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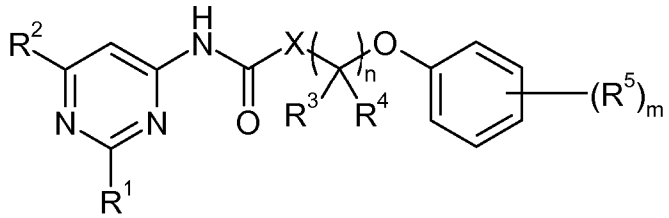
(54) Title: PHENOXY-SUBSTITUTED PYRIMIDINES AS ADENOSINE RECEPTOR ANTAGONISTS



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(57) Abstract: Compounds of formula (I), including pharmaceutically acceptable salts, esters, solvates, stereoisomers and prodrugs thereof thereof, wherein R^1, R^2, R^3, R^4, R^5, X, m and n are as defined herein. Pharmaceutical compositions containing a compound of structure (I), as well as methods relating to the use thereof, are also disclosed.

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PHENOXY-SUBSTITUTED PYRIMIDINES AS ADENOSINE RECEPTOR ANTAGONISTS

CROSS-REFERENCE TO RELATED APPLICATION

This application claims the benefit of U.S. Provisional Patent Application No. 60/759,692, filed January 17, 2006, which application is incorporated by reference herein in its entirety.

FIELD OF THE INVENTION

The present invention relates to new antagonists of adenosine receptors, in particular antagonists of the A_{2A} adenosine receptor subtype, and the use of said compounds in the treatment of diseases and disorders susceptible of being ameliorated by antagonism of adenosine receptors. In particular the present invention relates to the use of such compounds in the treatment of disorders of the central nervous system which are known to be improved by the use of antagonists of the A_{2A} adenosine receptors, more specifically movement disorders such as Parkinson's disease, restless leg syndrome and dyskinesia and to pharmaceutical compositions comprising said compounds.

DESCRIPTION OF THE RELATED ART

The effects of adenosine are mediated through at least four specific identified cell membrane receptors. Receptors A_1, A_{2A}, A_{2B} and A_3 belong to the G protein-coupled receptor family. The A_1 and A_3 receptors down-regulate cellular cAMP levels through their coupling to G proteins, which inhibit adenylate cyclase. In contrast, A_{2A} and A_{2B} receptors couple to G proteins that activate adenylate cyclase and increase intracellular levels of cAMP. Through these receptors, adenosine regulates a wide range of physiological functions.

Thus, in the cardiovascular system, the activation of the A_1 receptor protects cardiac tissue from the effects of ischemia and hypoxia. A similar protective effect is also produced by antagonism of the A_{2A} receptor, which enhances A_1-receptor-induced antiadrenergic responses and may also be useful in the treatment of acute myocardial ischemia and supraventricular arrhythmias (Norton GR et al. *Am J Physiol.* **1999**; 276(2 Pt 2):H341-9; Auchampach JA, Bolli R. *Am J Physiol.* **1999**; 276(3 Pt 2):H1113-6). In addition, the A_{2B} adenosine receptor subtype (Feoktistov, I. et al., *Pharmacol. Rev.* **1997**, 49, 381-402)

appears to be involved in the control of vascular tone and the regulation of vascular smooth muscle growth.

In the kidney, adenosine exerts a biphasic action, inducing vasodilation at high concentrations and vasoconstriction at low concentrations. Thus, adenosine plays a role in the pathogenesis of some forms of acute renal failure that may be ameliorated by A_1 receptor antagonists (Costello-Boerrigter LC, et al. *Med Clin North Am*. **2003** Mar; 87(2): 475-91; Gottlieb SS., Drugs. 2001; 61(10): 1387-93).

Adenosine is also involved in the physiopathology of the immune system. It can induce degranulation of activated human mast cells through the A_{2B} and /or A_3 receptor. Thus A_{2B} and /or A_3 antagonists prevent mast cell degranulation and are, therefore, useful in the treatment, prevention or suppression of disease states induced by activation of the A_{2B} and/or A_3 receptor and mast cell degranulation. These disease states include but are not limited to asthma, myocardial reperfusion injury, allergic reactions including but not limited to rhinitis, urticaria, scleroderm arthritis, other autoimmune diseases and inflammatory bowel diseases.

Furthermore, in the respiratory system adenosine induces bronchoconstriction, modulates airway inflammation and promotes neutrophil chemotaxis. Therefore, an adenosine antagonist would be particularly useful in the treatment of asthma.

In the gastrointestinal and metabolic system, the A_{2B} adenosine receptor subtype (Feoktistov, I. et al., *Pharmacol. Rev.* **1997**, 49, 381-402) seems to be involved in the regulation of hepatic glucose production, the modulation of intestinal tone, as well as intestinal secretion. Thus, A_{2B} antagonists may also be useful in the treatment of diabetes mellitus and obesity.

In the central nervous system adenosine is a potent endogenous neuromodulator, which controls the presynaptic release of many neurotransmitters and is thus involved in motor function, sleep, anxiety, pain and psychomotor activity. All adenosine receptor subtypes are present in the brain, with A_1 and A_{2A} subtypes being differentially distributed. The former are found predominantly in the hippocampus and cortex, whilst the latter are found mainly in the striatum. Adenosine A_{2A} receptors modulate the release of GABA in the striatum, which possibly regulates the activity of medium spiny neurons.

Thus, A_{2A} receptor antagonists may be a useful treatment for neurodegenerative movement disorders such as Parkinson and Huntington's disease (Tuite P, et al., *J. Expert Opin Investig Drugs*. **2003**; 12: 1335-52; Popoli P. et al. *J Neurosci.* **2002**; 22:1967-75), dystonias such as restless leg syndrome (Happe S, et al., *Neuropsychobiology*. **2003**; 48: 82-6), and dyskinesias such as those caused by prolonged use of neuroleptic and dopaminergic drugs (Jenner P. *J Neurol.* **2000**; 247 Suppl2: II43-50).

In the treatment of Parkinson's disease an A_{2A} antagonist may be useful not only as monotherapy, but also when administered in combination with L-DOPA and/or one or more of the following drugs: dopamine agonists, inhibitors of dopamine decarboxylase, catechol-O-methyltransferase inhibitors and inhibitors of monoamine oxidase.

In addition, A_{2A} antagonists may have therapeutic potential as neuroprotectants (Stone TW. et al., *Drug. Dev. Res.* **2001**; 52: 323-330), and in the treatment of sleep disorders (Dunwiddie TV et al., *Ann. Rev. Neurosci.* **2001**; 24: 31-55).

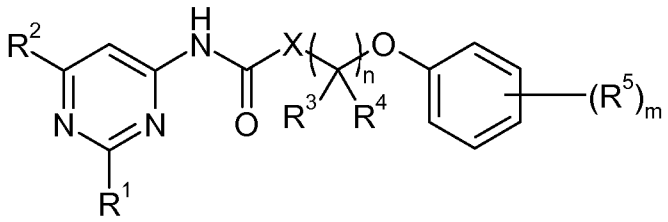
It has now been found that certain 4-aminopyrimidine derivatives are novel potent antagonists of the A_{2A} adenosine receptor and can therefore be used in the treatment or prevention of diseases susceptible to amelioration by antagonism of the adenosine receptor.

Further objectives of the present invention are to provide a method for preparing said compounds; pharmaceutical compositions comprising an effective amount of said compounds; the use of the compounds in the manufacture of a medicament for the treatment of pathological conditions or diseases susceptible of being improved by antagonism of an adenosine receptor, in particular by antagonism of the A_{2A} adenosine receptor; methods of treatment of pathological conditions or diseases susceptible to amelioration by antagonism of an adenosine receptor, in particular by antagonism of the A_{2A} adenosine receptor comprising the administration of the compounds of the invention to a subject in need of treatment and combinations of said compounds with one or more of the following drugs: L-DOPA, dopamine agonists, inhibitors of dopamine decarboxylase, catechol-O-methyltransferase inhibitors and inhibitors of monoamine oxidase.

BRIEF SUMMARY OF THE INVENTION

In brief, this invention is generally directed to adenosine receptor antagonists, as well as to methods for their preparation and use, and to pharmaceutical compositions containing the

same. More specifically, the adenosine receptor antagonists of this invention are compounds having the following general structure (I):



(I)

and pharmaceutically acceptable salts, esters, solvates, stereoisomers and prodrugs thereof, wherein R^1 , R^2 , R^3, R^4, R^5, X, m and n are as defined below.

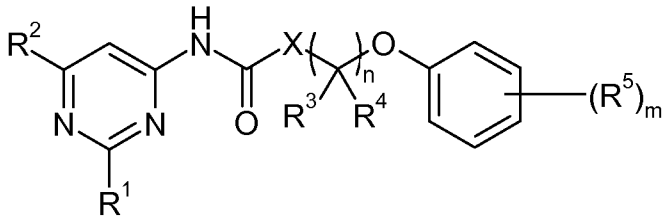
The compounds of this invention may generally be used to treat a variety of disorders or conditions, particularly those which benefit from inhibition of adenosine (particularly A_{2A}) receptors. Accordingly, in another embodiment, methods are disclosed for treating one or more of a variety of diseases or conditions, including (but not limited to) ischemia, supraventricular arrhythmias, acute renal failure, myocardial reperfusion injury, autoimmune disease, inflammatory bowel diseases, asthma, diabetes mellitus, obesity, Parkinson disease, Huntington's disease, dystonia or dyskinesia.

The methods of this invention generally involve administering an effective amount of one or more compounds of this invention, typically in the form of a pharmaceutical composition, to an animal (also referred to here as a "patient", including a human) in need thereof. Accordingly, in still another embodiment, compositions are disclosed containing one or more compounds of this invention and a pharmaceutically acceptable carrier and/or diluent.

These and other aspects of the invention will be apparent upon reference to the following detailed description. To that end, various references are set forth herein which describe in more detail certain procedures, compounds and/or compositions, and are hereby incorporated by reference in their entirety.

DETAILED DESCRIPTION OF THE INVENTION

As mentioned above, the present invention is directed generally to compounds useful as adenosine receptor antagonists. The compounds of this invention have the following structure (I):



(I)

and pharmaceutically acceptable salts, esters, solvates, stereoisomers and prodrugs thereof, wherein:

each of R^1 and R^2 independently is an aryl or heteroaryl group optionally substituted by one or more substituents selected from the group of lower alkyl, halogen, cycloalkyl, phenyl, hydroxy, lower alkoxy, -SH, NO_2, lower alkylthio, lower alkylamino, cyano, and amino, wherein the lower alkyl, cycloalkyl, phenyl, lower alkoxy, lower alkylthio and lower alkylamino groups are optionally substituted;

each of R^3 and R^4 independently is at each occurrence selected from the group of hydrogen, optionally substitituted alkyl, and optionally substituted alkoxy;

R^5 independently is at each occurrence selected from the group of halogen, optionally substituted hydroxyC_{1-6}alkyl, optionally substituted C_{1-6}alkoxyC_{1-6}alkyl, optionally substituted morpholinylC_{1-6}alkyl, optionally substituted mono(C_{1-6}alkyl)aminoC_{1-6}alkyl, optionally substituted di(C_{1-6}alkyl)aminoC_{1-6}alkyl, optionally substituted C_{1-6}alkoxyC_{1-6}alkylaminoC_{1-6}alkyl, optionally substituted C_{1-6}alkoxy, optionally substituted pyrrolidinyl, optionally substituted pyrazolidinyl, optionally substituted imidazolidinyl, optionally substituted piperidinyl and optionally substituted piperazinyl;

X is a bond, NH or O;

m is 1, 2 or 3;

and

n is 1, 2 or 3;

with the proviso that when X is NH or O, then n is 2 or 3.

Other aspects of the present invention are: a) pharmaceutical compositions containing a pharmaceutically effective amount of said compounds, b) the use of said compounds in the manufacture of a medicament for the treatment of diseases susceptible of being improved by antagonism of an adenosine receptor, in particular by antagonism of the A_{2A} adenosine receptor; c) methods of treatment of diseases susceptible to amelioration by antagonism of an adenosine receptor, in particular by antagonism of the A_{2A} adenosine receptor, which methods comprise the administration of the compounds of the invention to a subject in need of treatment and administration of combinations of said compounds with one or more of the following drugs: L-DOPA, dopamine agonists, inhibitors of dopamine decarboxylase, catechol-O-methyltransferase inhibitors and inhibitors of monoamine oxidase. A further aspect of the present invention includes use of a compound of the present invention to provide a physiological, functional, or biological assessment of a patient or provide disease or pathology detection and assessment. In such an aspect, a radioactive form of a compound of the present invention may be employed in scintigraphy, positron emission tomography (PET), computerized tomography (CT), and/or single photon emission computerized tomography (SPECT).

As used herein the term alkyl includes linear or branched alkyl radicals having 1 to 8 carbon atoms. Typically, alkyl groups have 1 to 6 or 1 to 4 carbon atoms. Examples of alky groups include methyl, ethyl, n-propyl, i-propyl, n-butyl, sec-butyl and tert-butyl, n-pentyl, 1-methylbutyl, 2-methylbutyl, isopentyl, 1-ethylpropyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, n-hexyl, 1-ethylbutyl, 2-ethylbutyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, 2-methylpentyl, 3-methylpentyl and iso-hexyl radicals.

As used herein, the term alkoxy includes linear or brached oxy-containing radicals each having alkyl portions of 1 to 8, typically 1 to 6 and more typically 1 to 4 carbon atoms. Examples of alkoxy groups include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, sec-butoxy and t-butoxy. Examples of substituted alkoxy groups include trifluoromethoxy, difluoromethoxy, hydroxymethoxy, 2-hydroxyethoxy and 2-hydroxypropoxy.

As used herein, the term alkylthio embraces radicals containing an optionally substituted, linear or brached alkyl radicals of 1 to 8, typically 1 to 6 and more typically 1 to 4 carbon atoms. Examples of alkylthio radicals include methylthio, ethylthio, n-propylthio, i-propylthio, n-butylthio, sec-butylthio and t-butylthio. Examples of substituted alkylthio

groups include trifluoromethylthio, difluoromethylthio, hydroxymethylthio, 2-hydroxyethylthio and 2-hydroxypropylthio.

As used herein, the term cyclic group embraces, unless otherwise specified, carbocyclic and heterocyclic radicals. The cyclic radicals can contain one or more rings. Carbocyclic radicals may be aromatic or alicyclic, for example cycloalkyl radicals. Heterocyclic radicals also include heteroaryl radicals.

As used herein, the term aromatic group embraces typically a 5- to 14- membered aromatic ring system, such as a 5- or 6- membered ring which may contain one or more heteroatoms selected from O, S and N. When no heteroatoms are present the radical is named aryl radical and when at least one heteroatom is present it is named heteroaryl radical. The aromatic radical can be monocyclic or polycyclic, such as phenyl or naphthyl. When an aromatic radical or moiety carries 2 or more substituents, the substituents may be the same or different.

As used herein, the term aryl radical embraces typically a C_5-C_{14} monocyclic or polycyclic aryl radical such as phenyl, naphthyl, anthranyl or phenanthryl. When an aryl radical carries 2 or more substituents, the substituents may be the same or different.

As used herein, the term heteroaryl radical embraces typically a 5- to 14- membered ring system comprising at least one heteroaromatic ring and containing at least one heteroatom selected from O, S and N. A heteroaryl radical may be a single ring or two or more fused rings wherein at least one ring contains a heteroatom.

Examples of heteroaryls include pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, furyl, oxadiazolyl, oxazolyl, isoxazolyl, imidazolyl, thiazolyl, thiadiazolyl, thienyl, pyrrolyl, benzothiazolyl, indolyl, indazolyl, purinyl, quinolyl, isoquinolyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, quinolizinyl, cinnolinyl, triazolyl, indolizinyl, indolinyl, isoindolinyl, isoindolyl, imidazolidinyl, pteridinyl and pyrazolyl. When a heteroaryl radical carries 2 or more substituents, the substituents may be the same or different.

As used herein, the term heterocycle radical embraces typically a 5- to 14- membered ring system comprising at least one heterocyclic ring and containing at least one heteroatom selected from O, S and N. A heterocycle radical may be a single ring or two or more fused rings wherein at least one ring contains a heteroatom. A heterocycle radical may be aromatic, in which case it is a heteroaryl radical, or it may be non-aromatic.

Examples of aromatic heterocycles (i.e., heteroaryls) are provided above. Examples of non-aromatic heterocycles include piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, oxazolidinyl, imidazolidinyl, thiazolidinyl, azepanyl, [1,4]diazepanyl, [1,4]oxazepanyl and thiazepanyl.

As used herein, the term cycloalkyl embraces saturated optionally substituted carbocyclic radicals and, unless otherwise specified, a cycloalkyl radical typically has from 3 to 7 carbon atoms. The preferred substituents in said cycloalkyl groups are selected from halogen atoms, hydroxy groups, alkyl groups and amino groups.

Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. It is preferably cyclopropyl, cyclopentyl or cyclohexyl. When a cycloalkyl radical carries 2 or more substituents, the substituents may be the same or different.

As used herein, some of the atoms, radicals, moieties, chains or cycles present in the general structures of the invention are “optionally substituted”. This means that these atoms, radicals, moieties, chains or cycles can be either unsubstituted or substituted in any position by one or more, for example 1, 2, 3 or 4, substituents, whereby the hydrogen atoms bound to the unsubstituted atoms, radicals, moieties, chains or cycles are replaced by chemically acceptable atoms, radicals, moieties, chains or cycles. When two or more substituents are present, each substituent may be the same or different.

The substituents of an “optionally substituted” structure may include, without limitation, one or more, typically one to four, and more typically one to two of the following substituents: alkyl, alkenyl, alkynyl, aryl, heteroaryl, alkoxy, aryloxy, alkylthio, arylthio, cycloalkyl, arylalkyl, amino, alkylamino, dialkylamino, amido (e.g. CONH2, CONHalkyl and CONHdialkyl and reverse NCOH or NCOalkyl), sulfoxide, sulfonyl, F, Cl, Br, I, CN, NO_2, NH_2, $NHCH_3$, $NHCH_2CH_3$, $N(CH_3)_2$, $N(CH_2CH_3)_2$, sulfoxide, sulfone, SH, SCH_3, OH, OCH_3, OCF_3, CH_3, and CF_3.

As used herein, the term halogen atom embraces chlorine, fluorine, bromine or iodine atoms typically a fluorine, chlorine or bromine atom, most preferably chlorine or fluorine. The term halo when used as a prefix has the same meaning.

As used herein, the term pharmaceutically acceptable salt embraces salts with a pharmaceutically acceptable acid or base. Pharmaceutically acceptable acids include both

inorganic acids, for example hydrochloric, sulphuric, phosphoric, diphosphoric, hydrobromic, hydroiodic and nitric acid and organic acids, for example citric, fumaric, maleic, malic, mandelic, ascorbic, oxalic, succinic, tartaric, benzoic, acetic, methanesulphonic, ethanesulphonic, benzenesulphonic or p-toluenesulphonic acid. Pharmaceutically acceptable bases include alkali metal (e.g. sodium or potassium) and alkali earth metal (e.g. calcium or magnesium) hydroxides and organic bases, for example alkyl amines, arylalkyl amines and heterocyclic amines.

Other preferred salts according to the invention are quaternary ammonium compounds wherein an equivalent of an anion (X-) is associated with the positive charge of the N atom. X- may be an anion of various mineral acids such as, for example, chloride, bromide, iodide, sulphate, nitrate, phosphate, or an anion of an organic acid such as, for example, acetate, maleate, fumarate, citrate, oxalate, succinate, tartrate, malate, mandelate, trifluoroacetate, methanesulphonate and p-toluenesulphonate. X- is preferably an anion selected from chloride, bromide, iodide, sulphate, nitrate, acetate, maleate, oxalate, succinate or trifluoroacetate. More preferably X- is chloride, bromide, trifluoroacetate or methanesulphonate.

As used herein, an N-oxide is formed from the tertiary basic amines or imines present in the molecule, using a convenient oxidising agent.

According to one embodiment of the present invention in the compounds of formula (I), R^1 represents a monocyclic aryl or heteroaryl group selected from the group of phenyl, pyridinyl, furanyl, thiophenyl, thiazolyl, pyrazolyl, imidiazolyl, oxazolyl, isoxazolyl and oxadiazolyl groups which are optionally substituted by one or more substituents selected from the group of halogen, hydroxyl, amino, alkylamino, optionally substituted lower alkoxy and optionally substituted lower alkyl.

According to another embodiment of the present invention in the compounds of formula (I), R^2 represents a monocyclic aryl or heteroaryl group selected from the group of phenyl, pyridinyl, furanyl, thiophenyl, thiazolyl, pyrazolyl, imidiazolyl, oxazolyl, isoxazolyl and oxadiazolyl groups which are optionally substituted by one or more substituents selected from the group of halogen, hydroxyl, amino, alkylamino, optionally substituted lower alkoxy and optionally substituted lower alkyl.

Particular individual compounds of the invention include:

2-(3-Dimethylaminomethyl-phenoxy)-N-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-acetamide (Compound 1-1);

N-[6-(3,5-Dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-2-(3-ethylaminomethyl-phenoxy)-acetamide (Compound 1-2);

2-(2-Dimethylaminomethyl-phenoxy)-N-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-acetamide (Compound 1-3);

2-(4-Dimethylaminomethyl-phenoxy)-N-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-acetamide (Compound 1-4);

2-(4-Dimethylaminomethyl-2-methoxy-phenoxy)-N-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-acetamide (Compound 1-5);

2-(4-Dimethylaminomethyl-3-methoxy-phenoxy)-N-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-acetamide (Compound 1-6);

2-(2-Dimethylaminomethyl-6-methoxy-phenoxy)-N-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-acetamide (Compound 1-7);

2-(5-Dimethylaminomethyl-2-methoxy-phenoxy)-N-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-acetamide (Compound 1-8);

2-(2-Dimethylaminomethyl-4-methoxy-phenoxy)-N-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-acetamide (Compound 1-9);

2-(3-Chloro-4-dimethylaminomethyl-phenoxy)-N-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-acetamide (Compound 1-10);

2-(2-Dimethylaminomethyl-4-methyl-phenoxy)-N-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-acetamide (Compound 1-11);

N-[6-(3,5-Dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-2-{3-[(ethyl-methyl-amino)-methyl]-phenoxy}-acetamide (Compound 1-12);

N-[6-(3,5-Dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-2-(3-morpholin-4-ylmethyl-phenoxy)-acetamide (Compound 1-13);

2-[3-(2-Dimethylamino-ethyl)-phenoxy]-N-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-acetamide (Compound 1-14);

N-[6-(3,5-Dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-2-[3-(2-morpholin-4-yl-ethyl)-phenoxy]-acetamide (Compound 1-15);

N-[6-(3,5-Dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-2-(3-fluoro-5-pyrrolidin-1-ylmethyl-phenoxy)-acetamide (Compound 1-16);

N-[6-(3,5-Dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-2-(3-fluoro-5-morpholin-4-ylmethyl-phenoxy)-acetamide (Compound 1-17);

2-(3-Dimethylaminomethyl-5-fluoro-phenoxy)-N-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-acetamide (Compound 1-18);

2-(3-Dimethylaminomethyl-phenoxy)-N-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-propionamide (Compound 1-19);
2-(3-Dimethylaminomethyl-phenoxy)-N-[2-(5-methyl-furan-2-yl)-6-thiazol-2-yl-pyrimidin-4-yl]-acetamide (Compound 2-1);
2-(3-Ethylaminomethyl-phenoxy)-N-[2-(5-methyl-furan-2-yl)-6-thiazol-2-yl-pyrimidin-4-yl]-acetamide (Compound 2-2);
2-[3-(Isopropylamino-methyl)-phenoxy]-N-[2-(5-methyl-furan-2-yl)-6-thiazol-2-yl-pyrimidin-4-yl]-acetamide (Compound 2-3);
2-(3-Cyclopropylaminomethyl-phenoxy)-N-[2-(5-methyl-furan-2-yl)-6-thiazol-2-yl-pyrimidin-4-yl]-acetamide (Compound 2-4);
2-(3-Cyclobutylaminomethyl-phenoxy)-N-[2-(5-methyl-furan-2-yl)-6-thiazol-2-yl-pyrimidin-4-yl]-acetamide (Compound 2-5); and
2-{3-[(2-Methoxy-ethylamino)-methyl]-phenoxy}-N-[2-(5-methyl-furan-2-yl)-6-thiazol-2-yl-pyrimidin-4-yl]-acetamide (Compound 2-6).

Additional compounds of the invention include:
2-(3-Dimethylaminomethyl-5-methoxy-phenoxy)-N-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-propionamide (Compound 1-20);
2-(5-Dimethylaminomethyl-2-methoxy-phenoxy)-N-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-propionamide (Compound 1-21);
2-(3-Dimethylaminomethyl-2-methoxy-phenoxy)-N-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-propionamide (Compound 1-22);
2-(3-Dimethylaminomethyl-4-methoxy-phenoxy)-N-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-propionamide (Compound 1-23);
2-(2-Dimethylaminomethyl-4-methoxy-phenoxy)-N-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-propionamide (Compound 1-24);
2-(2-Dimethylaminomethyl-3-methoxy-phenoxy)-N-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-propionamide (Compound 1-25);
2-(2-Dimethylaminomethyl-5-methoxy-phenoxy)-N-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-propionamide (Compound 1-26);
2-(2-Dimethylaminomethyl-6-methoxy-phenoxy)-N-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-propionamide (Compound 1-27);
2-(4-Dimethylaminomethyl-3-methoxy-phenoxy)-N-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-propionamide (Compound 1-28);
2-(4-Dimethylaminomethyl-2-methoxy-phenoxy)-N-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-propionamide (Compound 1-29);

1-[2-(2-Dimethylaminomethyl-6-methoxy-phenoxy)-ethyl]-3-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-urea (Compound 3-1);

1-[2-(2-Dimethylaminomethyl-5-methoxy-phenoxy)-ethyl]-3-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-urea (Compound 3-2);

1-[2-(2-Dimethylaminomethyl-4-methoxy-phenoxy)-ethyl]-3-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-urea (Compound 3-3);

1-[2-(2-Dimethylaminomethyl-3-methoxy-phenoxy)-ethyl]-3-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-urea (Compound 3-4);

1-[2-(3-Dimethylaminomethyl-2-methoxy-phenoxy)-ethyl]-3-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-urea (Compound 3-5);

1-[2-(3-Dimethylaminomethyl-4-methoxy-phenoxy)-ethyl]-3-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-urea (Compound 3-6);

1-[2-(3-Dimethylaminomethyl-5-methoxy-phenoxy)-ethyl]-3-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-urea (Compound 3-7);

1-[2-(5-Dimethylaminomethyl-2-methoxy-phenoxy)-ethyl]-3-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-urea (Compound 3-8);

1-[2-(4-Dimethylaminomethyl-3-methoxy-phenoxy)-ethyl]-3-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-urea (Compound 3-9);

1-[2-(4-Dimethylaminomethyl-2-methoxy-phenoxy)-ethyl]-3-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-urea (Compound 3-10);

[6-(3,5-Dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-carbamic acid 2-(2-dimethylaminomethyl-6-methoxy-phenoxy)-ethyl ester (Compound 4-1);

[6-(3,5-Dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-carbamic acid 2-(2-dimethylaminomethyl-5-methoxy-phenoxy)-ethyl ester (Compound 4-2);

[6-(3,5-Dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-carbamic acid 2-(2-dimethylaminomethyl-4-methoxy-phenoxy)-ethyl ester (Compound 4-3);

[6-(3,5-Dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-carbamic acid 2-(2-dimethylaminomethyl-3-methoxy-phenoxy)-ethyl ester (Compound 4-4);

[6-(3,5-Dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-carbamic acid 2-(5-dimethylaminomethyl-2-methoxy-phenoxy)-ethyl ester (Compound 4-5);

[6-(3,5-Dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-carbamic acid 2-(3-dimethylaminomethyl-5-methoxy-phenoxy)-ethyl ester (Compound 4-6);

[6-(3,5-Dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-carbamic acid 2-(3-dimethylaminomethyl-4-methoxy-phenoxy)-ethyl ester (Compound 4-7);

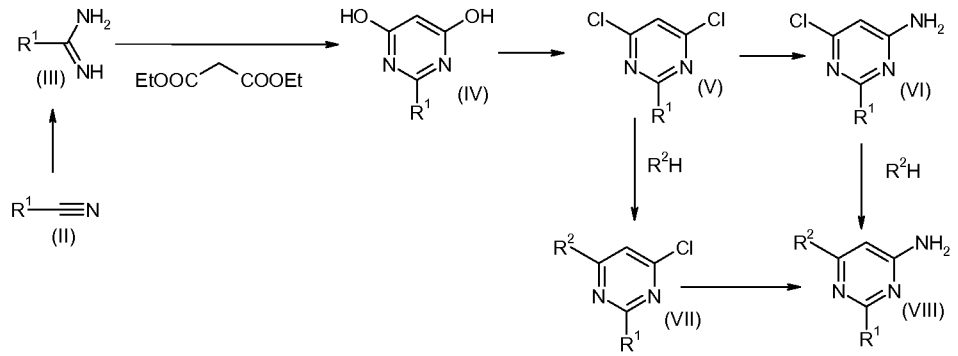
[6-(3,5-Dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-carbamic acid 2-(3-dimethylaminomethyl-2-methoxy-phenoxy)-ethyl ester (Compound 4-8);

[6-(3,5-Dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-carbamic acid 2-(4-dimethylaminomethyl-2-methoxy-phenoxy)-ethyl ester (Compound 4-9); and [6-(3,5-Dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-carbamic acid 2-(4-dimethylaminomethyl-3-methoxy-phenoxy)-ethyl ester (Compound 4-10).

The compounds of the present invention may be prepared by one of the processes described below.

Compounds of formula (I) where R^1 is a monocyclic or polycyclic heteroaryl group linked to the pyrimidine ring through a carbon atom and R^2 is a monocyclic or polycyclic heteroaryl group linked to the pyrimidine ring through a nitrogen atom can be obtained as shown is Scheme 1.

Scheme 1



The carboxyamidines of formula (III), wherein R^1 is a monocyclic or polycyclic heteroaryl group linked to the carboxyamidine group through a carbon atom can be obtained by reacting a nitrile of formula (II) with trimethylaluminum and ammonium chloride, in a solvent such as benzene, toluene or xylene, at a temperature from 80°C to 120°C. It also can be obtained by reaction of a nitrile of formula (II) with sodium methoxide in methanol at room temperature, followed by reaction with ammonium chloride at the same temperature.

The carboxyamidines of formula (III) can be reacted with diethyl malonate in a solvent such as methanol, ethanol, isopropyl alcohol, butyl alcohol or tetrahydrofuran, in the presence of a base, such as sodium methoxide, sodium ethoxide or potassium *tert*butoxide and at a temperature from room temperature to the boiling point of the solvent to yield the pyrimidine-4,6-diols of formula (IV).

The resulting pyrimidine-4,6-diols of formula (IV) can be reacted with a chlorinated agent such a phosphorus oxychloride, phosphorus pentachloride or a mixture of them, in a solvent such as phosphorus oxychloride, benzene or toluene, at a temperature from room temperature to the boiling point of the solvent to yield the 4,6-dichloropyrimidine compounds of formula (V). Optionally, the presence of a base such as dimethylaminoaniline, triethylamine or diisopropyl-ethylamine may be needed in this reaction step.

The reaction of the 4,6-dichloropyrimidine compounds of formula (V) with ammonium hydroxide in a solvent such as methanol, ethanol, isopropyl alcohol or tetrahydrofuran, at a temperature from 80°C to 140°C produces the 6-chloropyrimidin-4-amines of formula (VI).

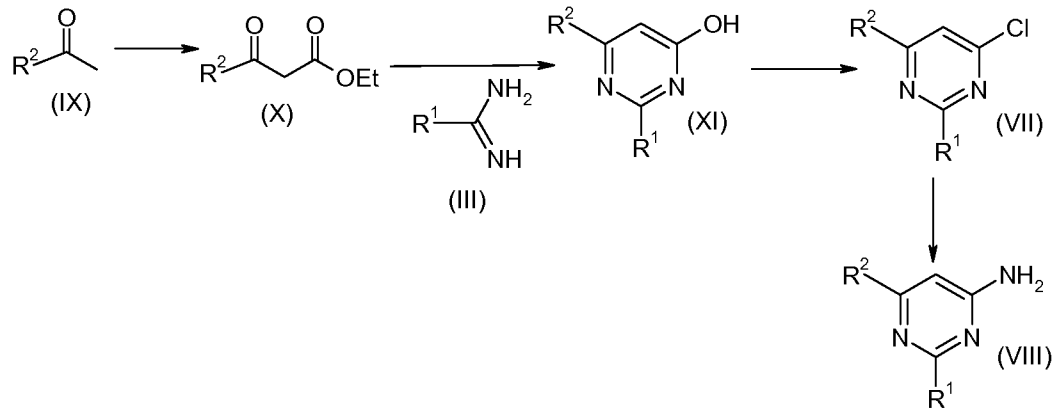
The resulting 6-chloropyrimidin-4-amines of formula (VI) are reacted with a compound of formula R^2-H wherein R^2 is a monocyclic or polycyclic heteroaryl group linked to the pyrimidine ring through a nitrogen atom to yield the compounds of formula (VIII). The reaction is carried out in a solvent such as dimethylformamide, dimethylacetamide or dimethylsulfoxide, in the presence of a base, such as sodium hydride, potassium carbonate or cesium carbonate, at a temperature from 60°C to 140°C.

The 4,6-dichloropyrimidine compounds of formula (V) can also be converted into the 4-chloropyrimidines of formula (VII) by reaction with a compound of formula R^2-H wherein R^2 is a monocyclic or polycyclic heteroaryl group linked to the pyrimidine ring through a nitrogen atom. The reaction is carried out in a solvent such as dimethylformamide, dimethylacetamide or dimethylsulfoxide, in the presence of a base, such as sodium hydride, potassium carbonate or cesium carbonate, at a temperature from 60°C to 140°C.

The resulting 4-chloropyrimidines of formula (VII) can then be converted to the compounds of formula (VIII) according to the invention by reaction with ammonium hydroxide in a solvent such as methanol, ethanol, isopropyl alcohol or tetrahydrofuran, at a temperature from 80°C to 140°C.

Compounds of formula (VIII) where R^1 is a monocyclic or polycyclic heteroaryl group linked to the pyrimidine ring through a carbon atom and R^2 is a monocyclic or polycyclic heteroaryl group linked to the pyrimidine ring through a carbon atom can be obtained as shown is Scheme 2.

Scheme 2



The reaction between methyl ketones of formula (IX), wherein R^2 is a monocyclic or polycyclic heteroaryl group linked to the pyrimidine ring through a carbon atom and diethyl carbonate can be carried out in the presence of a base, preferably sodium hydride, in a solvent such as benzene, toluene, ethyl ether, tetrahydrofuran or dioxane, and at a temperature from 40°C to 120°C to yield the substituted ethyl 3-oxo-propanoates of formula (X).

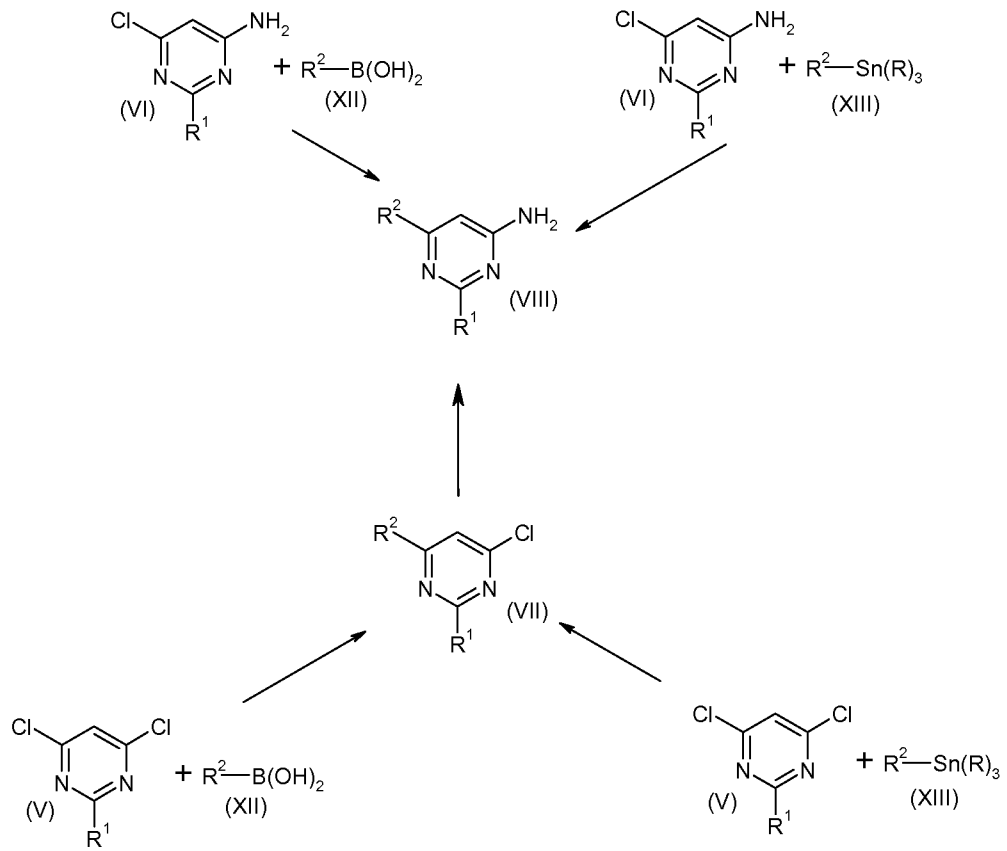
The pyrimidin-4-ol compounds of formula (XI) can be obtained from the substituted ethyl 3-oxo-propanoates of formula (X) by reaction with carboxyamidines of formula (III) in a solvent such as methanol, ethanol, isopropyl alcohol, butyl alcohol or tetrahydrofuran, in the presence of a base, such as sodium methoxide, sodium ethoxide or potassium *tert*butoxide and at a temperature from room temperature to the boiling point of the solvent.

The pyrimidin-4-ol compounds of formula (XI) can be reacted with a chlorinated agent such a phosphorus oxychloride, phosphorus pentachoride or a mixture of them, in a solvent such as phosphorus oxychloride, benzene or toluene, at a temperature from room temperature to the boiling point of the solvent to yield the 4-chloropyrimidines of formula (VII). Optionally, the presence of a base such as dimethylaminoaniline, triethylamine or diisopropyl-ethylamine may be needed in this reaction step.

The compounds of formula (VIII) according to the present invention can be prepared from 4-chloropyrimidines of formula (VII) by reaction with ammonium hydroxide in a solvent such as methanol, ethanol, isopropyl alcohol or tetrahydrofuran, at a temperature from 80°C to 140°C.

Compounds of formulae (VIII) where R^1 is a monocyclic or polycyclic heteroaryl group linked to the pyrimidine ring through a carbon atom and R^2 is a monocyclic or polycyclic heteroaryl group linked to the pyrimidine ring through a carbon atom can also be obtained as shown is Scheme 3.

Scheme 3



The Suzuki reaction between the 4-aminopirimidines of formulae (V) or (VI) and the boronic acid of formula (XII), wherein R^2 is a monocyclic or polycyclic heteroaryl group linked to the pyrimidine ring through a carbon atom, is preferably carried out in an organic solvent such as methanol, ethanol, acetonitrile, dioxane, tetrahydrofuran, dimethoxyethane, benzene or toluene, optionally in the presence of water, at a temperature between 60°C and 120°C, with a base such as sodium or potassium carbonate and a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0).

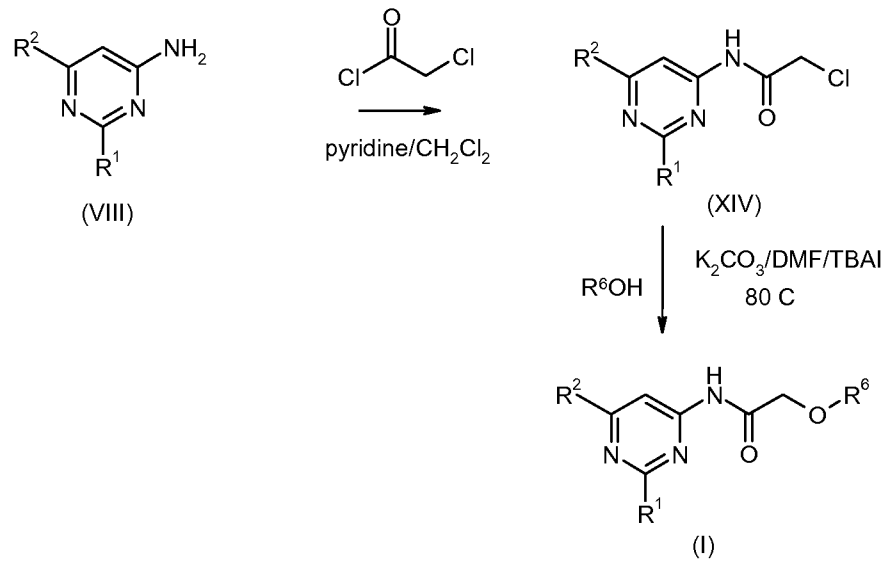
The Stille reaction between the 4-aminopirimidines of formulae (V) or (VI) and the organotin derivative of formula (XIII), wherein R^2 is a monocyclic or polycyclic heteroaryl group linked to the pyrimidine ring through a carbon atom, is preferably carried out in an organic solvent such as methanol, ethanol, acetonitrile, dioxane, tetrahydrofuran,

dimethoxyethane, benzene or toluene, optionally in the presence of water, at a temperature between 60°C and 120°C, with a base such as sodium or potassium carbonate and a catalyst such as tetrakis(triphenylphosphine)palladium(0) or bis(triphenylphosphine)palladium(II) chloride.

The 4-chloropyrimidine compounds of formula (VII) can be converted to the compounds of formula (VIII) by reaction with ammonium hydroxide in a solvent such as methanol, ethanol, isopropyl alcohol or tetrahydrofuran, at a temperature from 80°C to 140°C.

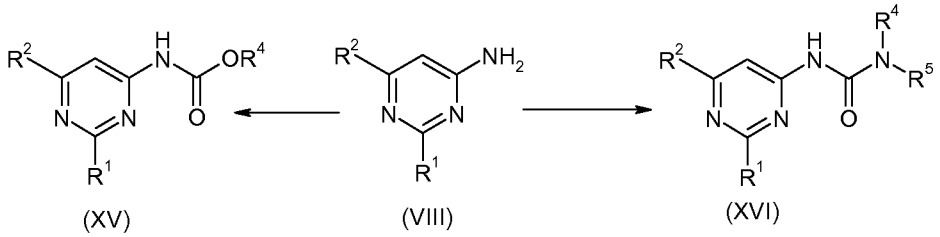
The synthesis of amides of formulae (XIV) can be prepared following Scheme 4

Scheme 4



The amides of formula (XIV) are obtained by reaction of a compound of formula (VIII) with chloroacetyl chloride in a solvent such as dichloromethane and base (e.g., pyridine). The resultant compound of formula (XIV) is reacted with the desired alcohol in the presence of potassium carbonate, TBAI and DMF to yield the desired amide of formula (I).

Scheme 5



The carbamates of formula (XV) are obtained by reaction of a compound of formula (VIII) with a compound of formula Z-$COOR^4$, wherein Z represents a leaving group such as halogen atom, preferably chlorine or a group selected from ethoxy, methoxy, p-nitrophenoxy and imidazolyl. The reaction is carried out in a solvent, such as tetrahydrofuran, chloroform, methylene chloride or dimethylformamide, in the presence of a base, preferably triethylamine, diisopropylethylamine, potassium carbonate or sodium hydroxide, at a temperature from –70°C to 100°C.

The compounds of formula (VIII) can also be converted to the ureas of formula (XVI) wherein R^5 is a hydrogen atom by reaction with an isocyanate of formula R^4-N=C=O in a solvent such as benzene, toluene or xylene, at a temperature from room temperature to 140°C.

When the defined groups R^1 to R^6 are susceptible to chemical reaction under the conditions of the hereinbefore described processes or are incompatible with said processes, conventional protecting groups may be used in accordance with standard practice, for example see T. W. Greene and P. G. M. Wuts in 'Protective Groups in Organic Chemistry', 3rd Edition, John Wiley & Sons (1999). It may be that deprotection will form the last step in the synthesis of compounds of formula (I).

PHARMACOLOGICAL ACTIVITY

Adenosine A2A receptor binding assays

Receptor cloning

The coding sequence of the human A2A receptor was amplified from a human brain cDNA library by the polymerase chain reaction. The amplicon was cloned into the pcDNA5/FRT/V5-His-TOPO expression vector (Invitrogen) and sequence confirmed using an ABI 3100 automated sequencer (Applied Biosystems). The expression construct was transfected into Flp-In HEK cells (Invitrogen) using Lipofectamine 2000 (Invitrogen). Cells stably expressing the human A2A receptor were selected using 1 mg/ml hygromycin in complete DMEM.

Membrane preparation

Crude membranes were prepared from Flp-In HEK cells transfected with the human A2A receptor by resuspending cells in lysis buffer (50 mM Tris-HCl pH 7.4, 5mM EDTA, 10 mM $MgCl_2$) and disrupting under N_2 at a pressure of 900 psi (Parr Cell disruption bomb,

cat.4639) for 30 min on ice followed by differential centrifugation. The resulting crude membrane pellet was resuspended in assay buffer (50 mM Tris HCl pH 7.4, 1 mM EDTA, 10 mM $MgCl_2$). Membrane protein concentration was determined by Bradford assay and aliquots were stored at –80°C.

Binding assay

An aliquot of membranes (5-10 μg of protein) was pre-incubated for 30 min at RT in the presence of 10 μg/ml Adenosine Deaminase (Type IV Calf Spleen, Sigma). Membranes were then incubated for 90 min with 1.0 nM [^{3}H]-ZM 241385 (27.40 Ci/mmol Tocris R1036) in the presence of varying concentrations of competing ligand. Non-specific binding was determined in the presence of excess (1 μM) of CGS15943. Bound and free ligand were separated by rapid vacuum filtration using a Packard 96-well cell harvester onto UniFilter GF/C filter plates (PerkinElmer) that had been pretreated with 0.5% polyethyleneimine. The filter plates were than washed 3 x 200 μl with 50mM Tris HCl, 50mM NaCl pH 7.4. Bound radioligand was determined by scintillation counting using a TopCount-NXT (Packard). Binding data was analyzed by nonlinear, least-squares curve fitting algorithms using GraphPad Prism (GraphPad Software, Inc. San Diego, CA) or ActivityBase (IDBS, Guildford, Surrey, UK). K_i values were calculated from IC_{50} values using the Cheng-Prusoff equation (Cheng, Y, Prusoff, W.H. Biochem. Pharm. 22:3099-3108, 1973.).

For A2A membrane assay:
ZM241385 measured Kd = 0.3 ± 0.2 nM; B_{max} = 33 ± 8 pmol/mg by Scatchard Analysis
Binding Ki = 0.25 ± 0.04 nM.

With reference to A2a receptor binding affinities, A2a receptor antagonists of this invention may have a IC_{50} of less than 10 μM. In one embodiment of this invention, a A2a receptor antagonist has a IC_{50} of less than 1μM. In another embodiment the IC_{50} is less than 0.25 μM (*i.e.,* 250 nM).

The pyrimidin-4-amine derivatives of the invention are useful in the treatment or prevention of diseases known to be susceptible to improvement by treatment with an antagonist of an adenosine receptor, in particular those susceptible to improvement by treatement with and antagonist of the A_{2A} adenosine receptor. Such diseases are, for example ischemia, supraventricular arrhythmias, acute renal failure, myocardial reperfusion injury, allergic reactions including but not limited to rhinitis, urticaria, scleroderm arthritis, other autoimmune diseases, inflammatory bowel diseases, asthma, diabetes mellitus, obesity, Parkinson disease, Huntington's disease, dystonias such as restless leg syndrome,

dyskinesias such as those caused by prolonged use of neuroleptic and dopaminergic drugs or sleep disorders.

Accordingly, the pyrimidin-4-amine derivatives of the invention and pharmaceutically acceptable salts thereof, and pharmaceutical compositions comprising such compound and/or salts thereof, may be used in a method of treatment of disorders of the human body which comprises administering to a subject requiring such treatment an effective amount of pyrimidin-4-amine derivative of the invention or a pharmaceutically acceptable salt thereof.

The present invention also provides pharmaceutical compositions which comprise, as an active ingredient, at least a pyrimidin-4-amine derivative of formula (I) or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable excipient such as a carrier or diluent. The active ingredient may comprise 0.001% to 99% by weight, preferably 0.01% to 90% by weight of the composition depending upon the nature of the formulation and whether further dilution is to be made prior to application. Preferably the compositions are made up in a form suitable for oral, topical, nasal, rectal, percutaneous or injectable administration.

The pharmaceutically acceptable excipients which are admixed with the active compound, or salts of such compound, to form the compositions of this invention are well-known *per se* and the actual excipients used depend *inter alia* on the intended method of administering the compositions.

Compositions of this invention are preferably adapted for injectable and oral administration. In this case, the compositions for oral administration may take the form of tablets, retard tablets, sublingual tablets, capsules, inhalation aerosols, inhalation solutions, dry powder inhalation, or liquid preparations, such as mixtures, elixirs, syrups or suspensions, all containing the compound of the invention; such preparations may be made by methods well-known in the art.

The diluents which may be used in the preparation of the compositions include those liquid and solid diluents which are compatible with the active ingredient, together with colouring or flavouring agents, if desired. Tablets or capsules may conveniently contain between 2 and 500 mg of active ingredient or the equivalent amount of a salt thereof.

The liquid composition adapted for oral use may be in the form of solutions or suspensions. The solutions may be aqueous solutions of a soluble salt or other derivative of the active

compound in association with, for example, sucrose to form a syrup. The suspensions may comprise an insoluble active compound of the invention or a pharmaceutically acceptable salt thereof in association with water, together with a suspending agent or flavouring agent.

Compositions for parenteral injection may be prepared from soluble salts, which may or may not be freeze-dried and which may be dissolved in pyrogen free aqueous media or other appropriate parenteral injection fluid.

Effective doses are normally in the range of 2-2000 mg of active ingredient per day. Daily dosage may be administered in one or more treatments, preferably from 1 to 4 treatments, per day.

In another embodiment, the present invention permits the diagnostic visualization of specific sites within the body by the use of radioactive or non-radioactive pharmaceutical agents Use of a compound of the present invention may provide a physiological, functional, or biological assessment of a patient or provide disease or pathology detection and assessment. Radioactive pharmaceuticals are employed in scintigraphy, positron emission tomography (PET), computerized tomography (CT), and single photon emission computerized tomography (SPECT.) For such applications, radioisotopes are incorporated of such elements as iodine (I) including ^{123}I (PET), ^{125}I (SPECT), and ^{131}I, technetium (Tc) including ^{99}Tc (PET), phosphorus (P) including ^{31}P and ^{32}P, chromium (Cr) including ^{51}Cr, carbon (C) including ^{11}C, fluorine (F) including ^{18}F, thallium (Tl) including ^{201}Tl, and like emitters of positron and ionizing radiation. Non-radioactive pharmaceuticals are employed in magnetic resonance imaging (MRI), fluoroscopy, and ultrasound. For such applications, isotopes are incorporated of such elements as gadolinium (Gd) including ^{153}Gd, iron (Fe), barium (Ba), manganese (Mn), and thallium (Tl). Such entities are also useful for identifying the presence of particular target sites in a mixture and for labeling molecules in a mixture.

The present invention will be further illustrated by the following examples. The examples are given by way of illustration only and are not to be construed as a limiting.

Reagents, starting materials, and solvents were purchased from commercial suppliers and used as received. Concentration refers to evaporation under vacuum using a Büchi rotatory evaporator. Reaction products were purified, when necessary, by flash chromatography on silica gel (40-63 μm) with the solvent system indicated.

Analytical HPLC-MS Method 1

Platform: Agilent 1100 series: equipped with an auto-sampler, an UV detector (220 nM and 254 nM), a MS detector (APCI);

HPLC column: YMC ODS AQ, S-5, 5µ, 2.0 x50 mm cartridge;

HPLC gradient: 1.0 mL/minute, from 10 % acetonitrile in water to 90 % acetonitrile in water in 2.5 minutes, maintaining 90 % for 1 minute. Both acetonitrile and water have 0.025% TFA.

Analytical HPLC-MS Method 2

Platform: Agilent 1100 series: equipped with an auto-sampler, an UV detector (220 nM and 254 nM), a MS detector (APCI);

HPLC column: Phenomenex Synergi-Max RP, 2.0 x 50 mm column;

HPLC gradient: 1.0 mL/minute, from 5 % acetonitrile in water to 95 % acetonitrile in water in 13.5 minutes, maintaining 95 % for 2 minute. Both acetonitrile and water have 0.025% TFA.

Analytical HPLC-MS Method 3

Platform: Agilent 1100 series: equipped with an auto-sampler, an UV detector (220 nM and 254 nM), a MS detector (electrospray);

HPLC column: XTerra MS, C_{18}, 5µ, 3.0 x 250 mm column;

HPLC gradient: 1.0 mL/minute, from 10 % acetonitrile in water to 90 % acetonitrile in water in 46 minutes, jump to 99% acetonitrile and maintain 99 % acetonitrile for 8.04 minutes. Both acetonitrile and water have 0.025% TFA.

Analytical HPLC-MS Method 4

Platform: Agilent 1100 series: equipped with an auto-sampler, an UV detector (220 nM and 254 nM), a MS detector (APCI) and Berger FCM 1200 CO_2 pump module;

HPLC column: Berger Pyridine, PYR 60A, 6µ, 4.6 x 150 mm column;

HPLC gradient: 4.0 mL/minute, 120 bar; from 10 % methanol in supercritical CO_2 to 60% methanol in supercritical CO_2 in 1.67 minutes, maintaining 60 % for 1 minute. Methanol has 1.5% water. Backpressure regulated at 140 bar.

Analytical HPLC-MS Method 5

Platform: Gilson 215 Auto-sampler, Dionex Thermostatted Column Compartment TCC-100 held at 30°C, Dionex PDA-100 Photodiode Array Detector (220 nm and 254 nm), Dionex P680 HPLC pump, Thermo Finnigan MSQ single quad Mass Spectrometer (APCI)

HPLC column: Phenomenex Gemini 5µ C18 110A, 3.0 x 150 mm

HPLC gradient: 1.5 mL/min, from 5% acetonitrile in water to 90% acetonitrile in water in 9.86 minutes, from 90% acetonitrile in water to 95% acetonitrile in water in 0.1 minutes, hold at 95% for 1.19 minutes. Both acetonitrile and water have 0.04% NH_4OH

Preparative HPLC-MS

Platform: Shimadzu HPLC equipped with a Gilson 215 auto-sampler/fraction collector, UV detector and a PE Sciez API150EX mass detector;

HPLC column: BHK ODS-O/B, 5 µ, 30x75 mm

HPLC gradient: 35 mL/minute, 10% acetonitrile in water to 100 % acetonitrile in 7 minutes, maintaining 100 % acetonitrile for 3 minutes, with 0.025% TFA.

Intermediate 1. 5-Methyl-furan-2-carboxamidine (HCl)

To a solution of sodium methoxide (5.55 mmol) in methanol (50 mL) was added 5-Methyl-furan-2-carbonitrile (5.0 g, 53.2 mmol). The mixture was stirred at room temperature for 3 hours. To the resulting solution was slowly added ammonium chloride (3.14 g, 58.7 mmol) and the mixture was stirred at room temperature for 68 hours. The resulting suspension was filtered and the solvent removed under reduced pressure. The solid obtained was washed with ethyl ether (3x25 mL) to give 7.5 g (96%) of 5-Methyl-furan-2-carboxamidine (HCl).

δ (200 MHz, DMSO-d_6): 6.88-6.86 (m, 1H); 7.89 (d, J=3.8 Hz, 1H); 8.19 (s, 1H); 9.22 (s, 3H).

Intermediate 2. 2-(5-Methyl-furan-2-yl)-pyrimidine-4,6-diol

To a solution of sodium ethoxide (0.191 mol) in ethanol (90 mL) was slowly added Intermediate 1 (5.6 g, 38.2 mmol). The mixture was stirred at room temperature for 30 minutes and then, diethyl malonate (4.87 g, 30.4 mmol) was added. The suspension was refluxed for 32 hours. The solvent was removed under reduced pressure, the residue was suspended in water (100 mL) and acidified to pH=6 with 5N hydrochloric acid. The resulting solid was filtered and washed with water (50 mL), ethanol/ethyl ether (4:1, 25 mL), ethyl ether (2x25 mL). 2-(5-Methyl-furan-2-yl)-pyrimidine-4,6-diol was obtained (4.2 g, 78%) as a pale yellow solid.

δ (300 MHz, DMSO-d_6): 5.00 (s, 1H); 6.60-6.70 (m, 1H); 7.40 (d, *J*=3.4 Hz, 1H); 7.80 (s, 1H).

Intermediate 3. 4,6-Dichloro-2-(5-methyl-furan-2-yl)-pyrimidine

A suspension of Intermediate 2 (3.0 g, 16.8 mmol) and *N,N*-diisopropylethylamine (3.85 g, 29.8 mmol) in phosphorous oxychloride (17 mL) was refluxed for 3 hours. The solvent was

removed under pressure and methylene chloride (50 mL) and ice were slowly added. The organic layer was washed with water (2x25 mL), saturated solution of sodium bicarbonate (2x25 mL), brine, and dried (Na_2SO_4). The solvent was removed under reduced pressure to give 4,6-Dichloro-2-(5-methyl-furan-2-yl)-pyrimidine (3.15 g, 87%) as a grey solid.

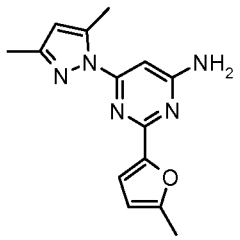
δ (300 MHz, $CDCl_3$): 6.63-6.61 (m, 1H); 7.22 (s, 1H); 7.46 (d, *J*=3.4 Hz, 1H); 7.68 (s, 1H).

Intermediate 4. 6-Chloro-2-(5-methyl-furan-2-yl)-pyrimidin-4-ylamine

A suspension of Intermediate 3 (2.0 g, 9.3 mmol) in methanol (14 mL) and 30% ammonium hydroxide (27 mL) was heated in a pressure reactor for 20 hours. The solvent was partially removed under reduced pressure. The resulting solid was filtered, washed with water (25 mL), ethyl ether (25 mL), and dried. 6-Chloro-2-(5-methyl-furan-2-yl)-pyrimidin-4-ylamine was obtained (1.48 g, 76%) as an off-white solid.

δ (400 MHz, $CDCl_3$): 5.21 (bs, 2H); 6.31 (s, 1H); 6.54 (m, 1H); 7.28 (d, *J1*=3.7 Hz, 1H); 7.58 (s, 1H).

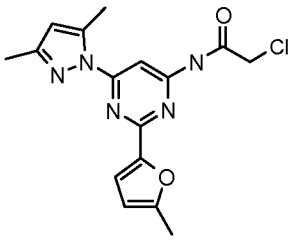
Intermediate 5. 6-(3,5-Dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-ylamine



To a solution of Intermediate 4 (1.0 g, 5.1 mmol) in anhydrous DMF (20 mL) was added 3,5-Dimethyl-pyrazol (0.7 g, 10.2 mmol) and cesium carbonate (3.34 g, 10.2 mmol). The mixture was heated at 85ºC for 21 hours. The solution was poured into water (50 mL) and extracted with ethyl acetate (2x25 mL). The organic layer was washed with water (2x25 mL) and brine (25 mL), dried (Na_2SO_4), and the solvent removed under reduced pressure. The resulting solid was purified by column chromatography with silica gel, eluting with methylene chloride/methanol (3%), to give 6-(3,5-Dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-ylamine (0.64 g, 55%) as an off-white solid.

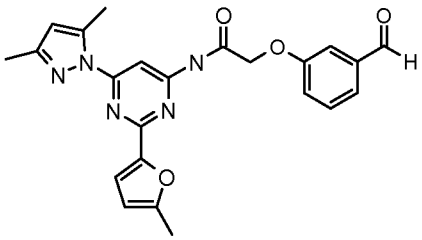
δ (250 MHz, $CDCl_3$): 5.12 (bs, 2H); 6.48-6.46 (m, 1H); 6.57-6.55 (m, 1H); 6.90 (s, 1H); 7.31 (d, *J*=3.6 Hz, 1H); 7.61 (s, 1H); 7.75 (d, *J*=1.2 Hz, 1H); 8.63 (d, *J*=3.0 Hz, 1H).

Intermediate 6. 2-Chloro-N-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-acetamide



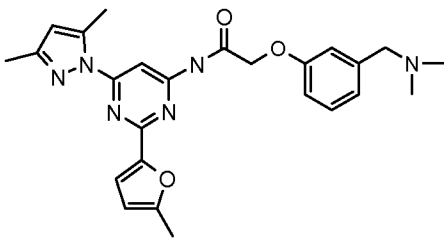
To 5 mL dichloromethane were added 0.3 g (1.3 mmol) of the compound of Intermediate 5, 0.22 g chloroacetyl chloride (0.20 mmol, 1.5 eq) and 0.16 g pyridine. The reaction mixture was stirred at r/t for 2 hours. The reaction was quenched with 5 mL saturated sodium bicarbonate and extracted; the aqueous solution was washed with an additional 5 mL dichloromethane. The organic layers combined and dried under sodium sulfate, concentrated to a yellow solid (0.4 g, 100% crude yield).

Intermediate 7. N-[6-(3,5-Dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-2-(3-formyl-phenoxy)-acetamide



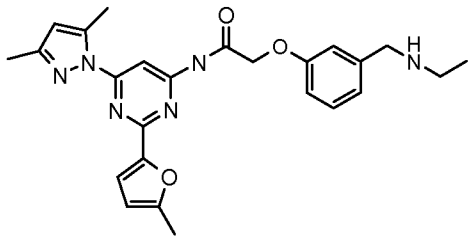
To 20 mL DMF were added 2 g (M.W. 345, 5.8 mmol, 1 eq) Intermediate 6, 0.78 g (M.W. 122, 1.1 eq) 3-hydroxybenzaldehyde, 0.8g (M.W. 138, 1eq) potassium carbonate, and 0.1g TBAI. The reaction mixture was stirred vigorously at room temperature overnight. The reaction was quenched with 100 mL water, extracted twice with 100 mL dichloromethane. The organic layers were combined, dried under sodium sulfate, and concentrated to driness. The solid thus obtained was resuspended in 15 mL methanol, filtered and washed twice with 10 mL ether. Obtained 1.1 g (44.0%) Intermediate 7 as a white solid. LCMS (APCI) *m/z* 432.0 (MH^+).

Compound 1-1. 2-(3-Dimethylaminomethyl-phenoxy)-N-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-acetamide



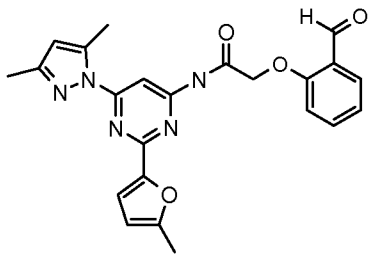
To a mixture of 5 mL THF and 5 mL ethanol were added 850 mg Intermediate 7 (M.W. 431, 2 mmol, 1 eq), 0.21 mL BH_3/pyridine complex (1.2 eq), 3 mL dimethylamine (2M in THF, 3 eq), and 10 drops of acetic acid. The reaction mixture was stirred at room temperature overnight. The reaction was quenched with 50 mL 1N HCl, extracted twice with 50 mL dichloromethane, the organic layers were combined, dried under sodium sulfate, concentrated and purified by silica gel column, using 200 mL dichloromethane, 500 mL 5% THF in dichloromethane, and 500 mL 5% MeOH (2N ammonia) in dichloromethane. Obtained 680 mg white solid (yield 74.2%). The solid was dissolved in 10 mL dichloromethane, chilled to –78°C and added 1.0 mL 2N HCl in ether and dried under nitrogen. LCMS (APCI) *m/z* 461.0 (MH^+). t_{ret} = 22.74 min, Method 3. δ (300 MHz, $CDCl_3$): 2.29 (s, 3H), 2.36 (s, 6H), 2.46 (s, 3H), 2.78 (s, 3H), 3.57 (s, 2H), 4.67 (s, 2H), 6.02 (s, 1H), 6.17 (d, J = 4.5Hz, 1H), 6.94 (dd, J = 9.0, 2.7 Hz, 1H), 7.03-7.09 (m, 1H), 7.18 (d, J = 3.0 Hz, 1H), 7.26-7.34 (m, 1H), 8.55 (s, 1H), 9.10 (s, 1H).

Compound 1-2. N-[6-(3,5-Dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-2-(3-ethylaminomethyl-phenoxy)-acetamide



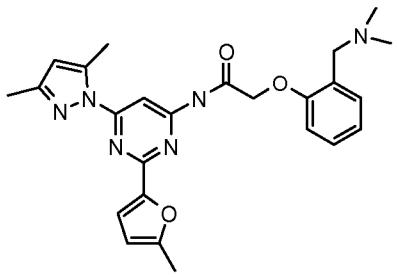
Compound 1-2 was prepared according to the procedures described in Compound 1-1, except that ethylamine was used instead of dimethylamine. LCMS (APCI) *m/z* 461.0 (MH^+). t_{ret} = 2.200 min, Method 4.

Intermediate 8. N-[6-(3,5-Dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-2-(2-formyl-phenoxy)-acetamide



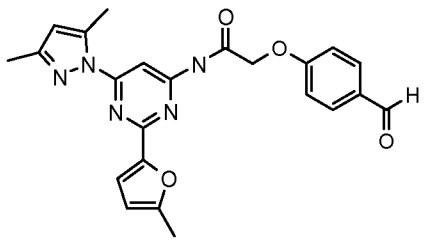
Intermediate 8 was prepared according to the procedures described in Intermediate 7, except that 2-hydroxybenzaldehyde was used instead of 3-hydroxybenzaldehyde.

Compound 1-3. 2-(2-Dimethylaminomethyl-phenoxy)-N-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-acetamide



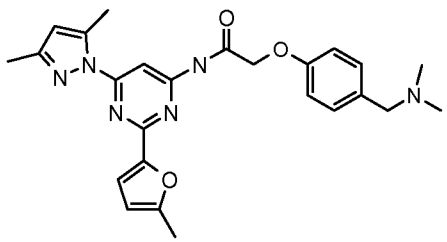
Compound 1-3 was prepared according to the procedures described in Compound 1-1, except that Intermediate 8 was used instead of Intermediate 7. LCMS (APCI) *m/z* 461.0 (MH^+). t_{ret} = 12.250 min, Method 5.

Intermediate 9. N-[6-(3,5-Dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-2-(4-formyl-phenoxy)-acetamide



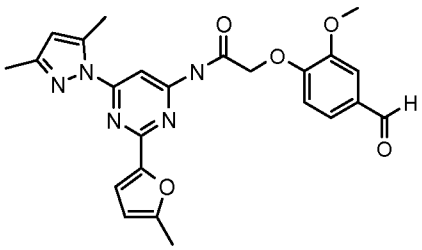
Intermediate 9 was prepared according to the procedures described in Intermediate 7, except that 4-hydroxybenzaldehyde was used instead of 3-hydroxybenzaldehyde.

Compound 1-4. 2-(4-Dimethylaminomethyl-phenoxy)-N-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-acetamide



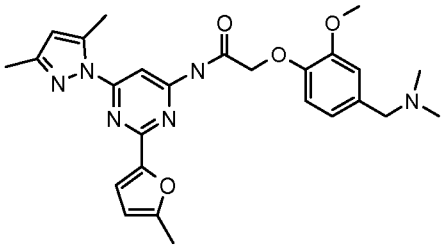
Compound 1-4 was prepared according to the procedures described in Compound 1-1, except that Intermediate 9 was used instead of Intermediate 7. LCMS (APCI) *m/z* 461.0 (MH^+). t_{ret} = 10.250 min, Method 2.

Intermediate 10. N-[6-(3,5-Dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-2-(4-formyl-2-methoxy-phenoxy)-acetamide



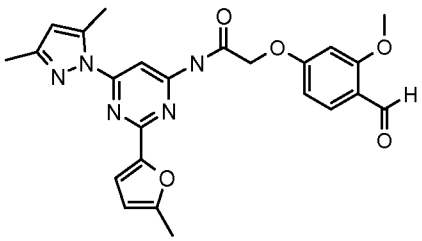
Intermediate 10 was prepared according to the procedures described in Intermediate 7, except that 4-hydroxy-3-methoxy-benzaldehyde was used instead of 3-hydroxybenzaldehyde.

Compound 1-5. 2-(4-Dimethylaminomethyl-2-methoxy-phenoxy)-N-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-acetamide



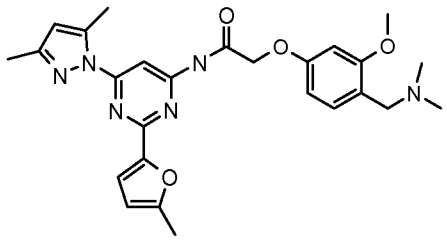
Compound 1-5 was prepared according to the procedures described in Compound 1-1, except that Intermediate 10 was used instead of Intermediate 7. LCMS (APCI) *m/z* 491.0 (MH^+). t_{ret} = 10.630 min, Method 2.

Intermediate 11. N-[6-(3,5-Dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-2-(4-formyl-3-methoxy-phenoxy)-acetamide



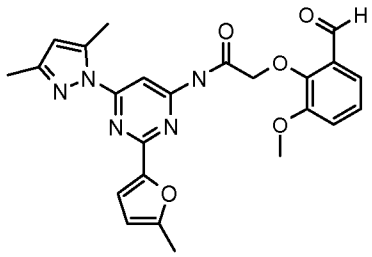
Intermediate 11 was prepared according to the procedures described in Intermediate 7, except that 4-hydroxy-2-methoxy-benzaldehyde was used instead of 3-hydroxybenzaldehyde.

Compound 1-6. 2-(4-Dimethylaminomethyl-3-methoxy-phenoxy)-N-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-acetamide



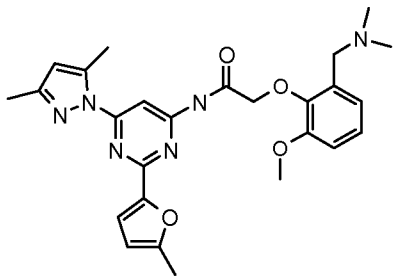
Compound 1-6 was prepared according to the procedures described in Compound 1-1, except that Intermediate 11 was used instead of Intermediate 7. LCMS (APCI) *m/z* 491.0 (MH^+). t_{ret} = 11.11 min, Method 2.

Intermediate 12. N-[6-(3,5-Dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-2-(2-formyl-6-methoxy-phenoxy)-acetamide



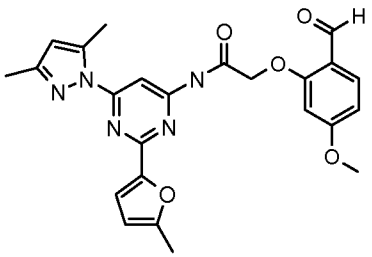
Intermediate 12 was prepared according to the procedures described in Intermediate 7, except that 2-hydroxy-3-methoxy-benzaldehyde was used instead of 3-hydroxybenzaldehyde.

Compound 1-7. 2-(2-Dimethylaminomethyl-6-methoxy-phenoxy)-N-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-acetamide



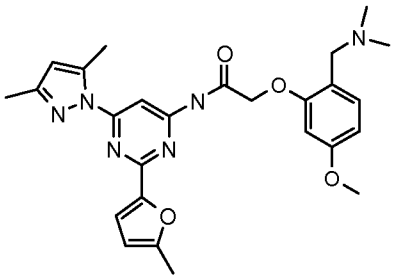
Compound 1-7 was prepared according to the procedures described in Compound 1-1, except that Intermediate 12 was used instead of Intermediate 7. LCMS (APCI) *m/z* 491.0 (MH^+). t_{ret} = 11.870 min, Method 2.

Intermediate 13. N-[6-(3,5-Dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-2-(2-formyl-5-methoxy-phenoxy)-acetamide



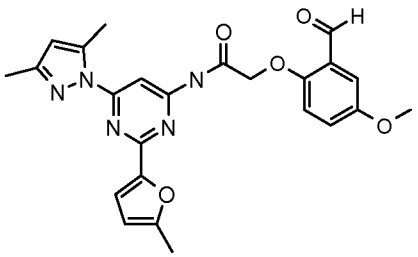
Intermediate 13 was prepared according to the procedures described in Intermediate 7, except that 2-hydroxy-4-methoxy-benzaldehyde was used instead of 3-hydroxybenzaldehyde.

Compound 1-8. 2-(2-Dimethylaminomethyl-5-methoxy-phenoxy)-N-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-acetamide



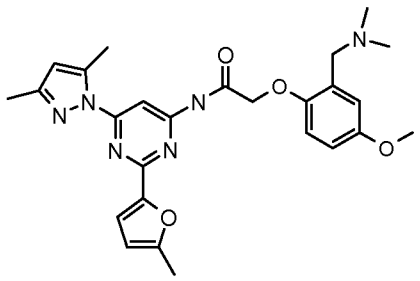
Compound 1-8 was prepared according to the procedures described in Compound 1-1, except that Intermediate 13 was used instead of Intermediate 7. LCMS (APCI) *m/z* 491.0 (MH^+). t_{ret} = 10.700 min, Method 2.

Intermediate 14. N-[6-(3,5-Dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-2-(2-formyl-4-methoxy-phenoxy)-acetamide



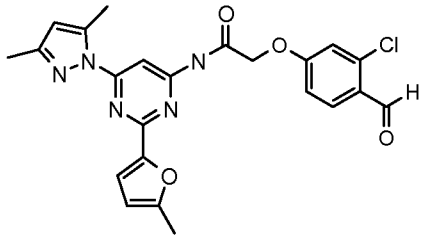
Intermediate 14 was prepared according to the procedures described in Intermediate 7, except that 2-hydroxy-5-methoxy-benzaldehyde was used instead of 3-hydroxybenzaldehyde.

Compound 1-9. 2-(2-Dimethylaminomethyl-5-methoxy-phenoxy)-N-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-acetamide



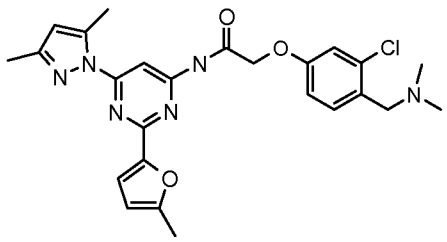
Compound 1-9 was prepared according to the procedures described in Compound 1-1, except that Intermediate 14 was used instead of Intermediate 7. LCMS (APCI) *m/z* 491.0 (MH^+). t_{ret} = 12.100 min, Method 2.

Intermediate 15. 2-(3-Chloro-4-formyl-phenoxy)-N-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-acetamide



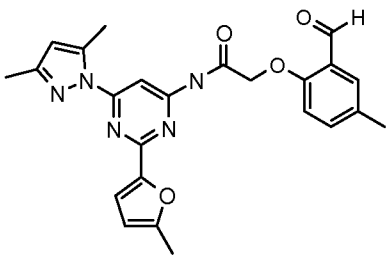
Intermediate 15 was prepared according to the procedures described in Intermediate 7, except that 2-chloro-4-hydroxy-benzaldehyde was used instead of 3-hydroxybenzaldehyde.

Compound 1-10. 2-(3-Chloro-4-dimethylaminomethyl-phenoxy)-N-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-acetamide



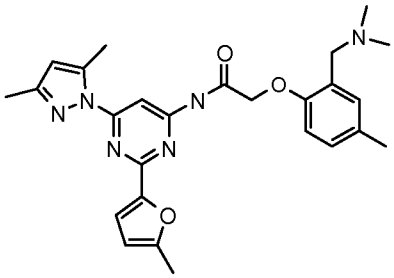
Compound 1-10 was prepared according to the procedures described in Compound 1-1, except that Intermediate 15 was used instead of Intermediate 7. LCMS (APCI) *m/z* 495.0 (MH^+). t_{ret} = 10.800 min, Method 2.

Intermediate 16. N-[6-(3,5-Dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-2-(2-formyl-4-methyl-phenoxy)-acetamide



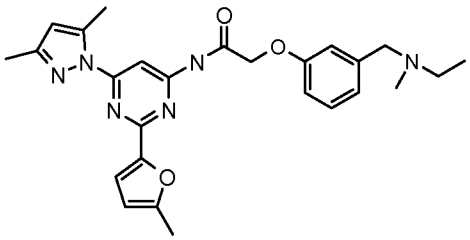
Intermediate 16 was prepared according to the procedures described in Intermediate 7, except that 2-hydroxy-5-methyl-benzaldehyde was used instead of 3-hydroxybenzaldehyde.

Compound 1-11. 2-(2-Dimethylaminomethyl-4-methyl-phenoxy)-N-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-acetamide



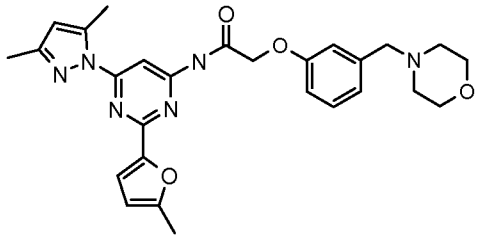
Compound 1-11 was prepared according to the procedures described in Compound 1-1, except that Intermediate 16 was used instead of Intermediate 7. LCMS (APCI) *m/z* 474.0 (MH^+). t_{ret} = 12.600 min, Method 2.

Compound 1-12. N-[6-(3,5-Dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-2-{3-[(ethyl-methyl-amino)-methyl]-phenoxy}-acetamide



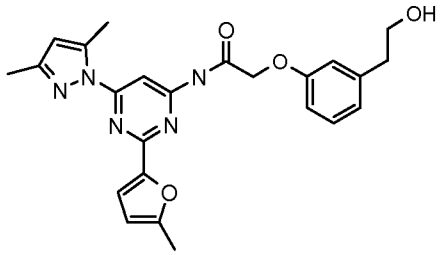
Compound 1-12 was prepared according to the procedures described in Compound 1-1, except that ethylmethylamine was used instead of dimethylamine. LCMS (APCI) *m/z* 475.0 (MH^+). t_{ret} = 10.900 min, Method 2.

Compound 1-13. N-[6-(3,5-Dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-2-(3-morpholin-4-ylmethyl-phenoxy)-acetamide



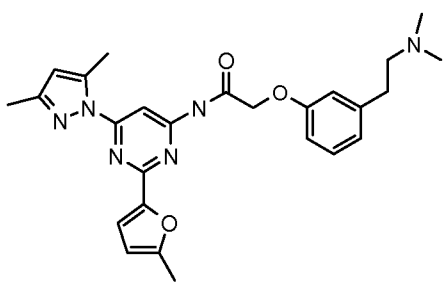
Compound 1-13 was prepared according to the procedures described in Compound 1-1, except that morpholine was used instead of dimethylamine. LCMS (APCI) *m/z* 503.8 (MH^+). t_{ret} = 10.000 min, Method 2.

Intermediate 17. N-[6-(3,5-Dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-2-[3-(2-hydroxy-ethyl)-phenoxy]-acetamide



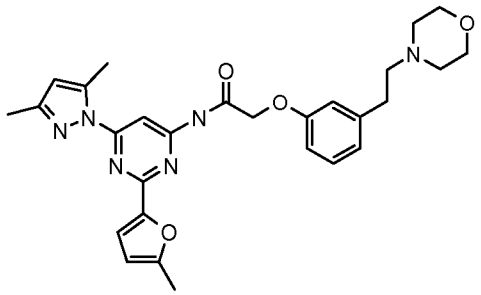
To 8 mL DMF were added 0.4g of Intermediate 6 (M.W. 345, 1.2 mmol, 1eq), 0.18g phenol (M.W. 138, 1.1eq), 0.16g potassium carbonate (M.W. 138, 1eq) and catalytical amount of TBAI. The reaction mixture was stirred at room temperature overnight. The reaction was quenched with 50 mL water, extracted twice with 50 mL dichloromethane. The organic layers were combined, dried under sodium sulfate, and concentrated to dryness. The solid was resuspended in 6 mL methanol, filtered, and washed with 5 mL ether twice. Obtained 110mg of Intermediate 17 as a white solid, yield 21.2%.

Compound 1-14. 2-[3-(2-Dimethylamino-ethyl)-phenoxy]-N-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-acetamide

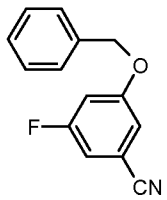


To 5 mL dichloromethane were added 110mg Intermediate 17 (M.W. 447, 0.25 mmol, 1 eq), 50 mg (2 eq) TFA and 0.05 mL MsCl. The reaction mixture was stirred at room temperature for one hour. HPLC showed clear conversion (M.S. 526). The reaction was quenched with 50 mL saturated sodium bicarbonate, extracted twice with 50 mL dichloromethane. The organic layers were combined, dried under sodium sulfate and concentrated to a white solid, used as is. The white solid obtained was dissolved in DMF/DCM (2/1), added catalytical amount of TBAI and dimethylamine, sealed and heated at 80°C overnight. The resulting product was purified by Prep-LCMS. LCMS (APCI) *m/z* 475.0 (MH^+). t_{ret} = 10.500 min, Method 2.

Compound 1-15. N-[6-(3,5-Dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-2-[3-(2-morpholin-4-yl-ethyl)-phenoxy]-acetamide

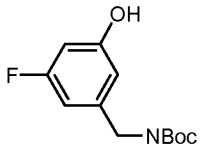


Compound 1-15 was prepared according to the procedures described in Compound 1-14, except that morpholine was used instead of dimethylamine. **Intermediate 18. 3-Benzyloxy-5-fluoro-benzonitrile**



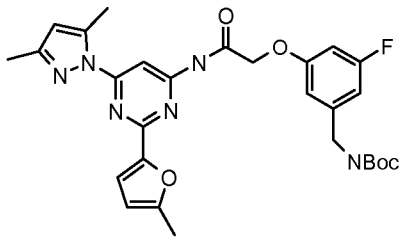
NaH (0.273 g, 60% suspension, 0.95 eq.) was suspended in 10 mL DMF at room temperature. Benzyl alcohol (0.621 g, 0.8 eq.) was added in three portions, at which time gas evolved from the solution. After stirring for 30 min. potassium benzoate (0.97 g, 0.77 eq.) was added, and the solution was stirred an additional 30 min. at room temperature. 3,5-Difluoronitrile (1 g, 1.0 eq.) was added slowly, then the solution was heated at 65 °C for 14 h. The reaction was cooled to room temperature, and quenched by slowly adding 25 mL H_2O and 25 mL brine. The mixture was extracted with EtOAc (2 x 200mL) and the organic layers were dried over MgSO4 and evaporated. The residue was purified by silica gel, eluting with 1:4 EtOAc:hexanes to give the final product as 1.15g colorless oil. GCMS (EI) *m/z* 227 (M^+).

Intermediate 19. (3-Fluoro-5-hydroxy-benzyl)-carbamic acid tert-butyl ester



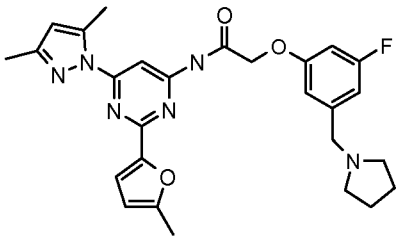
Intermediate 18 (0.5 g, 1 eq.) was dissolved in 10 mL acetic acid with 50 mg 5% Pd-C and the flask was pressurized to 50 psi with H_2 gas. The flask was shaken 14 h at room temperature. The mixture was filtered over Celite and concentrated. The residue was immediately dissolved in 10 mL DCM with DIEA (0.85 g, 3 eq.) and Boc_2O (0.528 g, 1.1 eq.). The pH was adjusted if necessary to pH > 7.5 by addition of DIEA. The reaction was judged complete after 2 h. The mixture was diluted with 75 mL of DCM then extracted with 10% $NaHSO_4$ (2 x 25 mL) then brine (25 mL). The organic layer was dried over $MgSO_4$ and evaporated to give the product as a colorless solid (0.45g). LCMS (APCI) *m/z* 242 (MH^+). NMR δ (300 MHz, $CDCl_3$): 1.46 (s, 9H), 4.22 (d, J = 6.0Hz, 2H), 4.3 (m, 1H), 4.93 (bs, 1H), 6.43-6.53 (m, 3H).

Intermediate 20. (3-{[6-(3,5-Dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-ylcarbamoyl]-methoxy}-5-fluoro-benzyl)-carbamic acid tert-butyl ester



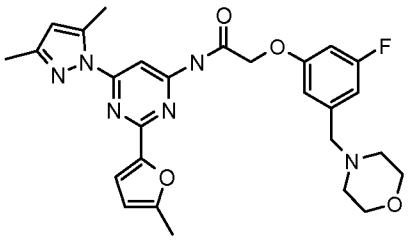
Intermediate 6 (0.42 g, 1.0 eq.), Intermediate 19 (0.44 g, 1.5 eq.) and DIEA (0.315 g, 2.0 eq.) were dissolved in 8 mL ACN and heated to 80 °C 14 h. The solvent was removed *in vacuo*, and the residue was extracted with EtOAc (200 mL) and 10% $NaHSO_4$ (30 mL) then brine (30 mL) then sat. $NaHCO_3$ (30 mL) and brine (30 mL). The organic layer was dried over $MgSO_4$ and evaporated and the residue was purified by silica gel eluting with 1:4 acetone:hexanes to give the product as a colorless solid (0.45g). LCMS (APCI) *m/z* 551.2 (MH^+).

Compound 1-16. N-[6-(3,5-Dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-2-(3-fluoro-5-pyrrolidin-1-ylmethyl-phenoxy)-acetamide



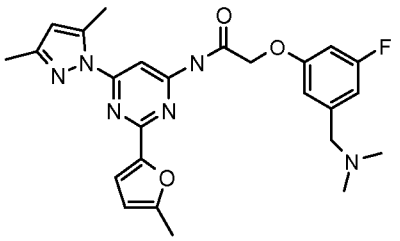
Intermediate 20 (0.25 g, 1 eq.) was dissolved in 5 mL DCM with TFA (1.03 g, 20 eq.). The solution was stirred at room temperature for 1 h. The solvent was removed in vacuo and the residue was immediately dissolved in ACN. DIEA (3 eq.) and 1,4-dibromobutane (2 eq) were added, and the solution was heated to reflux 14 h. The product was purified by prep-LCMS (15-75% ACN). LCMS rt = 6.41 min. (APCI) *m/z* 505.2 (MH^+).

Compound 1-17. N-[6-(3,5-Dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-2-(3-fluoro-5-morpholin-4-ylmethyl-phenoxy)-acetamide



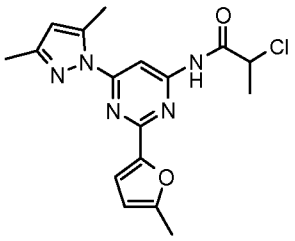
Compound 1-17 was synthesized by the same method as compound 1-16, except that bis(2-bromoethyl)ether was used in place of 1,4-dibromobutane. The product was purified by prep-LCMS (15-75% ACN). LCMS rt = 6.25 min. (APCI) *m/z* 521.2 (MH^+).

Compound 1-18. 2-(3-Dimethylaminomethyl-5-fluoro-phenoxy)-N-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-acetamide



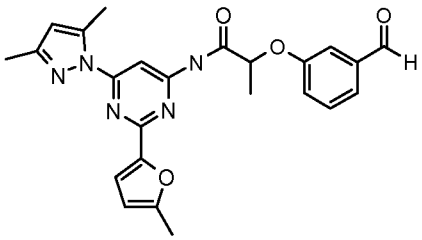
Intermediate 20 was treated with TFA in DCM as in the synthesis of compound 1-16. The crude amine was dissolved in ACN with formaldehyde (13 M solution, 10 eq.) and BH_3-pyridine (0.19 mL, 10 eq.) and the solution was stirred at room temperature 14 h. The product was purified by prep-LCMS (35-95% ACN). LCMS rt = 6.17 min. (APCI) *m/z* 479.1 (MH^+).

Intermediate 21. 2-Chloro-N-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-propionamide



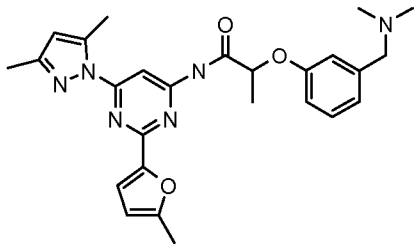
Intermediate 5 (1 g, 3.71 mmol) was suspended in 10 mL of anhydrous CH_2Cl_2. To this suspension was added pyridine (0.54 mL, 6.68 mmol, 1.8 eq.), followed by 2-chloropropionyl chloride (0.72 mL, 7.42 mmol, 2 eq.). The reaction mixture was stirred at room temperature for 16 hours after which the reaction was checked by LCMS to show the consumption of starting material. The reaction was diluted with CH_2Cl_2 (25 mL), washed with 10% aq. $NaHSO_4$ (50 mL), and the layers seperated. The aqueous layer was then extracted with CH_2Cl_2 (4 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over magnesium sulfate, filtered, and evaporated to dryness. The crude material was purified by flash chromatography eluting with 1:4 EtOAc/ Hexanes to yield 1.16 g (86.6%) of the product as an off-white solid. LCMS rt= 3.09 min. (APCI) *m/z* 360.0 (MH^+).

Intermediate 22. N-[6-(3,5-Dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-2-(3-formyl-phenoxy)-propionamide



Intermediate 21 (1 g, 2.78 mmol), 3-hydroxybenzaldehyde (0.36 g, 2.95 mmol, 1.05 eq.), K_2CO_3 (0.38 g, 2.75 mmol, 1 eq.), and TBAI (.051 g, 0.14 mmol, 0.05 eq.) were suspended in 10 mL of anhydrous acetone. The reaction mixture was refluxed at 60 °C for a total of 14 hours while monitoring the reaction every 3-4 hours by LCMS for the consumption of starting material. The reaction mixture was stopped and allowed to cool with about 20% unconsumed starting material remaining. The mixture was then diluted with Et_2O (30 mL), filtered through a medium fritted funnel washing with small aliquots of Et_2O, and the organic filtrate was evaporated to dryness. The crude material was purified by flash chromatography eluting with 1:3 EtOAc/ Hexanes to yield 0.27 g (21.7%) of the product as an off white foam. LCMS rt= 3.163 min. (APCI) *m/z* 446.1 (MH^+).

Compound 1-19. 2-(3-Dimethylaminomethyl-phenoxy)-N-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-propionamide



Intermediate 22 (0.25 g, 0.56 mmol) was dissolved in 1.5 mL of anhydrous THF and 1.5 ml of absolute EtOH. To this solution was added dimethylamine- 2M in THF (0.56 mL, 1.12 mmol, 2 eq.), BH_3•pyridine complex (0.11 mL, 0.88 mmol, 1.5 eq.), followed by 10 drops of glacial acetic acid added slowly dropwise. The reaction was stirred at room temperature for 20 hours after which it was checked by LCMS to show about 20% of unreacted starting material. The reaction was then stopped and stirred with aq. 2M HCl (2.5 mL) for 20 min. to quench the reaction. The solution was extracted with CH_2Cl_2 (25 mL) and the organic layer was then washed with brine (15 mL), dried over magnesium sulfate, filtered, and evaporated to dryness. The crude product was purified by flash chromatography eluting first with 2% MeOH in CH_2Cl_2 then gradually increasing the gradient to 5% MeOH in CH_2Cl_2 and finally with 10% MeOH in CH_2Cl_2 to yield the 0.044 g (16.5%) of the product as a white foam. The free base product was converted to the HCl salt by dissolving in CH_2Cl_2 (0.030 mL) and then adding 2M HCl in ether (0.12 mL, 0.23 mmol, 2.5 eq.). The excess solvent was removed in vacuo to give the HCl salt of the product as a white powder. LCMS rt= 2.490 min. (APCI) *m/z* 475.2 (MH^+).

^{1}H NMR δ (300 MHz, CD_3OD): 8.37 (s, 1H); 7.47 (t, *J*= 8.1 Hz, 1H); 7.27 (d, *J*= 3.0 Hz 1H); 7.22-7.14 (m, 3H); 6.30 (dd, *J*= 2.4, 0.9 Hz, 1H); 6.19 (s, 1H); 5.09 (q, 1H); 4.31 (d, *J*= 1.8 Hz, 2H); 2.85 (d, *J*= 7.8 Hz, 6H); 2.76 (s, 3H); 2.42 (s, 3H); 2.28 (s, 3H); 1.70 (d, *J*= 6.6 Hz, 3H).

Intermediate 23. Ethyl 3-oxo-3-(1,3-thiazol-2-yl)propanoate

To a solution of 60% sodium hydride (95.4 mmol) in diethyl carbonate (90 ml) was slowly added 2-acetylthiazole (5.0 g). The resulting solution was stirred at room temperature for 1 hour and at 90°C for 2 hours. The reaction mixture was poured into ice/water and acetic acid (5 mL) was added. The mixture was extracted with ethyl acetate (2x75 mL). The organic layer was washed with water (2x50 mL), brine (50 mL), dried (Na_2SO_4), and the solvent removed under reduced pressure. The title compound was obtained (4.4 g, 56%) as an oil by distillation under reduced pressure.

δ (250 MHz, $CDCl_3$): 1.23 (t, 3H); 4.15 (m, 4H); 7.71 (d, *J*=5.3 Hz, 1H); 7.99 (d, *J*=5.3 Hz, 1H). LCMS (APCI) *m/z* 517.0 (MH^+). t_{ret} = 9.840 min, Method 2.

Intermediate 24. 2-(5-Methyl-2-furyl)-6-(1,3-thiazol-2-yl)pyrimidin-4-ol

To a solution of potassium *tert*butoxide (0.57 g, 6.03 mmol) in butanol (2 mL) were added Intermediate 23 (0.85 g, 4.26 mmol) and Intermediate 1 (0.75 g, 4.69 mmol). The mixture was heated at 135ºC for 3 hours. The crude reaction was poured into water (20 mL) and acidified with 10% hydrochloric acid (25 mL). The resulting solid was filtered, washed with water (2x25 mL) and dried. The title compound was obtained (0.64 g, 50%) as an off-white solid.

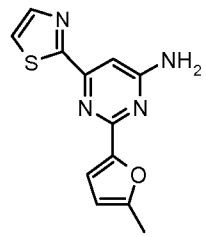
δ (250 MHz, $CDCl_3$): 2.45 (s, 3H); 6.38 (d, *J*=2.8 Hz, 1H); 6.77 (s, 1H); 7.44 (d, *J*=2.8 Hz, 1H); 7.98 (d, *J*=2.8 Hz, 1H); 8.03 (d, *J*=2.8 Hz, 1H).

Intermediate 25. 4-Chloro-2-(5-methyl-2-furyl)-6-(1,3-thiazol-2-yl)pyrimidine

A suspension of Intermediate 24 (0.63 g) in phosphorous oxychloride (20 mL) was refluxed for 24 hours. The solvent was removed under pressure and ice and water were slowly added. The resulting solid was filtered, washed with 2N sodium hydroxide, and dried. Purification by column chromatography with silica gel and methylene chloride as eluent gave 4-chloro-2-(5-methyl-2-furyl)-6-(1,3-thiazol-2-yl)pyrimidine (0.44 g, 66%) as an off-white solid.

δ (250 MHz, $CDCl_3$): 2.41 (s, 3H); 6.15 (d, *J*=4.8 Hz, 1H); 7.31 (d, *J*=3.2 Hz, 1H); 7.53 (d, *J*=3.2 Hz, 1H); 7.81 (s, 1H); 8.03 (d, *J*=4.8 Hz, 1H).

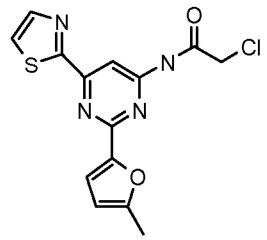
Intermediate 26. 2-(5-Methyl-2-furyl)-6-(1,3-thiazol-2-yl)pyrimidin-4-amine



A suspension of Intermediate 25 (0.25 g) in ethanol (22 mL) and 30% ammonium hydroxide (22 mL) was heated at 120ºC in a pressure reactor for 2.30 hours. The solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate (50 mL). The resulting solution was washed with water (2x25 mL), brine (25 mL), dried (Na_2SO_4), and the solvent removed under reduced pressure. Purification by trituration with ethyl ether gave 2-(5-methyl-2-furyl)-6-(1,3-thiazol-2-yl)pyrimidin-4-amine (0.12 g, 53%) as an off-white solid.

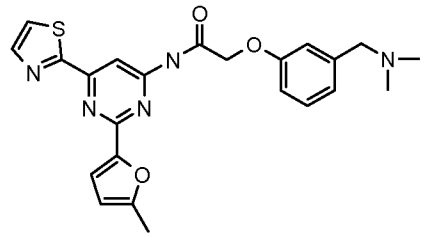
δ (250 MHz, DMSO-d_6): 2.38 (s, 3H); 6.29 (dd, *J*1=3.0 Hz, *J*2=1.0 Hz, 1H); 6.99 (m, 1H); 7.08 (d, *J*=3.4 Hz, 1H); 7.28 (bs, 2H); 7.93 (dd, *J*1=3.0 Hz, *J*2=1.0 Hz, 1H); 8.03 (dd, *J*1=3.0 Hz, *J*2=1.0 Hz, 1H).

Intermediate 27. 2-Chloro-N-[2-(5-methyl-furan-2-yl)-6-thiazol-2-yl-pyrimidin-4-yl]-acetamide



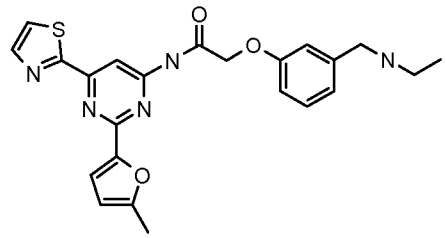
To 5 mL dichloromethane were added 0.34 g (1.3mmol) of Intermediate 26, 0.22g chloroacetyl chloride (2.0 mmol, 1.5 eq) and 0.16 g pyridine. The reaction mixture was stirred at r/t for 2 hours. The reaction was quenched with 5 mL saturated sodium bicarbonate and extracted; the aqueous solution was washed with an additional 5 mL dichloromethane. The organic layers combined and dried under sodium sulfate, concentrated to a off white solid (0.37 g, 85% yield).

Compound 2-1. 2-(3-Dimethylaminomethyl-phenoxy)-N-[2-(5-methyl-furan-2-yl)-6-thiazol-2-yl-pyrimidin-4-yl]-acetamide



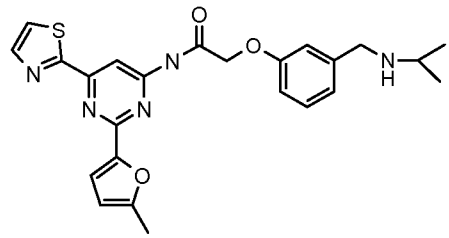
Compound 2-1 was prepared according to the procedures described in Compound 1-1, except that Intermediate 25 was used instead of Intermediate 6. LCMS (APCI) *m/z* 450.0 (MH^+). t_{ret} = 2.410 min, Method 4.

Compound 2-2. 2-(3-Ethylaminomethyl-phenoxy)-N-[2-(5-methyl-furan-2-yl)-6-thiazol-2-yl-pyrimidin-4-yl]-acetamide



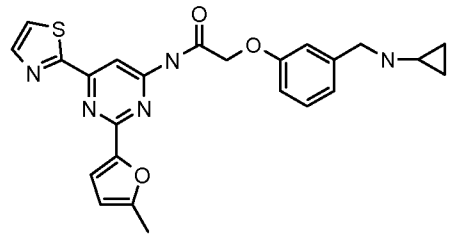
Compound 2-2 was prepared according to the procedures described in Compound 1-2, except that Intermediate 25 was used instead of Intermediate 6. LCMS (APCI) *m/z* 450.0 (MH^+). t_{ret} = 2.440 min, Method 4.

Compound 2-3. 2-[3-(Isopropylamino-methyl)-phenoxy]-N-[2-(5-methyl-furan-2-yl)-6-thiazol-2-yl-pyrimidin-4-yl]-acetamide



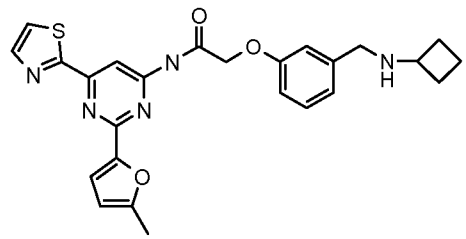
Compound 2-3 was prepared according to the procedures described in Compound 1-1, except that: (1) Intermediate 25 was used instead of Intermediate 6; and (2) isopropylamine was used instead of dimethylamine. LCMS (APCI) *m/z* 464.0 (MH^+). t_{ret} = 2.350 min, Method 4.

Compound 2-4. 2-(3-Cyclopropylaminomethyl-phenoxy)-N-[2-(5-methyl-furan-2-yl)-6-thiazol-2-yl-pyrimidin-4-yl]-acetamide



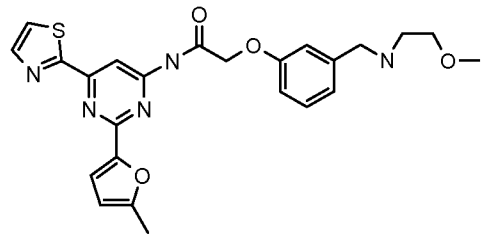
Compound 2-4 was prepared according to the procedures described in Compound 1-1, except that: (1) Intermediate 25 was used instead of Intermediate 6; and (2) cyclopropylamine was used instead of dimethylamine. LCMS (APCI) *m/z* 462.0 (MH^+). t_{ret} = 5.470 min, Method 2.

Compound 2-5. 2-(3-Cyclobutylaminomethyl-phenoxy)-N-[2-(5-methyl-furan-2-yl)-6-thiazol-2-yl-pyrimidin-4-yl]-acetamide



Compound 2-5 was prepared according to the procedures described in Compound 1-1, except that: (1) Intermediate 25 was used instead of Intermediate 6; and (2) cyclobutylamine was used instead of dimethylamine. LCMS (APCI) *m/z* 476.0 (MH^+). t_{ret} = 5.590 min, Method 2.

Compound 2-6. 2-{3-[(2-Methoxy-ethylamino)-methyl]-phenoxy}-N-[2-(5-methyl-furan-2-yl)-6-thiazol-2-yl-pyrimidin-4-yl]-acetamide

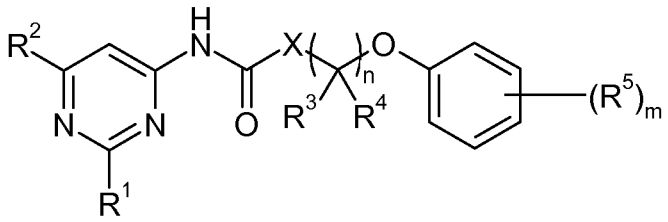


Compound 2-6 was prepared according to the procedures described in Compound 1-1, except that: (1) Intermediate 25 was used instead of Intermediate 6; and (2) 2-Methoxy-ethylamine was used instead of dimethylamine. LCMS (APCI) *m/z* 480.0 (MH^+). t_{ret} = 5.380 min, Method 2.

It will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without departing from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

WHAT IS CLAIMED IS:

1. A compound of formula (I)



(I)

or a pharmaceutically acceptable salt, ester, solvate, stereoisomer or prodrug thereof, wherein:

each of R^1 and R^2 independently is an aryl or heteroaryl group optionally substituted by one or more substituents selected from the group of lower alkyl, halogen, cycloalkyl, phenyl, hydroxy, lower alkoxy, -SH, NO_2, lower alkylthio, lower alkylamino, cyano, and amino, wherein the lower alkyl, cycloalkyl, phenyl, lower alkoxy, lower alkylthio and lower alkylamino groups are optionally substituted;

each of R^3 and R^4 independently is at each occurrence selected from the group of hydrogen, optionally substitituted alkyl, and optionally substituted alkoxy;

R^5 independently is at each occurrence selected from the group of halogen, optionally substituted hydroxyC_{1-6}alkyl, optionally substituted C_{1-6}alkoxyC_{1-6}alkyl, optionally substituted morpholinylC_{1-6}alkyl, optionally substituted mono(C_{1-6}alkyl)aminoC_{1-6}alkyl, optionally substituted di(C_{1-6}alkyl)aminoC_{1-6}alkyl, optionally substituted C_{1-6}alkoxyC_{1-6}alkylaminoC_{1-6}alkyl, optionally substituted C_{1-6}alkoxy, optionally substituted pyrrolidinyl, optionally substituted pyrazolidinyl, optionally substituted imidazolidinyl, optionally substituted piperidinyl and optionally substituted piperazinyl;

X is a bond, NH or O;

m is 1, 2 or 3;

and

n is 1, 2 or 3;

with the proviso that when X is NH or O, then n is 2 or 3.

2. A compound according to claim 1, wherein:
each of R^1 and R^2 is independently selected from the group of pyridinyl, furanyl, thiophenyl, thiazolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl and oxadiazolyl, all of which may be optionally substituted.

3. A compound according to claim 2, wherein n is 1 or 2.

4. A compound according to claim 3, wherein:
R^1 is selected from the group of pyridinyl, furanyl, thiophenyl, thiazolyl, pyrazolyl, imidazolyl, oxazolyl and isoxazolyl, all of which may be optionally substituted.

5. A compound according to claim 4, wherein:
R^2 is selected from the group of pyridinyl, thiazolyl and pyrazolyl, all of which may be optionally substituted.

6. A compound according to claim 5, wherein:
R^1 is selected from the group of pyridinyl, furanyl, 5-methyl-furanyl, thiophenyl, thiazolyl, pyrazolyl, imidazolyl, oxazolyl, 4-methyl-oxazolyl and isoxazolyl; and
R^2 is selected from the group of pyridinyl, thiazolyl, pyrazolyl and 3,5-dimethylpyrazolyl.

7. A compound according to claim 6, wherein:
R^1 is 5-methyl-furanyl, oxazolyl, 4-methyl-oxazolyl or pyridinyl and R^2 is pyrazolyl or 3,5-dimethylpyrazolyl.

8. A compound according to claim 7, wherein:
R^1 is 5-methyl-furanyl or pyridinyl and R^2 is 3,5-dimethylpyrazolyl.

9. A compound according to claim 8, wherein:
R^1 is 5-methyl-furanyl.

10. A compound according to claim 8, wherein:
R^1 is pyridinyl.

11. A compound according to claim 1, wherein the compound is a member selected from the group of:

2-(3-Dimethylaminomethyl-phenoxy)-N-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-acetamide;

N-[6-(3,5-Dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-2-(3-ethylaminomethyl-phenoxy)-acetamide;

2-(2-Dimethylaminomethyl-phenoxy)-N-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-acetamide;

2-(4-Dimethylaminomethyl-phenoxy)-N-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-acetamide;

2-(4-Dimethylaminomethyl-2-methoxy-phenoxy)-N-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-acetamide;

2-(4-Dimethylaminomethyl-3-methoxy-phenoxy)-N-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-acetamide;

2-(2-Dimethylaminomethyl-6-methoxy-phenoxy)-N-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-acetamide;

2-(5-Dimethylaminomethyl-2-methoxy-phenoxy)-N-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-acetamide;

2-(2-Dimethylaminomethyl-4-methoxy-phenoxy)-N-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-acetamide;

2-(3-Chloro-4-dimethylaminomethyl-phenoxy)-N-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-acetamide;

2-(2-Dimethylaminomethyl-4-methyl-phenoxy)-N-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-acetamide;

N-[6-(3,5-Dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-2-{3-[(ethyl-methyl-amino)-methyl]-phenoxy}-acetamide;

N-[6-(3,5-Dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-2-(3-morpholin-4-ylmethyl-phenoxy)-acetamide;

2-[3-(2-Dimethylamino-ethyl)-phenoxy]-N-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-acetamide;

N-[6-(3,5-Dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-2-[3-(2-morpholin-4-yl-ethyl)-phenoxy]-acetamide;

N-[6-(3,5-Dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-2-(3-fluoro-5-pyrrolidin-1-ylmethyl-phenoxy)-acetamide;

N-[6-(3,5-Dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-2-(3-fluoro-5-morpholin-4-ylmethyl-phenoxy)-acetamide;

2-(3-Dimethylaminomethyl-5-fluoro-phenoxy)-N-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-acetamide;
2-(3-Dimethylaminomethyl-phenoxy)-N-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-propionamide;
2-(3-Dimethylaminomethyl-phenoxy)-N-[2-(5-methyl-furan-2-yl)-6-thiazol-2-yl-pyrimidin-4-yl]-acetamide;
2-(3-Ethylaminomethyl-phenoxy)-N-[2-(5-methyl-furan-2-yl)-6-thiazol-2-yl-pyrimidin-4-yl]-acetamide;
2-[3-(Isopropylamino-methyl)-phenoxy]-N-[2-(5-methyl-furan-2-yl)-6-thiazol-2-yl-pyrimidin-4-yl]-acetamide;
2-(3-Cyclopropylaminomethyl-phenoxy)-N-[2-(5-methyl-furan-2-yl)-6-thiazol-2-yl-pyrimidin-4-yl]-acetamide;
2-(3-Cyclobutylaminomethyl-phenoxy)-N-[2-(5-methyl-furan-2-yl)-6-thiazol-2-yl-pyrimidin-4-yl]-acetamide;
2-{3-[(2-Methoxy-ethylamino)-methyl]-phenoxy}-N-[2-(5-methyl-furan-2-yl)-6-thiazol-2-yl-pyrimidin-4-yl]-acetamide;
2-(3-Dimethylaminomethyl-5-methoxy-phenoxy)-N-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-propionamide;
2-(5-Dimethylaminomethyl-2-methoxy-phenoxy)-N-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-propionamide;
2-(3-Dimethylaminomethyl-2-methoxy-phenoxy)-N-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-propionamide;
2-(3-Dimethylaminomethyl-4-methoxy-phenoxy)-N-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-propionamide;
2-(2-Dimethylaminomethyl-4-methoxy-phenoxy)-N-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-propionamide;
2-(2-Dimethylaminomethyl-3-methoxy-phenoxy)-N-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-propionamide;
2-(2-Dimethylaminomethyl-5-methoxy-phenoxy)-N-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-propionamide;
2-(2-Dimethylaminomethyl-6-methoxy-phenoxy)-N-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-propionamide;
2-(4-Dimethylaminomethyl-3-methoxy-phenoxy)-N-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-propionamide;
2-(4-Dimethylaminomethyl-2-methoxy-phenoxy)-N-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-propionamide;

1-[2-(2-Dimethylaminomethyl-6-methoxy-phenoxy)-ethyl]-3-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-urea;

1-[2-(2-Dimethylaminomethyl-5-methoxy-phenoxy)-ethyl]-3-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-urea;

1-[2-(2-Dimethylaminomethyl-4-methoxy-phenoxy)-ethyl]-3-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-urea;

1-[2-(2-Dimethylaminomethyl-3-methoxy-phenoxy)-ethyl]-3-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-urea;

1-[2-(3-Dimethylaminomethyl-2-methoxy-phenoxy)-ethyl]-3-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-urea;

1-[2-(3-Dimethylaminomethyl-4-methoxy-phenoxy)-ethyl]-3-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-urea;

1-[2-(3-Dimethylaminomethyl-5-methoxy-phenoxy)-ethyl]-3-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-urea;

1-[2-(5-Dimethylaminomethyl-2-methoxy-phenoxy)-ethyl]-3-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-urea;

1-[2-(4-Dimethylaminomethyl-3-methoxy-phenoxy)-ethyl]-3-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-urea;

1-[2-(4-Dimethylaminomethyl-2-methoxy-phenoxy)-ethyl]-3-[6-(3,5-dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-urea;

[6-(3,5-Dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-carbamic acid 2-(2-dimethylaminomethyl-6-methoxy-phenoxy)-ethyl ester;

[6-(3,5-Dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-carbamic acid 2-(2-dimethylaminomethyl-5-methoxy-phenoxy)-ethyl ester;

[6-(3,5-Dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-carbamic acid 2-(2-dimethylaminomethyl-4-methoxy-phenoxy)-ethyl ester;

[6-(3,5-Dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-carbamic acid 2-(2-dimethylaminomethyl-3-methoxy-phenoxy)-ethyl ester;

[6-(3,5-Dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-carbamic acid 2-(5-dimethylaminomethyl-2-methoxy-phenoxy)-ethyl ester;

[6-(3,5-Dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-carbamic acid 2-(3-dimethylaminomethyl-5-methoxy-phenoxy)-ethyl ester;

[6-(3,5-Dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-carbamic acid 2-(3-dimethylaminomethyl-4-methoxy-phenoxy)-ethyl ester;

[6-(3,5-Dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-carbamic acid 2-(3-dimethylaminomethyl-2-methoxy-phenoxy)-ethyl ester;

[6-(3,5-Dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-carbamic acid 2-(4-dimethylaminomethyl-2-methoxy-phenoxy)-ethyl ester; and
[6-(3,5-Dimethyl-pyrazol-1-yl)-2-(5-methyl-furan-2-yl)-pyrimidin-4-yl]-carbamic acid 2-(4-dimethylaminomethyl-3-methoxy-phenoxy)-ethyl ester.

12. A pharmaceutical composition comprising a compound according to claim 1 and a pharmaceutically acceptable carrier or diluent.

13. A pharmaceutical composition comprising a compound according to claim 3 and a pharmaceutically acceptable carrier or diluent.

14. A pharmaceutical composition comprising a compound according to claim 7, and a pharmaceutically acceptable carrier or diluent.

15. A pharmaceutical composition comprising a compound according to claim 11, and a pharmaceutically acceptable carrier or diluent.

16. A method for treating a subject having a condition susceptible to amelioration by antagonism of an adenosine receptor comprising administering to a subject in need thereof a pharmaceutical composition according to claim 12.

17. A method according to claim 16, wherein the condition is ischemia, supraventricular arrhythmias, acute renal failure, myocardial reperfusion injury, autoimmune disease, inflammatory bowel diseases, asthma, diabetes mellitus, obesity, Parkinson's disease, Huntington's disease, dystonia or dyskinesia.

18. A method for treating a subject having a condition susceptible to amelioration by antagonism of A_{2A} adenosine receptor comprising administering to a subject in need thereof a pharmaceutical composition according to claim 12.

19. A method according to claim 18, wherein the condition is ischemia, supraventricular arrhythmias, Parkinson's disease, Huntington's disease, dystonia or dyskinesia.

20. A method according to claim 18, wherein the condition is Parkinson's disease.