenoxy)-pyrimidine-2,4-diamine
290	5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-N,N-dimethyl-benzamide
291	5-[5-(2,5-Dimethyl-pyrrol-1-yl)-2-isopropyl-4-methoxy-phenoxy]-pyrimidine-2,4-diamine
292	5-(2-Ethyl-3-methoxy-benzyl)-pyrimidine-2,4-diamine
293	5-(2-Bromo-4,5-dimethoxy-phenoxy)-pyrimidine-2,4-diamine
294	6-(2,4-Diamino-pyrimidin-5-yloxy)-5-isopropyl-3-methyl-1*H*-indole-2-carboxylic acid ethyl ester

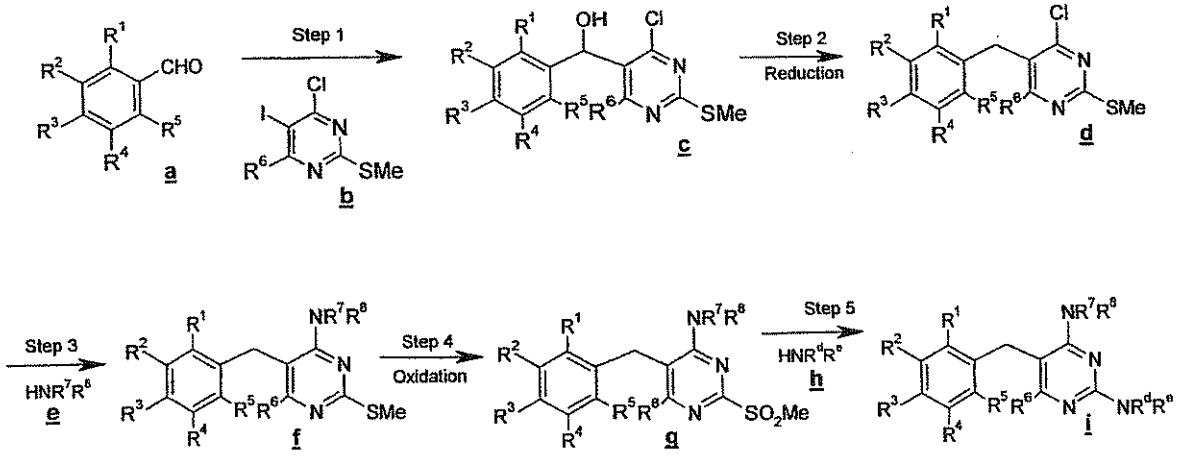
Compounds of the present invention can be made by a variety of methods depicted in the illustrative synthetic reaction schemes shown and described below.

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 (RT), e.g., about 20°C.

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



SCHEME A

In Step 1 of Scheme A, benzaldehyde a is alkylated with the Grignard reagent derived from 4-chloro-5-iodo-2-methylsulfanyl-pyrimidine b or like iodopyrimidine to provide an alpha-hydroxy benzyl pyrimidine c. The iodopyrimidine used in this step may be prepared according to the procedure described by Sakamoto et al., Chem. Pharm. Bull. 34:2719 (1986). 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 to allow introduction of desired functionalities to benzaldehyde a, after which the masked aldehyde is deprotected to provide the free aldehyde group. Aldehyde protection schemes of this sort are shown in the experimental examples below.

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

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

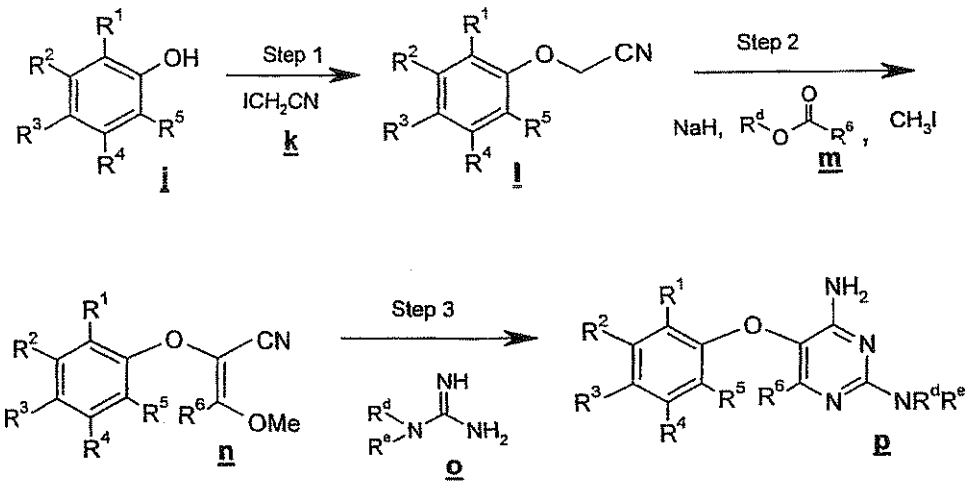
In step 3, a first amination by reaction of amine e with benzyl pyrimidine d yields benzyl aminopyrimidine f. Amine e may comprise any suitable primary or secondary amine having functionalities R^7 or R^8 in accordance with the invention. Amine e may comprise, e.g., ammonia, methylamine, ethylamine,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

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

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

Numerous variations on the above procedure are possible and will suggest themselves to those skilled in the art upon review of this disclosure. For example, various pyrimidine reagents may be used in place of iodopyrimidine b in step 1. In such variation, described in the experimental examples below, benzaldehyde a may be treated with 5-lithio-2,6-dimethoxypyrimidine [Mathson et al., JOC 55(10):3410-3412 (1990)] to form a dimethoxy benzyl pyrimidine alchohol which is subsequently oxidized with MnO_2. The resultant ketone can then be aminated to displace the methoxy groups to yield a diamino benzylpyrimidine in accordance with the invention.

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



SCHEME B

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

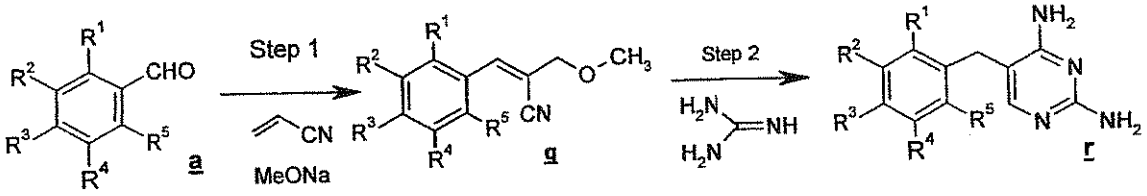
In step 2, a cyano enol ether compound n is formed by treatment of cyano ether l with a strong base such as sodium hydride, followed by introduction of ester m to form an enolate, that in turn is alkylated by addition of iodomethane or other alkyl halide. This step may be carried out under polar aprotic solvent conditions.

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

As in the case of Scheme A discussed above, numerous variations on the procedure of Scheme B are possible and will be readily apparent to those skilled in the art. For example, selective amination of the $-NH_2$ group of diamino pyrimidine p, using reductive amination

or like technique, may be used to introduce R^7 and R^8 functionalities in accordance with formula (I).

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



SCHEME C

In the procedure of Scheme C, benzaldehyde a is treated with acrylonitrile in the presence of sodium methoxide in step 1 to afford a phenyl methoxymethyl cinnamonitrile compound q, which in turn is reacted with guanidine in step 2 to yield the diaminopyrimidine r. Diamino pyrimidine r is a compound of formula (I) in which X is $-CH_2-$, Y is $-NH_2$ and R^6, R^7 and R^8 are hydrogen.

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

Table 2

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

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.

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 mouth-washes 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.

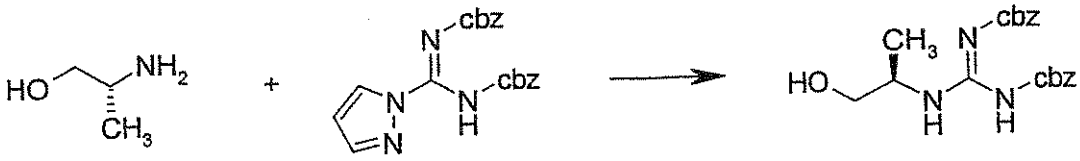
Other suitable pharmaceutical carriers and their formulations are described in *Remington: The Science and Practice of Pharmacy* 1995, edited by Martin, Mack Publishing Company, 19th edition, Easton, Pennsylvania. Representative pharmaceutical formulations containing a compound of the present invention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

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

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



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

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

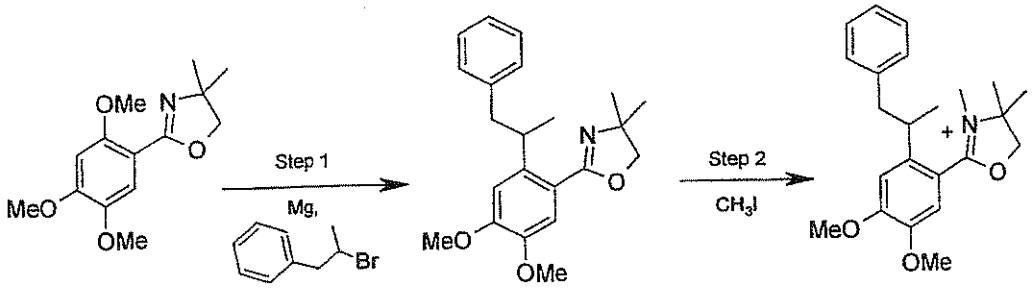


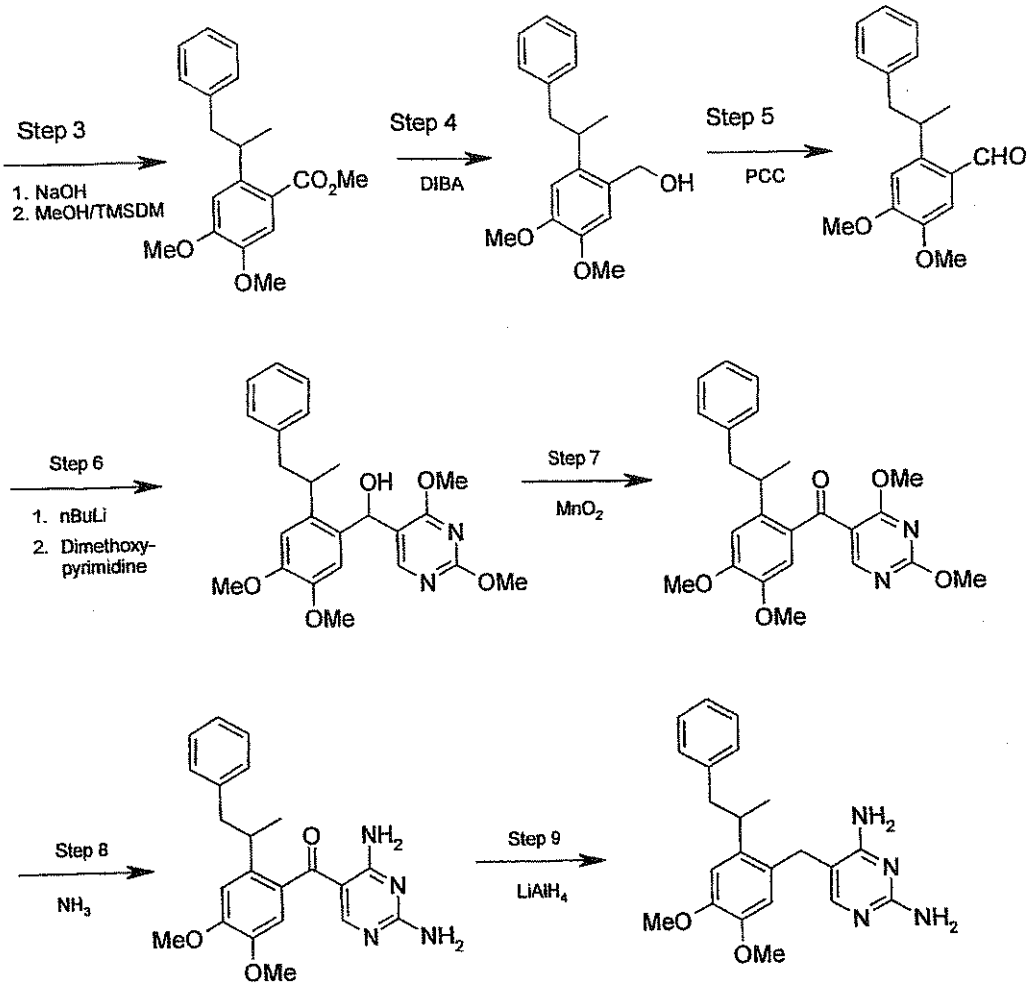
To a solution of bis-benzyloxycarbonyl-N-(2-(R)-hydroxy-1-methyl-ethyl)-guanidine in 75 mL EtOH was added 10% Pd/C (0.10 g). The mixture was stirred under 1 Atmosphere of H_2. After 16 hours the mixture was filtered through a pad of celite and concentrated in vacuo to give N-(2-(R)-hydroxy-1-methyl-ethyl)-guanidine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

Using the appropriate amines with the above procedure, the following guanidine compounds were also prepared:
N-(3-Ethanesulfonyl-1-methyl-propyl)-guanidine;
4-Guanidino-piperidine-1-carboxylic acid ethyl ester;
N-(1-Cyclopropyl-ethyl)-guanidine;
N-(Tetrahydro-thiopyran-4-yl)-guanidine;
N-[2-(4-Acetyl-piperazin-1-yl)-1-methyl-ethyl]-guanidine;
N-(1-Hydroxymethyl-propyl)-guanidine
N-(1-Methanesulfonyl-piperidin-4-yl)-guanidine; and
N-[3-Hydroxy-1-(2-hydroxy-ethyl)-propyl]-guanidine.

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

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





Scheme D

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

The 4,4-dimethyl-2-(2,4,5-trimethoxy-phenyl)-4,5-dihydro-oxazole used in this step was prepared according to the procedure reported by Meyers et al., J Org Chem 43:1372-1379 (1978). To a rapidly stirring suspension of magnesium turnings (1.32 g, 54.5 mol) and in 35 mL tetrahydrofuran (THF) was added 1,2-dibromoethane (0.10 mL) in one portion. 2-bromo-1-phenylpropane (10.86 g, 54.5 mmol) was added at a rate that maintained the internal temperature at 40°C. After 2.5 hours the cloudy suspension was transferred via canula to a solution of 4,4-dimethyl-2-(2,4,5-trimethoxy-phenyl)-4,5-dihydro-oxazole (10.013 g, 36.4 mmol) in 50 mL THF. After 18 hours the solution cooled to 0°C and quenched by the slow addition of 10% NH_4Cl. 500 mL H_2O was added and the mixture was extracted with ethyl acetate, washed with H_2O, and washed with brine. The combined organics were dried over Na_2SO_4, filtered and concentrated in vacuo to give a crude solid. Purifications via flash chromatography (4:1 hexane/ethyl acetate) afforded 2-[4,5-dimeth-

oxy-2-(1-methyl-2-phenyl-ethyl)-phenyl]-4,4-dimethyl-4,5-dihydro-oxazole as a clear viscous oil (7.833 g, 41%).

Step 2. 2-[4,5-Dimethoxy-2-(1-methyl-2-phenyl-ethyl)-phenyl]-3,4,4-trimethyl-4,5-dihydro-oxazolium iodide

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

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

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

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

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

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

A solution of pyridinium chlorochromate (1.253 g, 5.8 mmol) in 40 mL CH_2Cl_2 was cooled to 0°C. [4,5-Dimethoxy-2-(1-methyl-2-phenyl-ethyl)-phenyl]-methanol (1.110 g, 3.88

mmol) in 5.0 mL CH_2Cl_2 was added drop-wise and allowed to stir for 45 minutes. The mixture was diluted in 200 mL Et_2O, filtered through celite and concentrated in vacuo to afford a dark brown oil. Purification via flash chromatography (9:1 hexane/ethyl acetate) gave 4,5-dimethoxy-2-(1-methyl-2-phenyl-ethyl)-benzaldehyde (0.840 g, 76%) as a clear oil.

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

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

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

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

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

A solution of [4,5-dimethoxy-2-(1-methyl-2-phenyl-ethyl)-phenyl]-(2,4-dimethoxy-pyrimidin-5-yl)-methanone (0.212 g, 0.5 mmol) in 5.0 mL MeOH was added to ammonia (15 mL, 7.0M in MeOH) in a sealed tube. The mixture was heated to 80°C. After 16 hours the solution was cooled and concentrated in vacuo to give a dark solid. Purification via flash

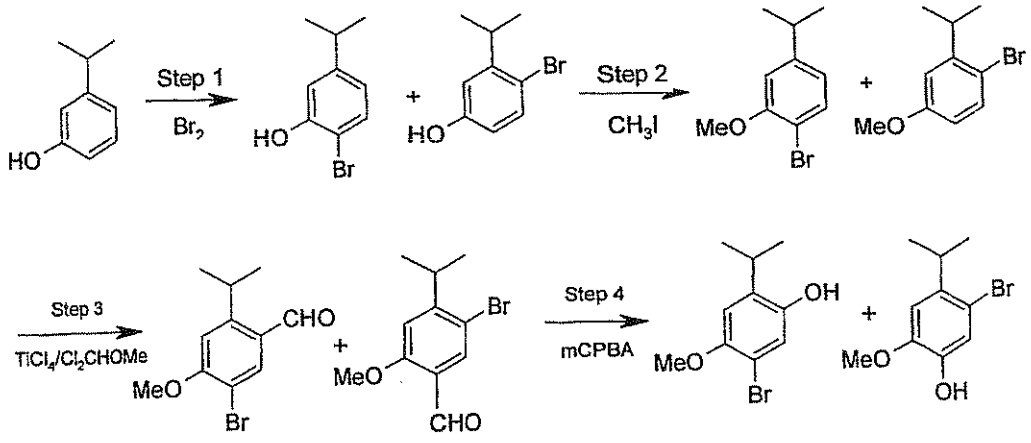
chromatography (95:5 CH_2Cl_2/MeOH) afforded (2,4-diamino-pyrimidin-5-yl)-[4,5-dimethoxy-2-(1-methyl-2-phenyl-ethyl)-phenyl]-methanone (0.162 g, 86%) as a white solid.

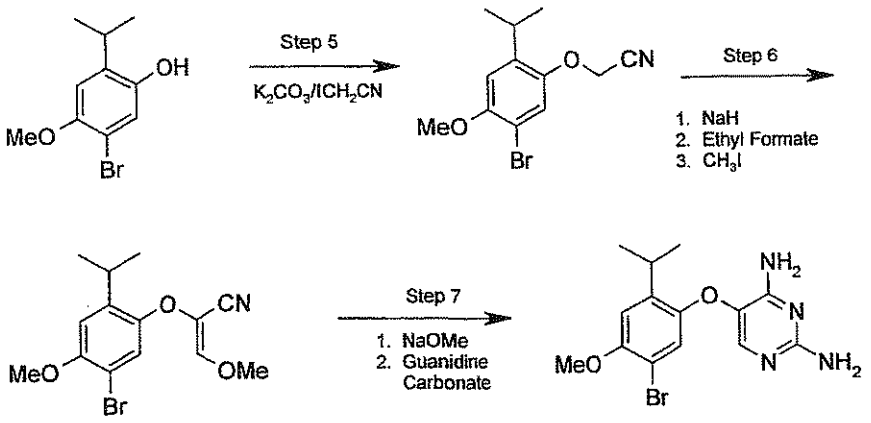
Step 9. 5-[4,5-Dimethoxy-2-(1-methyl-2-phenyl-ethyl)-benzyl]-pyrimidine-2,4-diamine
To a solution of (2,4-diamino-pyrimidin-5-yl)-[4,5-dimethoxy-2-(1-methyl-2-phenyl-ethyl)-phenyl]-methanone (0.413 g, 0.4 mmol) in 10 mL THF was added $LiAlH_4$ (0.73 mL, 1.0 M in THF) over 5 min. After gas evolution ceased the mixture was warmed to reflux. After 3 h the mixture was cooled to 0°C and quenched by the Fieser method. After 30 min the mixture was filtered through a pad of celite and concentrated in vacuo to give a crude white solid. To a solution of this solid in 5 mL CH_2Cl_2 was added TFA (1.1 mL, 14.0 mmol) followed by triethylsilane (0.4 mL, 2.8 mmol). After 30 min 50 mL 10% K_2CO_3 was added and the mixture was extracted with ethyl acetate and washed with brine. The combined organics were dried over Na_2SO_4, filtered and concentrated in vacuo. Purification via flash chromatography (95:5 CH_2Cl_2) afforded 5-[4,5-dimethoxy-2-(1-methyl-2-phenyl-ethyl)-benzyl]-pyrimidine-2,4-diamine (0.066 g, 58%) as a white foam; melting point (HCl salt) 227.1-227-4°C.

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

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

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





Scheme E

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

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

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

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

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

To a solution of 1-bromo-4-isopropyl-2-methoxy-benzene and 1-bromo-2-isopropyl-4-methoxy-benzene from step 2 (6.621 g, 28.9 mmol) in 100 mL 1,2 dichloroethane was added $TiCl_4$ (6.3 mL, 57.8 mmol) at 0°C. After 10 minutes, dichloromethoxymethane (Cl_2CHOMe) (2.6 mL, 28.9 mmol) was added and the mixture was warmed to reflux.

After 3 hours the mixture was cooled poured over ice and acidified with 50 mL 2 M HCl. The resulting slurry was extracted with CH_2Cl_2, and washed with brine. The combined organics were dried over $MgSO_4$, filtered and concentrated in vacuo to give a dark-green oil. Purification via flash chromatography (96:4 hexane/ethyl acetate) afforded 5-bromo-2-isopropyl-4-methoxy-benzaldehyde and 5-bromo-4-isopropyl-2-methoxy-benzaldehyde (2.876 g, 39%, 6.621 g, 72%) as a 1:1 mixture of inseparable isomers in the form of an orange oil, which was used directly in step 4.

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

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

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

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

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

Sodium hydride (0.122 g, 5.0 mmol, 60% w/w) was washed with dry hexanes and evaporated under a stream of nitrogen. 10 mL THF was added and the mixture was cooled to 0°C. (5-Bromo-2-isopropyl-4-methoxy-phenoxy)-acetonitrile (0.577 g, 2.03 mmol) was

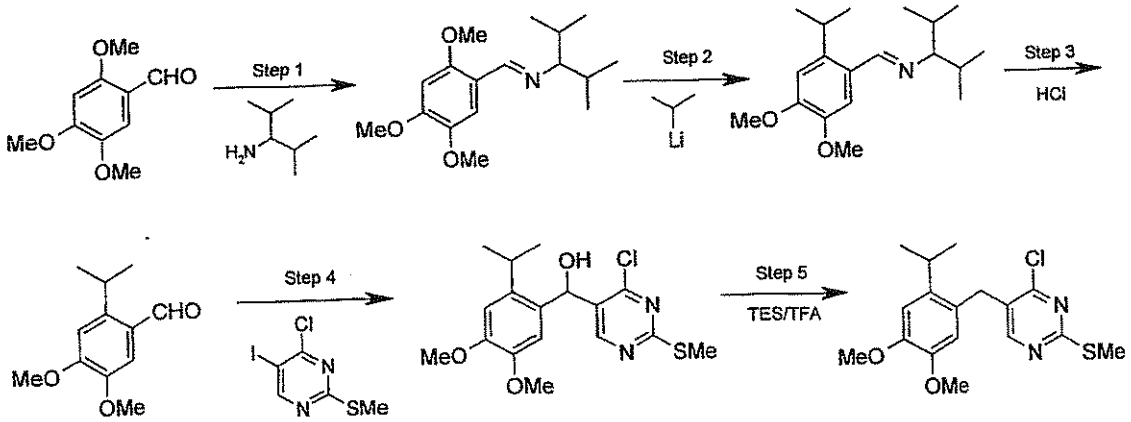
added in portions. After 30 min ethyl formate (4.9 mL, 60.9 mmol) was added and the solution was warmed to 80°C. After 4.5 hours the mixture was cooled and 5.0 mL iodomethane was added in one portion. After 16 hours the solution was quenched with H_2O, concentrated in vacuo, extracted with ethyl acetate, washed with H_2O and then washed with brine. The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. Purification via flash chromatography (9:1 hexane/ethyl acetate) afforded 2-(5-bromo-2-isopropyl-4-methoxy-phenoxy)-3-methoxy-acrylonitrile (0.319 g, 48%) as a white solid.

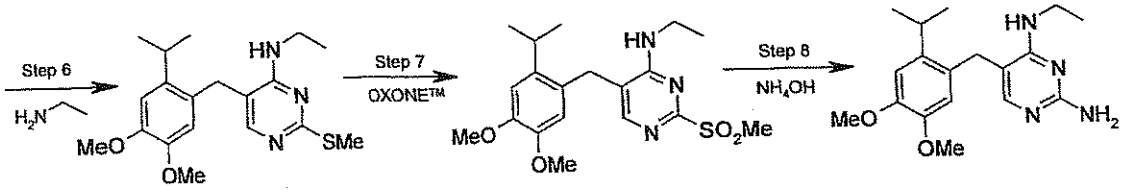
Step 7. 5-(5-Bromo-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine
To a solution of 2-(5-bromo-2-isopropyl-4-methoxy-phenoxy)-3-methoxy-acrylonitrile (0.282 g, 0.9 mmol) and guanidine carbonate (0.078 g, 0.4 mmol) in 10.0 mL dimethyl sulfoxide (DMSO) was added sodium methoxide (1.0 mL, 1.0M in MeOH). The mixture was warmed to 120°C. The methanol was collected via a short-path condenser. After 3 h the mixture was cooled and concentrated in vacuo to give a crude oil. Purification via flash chromatography (95:5 CH_2Cl_2/MeOH) afforded 17 (0.246 g, 77%) as a pink solid; Mass Spec M+H = 352.

The above procedure may be used with various different phenols in step 1 and/or substituted guanidines in step 7 under essentially the same reaction conditions to produce additional compounds. Additional compounds made according to the procedure of Example 2 are shown in Table 1.

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

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





Scheme F

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

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

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

To a solution of (1-isopropyl-2-methyl-propyl)-(2,4,5-trimethoxy-benzylidene)-amine (1.024 g, 3.5 mmol) in 35 ml THF at -78°C was added isopropyllithium (6.0 mL, 0.7 M in pentane) drop-wise over 5 minutes. The solution was allowed to stir 30 min at -78°C. After warming to RT over 45 minutes the mixture was quenched by the addition of 5 mL of 10% NH_4Cl and concentrated in vacuo. 100 mL of H_2O was added and the mixture was extracted with ethyl acetate, washed with H_2O and then brine. The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo to give (2-isopropyl-4,5-dimethoxy-benzylidene)-(1-isopropyl-2-methyl-propyl)-amine as a yellow oil.

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

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

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

The 4-chloro-5-iodo-2-methylsulfanyl-pyrimidine used in this step was prepared according to the procedure described by Sakamoto et al., Chem. Pharm. Bull. 34:2719

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

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

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

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

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

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

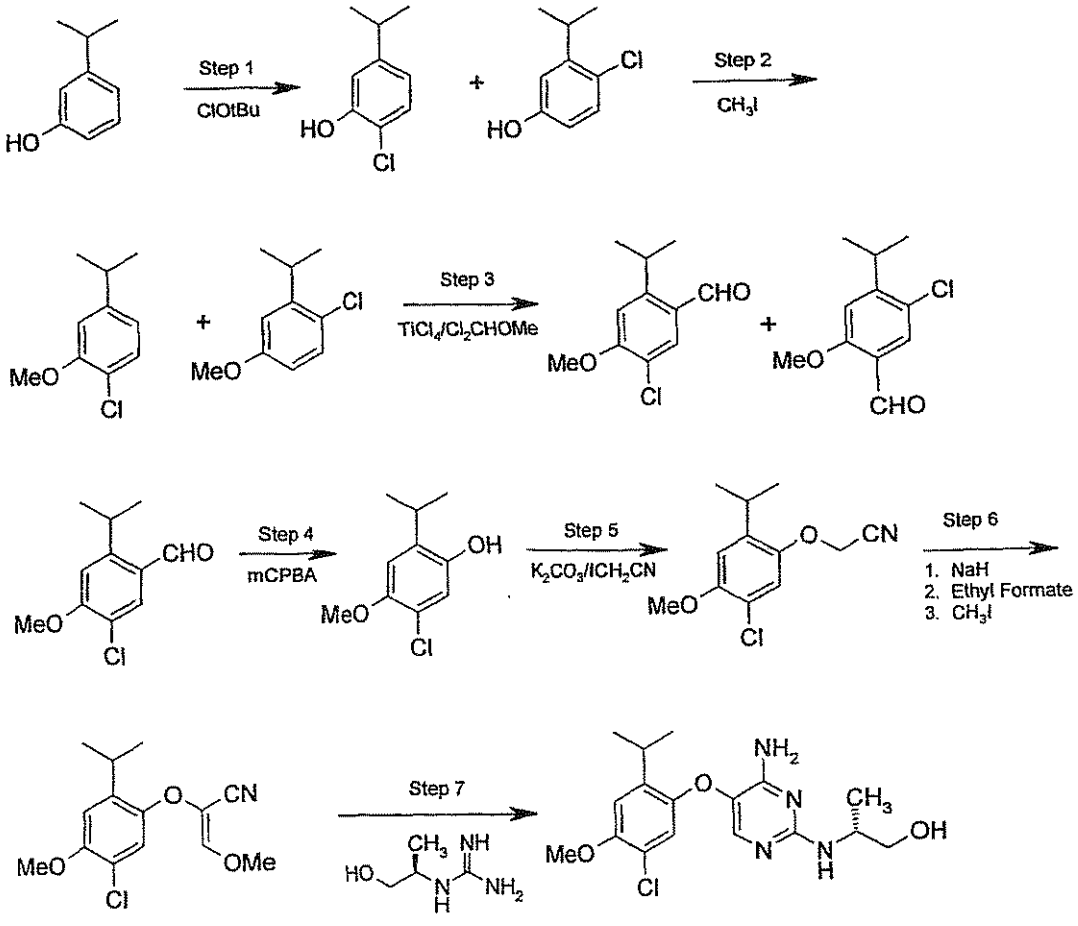
To a solution of ethyl-[5-(2-isopropyl-4,5-dimethoxy-benzyl)-2-methylsulfanyl-pyrimidin-4-yl]-amine (0.129 g, 0.4 mmol) in 20 mL 1:1 H_2O/THF was added OXONE® (0.461 g, 0.8 mmol) in 4.0 mL H_2O. After 2 hours, 50 mL H_2O was added and the mixture was extracted with ethyl acetate, washed with H_2O and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

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

Use of different alkyllithium reagents in step 1 and/or different substituted amines in steps 6 and 8 of the above procedure afforded additional compounds under the same or very similar reaction conditions. Additional compounds made by the procedure of Example 3 are shown in Table 1.

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

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



Scheme G

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

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

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

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

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

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

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

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

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

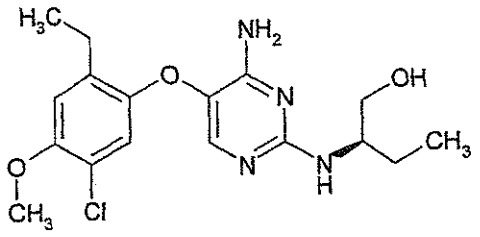
To a solution of 5-chloro-2-isopropyl-4-methoxy-phenol (10.36 g, 51.6 mmol) in 40 mL DMF was added K_2CO_3 (8.55 g, 62.0 mmol) and the mixture was heated to 65°C. After 15

minutes iodoacetonitrile (9.05 g, 54.2 mmol) was added and the mixture was heated to 80°C for 1 hour. The mixture was cooled, poured into an ice/H_2O mixture and extracted with 1:1 toluene/hexane. The combined organics were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by passing through a short plug of silica to afford (5-chloro-2-isopropyl-4-methoxy-phenoxy)-acetonitrile (11.97 g, 97%) as a white solid.

Step 6. 2-(5-Chloro-2-isopropyl-4-methoxy-phenoxy)-3-methoxy-acrylonitrile
To a solution of (5-chloro-2-isopropyl-4-methoxy-phenoxy)-acetonitrile (1.44 g, 6.0 mmol) and ethyl formate (2.2 g, 29.2 mmol) in 7 mL 1,2-dimethoxy ethane at 5°C was added 95% NaH (0.15 g, 6.0 mmol) in one portion. The mixture was warmed to RT. After 1 hour 95% NaH (0.15 g, 6.0 mmol) was added in one portion. After 1 hour 10 mL iodomethane was added and the mixture was allowed to stir for 16 hour. The mixture was concentrated in vacuo, 1N HCl was added and the mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. Purification via flash chromatography (85:15 hexane/ethyl acetate) afforded 2-(5-chloro-2-isopropyl-4-methoxy-phenoxy)-3-methoxy-acrylonitrile (1.41 g, 84%) as a white solid.

Step 7. 2-[4-Amino-5-(5-chloro-2-isopropyl-4-methoxy-phenoxy)-pyrimidin-2-ylamino]-(R)-propan-1-ol
To a solution of 2-(5-chloro-2-isopropyl-4-methoxy-phenoxy)-3-methoxy-acrylonitrile (0.20 g, 0.7 mmol) in 1 mL DMSO was added N-(2-(R)-hydroxy-1-methyl-ethyl)-guanidine from Preparation 1 (0.10 g, 0.8 mmol). The solution was warmed to 120°C. After 45 minutes the solution was cooled, taken up in H_2O, and extracted with ethyl acetate. The combined organic layers were washed with H_2O, dried over $NaSO_4$, filtered and concentrated in vacuo. Purification via flash chromatography (95:5 CH_2Cl_2/MeOH) afforded 2-[4-Amino-5-(5-chloro-2-isopropyl-4-methoxy-phenoxy)-pyrimidin-2-ylamino]-(R)-propan-1-ol (0.128 g, 50 %) as a solid; Mass Spec M+H = 366.

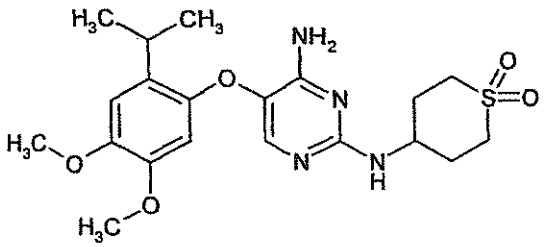
Example 5: 2-[4-Amino-5-(5-chloro-2-ethyl-4-methoxy-phenoxy)-pyrimidin-2-ylamino]-butan-1-ol



To a solution of N-(2-(R)-hydroxy-1-methyl-ethyl)-guanidine from Preparation 1 (0.15 g, 1.1 mmol) in 1 mL of dry DMSO was added 2-(5-chloro-2-isopropyl-4-methoxy-phenoxy)-3-methoxy-acrylonitrile (0.23 g, 0.9 mmol) from step 6 of Example 4. The mixture was heated at 120°C for 3.0 hours. The reaction mixture was cooled and 20 mL of water was added and was extracted with EtOAc (2 X 50 mL). The combined organic solution was then washed with water (3 X 50 mL), then with Brine. The solution was dried over $MgSO_4$, filtered and concentrated. The compound was purified by column chromatography on Silica Gel using 2% MeOH/dichloromethane. The fractions containing the product were combined and evaporated under reduced pressure to give crude product. This product was suspended in 2 mL of ether, and 0.6 mL of 1M HCl/ether (1.5 eq.) was added. 30 minutes later, the solid was filtered and washed with ether to give 160 mg of 2-[4-Amino-5-(5-chloro-2-isopropyl-4-methoxy-phenoxy)-pyrimidin-2-ylamino]-(R)-propan-1-ol as a hydrochloride salt: Mass Spec M+H = 367; MP; 111.4-116.9°C.

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

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

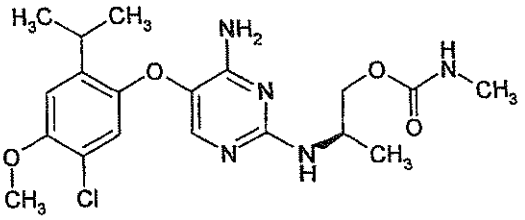


5-(2-Isopropyl-4,5-dimethoxy-phenoxy)-N*2*-(tetrahydro-thiopyran-4-yl)-pyrimidine-2,4-diamine was prepared according to the procedure of Example 5, using 2-(2-isopropyl-4,5-dimethoxy-phenoxy)-3-methoxy-acrylonitrile (prepared usingthe procedure of Example 4) together with N-(tetrahydro-thiopyran-4-yl)-guanidine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

To a mixture of 5-(2-isopropyl-4,5-dimethoxy-phenoxy)-N*2*-(tetrahydro-thiopyran-4-yl)-pyrimidine-2,4-diamine (0.19 g, 0.46 mmol) in 25 mL of methanol and 25 mL of water was added the OXONE (1.73 g, 1.4 mmol). This mixture was stirred at RT overnight. The reaction mixture was diluted with water (50 mL) and extracted with EtOAc (3 X 50 mL). The organic solution was washed with Brine, dried over $MgSO_4$. The solution was filtered and concentrated. The residue was purified on one preparative TLC plate (20 x 40 cm)

eluting with EtOAc. Product recovered was stirred with 1.5 eq of 1M HCl/ether to afford 25 mg of N*2*-(1,1-dioxo-hexahydro-1lambda*6*-thiopyran-4-yl)-5-(2-isopropyl-4,5-dimethoxy-phenoxy)-pyrimidine-2,4-diamine HCl salt): MS (M+H); 441: MP: 255.1 - 257.8°C.

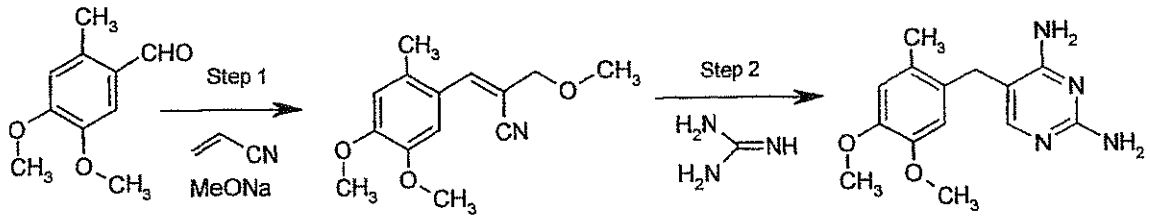
Example 7: **Methyl-carbamic acid 2-[4-amino-5-(5-chloro-2-isopropyl-4-methoxy-phenoxy)-pyrimidin-2-ylamino]-propyl ester**



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

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

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



Scheme H

This Example follows the procedure described by Manchand et al., J. Org. Chem. 57:3531-3535 (1992). Briefly, in step 1 4,5-dimethoxy-2-methyl-benzaldehyde and sodium methoxide were dissolved in cold methanol and stirred under nitrogen at RT for 18 hours. The

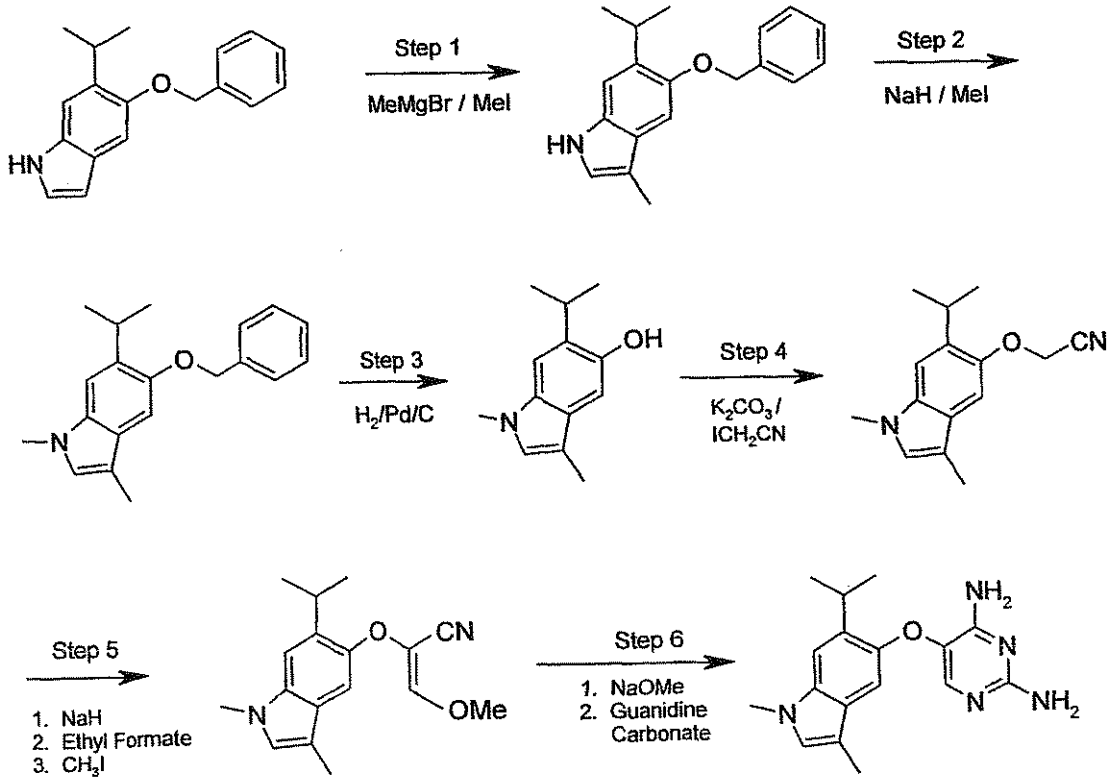
mixture was cooled to -15°C, and crude 3-(4,5-dimethoxy-2-methyl-phenyl)-2-methoxy-methyl-acrylonitrile was collected as filtrate.

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

Additional compounds made by the procedure of Example 8 are shown in Table 1.

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

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



SCHEME I

The 5-benzyloxy-6-isopropyl-1H-indole utilized in step 1 of this Example was prepared from 1-{2-[(5-benzyloxy)-4-(1-methylethyl)-2-nitrophenyl]ethenyl}-pyrrolidine according

to the procedure reported by Leonardi et al., Eur. J. Med. Chem. 29:551-559 (1994). The methylation of step 3 below also follows the procedure described by Leonardi et al.

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

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

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

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

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

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

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

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

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

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

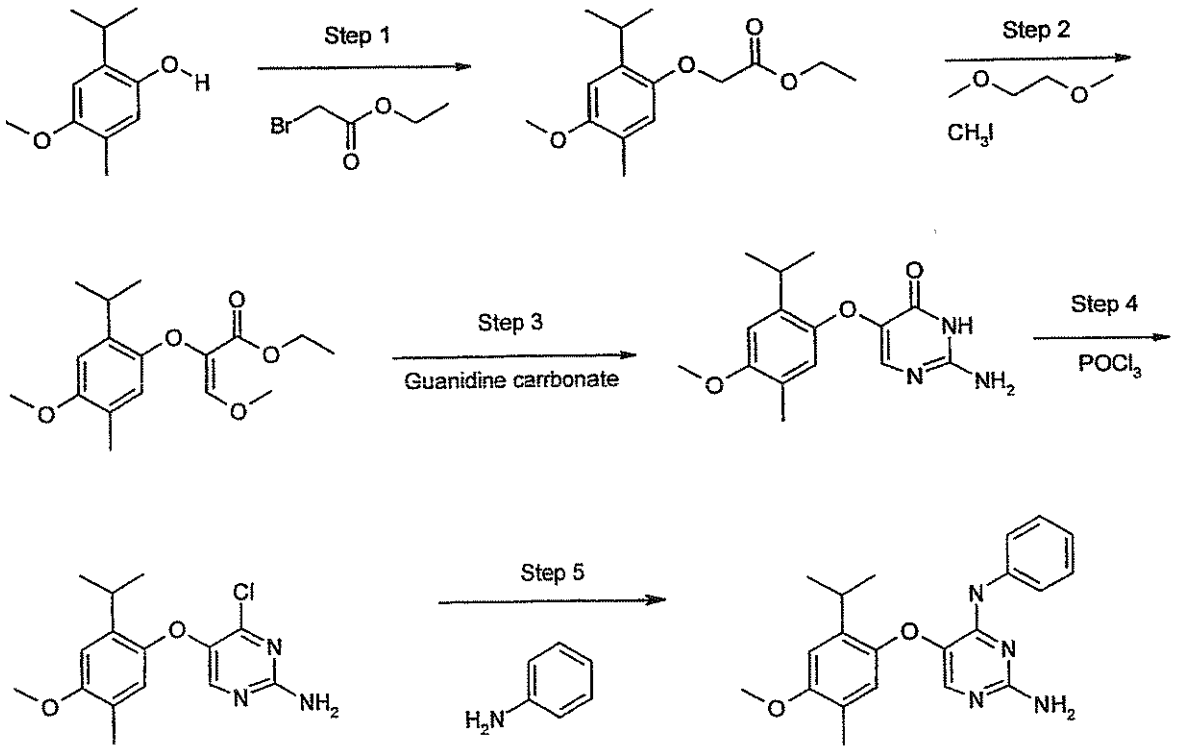
Step 6. 5-(6-Isopropyl-1,3-dimethyl-1H-indol-5-yloxy)-pyrimidine-2,4-diamine

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

5-(6-Isopropyl-1-methyl-1H-indol-5-yloxy)-pyrimidine-2,4-diamine was also prepared using the above procedure, but omitting the 3-methylation of step 1. MS (M+H): 298.

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

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



Scheme J

Step 1. (2-Isopropyl-4-methoxy-5-methyl-phenoxy)-acetic acid ethyl ester
To a solution of 2-isopropyl-4-methoxy-5-methyl-phenol (3.933 g, 21.8 mmol) in acetone (100 ml) was added potassium carbonate (20 g, 145 mmol) and ethyl bromoacetate (5ml, 45.1 mmol). The mixture was refluxed over night and was filtered through celite. The filtrate was concentrated under reduced pressure and the residue was partitioned between ethyl acetate and water. The organic phase was washed with brine and dried over anhydrous sodium sulfate. After removal of drying agent, the organic solution was concentrated under reduced pressure. The residue was purified with silica gel chromatography (10% to 15% methylene chloride in hexane) to yield (2-isopropyl-4-methoxy-5-methyl-phenoxy)-acetic acid ethyl ester as white solid (4.78 g, 82%).

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

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

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

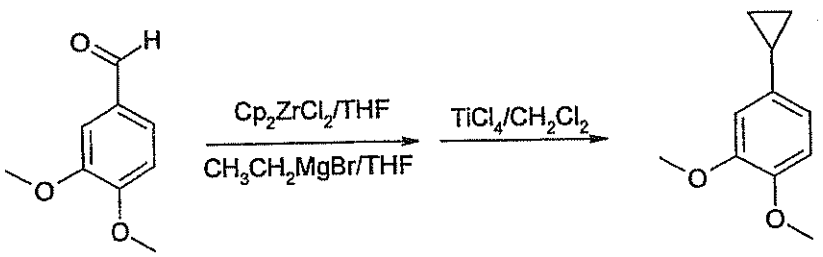
A mixture of 2-amino-5-(2-isopropyl-4-methoxy-5-methyl-phenoxy)-3H-pyrimidin-4-one in phosphorus oxychloride (5 ml) was heated at 110°C for 40 minutes and stirred at RT over night. Solvent was removed under reduced pressure and ice water was added. The aqueous solution was basified with potassium carbonate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

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

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

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

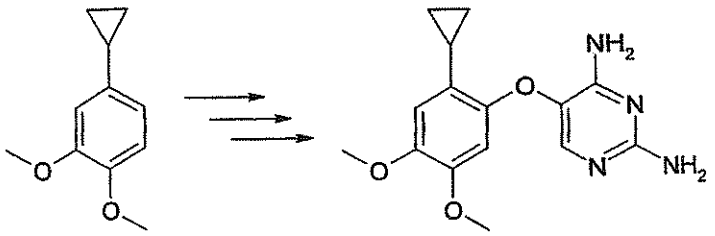
Step 1. 4-Cyclopropyl-1,2-dimethoxy-benzene



To a solution of zirconocene dichloride (1.76 g, 6.02 mmoles) in dry THF (25 ml), was slowly added ethylmagnesium bromide (12 ml, 1 M in THF, 12 mmol) at -78°C. The green solution was stirred for 15 minutes at -78°C and then warmed to 2°C until the reaction color turned red (15 minutes). A solution of 3,4-dimethoxy-benzaldehyde (1.00 g, 6.02 mmol) in dry THF (20 ml) was added and the reaction was allowed to warm up to RT over

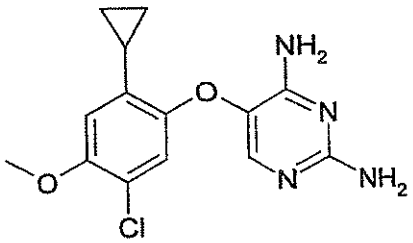
1.5 hours. Solvent was removed under reduced pressure, and dichloromethane (20 ml) was added. The reaction mixture was cooled to 0°C and titanium chloride (IV) (6 ml, 1M in dichloromethan, 6 mmol) was added. The reaction was allowed to warm up to RT over 30 minutes, and quenched with saturated ammonium chloride solution. The mixture was filtered through celite and portioned between dichloromethane and water. The combined dichloromethane was washed with saturated aqueous solution of ammonium chloride, saturated aqueous sodium bicarbonate and brine. The organic phase was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (gradient: 8% to 30%ethyl acetate in hexane) to yield 4-cyclopropyl-1,2-dimethoxy-benzene as yellow oily residue (0.2 g, 19%). Ref: Vincent Gandon et al. Eur. J. Org. Chem. 2000, 3713. ^{1}H NMR ($CDCl_3$) d: 0.60-0.66 (m, 2H), 0.87-0.92 (m, 2H), 1.81-1.91 (m, 1H), 3.85 (s, 3H), 3.87 (s, 3H), 6.62-6.79(m, 3H).

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

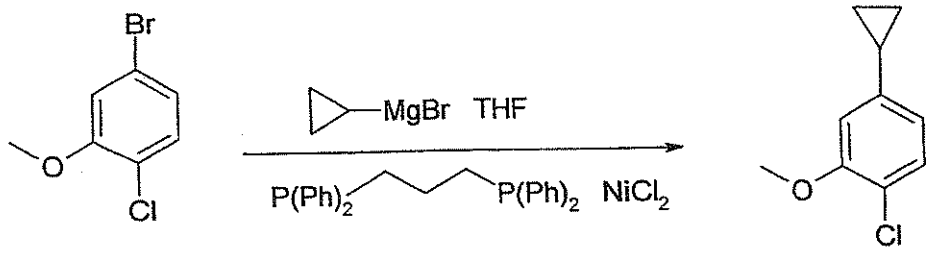


5-(2-Cyclopropyl-4,5-dimethoxy-phenoxy)-pyrimidine-2,4-diamine was prepared from 4-cyclopropyl-1,2-dimethoxy-benzene following the procedure of step 1 and steps 3-7 of Example 2 above.

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

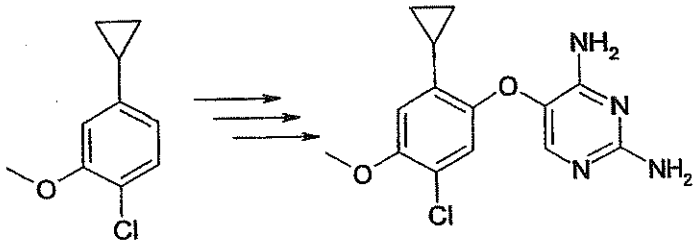


Step 1. 1-Chloro-4-cyclopropyl-2-methoxy-benzene



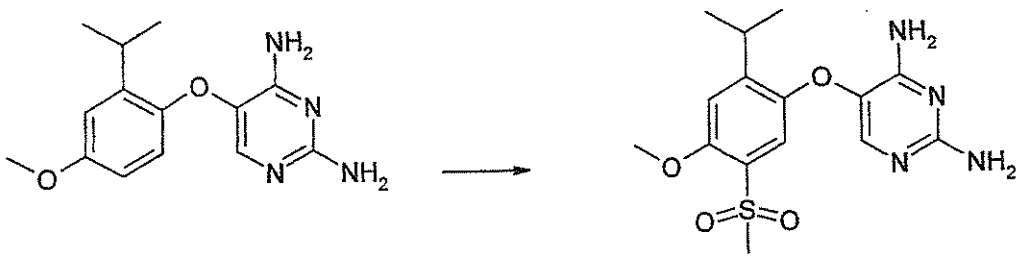
To a solution of 4-bromo-1-chloro-2-methoxy-benzene (1.45 g, 6.55 mmol) in dry THF (10 ml), was added {1,3-bis (diphenylphosphino)-propane} dichloronickel (II) and cyclopropylmagnesium bromide (46 ml,0.5 M in THF, 23 mmoles) at RT. The solution was stirred at RT for 2 hours, and then heated at 65°C for 48 hours. Aqueous hydrochloric acid solution (1 N, 20 mL) was aded, and the mixture was then cooled to RT and stirred for 30 minutes. The reaction mixture was partitioned between ethyl acetate and water. The combined organic phase was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (2% ethyl acetate in hexane) to yield 1-chloro-4-cyclopropyl-2-methoxy-benzene as yellow oily residue (0.81 g, 67%). ^{1}H NMR ($CDCl_3$) d: 0.65-0.70 (m, 2H), 0.94-1.00 (m, 2H), 1.85-1.89 (m, 1H), 3.89 (s, 3H), 6.57(dd, 1H, J=8.1 Hz, 2.0 Hz), 7.21 (d, 1H, J=8.1 Hz).

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



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

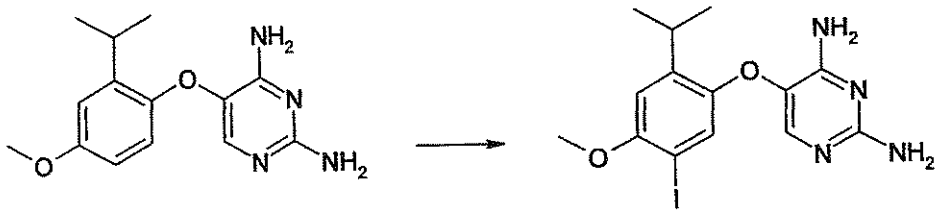
Example 13: 5-(2-Isopropyl-5-methanesulfonyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine



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

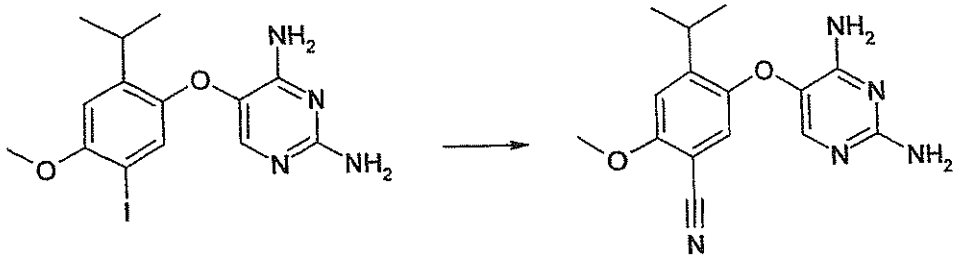
Example 14: 5-[5-(2,3-Dihydro-1H-tetrazol-5-yl)-2-isopropyl-4-methoxy-phenoxy]-pyrimidine-2,4-diamine

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



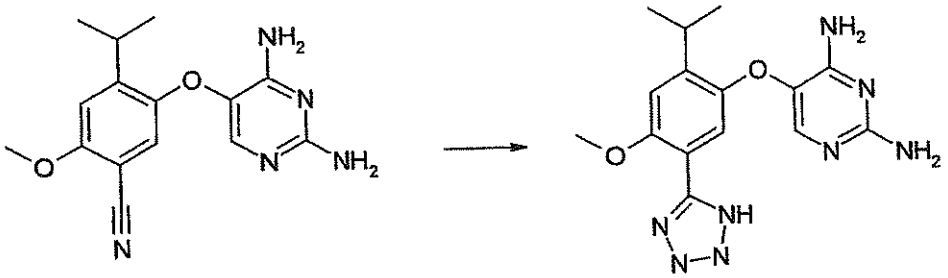
To a solution of 5-(2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine (0.40 g, 1.44 mmol) in glacial acetic acid (4 ml) at RT was added a solution of iodine monochloride (0.28 g, 1.76 mmol) in glacial acetic acid (4 ml). Water (6 ml) was also added, and the reaction was stirred for 16 hours, after which another portion of iodine monochloride (0.4g, 2.47mmole) in glacial acetic acid (4ml) was added. The reaction mixture was stirred for an additional hour at RT. The acidic mixture was basified with saturated $NaHCO_3$ solution and extracted into dichloromethane. The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified via flash chromatography (5%CH_3OH in CH_2CL_2 with 0.1% NH_4OH) to give 5-(5-iodo-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine as beige colored solid (0.536 g, 92%). M+H 400.

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



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

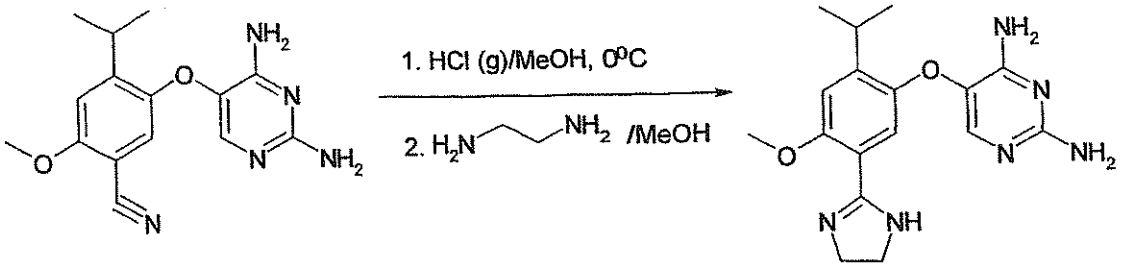
Step 3. 5-[5-(2,3-Dihydro-1H-tetrazol-5-yl)-2-isopropyl-4-methoxy-phenoxy]-pyrimidine-2,4-diamine



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

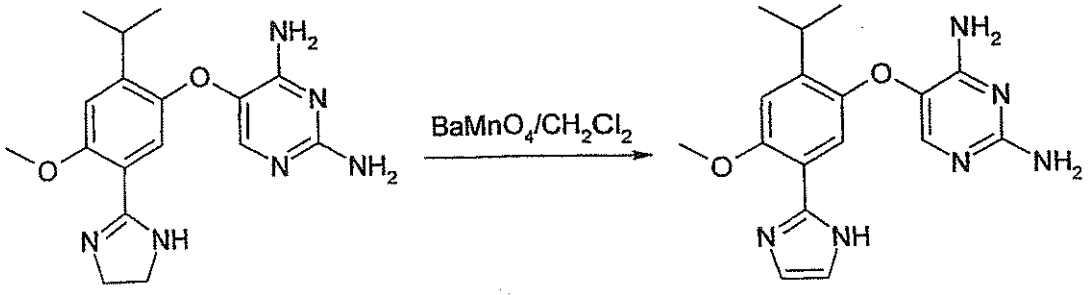
Example 15: 5-[5-(1H-Imidazol-2-yl)-2-isopropyl-4-methoxy-phenoxy]-pyrimidine-2,4-diamine

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



A cooled (0°C) suspension of 5-(2,4-diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-benzonitrile (0.138 g, 0.461 mmol) in dry methanol (15 ml) was bubbled with HCl gas for 10 minutes and refrigerated overnight. Solvent was evaporated under reduced pressure to give a yellow solid which was redissolved in dry methanol (10 ml). Ethylene diamine (0.034 ml, 0.509mmol) was added and the reaction mixture was refluxed for 20 hours and concentrated under reduced pressure. The residue was purified by silica gel chromatography (gradient: 7- 50% methanol in methylene chloride /0.1% concentrated NH_4OH) to yield 5-[5-(4,5-dihydro-1H-imidazol-2-yl)-2-isopropyl-4-methoxy-phenoxy]-pyrimidine-2,4-diamine which was crystalized from methanol /ethyl acetate /ether as a white solid, (0.053g, 33%). ^{1}H NMR (DMSO) delta: 1.26 (d, 6H, J=6.9 Hz), 3.33-3.48 (m, 5H), 3.85 (s, 3H), 5.83 (b, 2H), 6.30 (b, 2H), 6.56(b, 1H), 6.97 (s, 1H), 7.19 (s, 1H), 7.33 (s, 1H). M+H: 343.

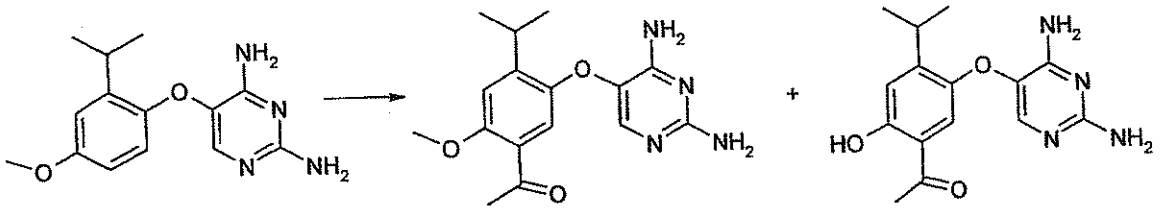
Step 2. 5-[5-(1H-Imidazol-2-yl)-2-isopropyl-4-methoxy-phenoxy]-pyrimidine-2,4-diamine



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

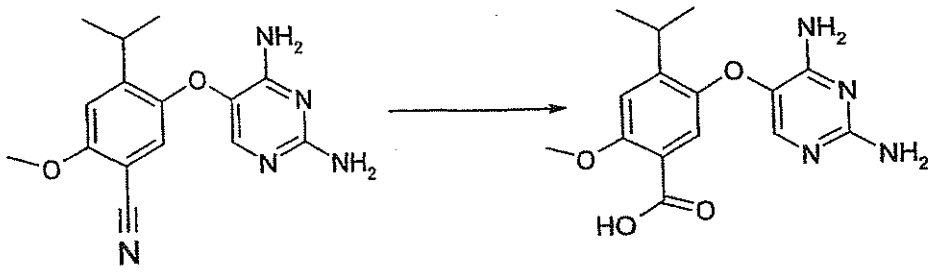
methanol in methylene chloride /0.1% concentrated ammonium hydroxide) to yield 5-[5-(1H-imidazol-2-yl)-2-isopropyl-4-methoxy-phenoxy]-pyrimidine-2,4-diamine as pale yellow solid (0.026 g, 41%). ^{1}H NMR (DMSO) delta: 1.29 (d, 6H, J=6.9 Hz), 3.3-3.39 (m, 1H), 3.94 (s, 3H), 5.53 (b, 2H), 6.00 (b, 2H), 7.01 (b, 3H), 7.36 (b, 1H), 7.45 (s, 1H). M+H: 341, M-H: 339.

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



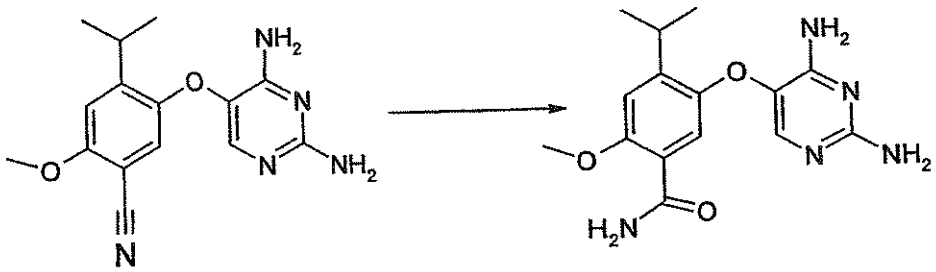
5-(2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine in anhydrous dichloroethane (20 mL) was added to TFA (0.06 mL, 0.77 mmol), acetyl chloride (0.31 mL, 4.37 mmol), and aluminum trichloride (583 mg, 4.37 mmol). After stirring for 22 hours at RT, water (1.2 mL) was added to the reaction at 0°C. The mixture was dried using anhydrous sodium sulfate and concentrated in vacuo. Aqueous sodium hydroxide (0.2M, 10 mL) was added to the residue and the mixture was heated at 100°C for 1 hour. After cooling, the reaction was extracted with dichloromethane. The dichloromethane layer was dried using anhydrous magnesium sulfate, concentrated, and purified with silica gel column chromatography eluting with 96/4/0.1 dichloromethane/ methanol/ ammonium hydroxide to yield 1-[5-(2,4-diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-ethanone (72 mg, 31%) as off-white solid, MS (M+H) = 317, ^{1}H NMR (hydrochloride salt) – (DMSO-d_6) δ: 1.24 (d, 6H, J = 6.9 Hz), 2.51 (s, 3H), 3.19 (m, 1H, J = 6.9 Hz), 3.93 (s, 3H), 7.13 (s, 1H), 7.18 (s, 1H), 7.29 (s, 1H), 7.62 (s, 2H), 8.30 (s, 1H), 8.60 (s, 1H), 12.01 (s, 1H). Also recovered was 1-[5-(2,4-diamino-pyrimidin-5-yloxy)-2-hydroxy-4-isopropyl-phenyl]-ethanone (43 mg, 20%) as pale yellow solid, MS (M+H) = 303, ^{1}H NMR (hydrochloride salt) – (DMSO-d_6) δ: 1.18 (d, 6H, J = 6.9 Hz), 2.59 (s, 3H), 3.10 (m, 1H, J = 6.9 H), 7.00 (s, 1H), 7.26 (s, 1H), 7.54 (s, 1H), 7.60 (s, 2H), 8.32 (s, 1H), 8.62 (s, 1H), 11.75 (s, 1H), 12.05 (s, 1H)

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



To a suspension of 5-(2,4-diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-benzonitrile (50 mg, 0.17 mmol, from Example 15) in ethanol (1 mL) was added sodium hydroxide (174 mg, 4.34 mmol, dissolved in 1 mL water). After refluxing overnight, the reaction was cooled in an ice bath. Aqueous hydrochloric acid (3M) was added until the pH of the reaction was 7. The white solid precipitate was collected, washed with small amounts of water and dichloromethane, and dried to yield 5-(2,4-diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-benzoic acid: (51 mg, 96%, MS (M+H) = 319), which was converted to the hydrochloride salt: ^{1}H NMR – (DMSO-d_6) : 1.23 (d, 6H, J = 6.9 Hz), 3.17 (m, 1H, J = 6.9 Hz), 3.85 (s, 3H), 7.08 (s, 1H), 7.26 (s, 2H), 7.53 (s, 2H), 8.33 (s, 1H), 8.60 (s, 1H), 11.65 (s, 1H).

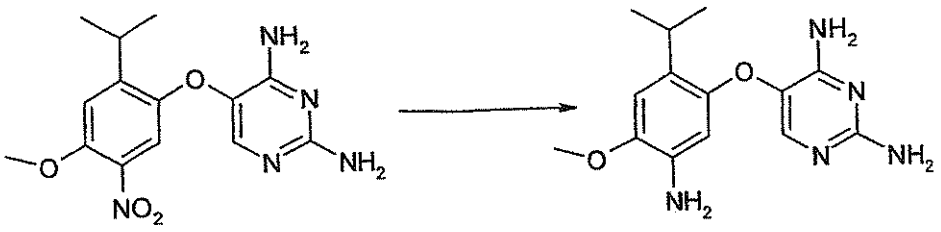
Example 18: 5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-benzamide



To 5-(2,4-diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-benzonitrile (49 mg, 0.16 mmol, from Example 15) suspended in ethanol (1 mL) was added sodium hydroxide (64 mg, 1.60 mmol, dissolved in 1 mL water). The reaction was heated at 110°C for 5 hours, cooled, and washed with dichloromethane (25 mL). The dichloromethane layer was concentrated and purified by preparatory TLC plates (92/8/0.5 dichloromethane/ methanol/ ammonium hydroxide) to yield 5-(2,4-diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-benzamide as white solid (9 mg, 17%, MS (M+H) = 318), which was converted to the hydrochloride salt: ^{1}H NMR – (DMSO-d_6) δ: 1.05 (d, 6H, J = 6.9 Hz), 3.00 (m, 1H, J = 6.9 Hz), 3.75 (s, 3H), 6.91 (s, 1H), 7.07 (s, 1H), 7.21 (s, 1H), 7.37 (s, 2H), 7.44 (s, 1H), 7.47 (s, 1H), 8.15 (s, 1H), 8.43 (s, 1H), 11.52 (s, 1H)

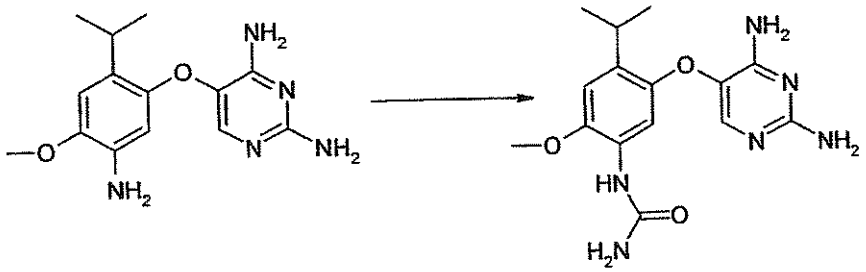
Example 19: [5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-urea

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



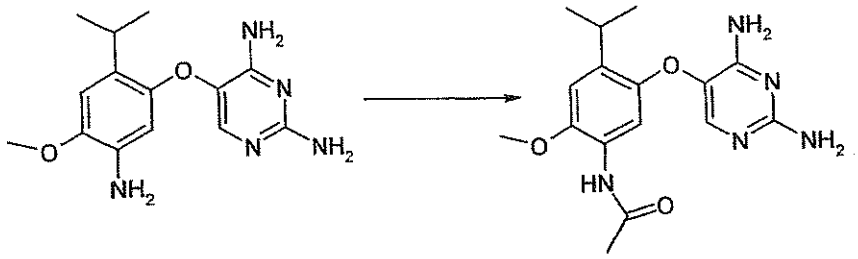
To 5-(2-isopropyl-4-methoxy-5-nitro-phenoxy)-pyrimidine-2,4-diamine (2.1 g, 6.58 mmol) suspended in ethanol (150 mL) in a Parr bomb, was added 10% palladium on charcoal (210 mg). After hydrogenation in the Parr hydrogenator overnight at 35 psi, the reaction was filtered through celite. The celite pad was washed with ethanol and ethyl acetate and the filtrate was concentrated. Purification with silica gel column chromatography (92/8/0.1 dichloromethane/ methanol/ ammonium hydroxide) gave 5-(5-amino-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine as a pale orange solid (468 mg, 25%, $(M+H)^+ = 290$), which was converted to the hydrochloride salt. ^1H NMR – (DMSO-d_6) δ: 0.99 (d, 6H, J = 6.9 Hz), 2.92 (m, 1H, J = 6.9 Hz), 3.66 (s, 3H), 6.64 (s, 1H), 6.82 (s, 1H), 7.05 (s, 1H), 7.40 (s, 2H), 8.10 (s, 1H), 8.42 (s, 1H).

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



To 5-(5-amino-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine (314 mg, 1.09 mmol) suspended in water (3 mL) was added acetic acid (0.25 mL, 4.34 mmol). Once all solids had dissolved, sodium cyanate (71 mg, 1.09 mmol, dissolved in 1.5 mL water) was added dropwise. After 30 minutes, the reaction was concentrated and purified with silica gel column chromatography eluting with 92/8/0.1 dichloromethane/ methanol/ ammonium hydroxide to yield [5-(2,4-diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-urea as an off-white solid (244 mg, 68%, $(M+H)^+ = 333$), which was converted to a hydrochloride salt: ^1H NMR – (DMSO-d_6) δ: 1.18 (d, 6H, J = 6.9 Hz), 3.02 (m, 1H, J = 6.9 Hz), 3.89 (s, 3H), 6.94 (s, 1H), 7.00 (s, 1H), 7.54 (s, 2H), 7.85 (s, 1H), 8.08 (s, 1H), 8.38 (s, 1H), 8.63 (s, 1H), 11.61 (s, 1H)

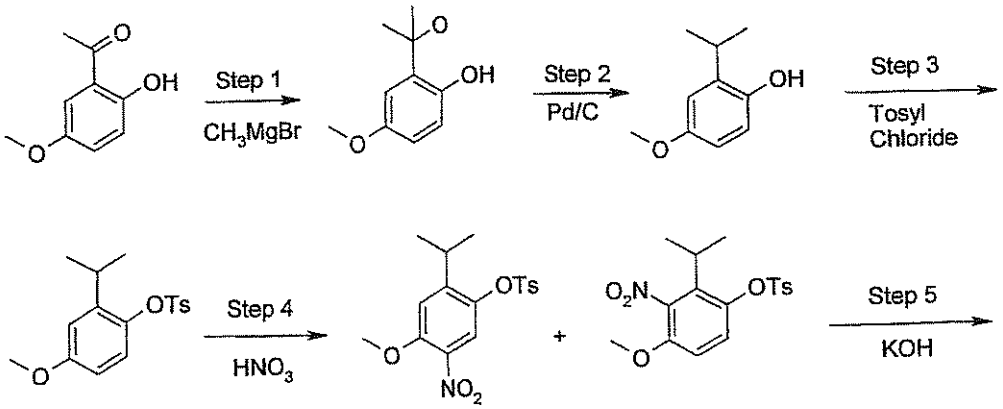
Example 20: N-[5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-acetamide

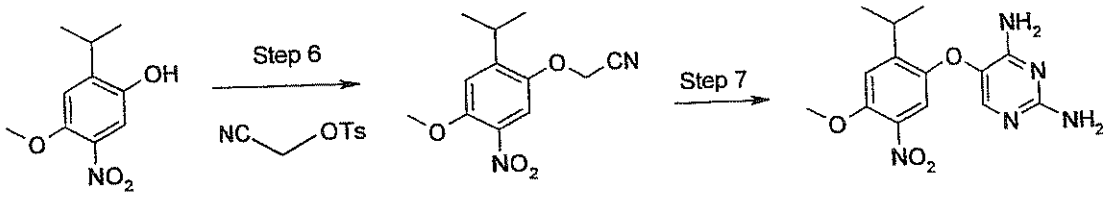


To 5-(5-amino-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine (100 mg, 0.35 mmol, from Example 17) dissolved in anhydrous dichloromethane (10 mL) was added anhydrous pyridine (0.03 mL, 0.38 mmol). To this reaction mixture at 0°C was added acetyl chloride (0.03 mL, 0.38 mmol). After stirring at RT for 1 hour, the reaction was concentrated and purified with preparatory TLC (93/7/0.5 dichloromethane/ methanol/ ammonium hydroxide) to yield an off-white solid (74 mg mixture of bis- and tris-acetylated products). To this solid was added aqueous sodium hydroxide (0.2 M, 2 mL), and the mixture was refluxed for 1 hour, cooled, and washed with dichloromethane (10 mL). The dichloromethane layer was dried using anhydrous magnesium sulfate and concentrated in vacuo to yield N-[5-(2,4-diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-acetamide as a white solid (53 mg, 46%, $M+H)^+$ =332) which was converted to a hydrochloride salt: ^{1}H NMR – (DMSO-d_6) δ: 1.21 (d, 6H, J = 6.9 Hz), 2.08 (s, 3H), 3.09 (m, 1H, J = 6.9 Hz), 3.88 (s, 3H), 7.00 (s, 1H), 7.09 (s, 1H), 7.57 (s, 2H), 7.74 (s, 1H), 8.36 (s, 1H), 8.63 (s, 1H), 9.26 (s, 1H), 11.75 (s, 1H).

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

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





SCHEME K

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

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

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

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

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

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

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

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

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

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

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

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

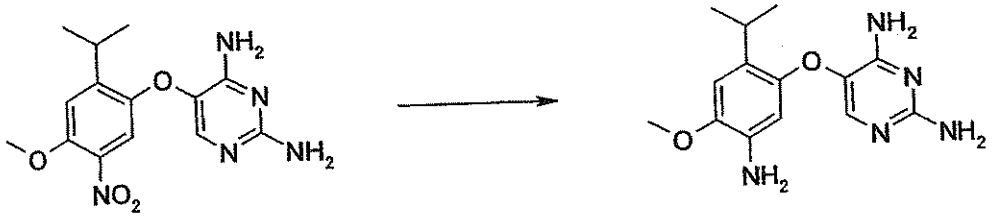
Step 7. 5-(2-Isopropyl-4-methoxy-5-nitro-phenoxy)-pyrimidine-2,4-diamine

A mixture of (2-isopropyl-4-methoxy-5-nitro-phenoxy)-acetonitrile (8.785 g, 35.5 mmol) and Brederick's reagent (14.6 mL, 70.9 mmol) was warmed to 100°C. After 45 min the mixture was evaporated under reduced pressure (50°C, 50 mtorr) to give an orange solid. The solid was added to a solution of aniline hydrochloride (9.19 g, 70.9 mmol) in 150 mL of EtOH. The mixture was warmed to reflux. After 16 hr additional aniline hydrochloride (4.596 g, 35.5 mmol) was added mixture was continued at reflux for 4 h. The solution was concentrated in vacuo and poured into H_2O. The mixture was extracted with ethyl acetate, washed with H_2O, washed with brine, dried over Na_2SO_4, and concentrated in vacuo to afford a yellow-green solid. This crude product was added to a mixture of 200 mL NMP

and guanidine carbonate (17.70 g, 98 mmol) and warmed to 130°C. After 5 hours the mixture was cooled then poured onto 2 l of an ice/H_2O mixture. The resulting precipitate was filtered, washed with H_2O and dried under vacuum (50°C). The crude solid was recrystallized from EtOH to afford 5-(2-isopropyl-4-methoxy-5-nitro-phenoxy)-pyrimidine-2,4-diamine (8.14 g, 63%, 3 steps) as a yellow crystalline solid (solvated 1:1 with EtOH). $M+H)^+ = 320$.

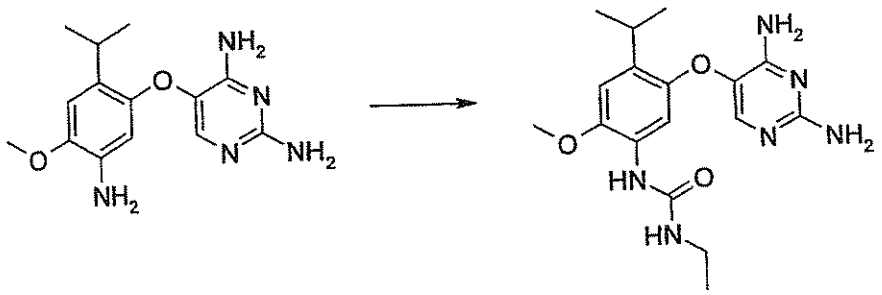
Example 22: 1-[5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-3-ethyl-urea

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



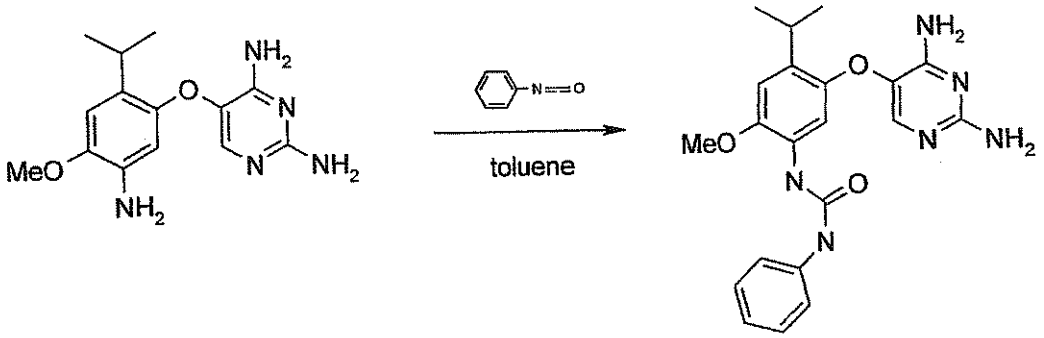
To a solution of 5-(2-isopropyl-4-methoxy-5-nitro-phenoxy)-pyrimidine-2,4-diamine (2.953 g, 9.2 mmol) in 250 mL EtOH and 25 AcOH was added 10% Pd/C. The mixture was placed under 50 psi of H_2 via a Parr hydrogenator. After 2.5 h the mixture was filtered through a pad of celite. The pad was washed with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

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



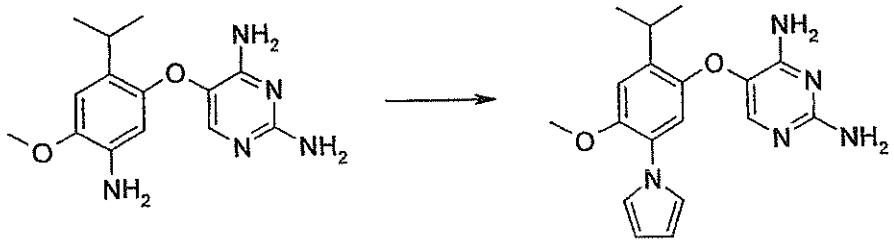
A solution of 5-(5-amino-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine (0.117 g, 0.4 mmol) and ethyl isocyanate (0.034 g, 0.5 mmol) in 4 mL of toluene was heated to 100°C in a sealed tube. After 5 h the solution was cooled and concentrated in vacuo gave a brown solid. Purification via flash chromatography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

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



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

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

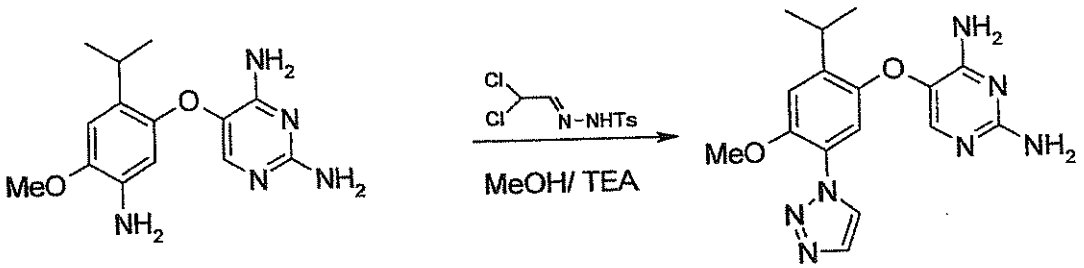


To a solution of 5-(5-amino-2-Isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine (0.303 g, 1.0 mmol) in 15 mL AcOH was added 2,5-dimethoxypyran (0.152 g, 1.2 mmol). The solution was warmed to reflux. After 2 h the solution was cooled and poured over ice/H_2O. The solution was converted to pH = 8 with 50% NaOH and extracted with ethyl acetate (3x75 mL). The combined organics were washed with H_2O, washed with brine, dried with Na_2SO_4, filtered and concentrated in vacuo to give a brown solid. Purification

via flash chromatography (CH_2Cl_2/MeOH 97:3) afforded 5-(2-isopropyl-4-methoxy-5-pyrrol-1-yl-phenoxy)-pyrimidine-2,4-diamine (0.244 g, 72%) as a pale yellow solid. (M+H) = 340.

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

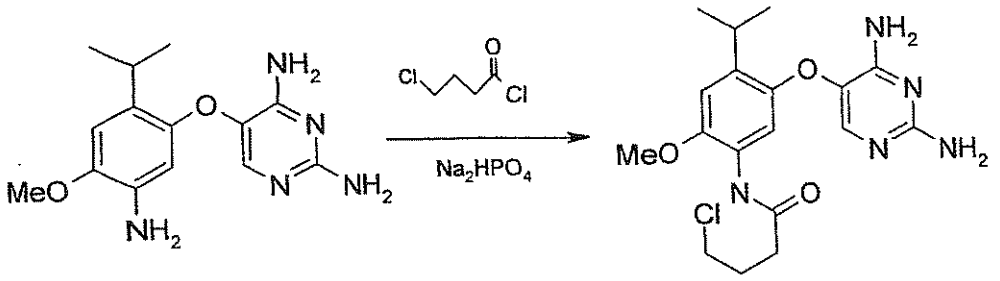
Example 25: 5-(2-Isopropyl-4-methoxy-5-[1,2,3]triazol-1-yl-phenoxy)-pyrimidine-2,4-diamine



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

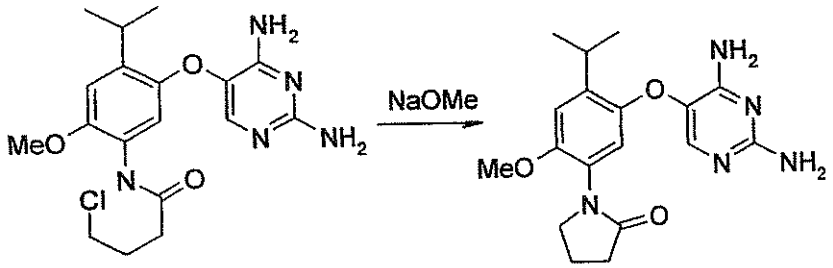
Example 26: 1-[5-(4-Amino-2-methyl-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-pyrrolidin-2-one

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



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

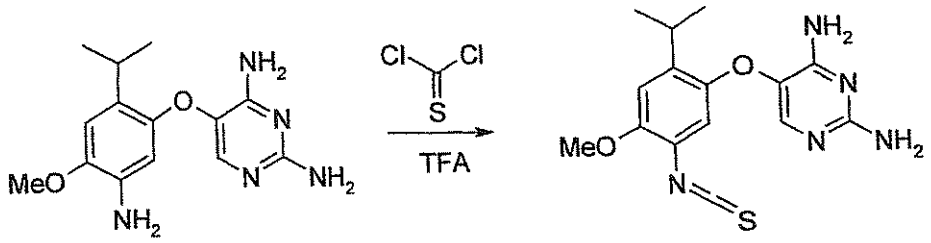
Step 2. 1-[5-(4-Amino-2-methyl-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-pyrrolidin-2-one



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

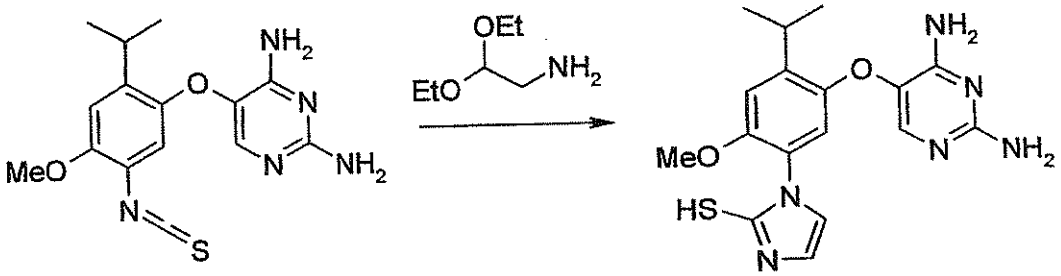
Example 27: 1-[5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-1H-imidazole-2-thiol

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



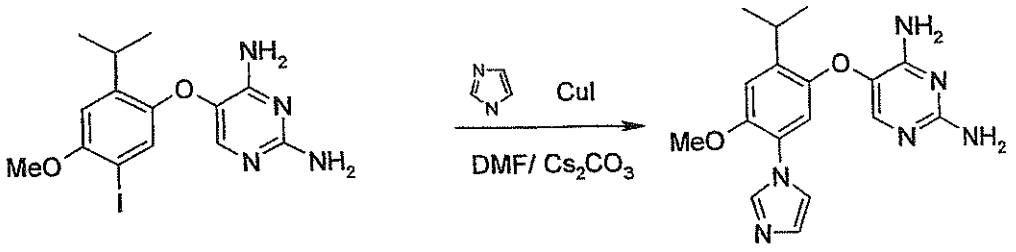
To a solution of 5-(5-amino-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine (0.100 g, 0.4 mmol) in 1 ml H_2O and TFA (0.040 g, 0.4 mmol) was added thiophosgene (0.040 g, 0.4 mmol) were added. After 1 h the mixture was neutralized with 2M NaOH and extracted with CH_2Cl_2. The combined organics were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

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



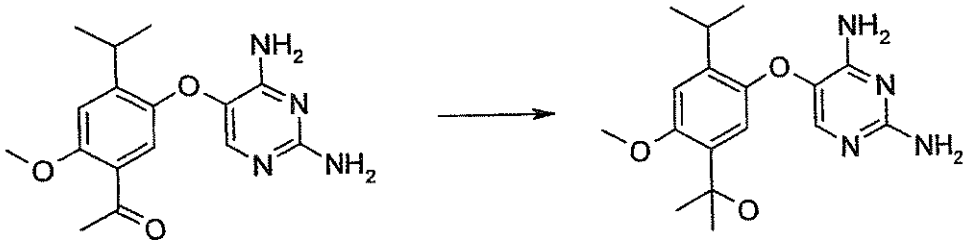
To a solution of amino acetal (0.173 g, 1.3 mmol) in 10 ml EtOH was added a solution of thio-isocyanate (0.430 g, 1.3 mmol) in 2 ml EtOH. The mixture was warmed to reflux. After 30 min the mixture was cooled, concentrated in vacuo and suspended in 1M HCl and refluxed again for another 30 min reaction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

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



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

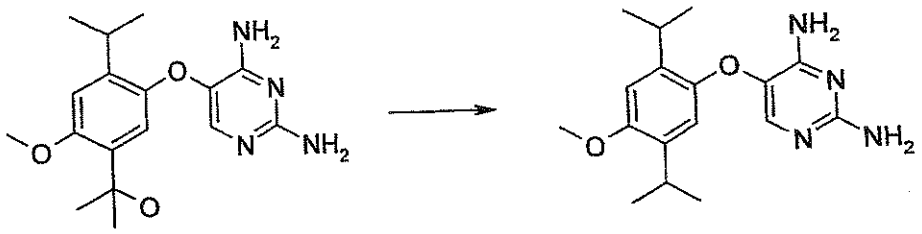
Example 29: 2-[5-(2,4-Diaminopyrimidin-5-yloxy)-4-isopropyl-2methoxy-phenyl]-propan-2-ol



To a solution of methylmagnesium bromide (83.4 mmol, 27.8 ml, 3.0 M in Et_2O) in 83 mL THF at 0°C was added 1-[5-(2,4-diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-ethanone (2.523 g, 8.3 mmol, from Example 16) in portions. After 16 h the mixture cooled to 0°C and was quenched by the addition 10% NH_4Cl. H_2O was added and the mixture was extracted with ethyl acetate. The combined organics were washed with H_2O, washed with brine, dried over $NaHCO_3$, filtered and concentrated in vacuo. The crude solid was purified via flash chromatography (94:6 CH_2Cl_2/MeOH) to afford acetophenone X (1.00 g, 40 % recovered) as a white solid and alcohol X (1.00 g, as a 1:1 mixture of methylated/demethylated). The mixture of alcohols were taken up in 31 ml DMF. K_2CO_3 (0.65 g, 4.7 mmol) and Iodomethane (0.098 ml, 1.6 mmol) were added and the mixture was warmed to 50°C. Additional portions of iodomethane (0.019 mL, 0.6 mmol) was added at 1, 2 and 3 hr. After 16 h the mixture was cooled and 10% NH_4Cl and extracted with ethyl acetate. The combined organics were washed with H_2O, washed with brine, dried with Na_2SO_4, filtered and concentrated in vacuo to give 2-[5-(2,4-diaminopyrimidin-

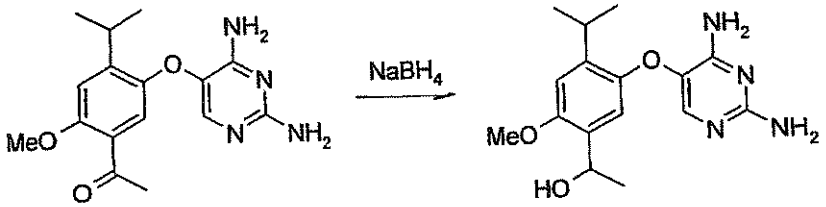
5-yloxy)-4-isopropyl-2-methoxy-phenyl]-propan-2-ol (0.711 g, yiled) as a white solid. $[MH]^+ = 333$.

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



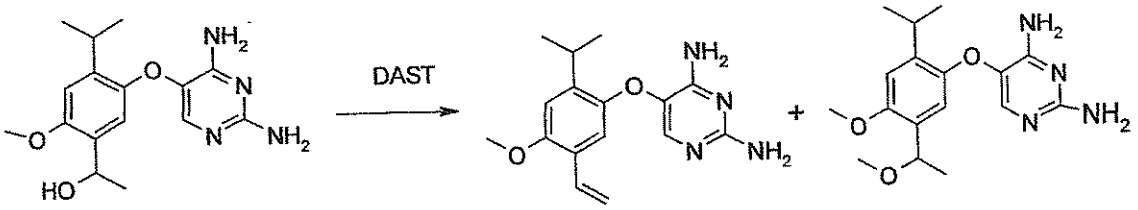
To a solution of 2-[5-(2,4-diaminopyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-propan-2-ol (0.350 g, 1.1 mmol) in 10 ml CH_2Cl_2 was added TFA (4.0 ml, 52.6 mmol) and triethylsilane (1.7 ml, 10.5 mmol). After 30 min saturated $NaHCO_3$ was added and the mixture was extracted with ethyl acetate. The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

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



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

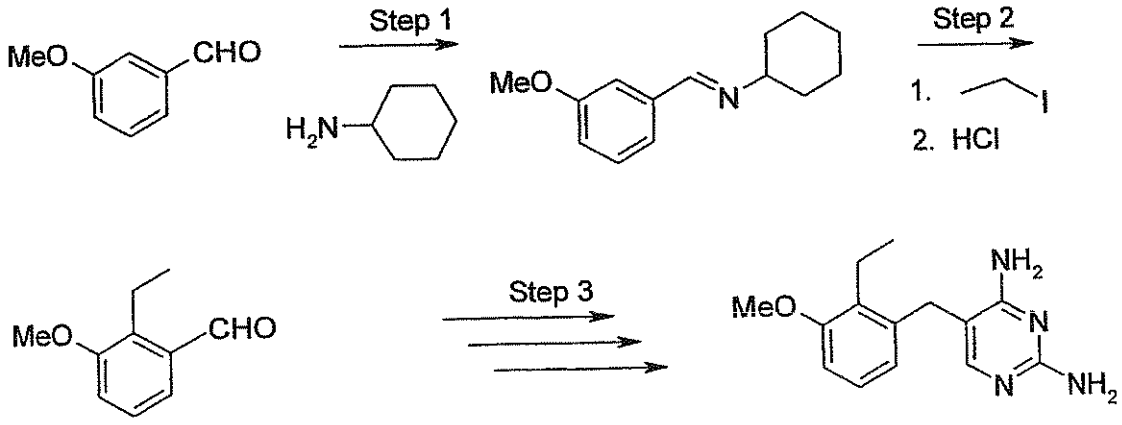
Example 32: 5-(2-Isopropyl-4-methoxy-5-vinyl-phenoxy)-pyrimidine-2,4-diamine and 5-[2-Isopropyl-4-methoxy-5-(1-methoxy-ethyl)-phenoxy]-pyrimidine-2,4-diamine



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

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

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



SCHEME M

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

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

Step 2. 2-Ethyl-3-methoxy benzaldehyde

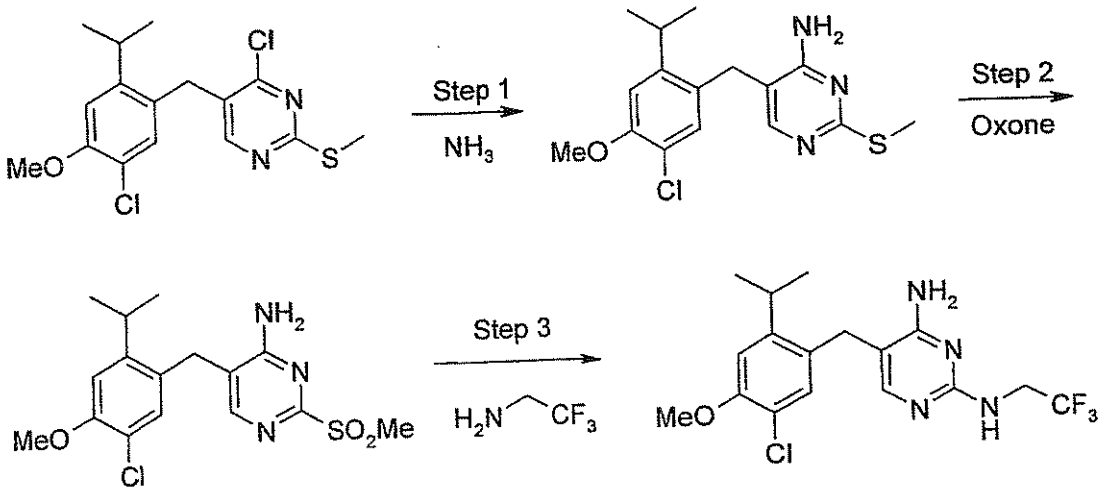
To a solution of 2,2,6,6-tetramethylpiperidine (4.67 g, 33 mmol) in 75 ml THF at –15°C was added *n*-butyllithium (12.6 ml, 32 mmol, 2.5 in hexanes) drop-wise maintaining the internal temperature below – 10°C. After 15 min a solution of cyclohexyl-(3-methoxy-benzylidene)-amine (3.259 g, 15.0 mmol) in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

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

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

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

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



SCHEME M

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

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

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

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

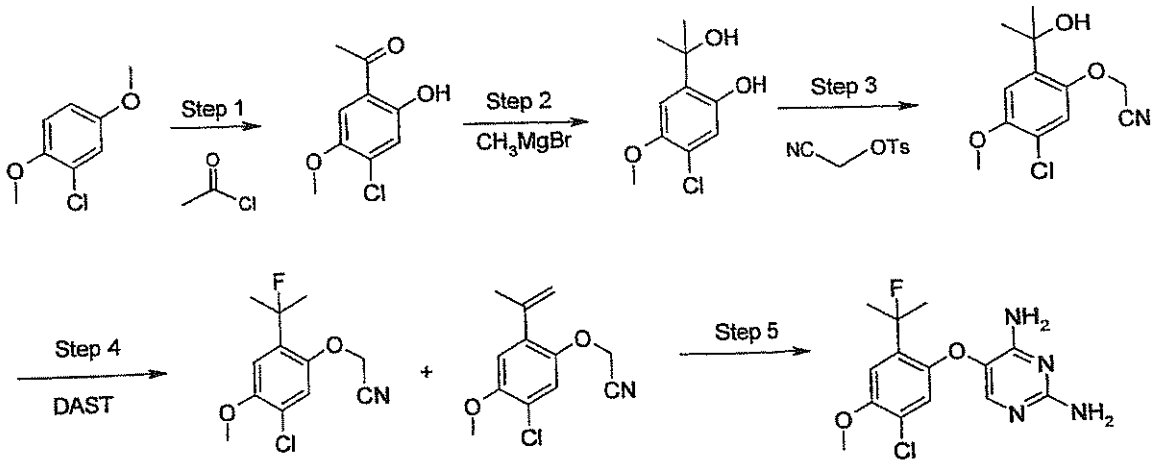
Step 3. 5-(5-Chloro-2-isopropyl-4-methoxy-benzyl)-N^2-(2,2,2-trifloro-ethyl)-pyrimidine-2,4-diamine

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

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

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

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



SCHEME N

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

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

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

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

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

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

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

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

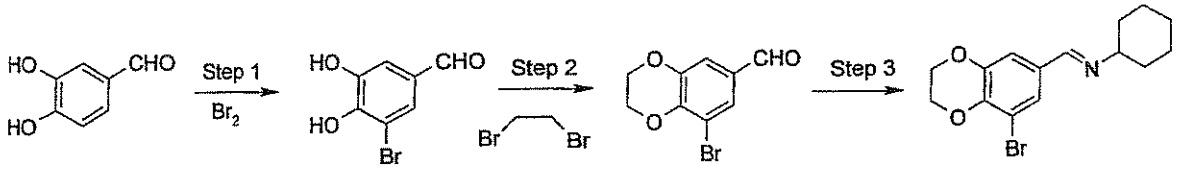
Step 5. 5-[5-Chloro-2-(1-fluoro-1-methyl-ethyl)-methoxy-phenoxy]-pyrimidine-2,4-diamine

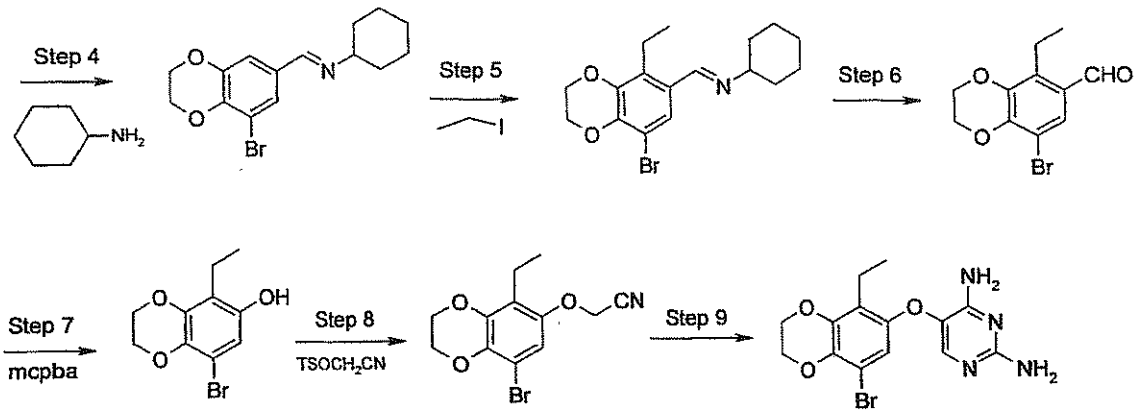
5-[5-Chloro-2-(1-fluoro-1-methyl-ethyl)-methoxy-phenoxy]-acetonitrile (1.447 g, 4.2 mmol) was converted, as describe in steps 6 and 7 of Example 2, to 5-[5-chloro-2-(1-fluoro-1-methyl-ethyl)-methoxy-phenoxy]-pyrimidine-2,4-diamine (0.263 g, 10 % for three steps) as a yellow solid; mp = 220.1-220.6°C (HCl salt); $[MH]^+ = 328$.

Similarly prepared, but starting with 3-fluoro-1,4-dimethoxybenzene, and using hydrogenation with Pd/C in step 4 instead of DAST, was 5-(5-Fluro-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine (0.778 g, 42%); mp (HCl salt) = 239-241°C; $[MH]^+ = 293$.

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

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





SCHEME O

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

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

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

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

Step 3. (8-Bromo-2,3-dihydro-benzo[1,4]dioxine-6-ylmethylene)-cyclohexyl-amine

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

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

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

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

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

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

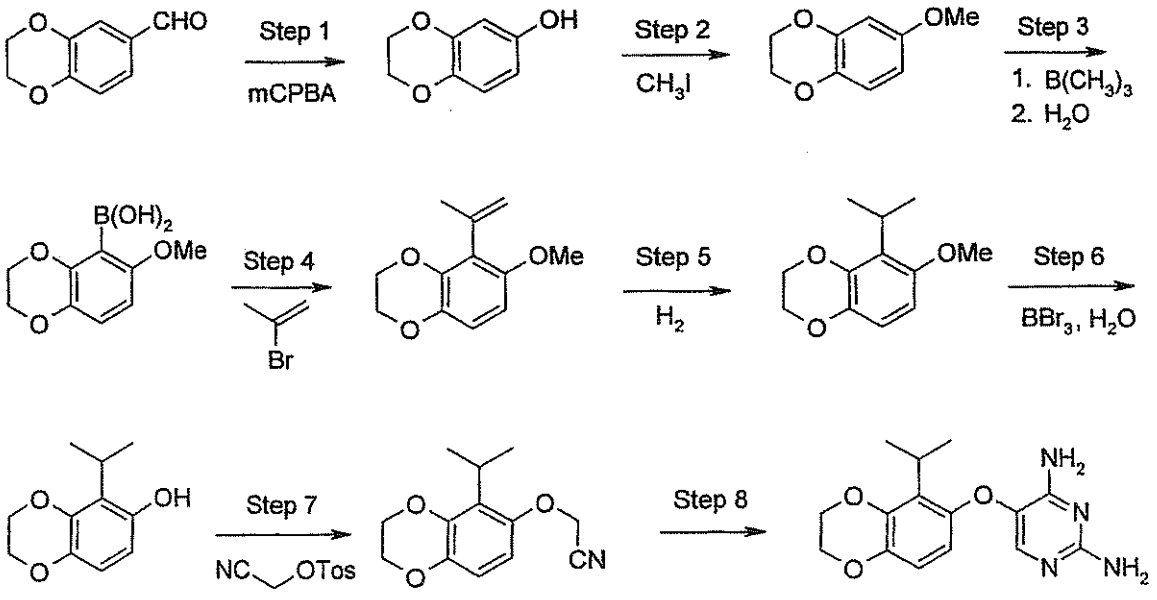
8-Bromo-5-ethyl-2,3-dihydro-benzo[1,4]dioxin-6-ol (3.182 g, 12.3 mmol), as described in the procedure of Step 6 of Example 21, was converted to cyanomethyl ether 8-Bromo-5-ethyl-2,3-dihydro-benzo[1,4]dioxin-6-yloxy)-acetonitrile (2.30 g, 63%).

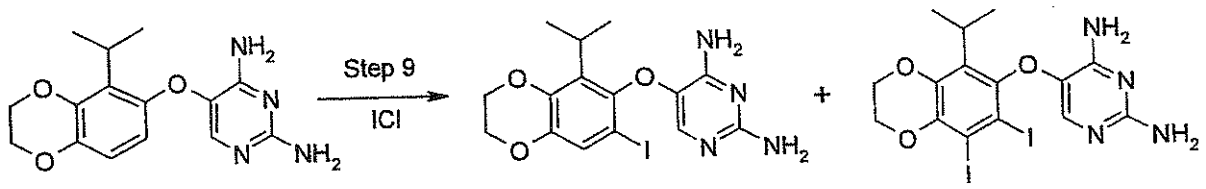
Step 7. 5-(8-Bromo-5-ethyl-2,3-dihydro-benzo[1.4]dioxin-6-yloxy)-pyrimidine-2,4-diamine

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

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

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





SCHEME P

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

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

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

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

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

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

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

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

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

Step 7. 5-Isopropyl-2,3-dihydro-benzo[1,4]dioxin -6-yloxy)acetonitrile
5-Isopropyl-6 hydroxy-2,3-dihydro-benzo[1,4]dioxine (0.622 g, 3.2 mmol) was converted, as described in Example 2 (step 5), to 5-Isopropyl-2,3-dihydro-benzo[1,4]dioxin-6-yloxy)-acetonitrile (0.544 g, 72%) as a clear oil.

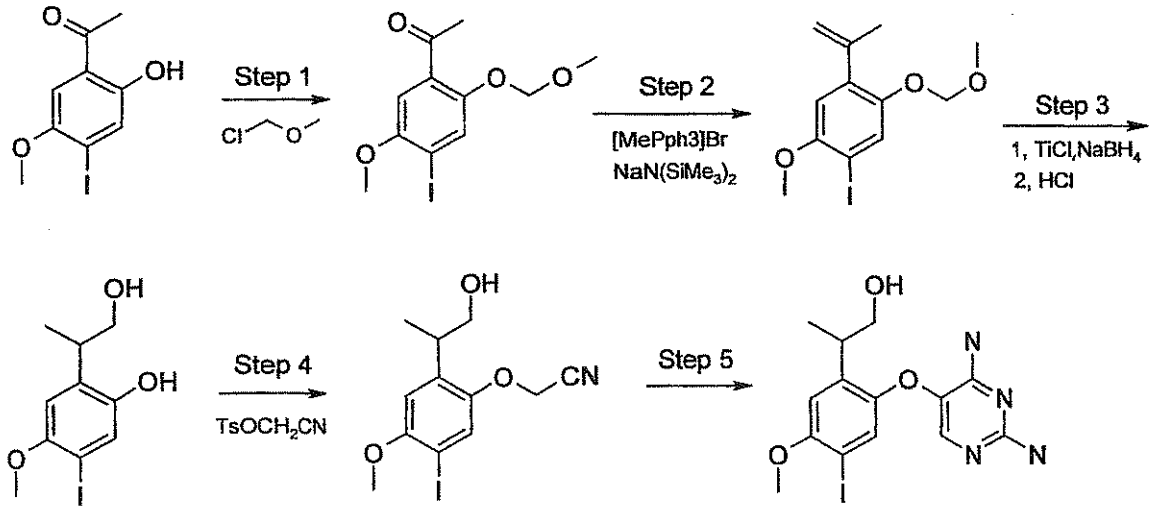
Step 8. 5-(5-Isopropyl-2,3-dihydro-benzo[1,4]dioxin-6-yloxy)-pyrimidine-2,4-diamine
5-Isopropyl-2,3-dihydro-benzo[1,4]dioxin -6-yloxy)acetonitrile (0.544 g, 2.3 mmol) was converted, as described in step 6 of Example 21, to 5-(5-isopropyl-2,3-dihydro-benzo[1,4]-dioxin-6-yloxy)-pyrimidine-2,4-diamine (0.560 g, 86%) as a yellow foam.

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

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

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

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



SCHEME Q

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

To suspension of sodium hydride (0.044 g , 1.1 mmol , 60% in mineral oil) in 0.5 ml DMF was added sodium 5-iodo-2-acetyl,4-methoxyphenol (0.292 g, 1 mmol, prepared as described in Example 35) as a solution in 1.5 ml DMF. After 10 minutes chloromethoxy methane (0.079 g, 1.0 mmol) was added. After 30 minutes the mixture was extracted with CH_2Cl_2 . The combined organics were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. Purification via flash chromatography (88:12= hexane/ethyl

acetate) afforded 1-(2-hydroxy-4-iodo-5-methoxy-phenyl)-ethanone (0.314 g, 85%) as yellow solid; $[MH]^+ = 337$.

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

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

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

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

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

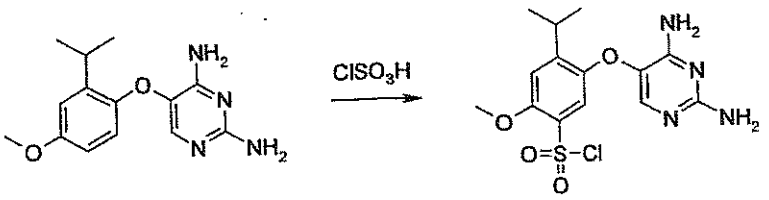
2-(2-Hydroxy-1-methyl-ethyl)-5-iodo-4-methoxy-phenol (0.080 g, 0.3 mmol) was converted, as described in step 6 of Example 21, to [2-(2-hydroxy-methyl-ethyl)-5-iodo-4-methoxy-phenoxy]-acetonitrile (0.076 g, 84%) as white solid; $[MH]^+ = 348$.

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

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

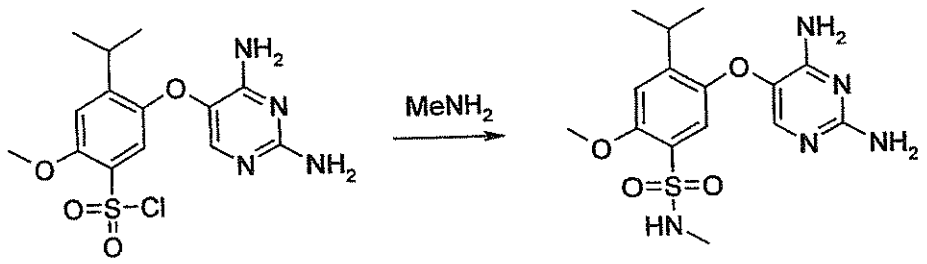
Example 39: 5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-N-methyl-benzenemethylsulfonamide

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



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

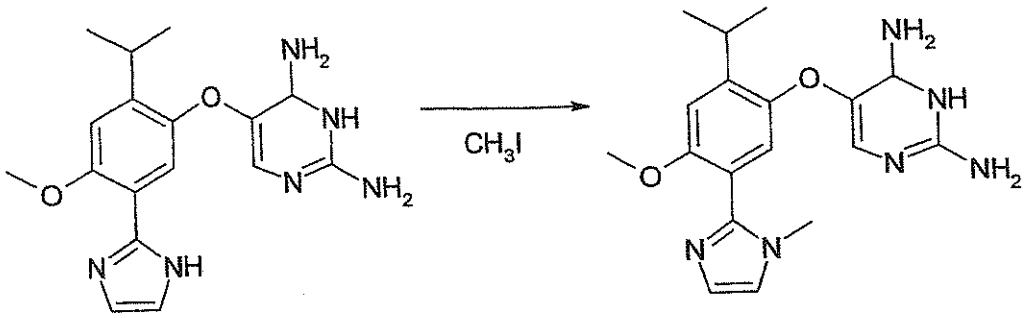
Step 2. 5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-N-methyl-benzenemethylsulfonamide



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

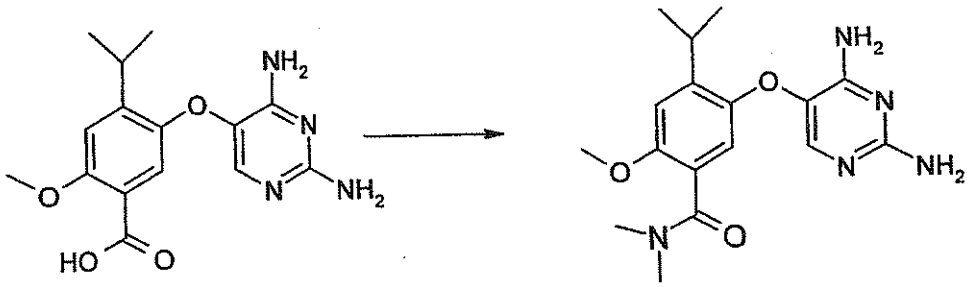
Similarly prepared, replacing methylamine with ethylamine, was 5-(2,4-Diamino-pyrimidin-5-yloxy)-N-ethyl-4-isopropyl-2-methoxy-benzenesulsonamide (0.186 g, 61%) as a white solid; mp (HCl salt)= 260-265°C; $[MH]^+ = 382$.

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



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

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



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

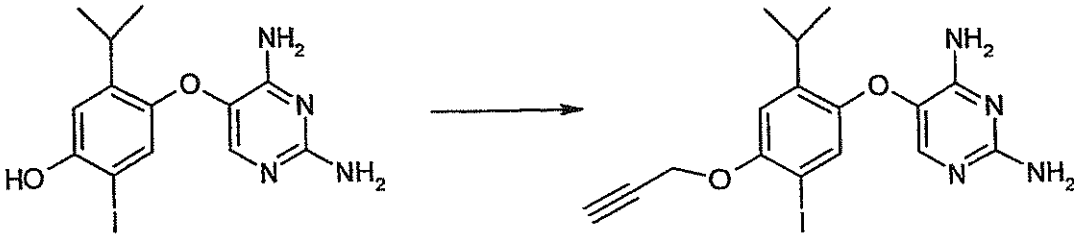
Similarly prepared using methylamine instead of dimethylamine, 5-(2,4-diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-N-methyl-benzamide (23 mg, 15%) was prepared as pale yellow solid, MS (M+H) = 332.

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



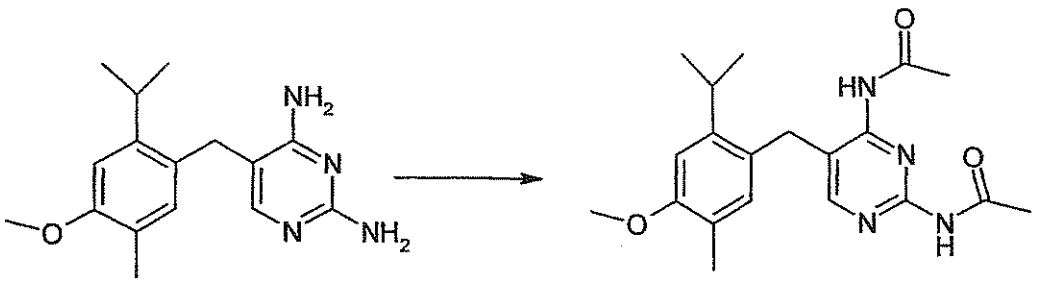
To a cold suspension of 1(0.21g, 0.52mmole) in dichloromethane (15ml) at 0°C was added BBr_3 (0.26g, 1.05mmole). The reaction mixture was stirred at RT for 16 hrs., quenched with water and basified with sat. $NaHCO_3$. The insoluble solid was collected by filtration. The filtrate was washed with water, dried over Na_2SO_4, filtered and concentrated in vacuo. The combined residue and the solid was flash chromatographed on silica gel (3 to 5% methanol in dichloromethane with 0.1% NH_4OH) gave desired product (0.174g, 86%) M+1 387

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



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

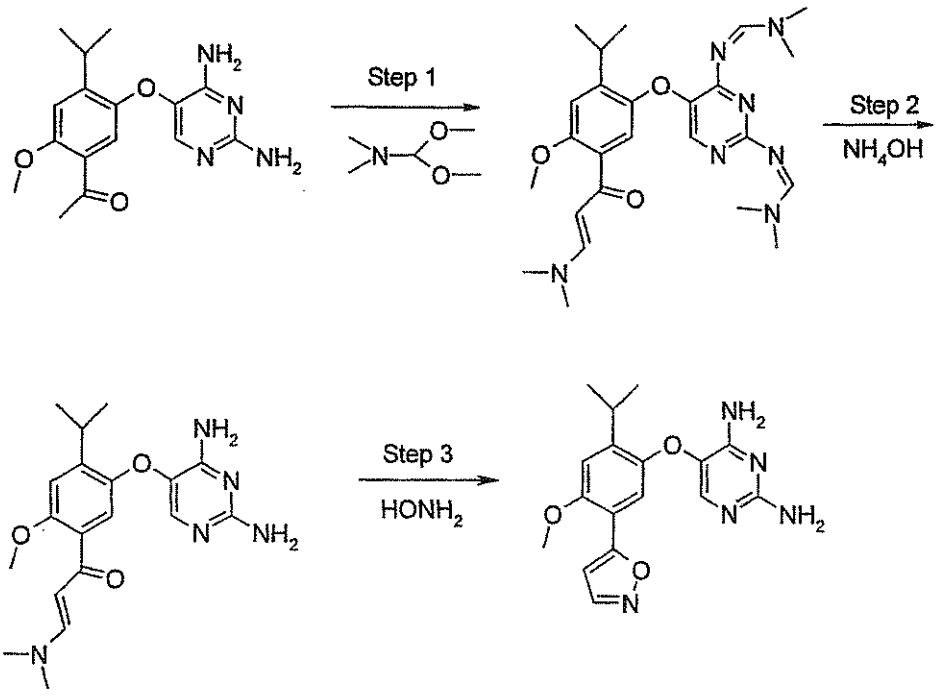
Example 44: N-[2-Acetylamino-5-(2-isopropyl-4-methoxy-5-methyl-benzyl)-pyrimidin-4-yl]-acetamide



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

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

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



SCHEME Q

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

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

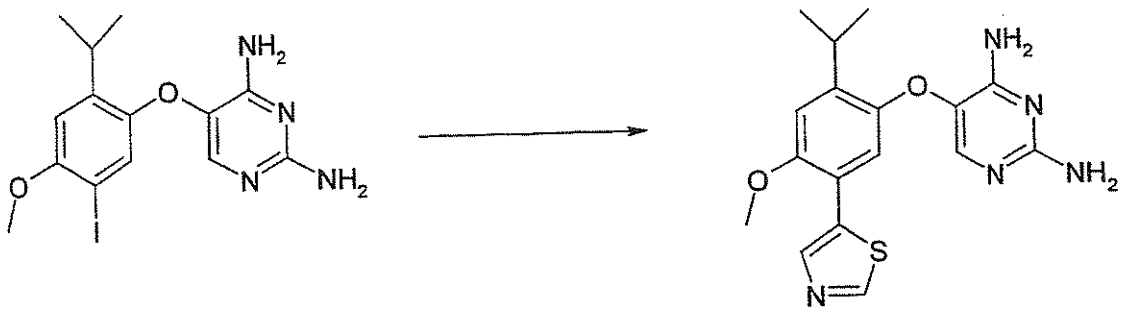
Step 2. 1-[5-(2,4-Diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-phenyl]-3-dimethylamino-propenone

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

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

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

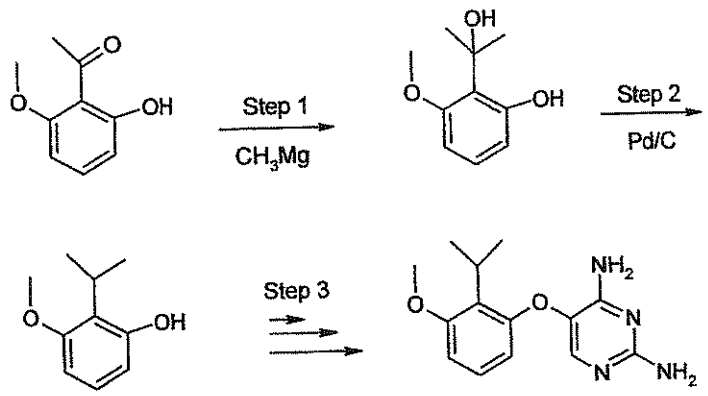
Example 46: 5-(2-Isopropyl-4-methoxy-5-thiazol-5-yl-phenoxy)-pyrimidine-2,4-diamine



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

Example 47: 5-(2-Isopropyl-3-methoxy-phenoxy)-pyrimidine-2,4-diamine

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



SCHEME R

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

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

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

To a solution of 1 (material from above Step 1) dissolved in acetic acid (50 mL) was added 10% palladium on charcoal (500 mg), water (6 mL), and ammonium formate (7.82 g, 124

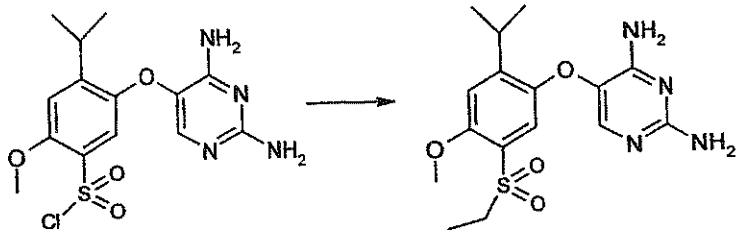
mmol). After refluxing for 1 hour, the reaction was cooled and filtered through celite. The celite pad was washed with ethyl acetate (500 mL). Water (300 mL) was added to the filtrate, and the mixture was basified (pH = 8) using solid sodium bicarbonate. The ethyl acetate layer was collected and washed with water, brine, dried using anhydrous sodium sulfate and concentrated to yield 2-Isopropyl-3-methoxy-phenol (3.68 g, 92%) as pale yellow solid.

Step 3.

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

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

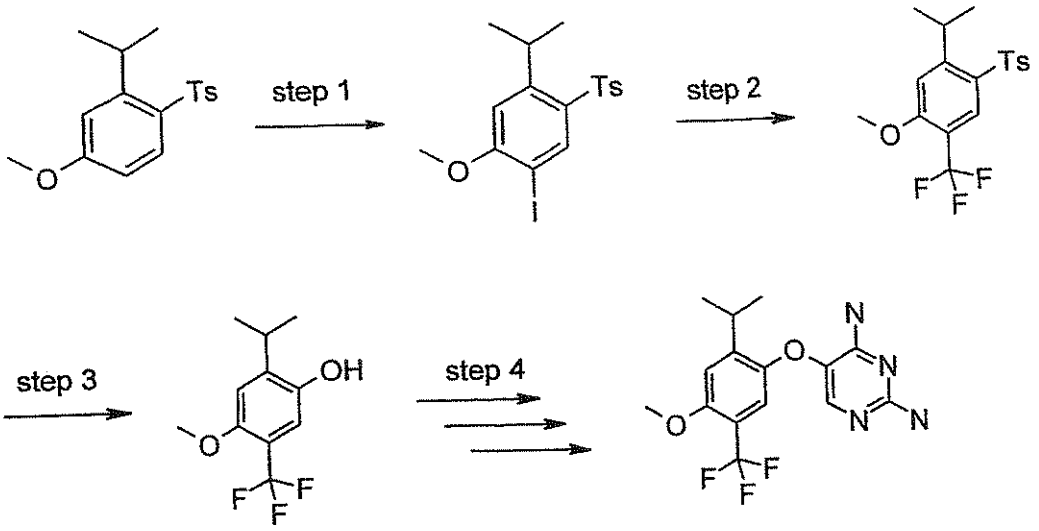
Example 48: 5-(5-Ethanesulfonyl-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine



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

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

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



SCHEME S

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

To a solution of 2-Isopropyl-4-methoxy-1-(toluene-4-sulfonyl)-benzene (10 g, 31.25 mmole) in HOAc (10ml) was added a solution of ICl (9.6g, 59.26mmole) in HOAc (10 ml) and H_2O (5 ml). The reaction mixture was stirred at RT for 16 hrs and basified by saturated NaHCO3 solution. The aqueous solution was extracted into EtOAc which was washed with water, brine, dried over Na2SO4, filtered and concentrated in vacuo to give 1-Iodo-4-isopropyl-2-methoxy-5-(toluene-4-sulfonyl)-benzene (12.35g, 89%).

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

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

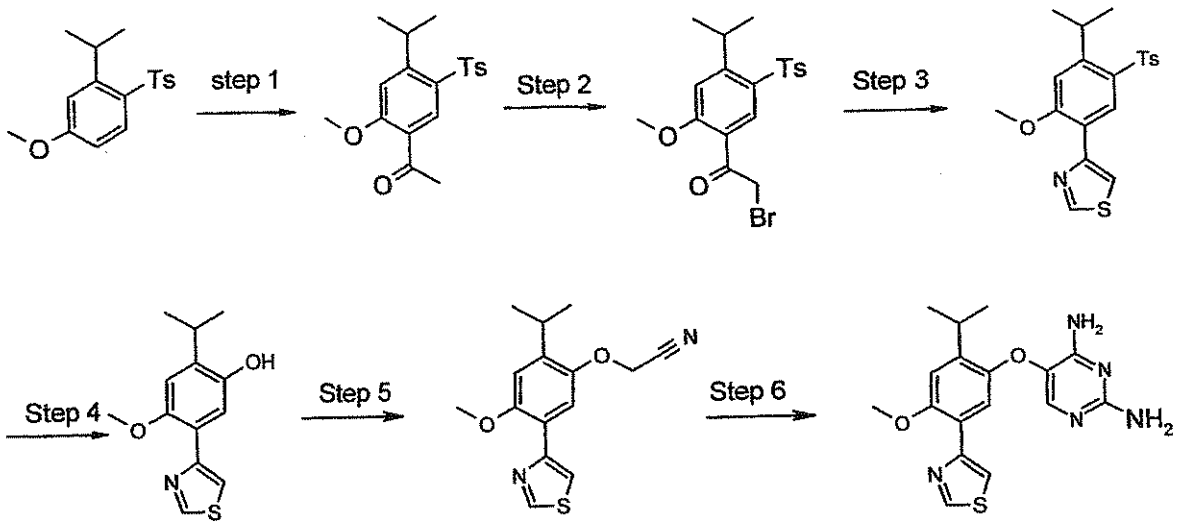
Step 3. 2-Isopropyl-4-methoxy-5-trifluoromethyl-phenol

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

Step 4. 5-(2-Isopropyl-4-methoxy-5-trifluoromethyl-phenoxy)-pyrimidine-2,4-diamine
Following the procedure of Example 2 steps 5-7, 2-Isopropyl-4-methoxy-5-trifluoro-methyl-phenol was converted to 5-(2-Isopropyl-4-methoxy-5-trifluoromethyl-phenoxy)-pyrimidine-2,4-diamine. M+H 343

Example 50: 5-(2-Isopropyl-4-methoxy-5-thiazol-4-yl-phenoxy)-pyrimidine-2,4-diamine

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



SCHEME T

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

Step 2. 2-Bromo-1-[4-isopropyl-2-methoxy-5-(toluene-4-sulfonyl)-phenyl]-ethanone
To a hot mixture of $CuBr_2$ (0.25 g, 1.10 mmole) in EtOAc (1 ml) was added a solution of 1-[4-Isopropyl-2-methoxy-5-(toluene-4-sulfonyl)-phenyl]-ethanone (0.2 g, 0.55 mmole) in CH_3Cl (1 ml). The reaction mixture was refluxed for 16 hrs, filtered, and concentrated to give 2-Bromo-1-[4-isopropyl-2-methoxy-5-(toluene-4-sulfonyl)-phenyl]-ethanone (0.23g, 95%) as an oil.

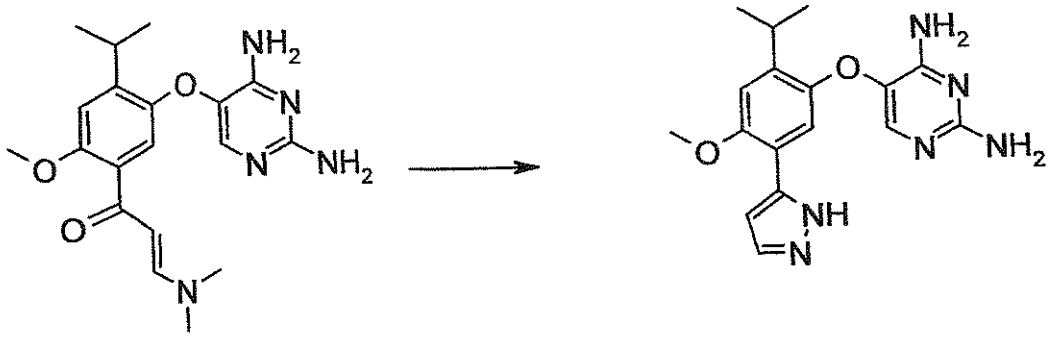
Step 3. 4-[4-Isopropyl-2-methoxy-5-(toluene-4-sulfonyl)-phenyl]-thiazole
To a solution of 2-Bromo-1-[4-isopropyl-2-methoxy-5-(toluene-4-sulfonyl)-phenyl]-ethanone (0.23 g, 0.51 mmole) in anhydrous dioxane (5 ml) was added Na_2CO_3 (1.1 g, 10.12 mmole) and thioamide (5 ml, 0.31g, 5.06 mmole). The reaction mixture was refluxed for 3 hrs and partitioned between H_2O and methylene chloride. The combined organic extracts was dried over Na2SO4, filtered and concentrated. Flash chromatography on silica(30% EtOAc in Hex) gave 4-[4-Isopropyl-2-methoxy-5-(toluene-4-sulfonyl)-phenyl]-thiazole (0.19g, 95%)as oil.

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

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

Step 6. 5-(2-Isopropyl-4-methoxy-5-thiazol-4-yl-phenoxy)-pyrimidine-2,4-diamine
A mixture of (2-Isopropyl-4-methoxy-5-thiazol-4-yl-phenoxy)-acetonitrile (0.27 g, 0.94 mmole) and Brederick's reagent (0.35 g, 2.01 mmole) was heated at 100°C for 2 hrs. Excess Brederick's reagent was removed under reduced pressure. The residue was dissolved in anhydrous EtOH (10 ml) and aniline HCl (0.38 g, 2.93 mmole) was added. The reaction mixture was heated at 80°C for 18 hrs and partitioned between EtOAc and water. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. Guanidine carbonate (0.27 g,1.49 mmole) and NMP (10 ml) were added and heated to 120°C for 10 hrs. The reaction mixture was poured into water and extracted into EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. Flash chromatography on silica (3% MeOH in methylene chloride with 0.1%NH_4OH) gave 5-(2-Isopropyl-4-methoxy-5-thiazol-4-yl-phenoxy)-pyrimidine-2,4-diamine (0.15g, 68%) as a solid. M+H 358.

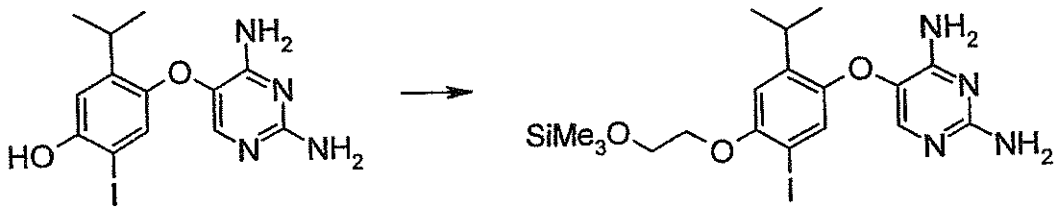
Example 51: 5-[5-(N'-Allylidene-hydrazinomethyl)-2-isopropyl-4-methoxy-phenoxy]-pyrimidine-2,4-diamine



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

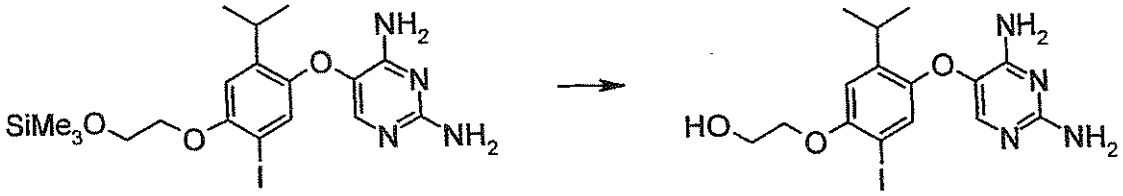
Example 52: 2-[4-(2,4-Diamino-pyrimidin-5-yloxy)-2-iodo-5-isopropyl-phenoxy]-ethanol

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



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

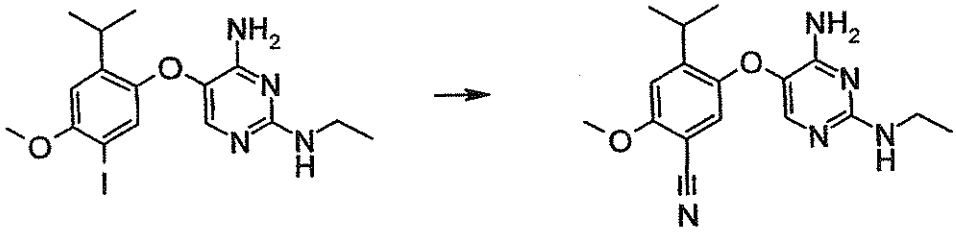
Step 2. 2-[4-(2,4-Diamino-pyrimidin-5-yloxy)-2-iodo-5-isopropyl-phenoxy]-ethanol



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

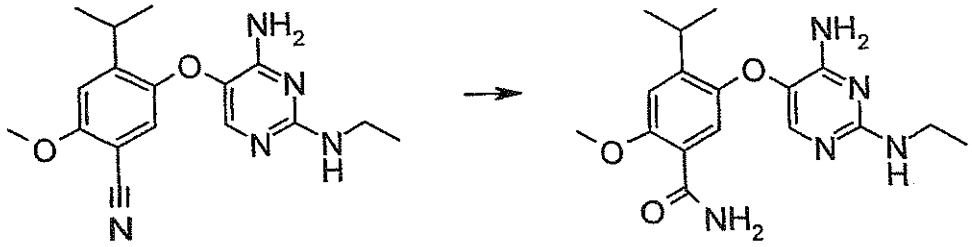
Example 53: 5-(4-Amino-2-ethylamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-benzamide

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



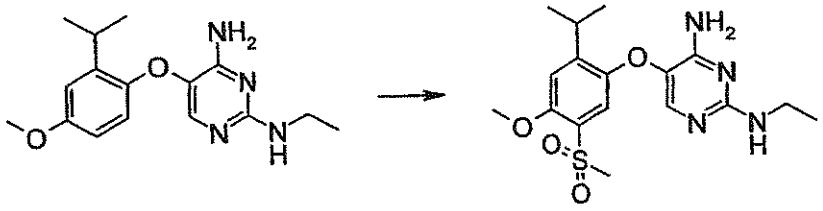
To a solution of N*2*-Ethyl-5-(5-iodo-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine (1.65 g, 4.12 mmole) in anhydrous DMF (10 ml) was added CuCN, and the reaction mixture was heated to 120°C for 3 hrs. The reaction mixture was poured into water (200 ml) and the insoluble portion was collected by filtration. The solid was triturated with 10%MeOH/methylene chloride/0.1%NH_4OH solution (100 ml) and filteded again. The filtrate was concentrated and flash chromatographed on silica (3% MeOH in methylene chloride with 0.1%NH_4OH) to give 5-(4-Amino-2-ethylamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-benzonitrile (0.87g, 71%) as a white solid.

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



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

Example 54: N*2*-Ethyl-5-(2-isopropyl-5-methanesulfonyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine



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

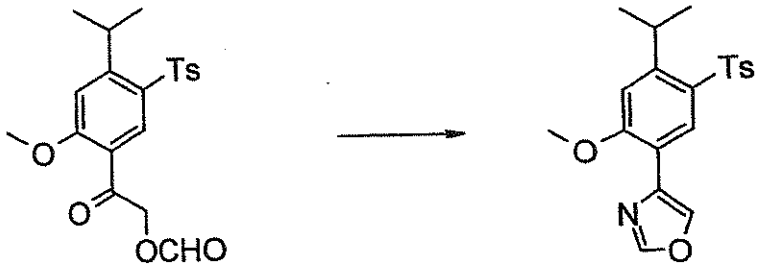
Example 55: 5-(2-Isopropyl-4-methoxy-5-oxazol-4-yl-phenoxy)-pyrimidine-2,4-diamine

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



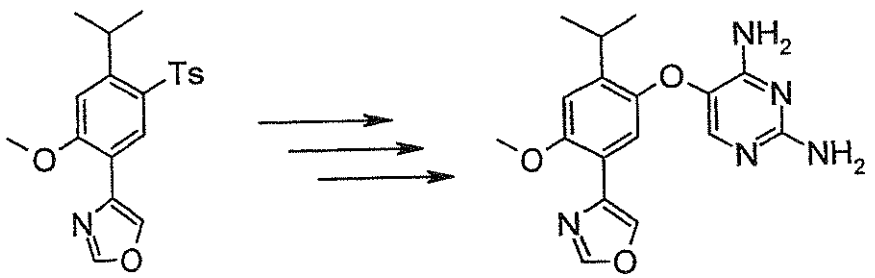
A mixture of 2-Bromo-1-[4-isopropyl-2-methoxy-5-(toluene-4-sulfonyl)-phenyl]-ethanone (0.2 g, 0.45 mmole) and sodium formate (0.040 g, 0.60 mmole) in anhydrous DMF (3 ml) was stirred at RT for 16 hours. The reaction mixture was poured into H_2O and extracted into EtOAc. The combined organic extract was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

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



A solution of the crude 2-Bromo-1-[4-isopropyl-2-methoxy-5-(toluene-4-sulfonyl)-phenyl]-ethanone from above and ammonium acetate (0.17 g, 2.25 mmole) in HOAc (5 ml) was heated at 100°C for 2 hrs. The reaction mixture was partitioned between methylene chloride and sat. $NaHCO_3$ solution. The combined organic extract was dried over Na_2SO_4, filtered and concentrated. Flash chromatography on silica (30 to 50%EtOAc in Hex) gave 4-[4-Isopropyl-2-methoxy-5-(toluene-4-sulfonyl)-phenyl]-oxazole (25mg, 14%) as a white solid.

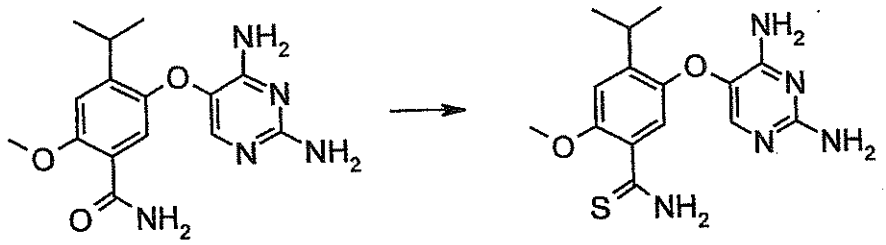
Step 3. 5-(2-Isopropyl-4-methoxy-5-oxazol-4-yl-phenoxy)-pyrimidine-2,4-diamine



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

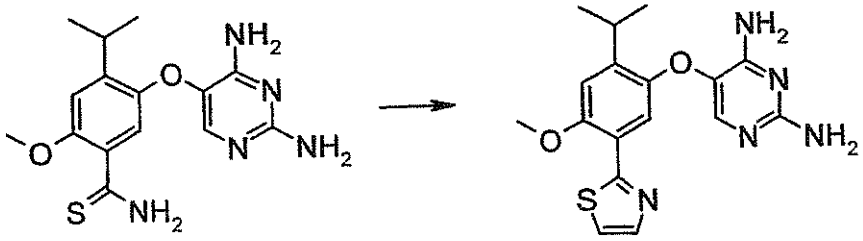
Example 56: 5-(2-Isopropyl-4-methoxy-5-thiazol-2-yl-phenoxy)-pyrimidine-2,4-diamine

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



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

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



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

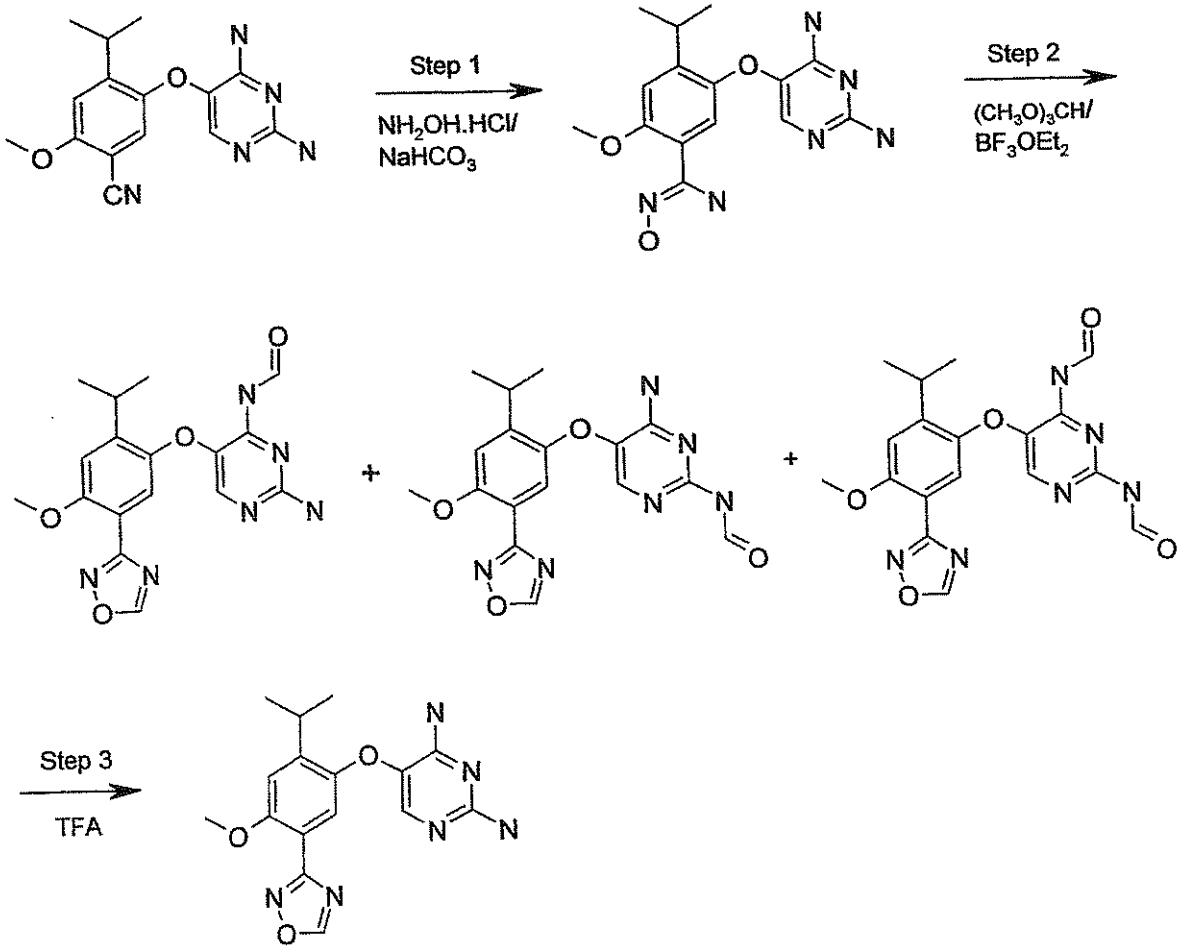
Example 57: 5-(4-Ethoxy-5-iodo-2-isopropyl-phenoxy)-pyrimidine-2,4-diamine



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

Example 58: 5-(2-Isopropyl-4-methoxy-5-[1,2,4]oxadiazol-3-yl-phenoxy)-pyrimidine-2,4-diamine

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



SCHEME U

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

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

The benzamidination carried out in this step follows the procedure reported by Meyer et al., Synthesis 6:899-905 (2003). To a stirred mixture of hydroxylamine hydrochloride (0.099 g, 1.43 mmol) and sodium hydrogen carbonate (0.119 g, 1.42 mmol) in ethanol (1.4 ml) and water (0.3 ml) was added 5-(2,4-diamino-pyrimidin-5-yloxy)-4-isopropyl-2-methoxy-benzonitrile (0.385 g, 1.29 mmol) and the mixture heated at reflux for 5 hours. A second portion of hydroxylamine hydrochloride (0.049 g, 0.71 mmol) and sodium hydrogen carbonate (0.060 g, 0.71 mmol) was added. After a further 2 hours the mixture was cooled, concentrated *in vacuo*, then diluted with water (10 ml) and extracted with ethyl acetate. The combined organic extracts were washed with brine then dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield 5-(2,4-diamino-pyrimidin-5-yloxy)-N-hydroxy-4-isopropyl-2-methoxy-benzamidine (355 mg) as a yellow foam. This material was used directly without further purification.

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

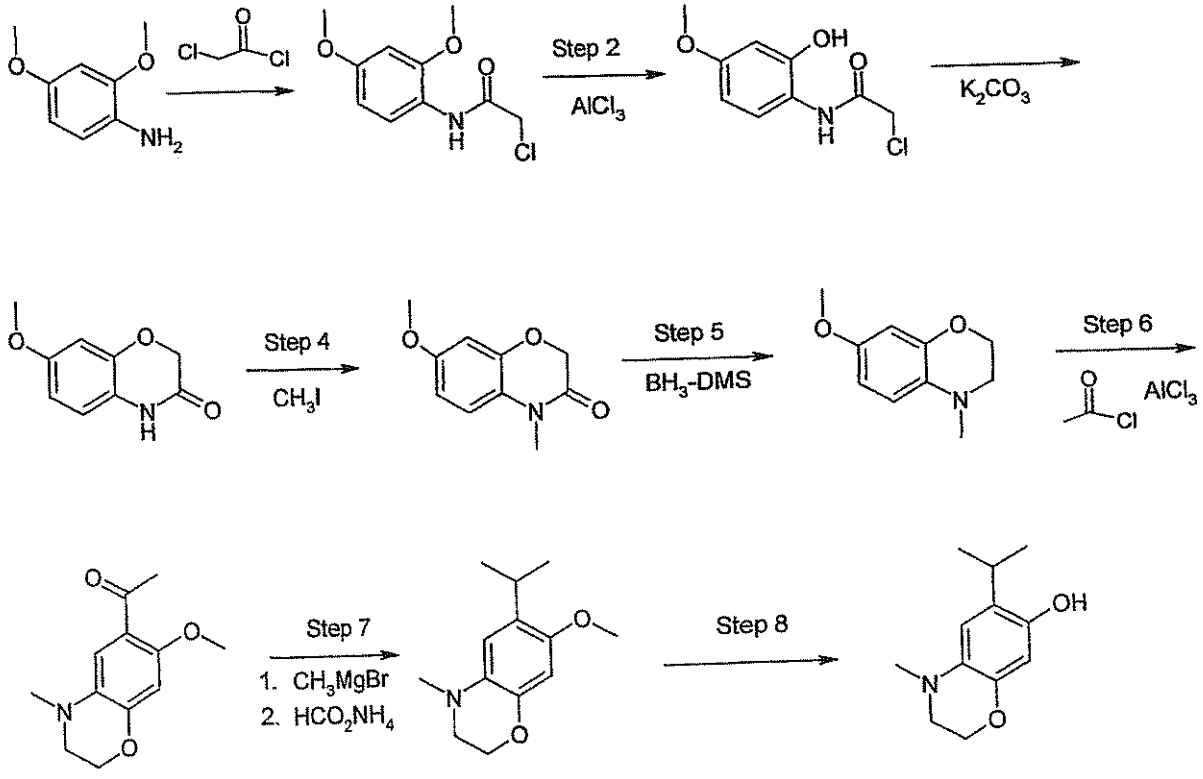
The formylation carried out in this step follows the procedure reported by Kitamura et al. Chem. Pharm. Bull. 49:268-277 (2001). Thus, to a suspension of 5-(2,4-diamino-pyrimidin-5-yloxy)-N-hydroxy-4-isopropyl-2-methoxy-benzamidine (0.350 g, 1.05 mmol) in trimethylorthoformate (1.12 g, 10.5 mmol) at RT and under nitrogen was added boron trifluoride diethyl etherate (1 drop) then the mixture heated at reflux for 1.5 hours. The resultant mixture was cooled, diluted with dichloromethane (60 ml), then washed with water (20 ml), brine (20 ml) and then dried ($MgSO_4$) filtered and concentrated *in vacuo* to provide a mixture of N-[2-amino-5-(2-isopropyl-4-methoxy-5-[1,2,4]oxadiazol-3-yl-phenoxy)-pyrimidin-4-yl]formamide, N-[4-amino-5-(2-isopropyl-4-methoxy-5-[1,2,4]oxadiazol-3-yl-phenoxy)-pyrimidin-2-yl]formamide and N-[4-formylamino-5-(2-isopropyl-4-methoxy-5-[1,2,4]oxadiazol-3-yl-phenoxy)-pyrimidin-2-yl]-formamide as a yellow solid (260 mg). This material was used directly without further purification.

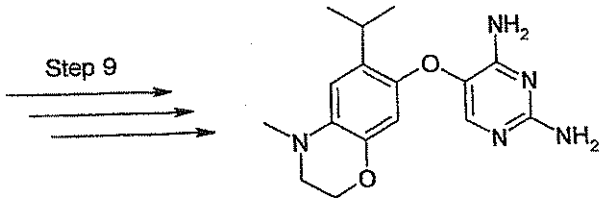
Step 3: 5-(2-Isopropyl-4-methoxy-5-[1,2,4]oxadiazol-3-yl-phenoxy)-pyrimidine-2,4-diamine

A mixture of N-[2-amino-5-(2-isopropyl-4-methoxy-5-[1,2,4]oxadiazol-3-yl-phenoxy)-pyrimidin-4-yl]formamide, N-[4-amino-5-(2-isopropyl-4-methoxy-5-[1,2,4]oxadiazol-3-yl-phenoxy)-pyrimidin-2-yl]formamide and N-[4-formylamino-5-(2-isopropyl-4-methoxy-5-[1,2,4]oxadiazol-3-yl-phenoxy)-pyrimidin-2-yl]-formamide (0.164 g) in TFA (10 mL) was heated at reflux for 24 h. The mixture was then cooled and concentrated *in vacuo*. The residue was purified by flash chromatography (0 - 5% methanol in dichloromethane) to yield 76 mg of 5-(2-isopropyl-4-methoxy-5-[1,2,4]oxadiazol-3-yl-phenoxy)-pyrimidine-2,4-diamine as its trifluoroacetic acid salt. M+H$^+$ =343; MP 135 – 138.5°C; ^{1}H NMR – ($CDCl_3$) δ: 1.27 (app d, 6H, J = 7.0 Hz), 3.11 (quintet, 1H, J = 7.0 Hz), 4.04 (s, 3H), 6.02 – 6.24 (br. D, 2H), 6.93 (s, 1H), 7.02 (s, 1H), 7.68 (s, 1H), 8.74 (s, 1H).

Example 59: 5-(6-Isopropyl-4-methyl-3,4-dihydro-2H-benzo[1,4]oxazin-7-yloxy)-pyrimidine-2,4-diamine

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





SCHEME V

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

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

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

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

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

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

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

7-Methoxy-4H-benzo[1,4]oxazin-3-one (11.61 g, 0.065 mol) in 100 mL dry DMF was stirred at 0°C under nitrogen. Sodium hydride (60%, 2.85 g, 0.0713 mol) was added in

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

Step 5. 7-Methoxy-4-methyl-3,4-dihydro-2H-benzo[1,4]oxazine
7-Methoxy-4-methyl-4H-benzo[1,4]oxazin-3-one (13.07 g, 0.68 mol) was added to 100 mL dry THF, and the reaction mixture was refluxed under nitrogen. Borane-dimethyl sulfide (13.6 mL, 0.136 mol) was added dropwise over one hour, and the reaction mixture was allowed to reflux for two hours. The reaction mixture was cooled and then quenched by addition of 50 mL of 10% aqueous HCl. Precipitate was removed by filtration, and the liquid was concentrated under reduced pressure to give 11.17 g of 7-Methoxy-4-methyl-3,4-dihydro-2H-benzo[1,4]oxazine. (M+H) = 180.

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

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

mixture was cooled, solids were removed by filtration, and the filtrate was diluted with water, and made neutral by addition of solid sodium bicarbonate. The resulting aqueous solution was extracted with EtOAc, and the combined organic layers were dried ($MgSO_4$), filtered, and evaporated under reduced pressure to yield 9.97 g of 6-Isopropyl-7-methoxy-4-methyl-3,4-dihydro-2H-benzo[1,4]oxazine.

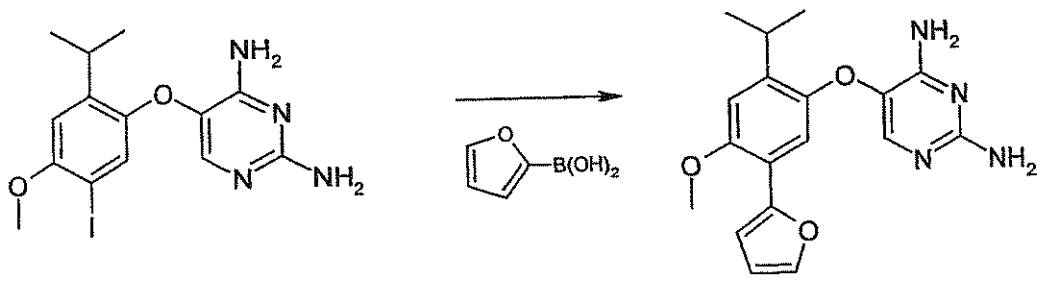
Step 8. 5-(6-Isopropyl-4-methyl-3,4-dihydro-2H-benzo[1,4]oxazin-7-yloxy)-pyrimidine-2,4-diamine

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

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

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

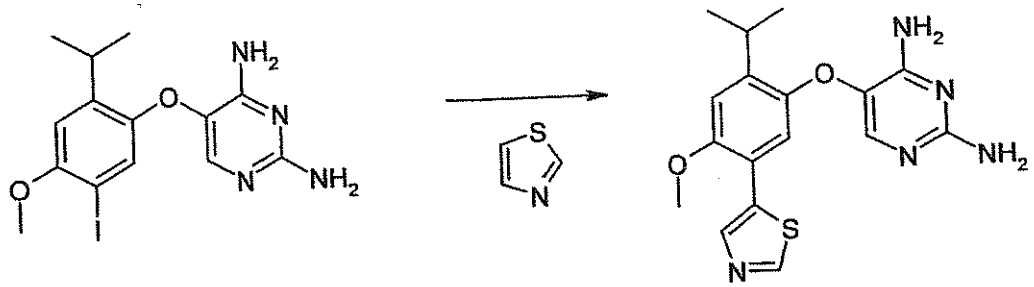
Example 60: 5-(5-Furan-2-yl-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine



5-(5-Iodo-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine (400 mg, 1 mmol), furan 2-boronic acid (285 mg, 1.5 mmol) and $Pd(Ph_3)_2Cl_2$ (50 mg) were taken up in 13 mL of degassed dioxane in a screw cap pressure flask. Sodium bicarbonate (2 mL of 2M

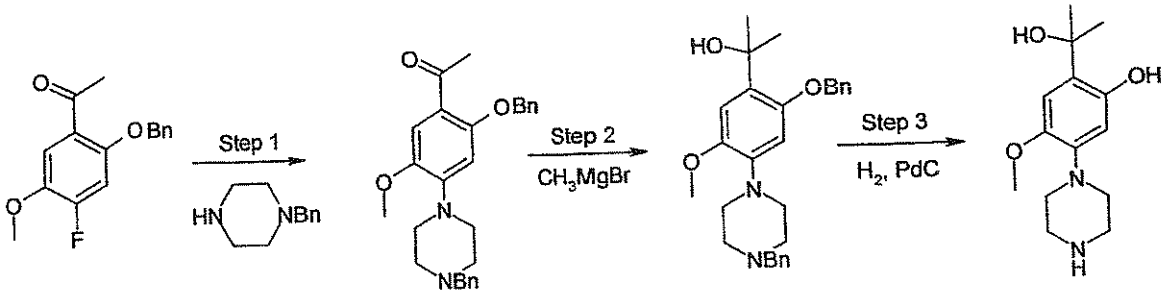
aqueous solution) was added, and the reaction mixture was heated to 105°C for 40 hours. The reaction mixture was cooled and partitioned between water and ethyl acetate. The organic phase was separated, dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography (3% to 5% MeOH in methylene chloride with 1% ammonium hydroxide) to yield 53 mg of 5-(5-Furan-2-yl-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine. (M+H) = 339. Mp = 253.7 - 254.6°C.

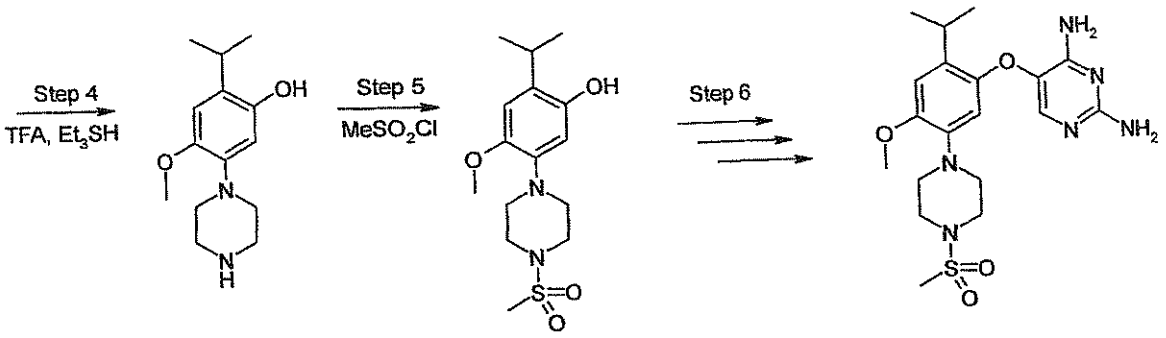
Example 61: 5-(5-Furan-2-yl-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine



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

Example 62: 5-[2-Isopropyl-5-(4-methanesulfonyl-piperazin-1-yl)-4-methoxy-phenoxy]-pyrimidine-2,4-diamine





SCHEME W

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

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

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

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

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

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

concentrated uner reduced pressure to yield 1.1g (92%) of 2-(1-Hydroxy-1-methyl-ethyl)-4-methoxy-5-piperazin-1-yl-phenol.

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

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

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

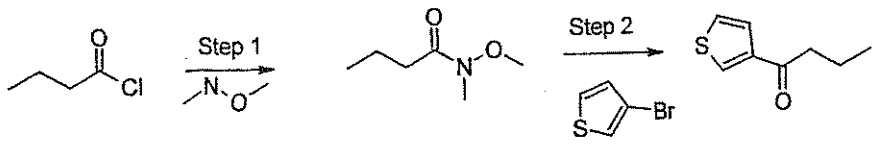
To a stirring solution of 2-Isopropyl-4-methoxy-5-piperazin-1-yl-phenol (0.47 g, 1.88 mmol) in dichloromethane at 0°C under nitrogen was added triethylamine (0.26 mL, 1.89 mmol), followed by methanesulfonyl chloride (0.15 mL, 1.89 mmol). The reaction mixture was stirred at 0°C for five minutes, and then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

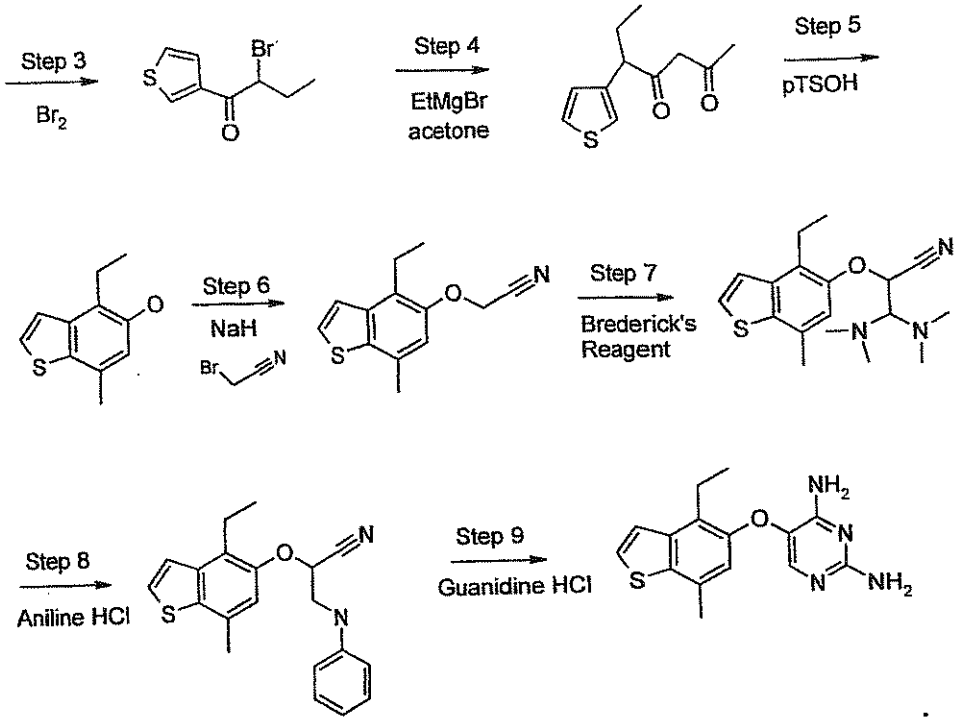
Step 6. 5-[2-Isopropyl-5-(4-methanesulfonyl-piperazin-1-yl)-4-methoxy-phenoxy]-pyrimidine-2,4-diamine

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

Example 63: 5-(4-Ethyl-7-methyl-benzo[b]thiophen-5-yloxy)-pyrimidine-2,4-diamine

The synthetic procedure used in this Example is outlined in Scheme X





SCHEME X

Step 1: N-Methoxy-N-methyl-butyramide

Pyridine (100 mL) was cooled to 0°C, and N,O-dimethylhydroxylamine hydrochloride (20.14g, 206 mmol) was added with stirring. This solution was stirred for 10 minutes, and then a solution of butyryl chloride (19.5 ml, 20g, 188 mmol) dissolved in 50 ml methylene chloride was added via addition funnel over 30 minutes. A precipitate formed after 5 minutes. This suspension was stirred and allowed to warm to RT. Stirring was continued for 2.0 hours, and the reaction was diluted with water, extracted with methylene chloride twice. The methylene chloride layers were combined and washed with 1 N HCl twice and once with brine. Diethyl ether (100 mL) was added to facilitate emulsion separation, and the organic layer was separated and washed with saturated bicarbonate solution, brine, and dried over magnesium sulfate. The solution was filtered and the solvent removed in vacuo to give N-Methoxy-N-methyl-butyramide as an oil (22.1 g, 89%).

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

3-Bromothiophene (11 g, 67 mmol) dissolved in hexanes (110 ml) was cooled to -20°C in acetone/water bath, and n-BuLi (28 ml, 71 mmol, 2.5 n solution in hexanes)was added slowly, over 10 min, then stirred 10 min at -20°C. THF was added (10 ml) over 5 min with rapid stirring. Precipitate formed after about 2/3 of addition. After adding all of the THF, the reaction mixture was stirred 20 min at -20°C, then 20 ml Hexanes was added and the reaction mixture was allowed to warm to 0°C. N-Methoxy-N-methyl-butyramide (9.29 g,

71 mmol) dissolved in 20 ml hexanes was added via cannula over 5 minutes, and the reaction mixture was stirred at 0°C for 1.5 hours. The reaction mixture was quenched with water, then 1 N HCl (75 ml), extracted twice with ether, washed 1 N HCl, brine, and dried over magnesium sulfate. Solvent was removed under reduced pressure to give an oil, which was chromatographed by flash chromatography (5% EtOAc/hexanes) to give 6.7 g, 64% of 1-Thiophen-3-yl-butan-1-one as an oil.

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

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

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

Step 6. (4-Ethyl-7-methyl-benzo[b]thiophen-5-yloxy)-acetonitrile
4-Ethyl-7-methyl-benzo[b]thiophen-5-ol (438 mg, 2 mmol) was dissolved in 10 ml DMF, and the reaction mixture was cooled to 0°C. Sodium hydride (66 mg, 3 mmol) was added

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

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

3,3-Bis-dimethylamino-2-(4-ethyl-7-methyl-benzo[b]thiophen-5-yloxy)-propionitrile (422 mg, 2 mmol) was dissolved in 2.5 ml tert-ButoxyBis (dimethylamino) methane, and the reaction mixture was heated to 100°C for 1 hour. The reaction was cooled to RT and the volume reduced under 1 mm vacuum while heating at 60°C. The residue was then placed on a high vacuum pump for 1 hour to give 3,3-Bis-dimethylamino-2-(4-ethyl-7-methyl-benzo[b]thiophen-5-yloxy)-propionitrile, 595 mg, 98 %, as an oil.

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

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

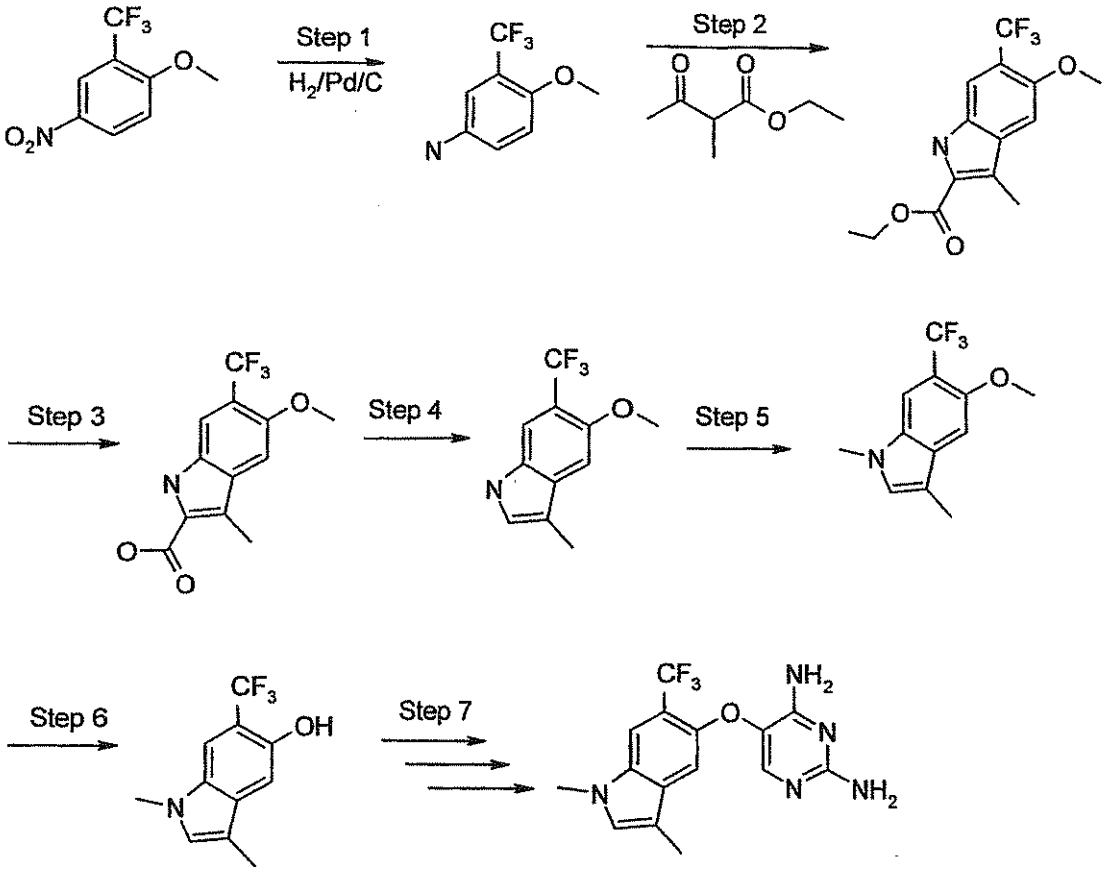
Step 9

2-(4-Ethyl-7-methyl-benzo[b]thiophen-5-yloxy)-3-phenylamino-acrylonitrile (360 mg, 1 mmol), guanidine HCl (411 mg, 4 mmol) and sodium methoxide (880 ul, 4 mmol, 4.9 M solution in methanol) in 5 mL absolute ethanol were heated to reflux in 5 ml absolute ethanol for 2 hours. Premixed guanidine HCl (411 mg, 4 mmol) and sodium methoxide (880 ul, 4 mmol, 4.9 M solution in methanol) in 1 ml EtOH was added via pipette, and the reaction mixture was heated to reflux for 2 hours. The reaction mixture was cooled, diluted with water, extracted twice with EtOAc, washed with brine, and dried over magnesium sulfate. Solvent was removed in vacuo to give 241 mg of 5-(4-Ethyl-7-methyl-benzo-[b]thiophen-5-yloxy)-pyrimidine-2,4-diamine as a white solid (74%). Mass Spec M+H =

301, M.P. = 181°C. Recrystallization of 175 mg of this product from MeOH and HCl/diethyl ether afforded 98 mg of the corresponding HCl salt 49%. , Mass Spec M+H = 301, M.P. > 300°C.

Example 64: 5-(1,3-Dimethyl-6-trifluoromethyl-1H-indol-5-yloxy)-pyrimidine-2,4-diamine

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



SCHEME Y

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

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

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

4-Methoxy-3-trifluoromethyl-phenylamine (5g, 26 mmol) in 12 mL water was cooled to -5°C (Ice/Methanol bath). Conc. HCl was added dropwise (7 ml), and the reaction mix-

ture was stirred for five minutes. A solution of $NaNO_2$ (2.0 g, 29 mmol) dissolved in 3 ml water was added dropwise over 10 minutes, and the reaction mixture was tirred for 30 min. Sodium acetate (1.8 g, 22 mmol) was then added, and stirring was continued at -5°C. In a separate flask, ethyl alpha-acetoacetate (4.55 g, 29 mmol) in 20ml absolute ethanol was stirred, and KOH (1.6 g, 29 mmol) dissolved in 3 ml water was added, followed by ice (30g). The resulting diazonium salt was added quickly to the reaction mixture, rinsing in with 5 ml EtOH, and the reaction mixture was stirred at 0°C for 3.5 hours, then stored at -10°C) for 16 hours. The reaction mixture was warmed to RT and extracted with ethyl acetate, washed with brine, and dried over magnesium sulfate. Solvent was removed under reduced pressure to leave a liquid residue. In a separate flask 100 ml EtOH and 21 ml acetyl chloride were mixed, with cooling in an ice bath, then heated to 70°C. The liquid residue was added via pipette over 15 minutes to the acetyl chloride solution. This reaction mixture was heated to reflux for 2.5 hours, cooled, evaporated under reduced pressure. The residue was purified by column chromatography (10% ethyl acetate/hexane) to give 3.0 g 5-Methoxy-3-methyl-6-trifluoromethyl-1H-indole-2-carboxylic acid ethyl ester, 38% as a white solid. And triturated with diethyl ether to give 5-Methoxy-3-methyl-6-trifluoromethyl-1H-indole-2-carboxylic acid ethyl ester (1.0g) as a white solid, and 5-Methoxy-3-methyl-4-trifluoromethyl-1H-indole-2-carboxylic acid ethyl ester (13.9%) as a white solid.

Step 3. 5-Methoxy-3-methyl-6-trifluoromethyl-1H-indole-2-carboxylic acid. 5-Methoxy-3-methyl-6-trifluoromethyl-1H-indole-2-carboxylic acid ethyl ester (3.0 g, 10 mmol) was dissolved in 10 ml absolute ethanol, and a solution of KOH (1.7 g, 30 mmol) in 7 ml water was added. The reaction mixture was heated to reflux for 2.5 hours, then cooled, acidified slowly with 6 N HCl to pH = 2, and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give 2.0 g, (73 %) 5-Methoxy-3-methyl-6-trifluoromethyl-1H-indole-2-carboxylic acid.

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

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

pressure. The residue was chromatographed (10% ErOAc/Hexanes) to give 5-Methoxy-3-methyl-6-trifluoromethyl-1H-indole (850 mg, 51%) as a solid.

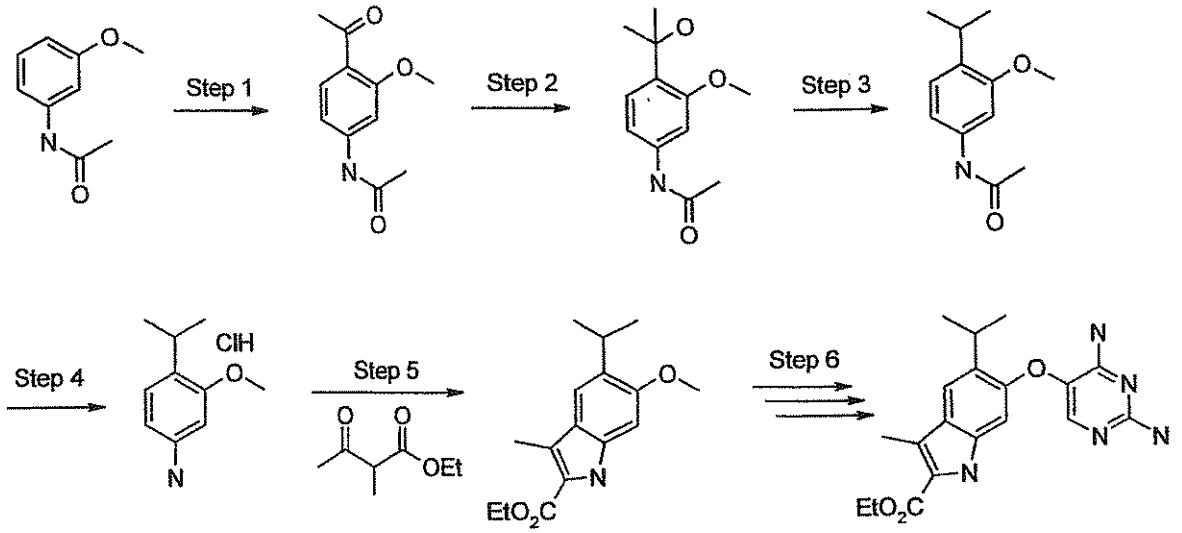
Step 5. 5-Methoxy-1,3-dimethyl-6-trifluoromethyl-1H-indole
A solution of 5-Methoxy-3-methyl-6-trifluoromethyl-1H-indole (900 mg, 4 mmol) in 7 ml DMF was cooled to 0°C, and sodium hydride (104 mg, 4 mmol, 95% powder) was added. The reaction mixture was stirred 15 minutes at 0°C, and then iodomethane (270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

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

Step 7
1,3-Dimethyl-6-trifluoromethyl-1H-indol-5-ol was converted to 5-(1,3-Dimethyl-6-trifluoromethyl-1H-indol-5-yloxy)-pyrimidine-2,4-diamine using the procedure of steps 6-9 of Example 62 (70 mg). The corresponding hydrochloride salt was recrystallized from MeOH/diethyl ether. Mass Spec M+H = 338, M.P. 256°C.

Example 65: 6-(2,4-Diamino-pyrimidin-5-yloxy)-5-isopropyl-3-methyl-1H-indole-2-carboxylic acid

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



SCHEME Z

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

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

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

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

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

N-[4-(1-Hydroxy-1-methyl-ethyl)-3-methoxy-phenyl]-acetamide (16.4 g) in 100 ml glacial acetic acid was stirred at room temp under N_2, Palladium on activated carbon (3 g 10Wt%) was added, followed by 5 g of ammonium formate. The reaction mixture was heated to reflux. After 30 minutes 5 g ammonium formate was added, and after 45 minutes another 8.5 g ammonium formate was added. Reflux was continued for another hour, then the reac-

tion mixture was cooled, and filtered through Celite. The filtrate was diluted with water, extracted with EtOAc, and the combinded organic layers were washed with brine and dried over magnesium sulfate. Evaporation under reduced pressure gave N-(4-Isopropyl-3-methoxy-phenyl)-acetamide (15.1 g, 99%).

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

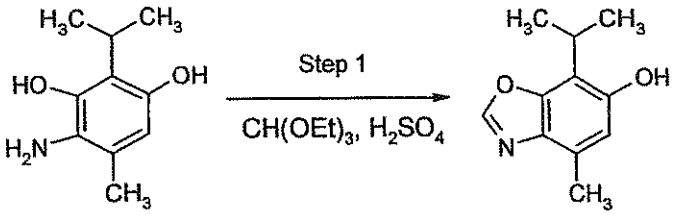
Step 5. 5-Isopropyl-6-methoxy-3-methyl-1H-indole-2-carboxylic acid ethyl ester
4-Isopropyl-3-methoxy-phenylamine HCl salt (3.1g, 19 mmol) was cooled to -5°C (Ice/-Methanol bath), and a mixture of 8 ml water and 5 ml concentrated. HCl was added dropwise. The reaction mixture was stirred for five minutes, and sodium nitrite (1.42g, 21 mmol) dissolved in 3 ml water was added dropwise over 10 minutes. The reaction mixture was stirred for 45 min, then sodium acetate (1.3 g, 16 mmol) was added. In a separate flask, to a stirring mixture of ethyl alpha-acetoacetate (3.26g, 21 mmol) in 15 ml absolute ethanol was added KOH (1.2 g, 21 mmol) dissolved in 3 ml water and then added ice (10 g). This mixture was added to the diazonium salt, and the reaction mixture was stirred at 0°C for 3.5 hours. The reaction mixture was stored at -10°C for 16 hours, then extracted with EtOAC. The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure to a liquid residue. In a separate flask, mixed 100 ml EtOH was mixed slowly with 22 ml acetyl chloride, with cooling in an ice bath. The EtOH/acetyl chloride solution was heated to 70°C, and added the residue was added via pipette over 10 min. The reaction mixture was heated to reflux for 2.5 hours, cooled, evaporated under reduced pressure to give slurry; diluted with water (100 ml) and filtered. The solid was washed with water. The solid was triturated with hexanes to give 5-Isopropyl-6-methoxy-3-methyl-1H-indole-2-carboxylic acid ethyl ester (1.7 g, 34%) as a solid.

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

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

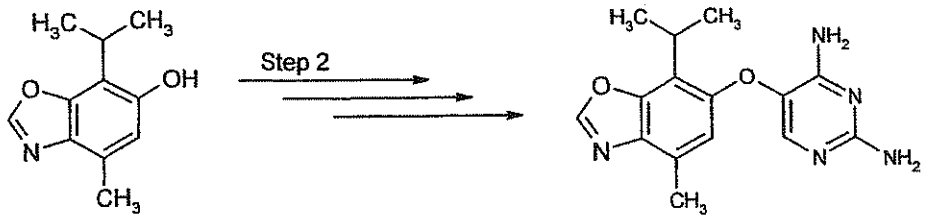
Example 66: 5-(7-Isopropyl-4-methyl-benzooxazol-6-yloxy)-pyrimidine-2,4-diamine

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



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

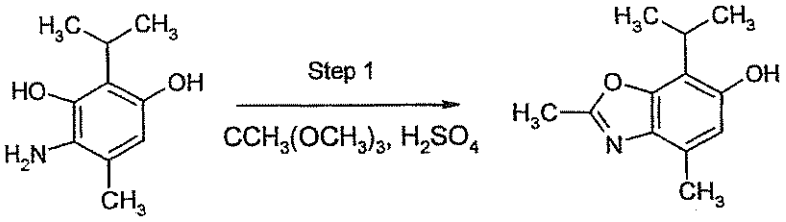
Step 2. 5-(7-Isopropyl-4-methyl-benzooxazol-6-yloxy)-pyrimidine-2,4-diamine



Using the procedure of steps 5-7 of Example 2, 7-isopropyl-4-methyl-benzooxazol-6-ol was converted to 5-(7-isopropyl-4-methyl-benzooxazol-6-yloxy)-pyrimidine-2,4-diamine. The hydrochloride salt was recrystallized from EtOH/diethyl ether. MS (M+H): 300.

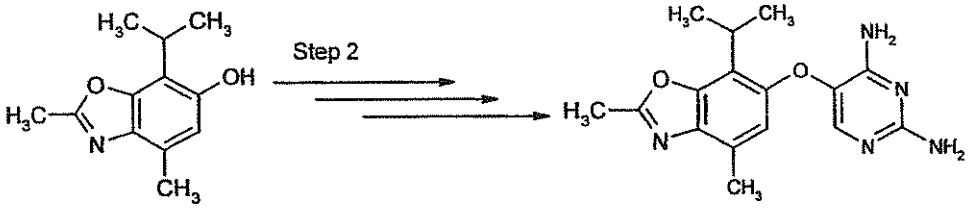
Example 67: 5-(7-Isopropyl-2,4-dimethyl-benzooxazol-6-yloxy)-pyrimidine-2,4-diamine

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



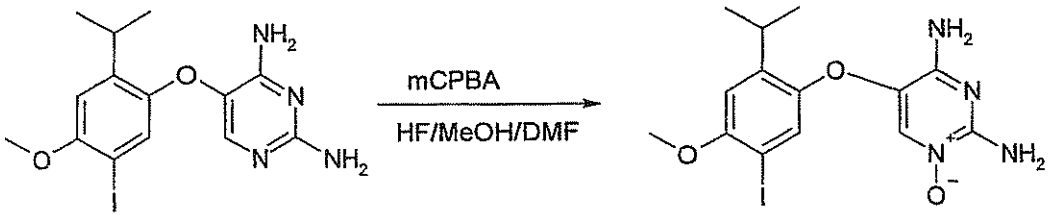
To a flask charged with 4-amino-2-isopropyl-5-methyl-benzene-1,3-diol (250 mg, 1.4 mmol) [Treibs and Albrecht, Journal fuer Praktische Chemie 13:291-305 (1961)], purged with argon, and cooled to 0°C, was sequentially added triethylorthoformate (0.53 mL, 4.2 mmol), MeOH (2.5 mL), and a 10% v/v solution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

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



Using the procedure of steps 5-7 of Example 2, 7-isopropyl-2,4-dimethyl-benzooxazol-6-ol was converted to 5-(7-Isopropyl-2,4-dimethyl-benzooxazol-6-yloxy)-pyrimidine-2,4-diamine. The hydrochloride salt was recrystallized from EtOH/diethyl ether. MS (M+H): 314, MP >300°C.

Example 68: 5-(5-Iodo-2-isopropyl-4-methoxy-phenoxy)-1-oxy-pyrimidine-2,4-diamine



To a solution of compound 5-(5-Iodo-2-isopropyl-4-methoxy-phenoxy)-pyrimidine-2,4-diamine (1.6g, 4.0 mmoles) in DMF/MeOH (30 ml/10 ml) was added HF (48% aqueous solution, 0.3 ml, 8.3 mmoles). After 3 minutes, m-chloroperoxybenzoic acid (80%, 2.16 g,

10.0 mmoles) was added, the mixture was stirred at RT for one hour. Cold 1N NaOH aqueous solution was added, and the reaction mixture was partitioned between ethyl acetate and water. The organic phase was washed with brine, dried over anhydrous sodium sulfate, filtered, concentrated in vacuo. The residue was purified by silica gel chromatography (2%, 5%, 6%, 8% MeOH in CH_2Cl_2 with 0.1 % NH_4OH) to give 5-(5-Iodo-2-isopropyl-4-methoxy-phenoxy)-1-oxy-pyrimidine-2,4-diamine (0.2g, 12%) as a yellow solid. M+H: 417.

Example 69: Formulations

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

Composition for Oral Administration

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, e.g., microcrystalline cellulose, sodium carboxymethylcellulose, dextrose, and the like. Hydrochloric acid may be added to adjust pH. The nasal spray formulations may be delivered via a nasal spray metered pump typically delivering about 50-100 microliters of formulation per actuation. A typical dosing schedule is 2-4 sprays every 4-12 hours.

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

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 minutes 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 pro-

ducing a final concentration of 1 μM ($P2X_3$) or 5 μM ($P2X_{2/3}$). Fluorescence was measured for an additional 2 minutes at 1 second intervals after agonist addition. A final addition of ionomycin (5 μM, final concentration) was made to each well of the FLIPR test plate to establish cell viability and maximum fluorescence of dye-bound cytosolic calcium. Peak fluorescence in response to the addition of α,β-meATP (in the absence and presence of test compounds) was measured and inhibition curves generated using nonlinear regression. PPADS, a standard P2X antagonist, was used as a positive control.

Using the above procedure, compounds of the invention exhibited activity for the $P2X_3$ receptor. The compound N*2*-Isopropyl-5-(2-isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine, e.g., exhibited a pIC_{50} of approximately 7.54 using the above assay.

Surprisingly and unexpectedly, compounds of formulae (I - IV) wherein R^1 is isopropyl exhibit better affinity for $P2X_3$ than compounds wherein R^1 is any other alkyl or other substituent. Table 3 below provides comparison pIC_{50} data for various compounds of different R^1 substituents.

TABLE 3

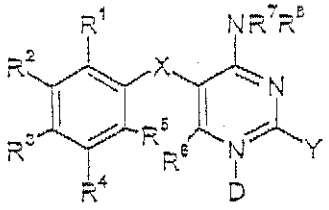
Compound	R^1	pIC_{50}
5-(2-tert-Butyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine	-tert-butyl	< 5.00
5-(4,5-Dimethoxy-2-propyl-benzyl)-pyrimidine-2,4-diamine	-n-propyl	< 5.00
5-(2-Isopropyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine	-isopropyl	6.94
5-(2-Ethyl-4,5-dimethoxy-benzyl)-pyrimidine-2,4-diamine	-ethyl	5.85
5-(4,5-Dimethoxy-2-methyl-benzyl)-pyrimidine-2,4-diamine	-methyl	< 5.00

As can be seen from Table 3, compounds of the invention wherein R^1 is isopropyl exhibit better affinity for the $P2X_3$ receptor than analogous compounds having other alkyl substituents as R^1.

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

What is claimed is:

1. A compound of formula (I)



(I)

or a pharmaceutically acceptable salt thereof,

wherein:

X is -O-;

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

D is an optional oxygen;

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

R^2, R^4 and R^5 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; $-(CH_2)_m-(Z)_n-(CO)-R^f$ or $-(CH_2)_m-(Z)_n-SO_2-(NR^g)_n-R^f$ where m and n each independently is 0 or 1, Z is O or NR^g, R^f is hydrogen, alkyl, hydroxy, alkoxy, amino, hydroxyalkyl or alkoxyalkyl, and each R^g is independently hydrogen or alkyl;

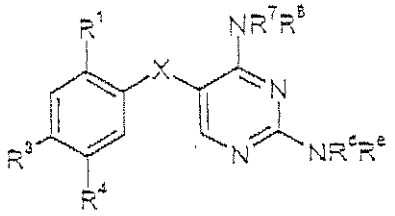
R^3 is methoxy;

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

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

2. The compound of claim 1 wherein said compound is

(a) of the formula (II)



(II)

wherein:

X is -O-;

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

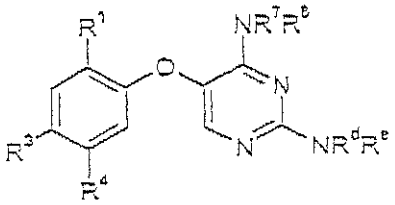
R^3 is methoxy;

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

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

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

(b) a compound of the formula (IV)



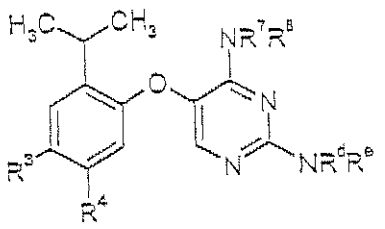
(IV)

wherein:

R^1 is: alkyl; alkenyl; cycloalkyl; or cycloalkenyl;

R^3, R^4, R^7, R^8, R^d and R^e are as defined in (a); or

(c) a compound of the formula (VI)



(VI)

wherein:
R^3, R^4, R^7, R^8, R^d and R^e are as defined in (a).

3. A pharmaceutical composition comprising a pharmaceutically acceptable excipient; and a compound of Claim 1 according to claim 1.

4. Use of a compound according to claim 1 for the manufacture of a medicament for the treatrnent of a disease mediated by a $P2X_3$ or $P2X_{2/3}$ receptor antagonist.

5. The use according to claim 4 wherein the disease is a genitourinary disease or a disease which is associated with pain.

6. The use according to claim 5, wherein said genitourinary disease is 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; prostatotis,; pelvic pain syndrome; prostatodynia; cystitis; or idiophatic bladder hypersensitivity; and the disease which is associated with pain is 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.