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(54) Title: 2-ANILINO-4-AMINOALKYLENEAMINOPYRIMIDINES

(57) Abstract: The present invention relates to 2-arylamino-4-(aminoalkylene)aminopyrimidines inhibitors which are inhibitors and therefore inhibit Protein Kinase C-alpha (PKC-a). The PKC-a inhibitors of the present invention are important for improving myocardial intracellular calcium cycling, resulting in improved myocardial contraction and relaxation performance and thereby slowing the progression of heart failure. The present invention further relates to compositions comprising said 2-arylamino-4-(aminoalkylene)amino-pyrimidines and to methods for controlling, abating, or otherwise slowing the progression of heart failure.

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2-ANILINO-4-AMINOALKYLENEAMINOPYRIMIDINES

RELATED CASES

Benefit is claimed to US provisional Application No. 60/813,875 filed June 15, 2006 the contents of which are incorporated herein.

FIELD OF THE INVENTION

The present invention relates to 2-arylamino-4-(aminoalkylene)aminopyrimidines which are inhibitors of Protein Kinase C-alpha (PKC-α). The PKC-α inhibitors of the present invention are important for improving myocardial intracellular calcium cycling, resulting in improved myocardial contraction and relaxation performance and thereby slowing the progression of heart failure. The present invention further relates to compositions comprising said 2-arylamino-4-(aminoalkylene)amino-pyrimidines and to methods for controlling, abating, or otherwise slowing the progression of heart failure.

BACKGROUND OF THE INVENTION

Many biologically active substances, for example, hormones, neurotransmitters and peptides are known to exert functions via intracellular mediators such as, cyclic adenosine monophosphate (cAMP), cyclic guanosine monophosphate (cGMP), diacylglycerol (DAG) and calcium. In many cases, these mediators activate or inactivate intracellular kinases or phosphatases that are important in protein phosphorylation/ dephosphorylation, and thus play important roles in regulating cellular processes and functions. The protein kinase C (PKC) family of calcium and/or lipid-activated serine-threonine kinases function downstream of nearly all membrane-associated signal transduction pathways.[1] Approximately 12 different isozymes comprise the PKC family, which are broadly classified by their activation characteristics. The conventional PKC isozymes (PKCα, βI, βII, and γ) are calcium- and lipid-activated, while the novel isozymes (ε, θ, η, and δ) and atypical isozymes (ζ, ι, υ, and μ) are calcium independent but activated by distinct lipids.[2] For example, stimulation of Gαq-coupled G-protein coupled receptors (GPCR) can activate phospholipase C (PLC) which in turn mediates hydrolysis of inositol phospholipids resulting in the generation of inositol 1,4,5-triphosphate (IP_3)

and DAG. IP_3 and DAG can activate the different isoforms of PKC by mobilizing calcium (calcium sensitive enzymes) or by directly activating PKC, respectively. Once activated, PKC isozymes translocate to discrete subcellular locations through direct interactions with docking proteins termed RACKs (Receptor for Activated C Kinases), which permit specific substrate recognition and subsequent signal transduction.[3]

Alterations in PKC activity has been suggested to contribute to human diseases, *inter alia*, diabetes, numerous forms of cancer, microalbinuria, endothelial dysfunction, cerebrovascular disease, stroke, coronary heart disease, cardiovascular disease and sequela (e.g. arrhythmia, sudden death, increased infarct size, congestive heart failure, angina), myocardial ischemic states, hypertension, lipid disorders, ischemia-reperfusion injury, atherosclerosis, peripheral artery/vascular disease, microvascular complications of diabetes (neuropathy, nephropathy, retinopathy), restenosis, renal disease, blood coagulation disorders, inflammatory diseases and heart failure and inhibition of PKC in these settings could be used to treat or prevent human disease. Lending support to the modulation of PKC in cardiac disease, PKC activation has been associated with cardiac hypertrophy, dilated cardiomyopathy, ischemic injury and mitogen stimulation.

Heart disease is the leading cause of death in industrialized nations. Historically heart failure (HF) has been a product of hypertension, coronary heart disease, genetic disorders, valvular deformities, diabetes or cardiomyopathy. While the root cause of heart failure is multifaceted, it uniformly is marked by impaired diastolic and/or systolic function and can be accompanied by chamber enlargement which ultimately manifest in symptomatic heart failure (fatigue, pulmonary edema, circulatory congestion, etc.)

The risk of death due to heart failure is 5-10% annually in patients with mild symptoms of heart failure, and increases to 30-40% annually in patients with advanced heart failure, with a 50% overall mortality rate at 5 years. The current mainstays of heart failure therapy are drugs that act on the renin-angiotensin-aldosterone system (ACEI, ARB, aldosterone inhibitor), diuretics, digoxin and β-adrenergic receptor blockers. Despite the fact that multiple drug classes are used to treat heart failure patients, new cases of heart failure are growing at over 10% per year.

Patients with acute decompensated heart failure (ADHF) are a treatment challenge to physicians and can present with volume overload and/or diminished cardiac output. Initial treatments for ADHF patients include intravenous diuretics, vasodilators, natriuretic peptides and inotropic agents. Despite the widespread use of these agents, long-term safety and benefit of these drugs have been questioned. In the case of inotropes, drugs that increases cardiac output and cardiac contractility without increasing myocardial oxygen consumption or heart rate are desirous. Despite the available treatments for patients with ADHF, hospital readmission rates are approximately 50% within 6 months and mortality is approximately 20-40% at 1 year.

The primary function of the heart is to generate and sustain an arterial blood pressure necessary to provide adequate perfusion of organs. It has, therefore, become an area of intense investigation to decipher the mechanism(s) which initiate and contribute to the development of heart failure rather than relying on a means for treating the symptoms of heart failure alone. At the cardiomyocyte (cardiac contractile cells) level, impaired calcium cycling is a hallmark of heart failure as is the basis of contractile abnormalities. Calcium plays a key role in regulating kinases, phosphatases and transcription factors believed to influence the remodeling process indicating that both acute and sustained alterations in intracellular calcium levels may have profound effect on cardiac function and remodeling (i.e., changes in wall thickness or chamber volume). This theory would support the proposition that the development of new therapies addressing the slowing and preventing of the disease progression, would be perhaps more effective against heart failure than palliation of heart failure.

Therefore, there is a limited means to treat patients with various forms and stages of heart failure and there is incentive to develop novel, safe and effective treatments to prevent or treat patients with symptoms of heart failure, acute exacerbation of heart failure and chronic heart failure and other cardiovascular diseases. An agent that has benefits in the treating acute exacerbations of heart failure as well as treating chronic heart failure is desirous.

1. Molkentin *et al.* (2001) *Annu. Rev. Physiol.* 63:391-426.
2. Dempsey *et al.* (2000) *Am. J. Physiol. Lung Mol. Physiol.* 279:247-251.

3. Mochly-Rosen, D. (1995) *Science* 268:247-251.

SUMMARY OF THE INVENTION

The present invention meets the aforementioned needs in that it has been found that certain 2-arylamino-4-(aminoalkylene)aminopyrimidines are effective for inhibiting Protein Kinase C-alpha (PKC-α) thereby improving myocardial contraction and relaxation performance and slowing the progression of heart failure.

The present invention encompasses three major aspects each of which have their own separate categories, aspects, iterations, and specific iterative examples. The major aspects of the present invention include:

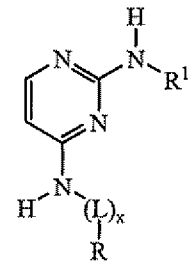
i) novel compositions of matter which are effective in inhibiting PKC-α;

ii) compositions or pharmaceutical compositions (matrices) comprising said compositions of matter;

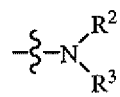
iii) methods for controlling, abating, or alleviating one or more of the causes of progressive heart failure which is affected by administration of a PKC-α inhibitors, whether administered alone or in a composition or within a pharmaceutical composition (matrix); and

iv) a process for preparing the PKC-α inhibitors of the present invention.

The first aspect of the present invention as a whole, relates to compounds, which include all enantiomeric and diastereomeric forms and pharmaceutically acceptable salts thereof, said compounds having the formula:



wherein R is a unit having the formula:



R^2 and R^3 are each independently chosen from:

i) hydrogen; or

ii) C_1-C_4 substituted or unsubstituted linear, branched, or cyclic alkyl;

L is a linking unit having the formula:

$$-[C(R^{4a}R^{4b})]_n-$$

each R^4 is independently chosen from

i) hydrogen; or

ii) C_1-C_4 alkyl;

the index n is from 1 to 4; and

R^1 is substituted or unsubstituted aryl.

The second major aspect of the present invention relates to compositions comprising:

a) an effective amount of one or more compounds according to the present invention; and

b) one or more acceptable excipients.

The third major aspect of the present invention relates to methods of use. As described herein below, the PKC-α inhibitors of the present invention are important for improving myocardial contraction and relaxation performance and thereby slowing the progression of heart failure and their administration to humans is, therefore, an effective treatment for humans suffering from acute heart failure.

These and other objects, features, and advantages will become apparent to those of ordinary skill in the art from a reading of the following detailed description and the appended claims. All percentages, ratios and proportions herein are by weight, unless otherwise specified. All temperatures are in degrees Celsius (° C) unless otherwise specified. All documents cited are in relevant part, incorporated herein by reference; the citation of any document is not to be construed as an admission that it is prior art with respect to the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention addresses several unmet medical needs, *inter alia*:

1) improving cardiac contraction/relaxation parameters in heart failure patients, leading to reduction of symptoms; and

2) attenuating adverse cardiac remodeling in heart failure patients, ultimately providing prolonged patient survival.

These and other unmet medical needs are resolved by the PKC-α inhibitors of the present invention, which are capable of blocking Protein Kinase C-alpha from impairing sarcoplasmic reticulum Ca^{2+} uptake. By providing heart failure patients with a PKC-α inhibitor, it is believed the patients will derive an improvement in cardiac function, thus resulting in improved myocardial contraction and relaxation performance and could result in slowing the progression to heart failure.

The following chemical hierarchy is used throughout the specification to describe and enable the scope of the present invention and to particularly point out and distinctly claim the units which comprise the compounds of the present invention. The term "hydrocarbyl" stands for any carbon atom-based unit (organic molecule), said units optionally containing one or more organic functional group, including inorganic atom comprising salts, *inter alia*, carboxylate salts, quaternary ammonium salts. Within the broad meaning of the term "hydrocarbyl" are the classes "acyclic hydrocarbyl" and "cyclic hydrocarbyl" which terms are used to divide hydrocarbyl units into cyclic and non-cyclic classes.

As it relates to the following definitions, "cyclic hydrocarbyl" units may comprise only carbon atoms in the ring (hydrocarbyl and aryl rings) or may comprise one or more heteroatoms in the ring (heterocyclic and heteroaryl). For "hydrocarbyl" rings the lowest number of carbon atoms in a ring are 3 carbon atoms; cyclopropyl. For "aryl" rings the lowest number of carbon atoms in a ring are 6 carbon atoms; phenyl. For "heterocyclic" rings the lowest number of carbon atoms in a ring is 1 carbon atom; diazirinyl, epoxy. For "heteroaryl" rings the lowest number of carbon atoms in a ring is 1 carbon atom; 1,2,3,4-tetrazolyl. The following is a non-limiting description of the terms "acyclic hydrocarbyl" and "cyclic hydrocarbyl" as used herein.

A. Substituted and unsubstituted C_1-C_{20} acyclic hydrocarbyl:

For the purposes of the present invention the term "substituted and unsubstituted C_1-C_{20} acyclic hydrocarbyl" encompasses 3 categories of units:

1) C_1-C_{20} linear or branched alkyl, non-limiting examples of which include, methyl (C_1), ethyl (C_2), n-propyl (C_3), *iso*-propyl (C_3), n-butyl (C_4), *sec*-butyl (C_4), *iso*-butyl (C_4), *tert*-butyl (C_4), and the like; substituted C_1-C_{20} linear or branched alkyl, non-limiting examples of which includes, hydroxymethyl (C_1), chloromethyl (C_1), trifluoromethyl (C_1), aminomethyl (C_1), 1-chloroethyl (C_2), 2-hydroxyethyl (C_2), 1,2-difluoroethyl (C_2), 3-carboxypropyl (C_3), and the like.

2) C_2-C_{20} linear or branched alkenyl, non-limiting examples of which include, ethenyl (C_2), 3-propenyl (C_3), 1-propenyl (*also* 2-methylethenyl) (C_3), isopropenyl (*also* 2-methylethen-2-yl) (C_3), buten-4-yl (C_4), and the like; substituted C_2-C_{20} linear or branched alkenyl, non-limiting examples of which include, 2-chloroethenyl (*also* 2-chlorovinyl) (C_2), 4-hydroxybuten-1-yl (C_4), 7-hydroxy-7-methyloct-4-en-2-yl (C_9), 7-hydroxy-7-methyloct-3,5-dien-2-yl (C_9), and the like.

3) C_2-C_{20} linear or branched alkynyl, non-limiting examples of which include, ethynyl (C_2), prop-2-ynyl (*also* propargyl) (C_3), propyn-1-yl (C_3), and 2-methyl-hex-4-yn-1-yl (C_7); substituted C_2-C_{20} linear or branched alkynyl, non-limiting examples of which include, 5-hydroxy-5-methylhex-3-ynyl (C_7), 6-hydroxy-6-methylhept-3-yn-2-yl (C_8), 5-hydroxy-5-ethylhept-3-ynyl (C_9), and the like.

B. Substituted and unsubstituted C_1-C_{20} cyclic hydrocarbyl:

For the purposes of the present invention the term "substituted and unsubstituted C_1-C_{20} cyclic hydrocarbyl" encompasses 5 categories of units:

1) The term "carbocyclic" is defined herein as "encompassing rings comprising from 3 to 20 carbon atoms, wherein the atoms which comprise said rings are limited to carbon atoms, and further each ring can be independently substituted with one or more moieties capable of replacing one or more hydrogen atoms." The following are non-limiting examples of "substituted and unsubstituted C_3-C_{20} carbocyclic rings" which encompass the following categories of units:

i) carbocyclic rings having a single substituted or unsubstituted hydrocarbon ring, non-limiting examples of which include, cyclopropyl (C_3), 2-methyl-cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), 2,3-dihydroxycyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclopentadienyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cycloheptyl (C_7), cyclooctanyl (C_8), decalinyl (C_{10}), 2,5-dimethylcyclopentyl (C_5), 3,5-dichlorocyclohexyl (C_6), 4-hydroxycyclohexyl (C_6), and 3,3,5-trimethylcyclohex-1-yl (C_6).

ii) carbocyclic rings having two or more substituted or unsubstituted fused hydrocarbon rings, non-limiting examples of which include, octahydropentalenyl (C_8), octahydro-1*H*-indenyl (C_9), 3a,4,5,6,7,7a-hexahydro-3*H*-inden-4-yl (C_9), decahydroazulenyl (C_{10}); bicyclo[6.2.0]decanyl (C_{10}), decahydronaphthalenyl (C_{10}), and dodecahydro-1*H*-fluorenyl (C_{13}).

iii) carbocyclic rings which are substituted or unsubstituted bicyclic hydrocarbon rings, non-limiting examples of which include, bicyclo-[2.1.1]hexanyl, bicyclo[2.2.1]heptanyl, bicyclo[3.1.1]heptanyl, 1,3-dimethyl[2.2.1]heptan-2-yl, bicyclo[2.2.2]octanyl, and bicyclo[3.3.3]undecanyl.

2) The term "aryl" is defined herein as "units encompassing at least one phenyl or naphthyl ring and wherein there are no heteroaryl or heterocyclic rings fused to the phenyl or naphthyl ring and further each ring can be independently substituted with one or more moieties capable of replacing one or more hydrogen atoms." The following are non-limiting examples of "substituted and unsubstituted C_6-C_{14} aryl rings" which encompass the following categories of units:

i) C_6 or C_{10} substituted or unsubstituted aryl rings; phenyl and naphthyl rings whether substituted or unsubstituted, non-limiting examples of which include, phenyl (C_6), naphthylen-1-yl (C_{10}), naphthylen-2-yl (C_{10}), 4-fluorophenyl (C_6), 2-hydroxyphenyl (C_6), 3-methylphenyl (C_6), 2-amino-4-fluorophenyl (C_6), 2-(*N*,*N*-diethylamino)phenyl (C_6), 2-cyanophenyl (C_6), 2,6-di-*tert*-butylphenyl (C_6), 3-methoxyphenyl (C_6), 8-hydroxynaphthylen-2-yl (C_{10}), 4,5-dimethoxynaphthylen-1-yl (C_{10}), and 6-cyano-naphthylen-1-yl (C_{10}).

ii) C_6 or C_{10} aryl rings fused with 1 or 2 saturated rings non-limiting examples of which include, bicyclo[4.2.0]octa-1,3,5-trienyl (C_8), and indanyl (C_9).

3) The terms "heterocyclic" and/or "heterocycle" are defined herein as "units comprising one or more C_1-C_{20} rings having from 3 to 20 atoms wherein at least one atom in at least one ring is a heteroatom chosen from nitrogen (N), oxygen (O), or sulfur (S), or mixtures of N, O, and S, and wherein further the ring which comprises the heteroatom is also not an aromatic ring." The following are non-limiting examples of "substituted and unsubstituted C_1-C_{20} heterocyclic rings" which encompass the following categories of units:

i) heterocyclic units having a single ring containing one or more heteroatoms, non-limiting examples of which include, diazirinyl (C_1), aziridinyl (C_2), urazolyl (C_2), azetidinyl (C_3), pyrazolidinyl (C_3), imidazolidinyl (C_3), oxazolidinyl (C_3), isoxazolinyl (C_3), isoxazolyl (C_3), thiazolidinyl (C_3), isothiazolyl (C_3), isothiazolinyl (C_3), oxathiazolidinonyl (C_3), oxazolidinonyl (C_3), hydantoinyl (C_3), tetrahydrofuranyl (C_4), pyrrolidinyl (C_4), morpholinyl (C_4), piperazinyl (C_4), piperidinyl (C_4), dihydropyranyl (C_5), tetrahydropyranyl (C_5), piperidin-2-onyl (valerolactam) (C_5), 2,3,4,5-tetrahydro-1*H*-azepinyl (C_6), 2,3-dihydro-1*H*-indole (C_8), and 1,2,3,4-tetrahydro-quinoline (C_9).

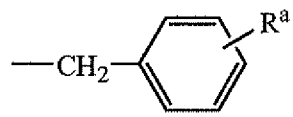
ii) heterocyclic units having 2 or more rings one of which is a heterocyclic ring, non-limiting examples of which include hexahydro-1*H*-pyrrolizinyl (C_7), 3a,4,5,6,7,7a-hexahydro-1*H*-benzo[d]imidazolyl (C_7), 3a,4,5,6,7,7a-hexahydro-1*H*-indolyl (C_8), 1,2,3,4-tetrahydroquinolinyl (C_9), and decahydro-1*H*-cycloocta[b]pyrrolyl (C_{10}).

4) The term "heteroaryl" is defined herein as "encompassing one or more C_1-C_{20} rings comprising from 5 to 20 atoms wherein at least one atom in at least one ring is a heteroatom chosen from nitrogen (N), oxygen (O), or sulfur (S), or mixtures of N, O, and S, and wherein further at least one of the rings which comprises a heteroatom is an aromatic ring." The following are non-limiting examples of "substituted and unsubstituted C_1-C_{20} heterocyclic rings" which encompass the following categories of units:

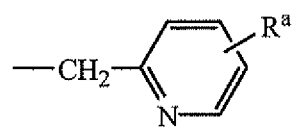
i) heteroaryl rings containing a single ring, non-limiting examples of which include, 1,2,3,4-tetrazolyl (C_1), [1,2,3]triazolyl (C_2), [1,2,4]triazolyl (C_2), triazinyl (C_3), thiazolyl (C_3), 1*H*-imidazolyl (C_3), oxazolyl (C_3), furanyl (C_4), thiopheneyl (C_4), pyrimidinyl (C_4), 2-phenylpyrimidinyl (C_4), pyridinyl (C_5), 3-methylpyridinyl (C_5), and 4-dimethylaminopyridinyl (C_5).

ii) heteroaryl rings containing 2 or more fused rings one of which is a heteroaryl ring, non-limiting examples of which include: 7*H*-purinyl (C_5), 9*H*-purinyl (C_5), 6-amino-9*H*-purinyl (C_5), 5*H*-pyrrolo[3,2-*d*]pyrimidinyl (C_6), 7*H*-pyrrolo[2,3-*d*]pyrimidinyl (C_6), pyrido[2,3-*d*]pyrimidinyl (C_7), 2-phenylbenzo[d]thiazolyl (C_7), 1*H*-indolyl (C_8), 4,5,6,7-tetrahydro-1-*H*-indolyl (C_8), quinoxalinyl (C_8), 5-methylquinoxalinyl (C_8), quinazolinyl (C_8), quinolinyl (C_9), 8-hydroxy-quinolinyl (C_9), and isoquinolinyl (C_9).

5) C_1-C_6 tethered cyclic hydrocarbyl units (whether C_3-C_{10} carbocyclic units, C_6 or C_{10} aryl units, C_1-C_{10} heterocyclic units, or C_1-C_{10} heteroaryl units) which connected to another moiety, unit, or core of the molecule by way of a C_1-C_6 alkylene unit. Non-limiting examples of tethered cyclic hydrocarbyl units include benzyl C_1-(C_6) having the formula:

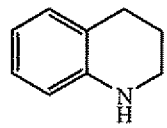


wherein R^a is optionally one or more independently chosen substitutions for hydrogen. Further examples include other aryl units, *inter alia*, (2-hydroxyphenyl)hexyl C_6-(C_6); naphthalen-2-ylmethyl C_1-(C_{10}), 4-fluorobenzyl C_1-(C_6), 2-(3-hydroxy-phenyl)ethyl C_2-(C_6), as well as substituted and unsubstituted C_3-C_{10} alkylenecarbocyclic units, for example, cyclopropylmethyl C_1-(C_3), cyclopentylethyl C_2-(C_5), cyclohexylmethyl C_1-(C_6);. Included within this category are substituted and unsubstituted C_1-C_{10} alkylene-heteroaryl units, for example a 2-picolyl C_1-(C_6) unit having the formula:

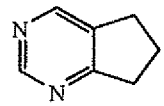


wherein R^a is the same as defined above. In addition, C_1-C_{12} tethered cyclic hydrocarbyl units include C_1-C_{10} alkyleneheterocyclic units and alkylene-heteroaryl units, non-limiting examples of which include, aziridinylmethyl C_1-(C_2) and oxazol-2-ylmethyl C_1-(C_3).

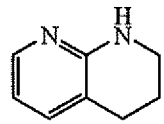
For the purposed of the present invention fused ring units, as well as spirocyclic rings, bicyclic rings and the like, which comprise a single heteroatom will be considered to belong to the cyclic family corresponding to the heteroatom containing ring. For example, 1,2,3,4-tetrahydroquinoline having the formula:



is, for the purposes of the present invention, considered a heterocyclic unit. 6,7-Dihydro-5*H*-cyclopentapyrimidine having the formula:



is, for the purposes of the present invention, considered a heteroaryl unit. When a fused ring unit contains heteroatoms in both a saturated and an aryl ring, the aryl ring will predominate and determine the type of category to which the ring is assigned. For example, 1,2,3,4-tetrahydro-[1,8]naphthyridine having the formula:



is, for the purposes of the present invention, considered a heteroaryl unit.

The term "substituted" is used throughout the specification. The term "substituted" is defined herein as "a hydrocarbyl moiety, whether acyclic or cyclic, which has one or more hydrogen atoms replaced by a substituent or several substituents as defined herein below." The units, when substituting for hydrogen atoms are capable of replacing one hydrogen atom, two hydrogen atoms, or three hydrogen atoms of a hydrocarbyl moiety at a time. In addition, these substituents can replace two hydrogen atoms on two adjacent carbons to form said substituent, new moiety, or unit. For

example, a substituted unit that requires a single hydrogen atom replacement includes halogen, hydroxyl, and the like. A two hydrogen atom replacement includes carbonyl, oximino, and the like. A two hydrogen atom replacement from adjacent carbon atoms includes epoxy, and the like. Three hydrogen replacement includes cyano, and the like. The term substituted is used throughout the present specification to indicate that a hydrocarbyl moiety, *inter alia*, aromatic ring, alkyl chain; can have one or more of the hydrogen atoms replaced by a substituent. When a moiety is described as "substituted" any number of the hydrogen atoms may be replaced. For example, 4-hydroxyphenyl is a "substituted aromatic carbocyclic ring", (N,N-dimethyl-5-amino)octanyl is a " substituted C_8 alkyl unit, 3-guanidinopropyl is a "substituted C_3 alkyl unit," and 2-carboxypyridinyl is a "substituted heteroaryl unit."

The following are non-limiting examples of categories and examples herewith of units which can suitably substitute for hydrogen atoms on a cyclic or acyclic hydrocarbyl unit, described herein below as R^5 units, wherein in the non-limiting examples provided herein below, R^6 is hydrogen, C_1-C_{10} linear or branched alkyl, C_2-C_{10} linear or branched alkenyl, C_2-C_{10} linear or branched alkynyl, and C_6 or C_{10} aryl.

R^5 units according to the present invention include the following:

i) $-NHCOR^6$; for example, $-NHCOCH_3$, $-NHCOCH_2CH_3$, $-NHCOC_6H_5$;

ii) $-COR^6$; for example, $-COCH_3$, $-COCH_2CH_3$, $-COCH_2CH_2CH_3$;

iii) $-CO_2R^6$; for example, $-CO_2CH_3$, $-CO_2CH_2CH_3$, $-CO_2CH_2CH_2CH_3$;

iv) $-OCOR^6$; for example, $-OCOCH_3$, $-OCOCH_2CH_3$, $-OCOCH_2CH_2CH_3$;

v) $-C(=NH)NH_2$;

vi) $-NHC(=NH)NH_2$;

vii) $-N(R^6)_2$; for example, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NH(CH_2CH_3)$;

viii) $-NHC_6H_5$;

ix) C_1-C_4 linear, branched, or cyclic alkyl; for example, methyl, ethyl;

x) $-CON(R^6)_2$; for example, $-CONH_2$, $-CONHCH_3$, $-CON(CH_3)_2$;

xi) $-CONHNH_2$;

xii) $-NHCN$;

xiii) $-CN$;

xiv) halogen: –F, –Cl, –Br, and –I;

xv) $-NHN(R^6)_2$; for example, $-NHNH_2$, $-NHNHCH_3$, $-NHN(CH_3)_2$;

xvi) $-OR^6$; for example, –OH, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2CH_2CH_3$;

xvii) $-NO_2$;

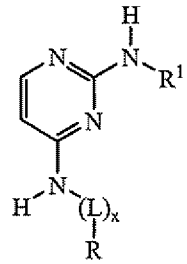
xviii) $-CH_mX_n$; wherein X is halogen, m is from 0 to 2, m+n =3; for example, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CCl_3$, or $-CBr_3$; and

xix) $-SO_2N(R^6)_2$; for example, $-SO_2NH_2$; $-SO_2NHCH_3$; $-SO_2NHC_6H_5$.

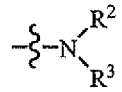
For the purposes of the present invention the terms "compound" and "analog" stand equally well for the novel compositions of matter described herein, including all enantiomeric forms, diastereomeric forms, salts, and the like, and the terms "compound" and "analog" are used interchangeably throughout the present specification.

Pharmaceutically acceptable salts of the compounds of this invention include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acids include hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycolic, lactic, salicylic, succinic, toluene-p-sulfonic, tartaric, acetic, citric, methanesulfonic, formic, benzoic, malonic, naphthalene-2-sulfonic and benzenesulfonic acids. Other acids, such as oxalic acid, while not themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds of this invention and their pharmaceutically acceptable acid addition salts. Salts derived from appropriate bases include alkali metal (*e.g.*, sodium), alkaline earth metal (*e.g.*, magnesium), ammonium and *N*-$(C_1$-C_4 alkyl$)_4^+$ salts.

The compounds of the present invention are 2-arylamino-4-(aminoalkylene)-aminopyrimidines having the core scaffold:



R units are amino units having the formula:



wherein R^2 and R^3 are each independently chosen from:

i) hydrogen; or

ii) C_1-C_4 substituted or unsubstituted linear, branched, or cyclic alkyl.

The first aspect of R units relates to amino units wherein R^2 and R^3 are independently chosen from hydrogen, methyl (C_1), or ethyl (C_2), said units having the formula:

i) $-NH_2$;

ii) $-NHCH_3$;

iii) $-N(CH_3)_2$;

iv) $-NH(CH_2CH_3)$;

v) $-N(CH_2CH_3)_2$; and

vi) $-N(CH_3)(CH_2CH_3)$.

The second aspect of R units relates to amino units wherein R^2 and R^3 are independently chosen from hydrogen, n-propyl (C_3), or *iso*-propyl (C_3), said units having the formula:

i) $-NH(CH_2CH_2CH_3)$;

ii) $-N(CH_2CH_2CH_3)_2$;

iii) $-NH[CH(CH_3)_2]$;

iv) $-N[CH(CH_3)_2]_2$; and

v) $-N(CH_2CH_2CH_3)[CH(CH_3)_2]$.

vi)

The third aspect of R units relates to amino units wherein R^2 is chosen from methyl (C_1) or ethyl (C_2), and R^3 is chosen from n-propyl (C_3) or *iso*-propyl (C_3), said units having the formula:

i) $-N(CH_3)(CH_2CH_2CH_3)$;

ii) $-N(CH_2CH_3)(CH_2CH_2CH_3)$;

iii) $-N(CH_3)[CH(CH_3)_2]$; and

iv) $-N(CH_2CH_3)[CH(CH_3)_2]_2$.

v)

The fourth aspect of R units relates to amino units wherein R^2 and R^3 are independently chosen from hydrogen, n-butyl (C_4), *iso*-butyl (C_4), *sec*-butyl (C_4), and *tert*-butyl (C_4), non-limiting examples of said units having the formula:

i) $-NH(CH_2CH_2CH_2CH_3)$;

ii) $-N(CH_2CH_2CH_2CH_3)_2$;

iii) $-NH[CH_2CH(CH_3)_2]$;

iv) $-N[CH_2CH(CH_3)_2]_2$;

v) $-NH[CH(CH_3)CH_2CH_3]$;

vi) $-N[CH(CH_3)CH_2CH_3]_2$;

vii) $-NH[C(CH_3)_3]$;

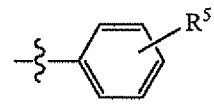
viii) $-N[C(CH_3)_3]_2$

ix) $-N(CH_2CH_2CH_2CH_3)[CH_2CH(CH_3)_2]$;

x) $-N(CH_2CH_2CH_2CH_3)[CH(CH_3)CH_2CH_3]$; and

xi) $-N(CH_2CH_2CH_2CH_3)[C(CH_3)_3]$.

R^1 is substituted or unsubstituted aryl having the formula:



wherein R^5 represents one or more (from 1 to 5) optionally present, and independently selected, substitutes for hydrogen as outlined herein above and described in the categories, aspects, iterations, examples, and tables herein below.

The first category of R^1 units relates to aryl units which are substituted by one or more R^5 units chosen from:

i) C_1-C_4 linear, branched, or cyclic alkyl; for example, methyl (C_1), ethyl (C_2), n-propyl (C_3), isopropyl (C_3), n-butyl (C_4), and the like;

ii) halogen; for example, –F, –Cl, –Br, and –I;

iii) $-OR^6$; for example, $-OCH_3$ (C_1), $-OCH_2CH_3$ (C_2), $-OCH_2CH_2CH_3$ (C_3), $-OCH(CH_3)_2$ (C_3), and the like;

iv) $-SO_2N(R^6)_2$; for example, $-SO_2NH_2$, $-SO_2NHCH_3$, $-SO_2NHC_6H_5$, and the like;

v) $-CH_mX_n$; wherein each X is independently F, Cl, Br, or I, m is from 0 to 2, m+n =3; for example, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CCl_3$, $-CBr_3$, and the like; and

vi) $-NO_2$;

wherein each R^6 is independently hydrogen, or C_1-C_4 linear, branched, or cyclic alkyl.

The first aspect of the first category of R^1 units relates to substituted phenyl units chosen from: 3-chlorophenyl, 4-chlorophenyl, 3,4-dichlorophenyl, 3-chloro-4-methyl-phenyl, 3-chloro-4-fluorophenyl, 3,4-difluorophenyl, 3-trifluoromethylphenyl, 3-trifluoro-methyl-4-chlorophenyl, 3-methoxyphenyl, 3-methylphenyl, 3-ethylphenyl, and 3-iso-propylphenyl.

The second aspect of the first category of R^1 units relates to substituted phenyl units chosen from: 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,3-difluorophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, 2,3,4-trifluorophenyl, 2,3,5-trifluorophenyl, 2,3,6-trifluorophenyl, 2,4,5-trifluorophenyl, 2,4,6-trifluorophenyl, 2-chlorophenyl, 2,3-dichlorophenyl, 2,4-dichlorophenyl, 2,5-dichlorophenyl, 2,6-dichloro-phenyl, 2,3,4-trichlorophenyl, 2,3,5-trichlorophenyl, 2,3,6-trichlorophenyl, 2,4,5-tri-chlorophenyl, and 2,4,6-trichlorophenyl.

The third aspect of the first category of R^1 units relates to substituted phenyl units chosen from: 2-methylphenyl, 4-methylphenyl, 2,3-dimethylphenyl, 2,4-dimethylphenyl,

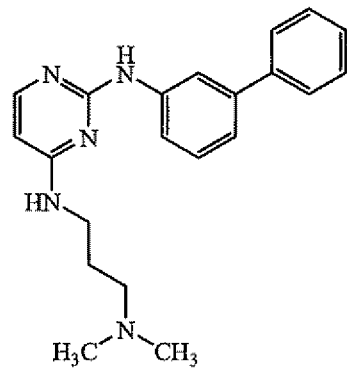
2,5-dimethyl-phenyl, 2,6-dimethylphenyl, 3,4-dimethyl-phenyl, 2,3,4-trimethylphenyl, 2,3,5-trimethyl-phenyl, 2,3,6-trimethylphenyl, 2,4,5-trimethylphenyl, 2,4,6-trimethyl-phenyl, 2-ethylphenyl, 4-ethylphenyl, 2,3-diethylphenyl, 2,4-diethylphenyl, 2,5-diethyl-phenyl, 2,6-diethylphenyl, 3,4-diethylphenyl, 2,3,4-triethylphenyl, 2,3,5-triethylphenyl, 2,3,6-triethylphenyl, 2,4,5-triethylphenyl, and 2,4,6-triethylphenyl.

The fourth aspect of the first category of R^1 units relates to substituted phenyl units chosen from: 2-methoxyphenyl, 4-methoxyphenyl, 2,3-dimethoxyphenyl, 2,4-dimethoxyphenyl, 2,5-dimethoxyphenyl, 2,6-dimethoxyphenyl, 3,4-dimethoxyphenyl, 2,3,4-trimethoxyphenyl, 2,3,5-trimethoxyphenyl, 2,3,6-trimethoxy-phenyl, 2,4,5-tri-methoxyphenyl, 2,4,6-trimethoxyphenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 4-hydroxy-phenyl, 2,3-dihydroxyphenyl, 2,4-dihydroxyphenyl, 2,5-dihydroxyphenyl, 2,6-dihydroxy-phenyl, 3,4-dihydroxy-phenyl, 2,3,4-trihydroxyphenyl, 2,3,5-trihydroxy-phenyl, 2,3,6-trihydroxyphenyl, 2,4,5-trihydroxyphenyl, and 2,4,6-trihydroxyphenyl.

However, other combinations of R^5 units not specifically exemplified are encompassed within the first category of R^1.

The second category of R^1 units relates to aryl units which are substituted by one or more R^5 units which are substituted or unsubstituted C_6 (phenyl) or C_{10} (naphthyl) aryl units.

The first aspect of this category relates to R^1 units which are biphenyl wherein R^5 is phenyl, for example, a compound having the formula:

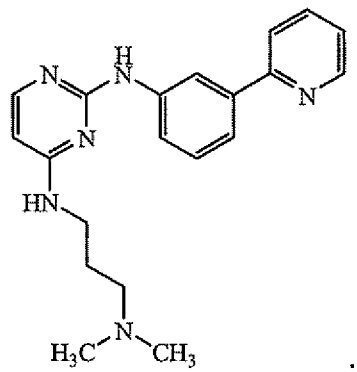


The second aspect of this category relates to R^1 units which are substituted biphenyl non-limiting examples of which include 2'-fluoro-biphenyl-2-yl, 2'-fluoro-biphenyl-3-yl, 2'-fluoro-biphenyl-4-yl, 3'-fluoro-biphenyl-2-yl, 3'-fluoro-biphenyl-3-yl, 3'-fluoro-biphenyl-4-yl, 4'-fluoro-biphenyl-2-yl, 4'-fluoro-biphenyl-3-yl, 4'-fluoro-biphenyl-4-yl, 2'-chloro-biphenyl-2-yl, 2'-chloro-biphenyl-3-yl, 2'-chloro-biphenyl-4-yl, 3'-chloro-biphenyl-2-yl, 3'-chloro-biphenyl-3-yl, 3'-chloro-biphenyl-4-yl, 4'-chloro-biphenyl-2-yl, 4'-chloro-biphenyl-3-yl, 4'-chloro-biphenyl-4-yl, 2'-methyl-biphenyl-2-yl, 2'-methyl-biphenyl-3-yl, 2'-methyl-biphenyl-4-yl, 3'-methyl-biphenyl-2-yl, 3'-methyl-biphenyl-3-yl, 3'-methyl-biphenyl-4-yl, 4'-methyl-biphenyl-2-yl, 4'-methyl-biphenyl-3-yl, and 4'-methyl-biphenyl-4-yl.

However, other combinations of R^5 units not specifically exemplified are encompassed within the second category of R^1.

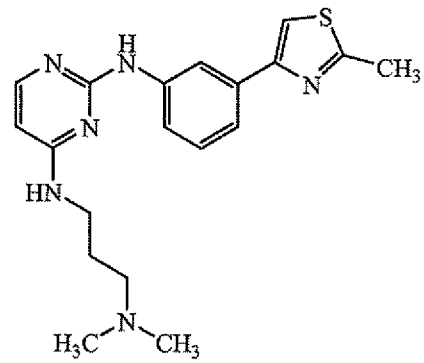
The third category of R^1 units relates to phenyl units which are substituted by one or more R^5 units which are substituted or unsubstituted C_3, C_4 or C_5 heteroaryl units.

The first aspect of this category relates to R^1 units which are C_4 or C_5 heteroaryl substituted phenyl units wherein R^5 is, for example, pyridin-2-yl thereby forming a compound having the formula:



Non-limiting examples or this category of R^1 include 2-pyridin-2-yl-phenyl, 3-pyridin-2-yl-phenyl, 4-pyridin-2-yl-phenyl, 2-pyridin-3-yl-phenyl, 3-pyridin-3-yl-phenyl, 4-pyridin-3-yl-phenyl, 2-pyridin-4-yl-phenyl, 3-pyridin-4-yl-phenyl, 4-pyridin-4-yl-phenyl, 2-pyrimidin-2-yl-phenyl, 3-pyrimidin-2-yl-phenyl, 4-pyrimidin-2-yl-phenyl, 2-pyrimidin-3-yl-phenyl, 3-pyrimidin-3-yl-phenyl, 4-pyrimidin-3-yl-phenyl, 2-pyrimidin-4-yl-phenyl, 3-pyrimidin-4-yl-phenyl, and 4-pyrimidin-4-yl-phenyl.

The second aspect of this category relates to R^1 units which are C_3 heteroaryl substituted phenyl wherein R^5 is, for example, 2-methyl-thiazol-4-yl thereby forming a compound having the formula:



Non-limiting examples of this aspect of the third category of R^1 include imidazol-1-yl, imidazol-2-yl, imidazol-4-yl, thiazol-2-yl, thiazol-4-yl, and the like.

L is a linking unit having the formula:

$$-[C(R^{4a}R^{4b})]_n-$$

wherein each R^{4a} and R^{4b} unit is independently chosen from:

i) hydrogen; or

ii) C_1-C_4 linear, branched, or cyclic alkyl; for example, methyl (C_1), ethyl (C_2), n-propyl(C_3), *iso*-propyl (C_3), cyclopropyl (C_3), n-butyl (C_4), *iso*-butyl (C_4), *sec*-butyl (C_4), and *tert*-butyl (C_4);

the index n is from 1 to 4. The index n indicates the number of units which comprise L linking units, for example, a linking unit having the formula $-CH_2-$ (methylene) would have an index n equal to 1. A linking unit having the formula $-CH_2CH_2-$ (ethylene) or the unit having the formula $-CH(CH_3)CH_2-$ (2-propylene) each have an index n equal to 2.

The first category of L units relates to unsubstituted alkylene units chosen from:

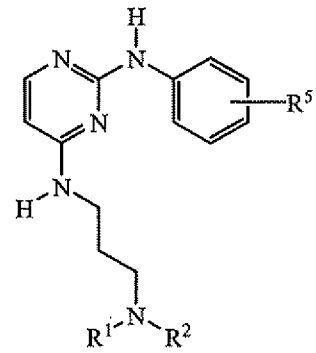
i) $-CH_2-$, methylene;

ii) $-CH_2CH_2-$, ethylene;

iii) $-CH_2CH_2CH_2-$, propylene; and

iv) $-CH_2CH_2CH_2CH_2-$, butylene.

The first aspect of the first category of L units encompasses linking groups which are $-CH_2CH_2CH_2-$, propylene; as exemplified in the generic formula:



The second aspect of the first category of L units encompasses linking groups which are $-CH_2CH_2-$, ethylene.

The second category of L units relates to alkyl substituted alkylene units chosen from:

i) $-CH(CH_3)CH_2-$, 1-methylethylene;

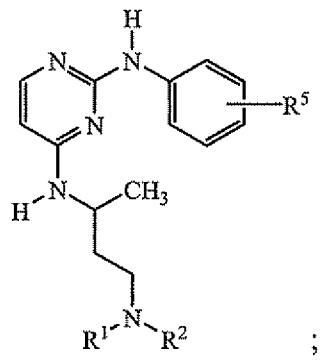
ii) $-CH_2CH(CH_3)-$, 2-methylethylene;

iii) $-CH(CH_3)CH_2CH_2-$, 1-methylpropylene;

iv) $-CH_2CH(CH_3)CH_2-$, 2-methylpropylene; and

v) $-CH_2C(CH_3)_2CH_2-$, 2,2-dimethylpropylene.

The first aspect of the second category of L units encompasses linking groups which are $-CH(CH_3)CH_2CH_2-$, 1-methylpropylene; as exemplified in the generic formula:



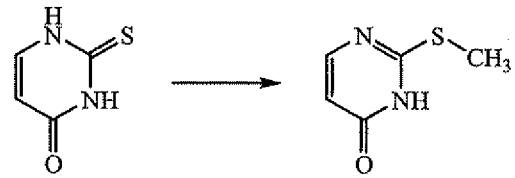
;

wherein the above formula encompasses both the R and the S enantiomers of the linking unit.

SYNTHESIS PROCEDURE

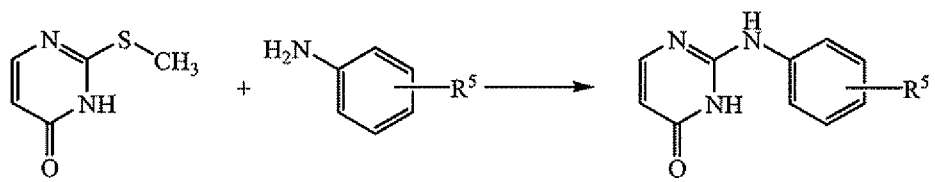
The compounds of the present invention can be prepared by the following general procedure, the formulator adjusting the reaction conditions as is necessary and which one skilled in the art will be able to accomplish without undo experimentation.

Step 1: Preparation of intermediate 2-(methylthio)pyrimidine-4(3*H*)-one. This compound can be used in the preparation of each analog encompassed by the present invention. The general procedure follows.



To a solution of sodium hydroxide (8 g, 200 mmol) in H_2O (75 mL) at room temperature is added thiouridine (14.2g, 100 mmol). The resulting mixture is stirred at room temperature for 20 minutes. Methyl iodide (6.86 mL, 110 mmol) is slowly added dropwise in THF (10 mL) and the mixture is stirred at room temperature for 18 hours. A white solid forms upon acidifying the mixture to pH 5 with glacial acetic acid. At this point the mixture is cooled in an ice bath and allowed to stand for approximately 2 hours after which the final product separates as a white solid and can be collected by filtration. First crop of crystals typically yields the desired product in an excess of 60% yield. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.45 (s, 3H), 6.07 (d, J= 6.6 Hz, 1H), 7.85 (d, J = 6.6 Hz, 1H).

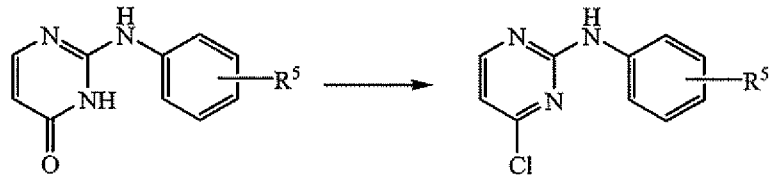
Step 2: Formation of 2-anilino intermediate.



2-(Substituted or unsubstituted phenylamino)pyrimidin-4(3*H*)-one: To a 2-(methyl-thio)pyrimidine-4(3*H*)-one (14.2 g, 100 mmol) in diglyme (60 mL) is added the substituted or unsubstituted aniline of choice (200 mmol). The resulting mixture is heated

to reflux and stirred for approximately 18 hours. The product which typically forms as a solid upon cooling the mixture to room temperature, is washed with solvent (pentane, hexane, or isopentane). However, solvent can be added to the reaction mixture to induce crystallization if necessary.

Step 3. Formation of 4-chloro-2-anilino intermediate.

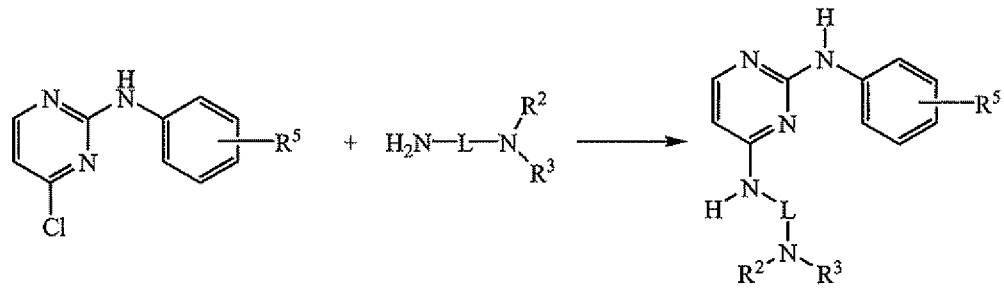


2-(Substituted or unsubstituted phenylamino)-4-chloro-pyrimidine: To a 2-(Substituted or unsubstituted phenylamino)pyrimidin-4(3*H*)-one (5.02 g, 22.6 mmol) and *N,N*-dimethyl-aniline (450 mL) is added of phosphorus oxychloride (450 mL). The resulting mixture is heated to reflux for 15 minutes, cooled to room temperature and concentrated *in vacuo*. The residue is neutralized to pH 7 with 1M NaOH (aqueous). The organic layer is extracted with EtOAc (3 x 250 mL). The combined organic layers are dried ($MgSO_4$) and concentrated *in vacuo*. The residue can be conveniently purified over silica (5% EtOAc in hexanes) to afford the desired compound.

Alternatively, the 4-chloro-2-anilino intermediate can be synthesized the following way:

2-(Substituted or unsubstituted phenylamino)-4-chloro-pyrimidine: To a 2-(Substituted or unsubstituted phenylamino)pyrimidin-4(3*H*)-one (3.00 g, 13.5 mmol) in toluene (30 mL) is added *N,N*-dimethyl-aniline (3.57 mL, 28.4 mmol) and phosphorus oxychloride (1.24 mL, 13.5 mmol). The resulting mixture is heated to reflux for 15 minutes, cooled to room temperature and neutralized to pH 7 with 1M NaOH (aqueous). The organic layer is extracted with EtOAc (3 x 250 mL). The combined organic layers are dried ($MgSO_4$) and concentrated *in vacuo*. The residue can be conveniently purified over silica (5% EtOAc in hexanes) to afford the desired compound.

Step 4. Formation of final compounds (analogs) of the present invention.



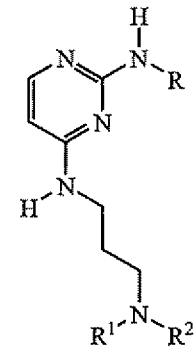
To the 2-(Substituted or unsubstituted phenylamino)pyrimidin-4(3*H*)-one formed in Step (2) (100 mmol) in THF (500 mL) is added diisopropylethylamine (200 mmol) followed by the desired diamine (200 mmol). The resulting mixture is heated to reflux for approximately 18 hours. The reaction is cooled to room temperature and concentrated *in vacuo*. The residue which forms is diluted with water and extracted with solvent. The combined organic layers are dried ($MgSO_4$) and concentrated *in vacuo*. This residue can be crystallized or purified over silica to afford the final compound.

Schemes I-IV herein below provide illustrative examples of the preparation of compounds encompassed by the various categories of the present invention.

The analogs (compounds) of the present invention are arranged into several categories to assist the formulator in applying a rational synthetic strategy for the preparation of analogs which are not expressly exampled herein. The arrangement into categories does not imply increased or decreased efficacy for any of the compositions of matter described herein.

ANALOG CATEGORIES

The compounds which comprise Category I of the present invention are 2-(substituted phenylamino)-4-(amino- or substituted amino-propylene)aminopyrimidines having the formula:



wherein R, R^1, and R^2 are defined herein below in Table I.

TABLE I

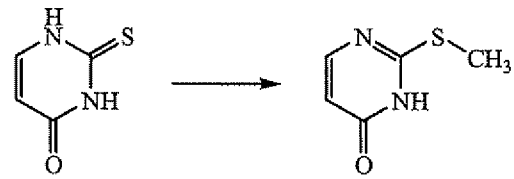
No	R	R^1	R^2
1	3-chlorophenyl	–H	–H
2	3-chlorophenyl	$–CH_3$	–H
3	3-chlorophenyl	$–CH_3$	$–CH_3$
4	3-chlorophenyl	$–CH_2CH_3$	–H
5	3-chlorophenyl	$–CH_2CH_3$	$–CH_3$
6	3-chlorophenyl	$–CH_2CH_3$	$–CH_2CH_3$
7	4-chlorophenyl	–H	–H
8	4-chlorophenyl	$–CH_3$	–H
9	4-chlorophenyl	$–CH_3$	$–CH_3$
10	4-chlorophenyl	$–CH_2CH_3$	–H
11	4-chlorophenyl	$–CH_2CH_3$	$–CH_3$
12	4-chlorophenyl	$–CH_2CH_3$	$–CH_2CH_3$
13	3,4-dichlorophenyl	–H	–H
14	3,4-dichlorophenyl	$–CH_3$	–H
15	3,4-dichlorophenyl	$–CH_3$	$–CH_3$
16	3,4-dichlorophenyl	$–CH_2CH_3$	–H
17	3,4-dichlorophenyl	$–CH_2CH_3$	$–CH_3$
18	3,4-dichlorophenyl	$–CH_2CH_3$	$–CH_2CH_3$
19	3-chloro-4-methylphenyl	–H	–H

20	3-chloro-4-methylphenyl	$-CH_3$	–H
21	3-chloro-4-methylphenyl	$-CH_3$	$-CH_3$
22	3-chloro-4-methylphenyl	$-CH_2CH_3$	–H
23	3-chloro-4-methylphenyl	$-CH_2CH_3$	$-CH_3$
24	3-chloro-4-methylphenyl	$-CH_2CH_3$	$-CH_2CH_3$
25	3-chloro-2-fluorophenyl	$-CH_3$	$-CH_3$
26	3-chloro-2-fluorophenyl	$-CH_2CH_3$	$-CH_3$
27	3-chloro-2-fluorophenyl	$-CH_2CH_3$	$-CH_2CH_3$
28	3-chloro-4-fluorophenyl	$-CH_3$	$-CH_3$
29	3-chloro-4-fluorophenyl	$-CH_2CH_3$	$-CH_3$
30	3-chloro-4-fluorophenyl	$-CH_2CH_3$	$-CH_2CH_3$
31	3,4-difluorophenyl	–H	–H
32	3,4-difluorophenyl	$-CH_3$	–H
33	3,4-difluorophenyl	$-CH_3$	$-CH_3$
34	3,4-difluorophenyl	$-CH_2CH_3$	–H
35	3,4-difluorophenyl	$-CH_2CH_3$	$-CH_3$
36	3,4-difluorophenyl	$-CH_2CH_3$	$-CH_2CH_3$
37	3-trifluoromethylphenyl	–H	–H
38	3-trifluoromethylphenyl	$-CH_3$	–H
39	3-trifluoromethylphenyl	$-CH_3$	$-CH_3$
40	3-trifluoromethylphenyl	$-CH_2CH_3$	–H
41	3-trifluoromethylphenyl	$-CH_2CH_3$	$-CH_3$
42	3-trifluoromethylphenyl	$-CH_2CH_3$	$-CH_2CH_3$
43	3-trifluoromethyl-4-chlorophenyl	–H	–H
44	3-trifluoromethyl-4-chlorophenyl	$-CH_3$	–H
45	3-trifluoromethyl-4-chlorophenyl	$-CH_3$	$-CH_3$
46	3-trifluoromethyl-4-chlorophenyl	$-CH_2CH_3$	–H
47	3-trifluoromethyl-4-chlorophenyl	$-CH_2CH_3$	$-CH_3$
48	3-trifluoromethyl-4-chlorophenyl	$-CH_2CH_3$	$-CH_2CH_3$

49	3-methoxyphenyl	–H	–H
50	3-methoxyphenyl	$–CH_3$	–H
51	3-methoxyphenyl	$–CH_3$	$–CH_3$
52	3-methoxyphenyl	$–CH_2CH_3$	–H
53	3-methoxyphenyl	$–CH_2CH_3$	$–CH_3$
54	3-methoxyphenyl	$–CH_2CH_3$	$–CH_2CH_3$
55	3-methylphenyl	$–CH_3$	$–CH_3$
56	3-methylphenyl	$–CH_2CH_3$	$–CH_3$
57	3-methylphenyl	$–CH_2CH_3$	$–CH_2CH_3$
58	3-ethylphenyl	$–CH_3$	$–CH_3$
59	3-ethylphenyl	$–CH_2CH_3$	$–CH_3$
60	3-ethylphenyl	$–CH_2CH_3$	$–CH_2CH_3$

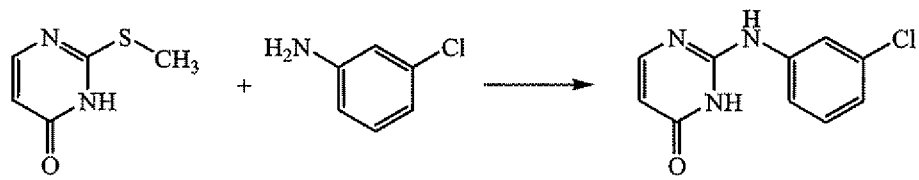
The compounds which comprise Category I of the present invention can be prepared by the procedure outlined herein below in Scheme I.

Scheme I



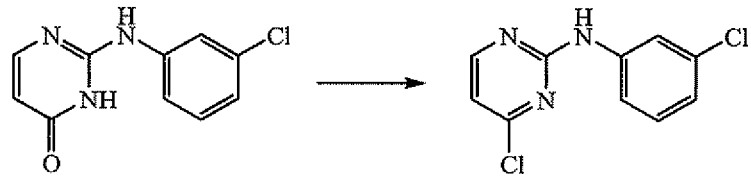
1

Reagents and conditions: (a) NaOH, THF, H_2O, MeI, rt, 18 h.



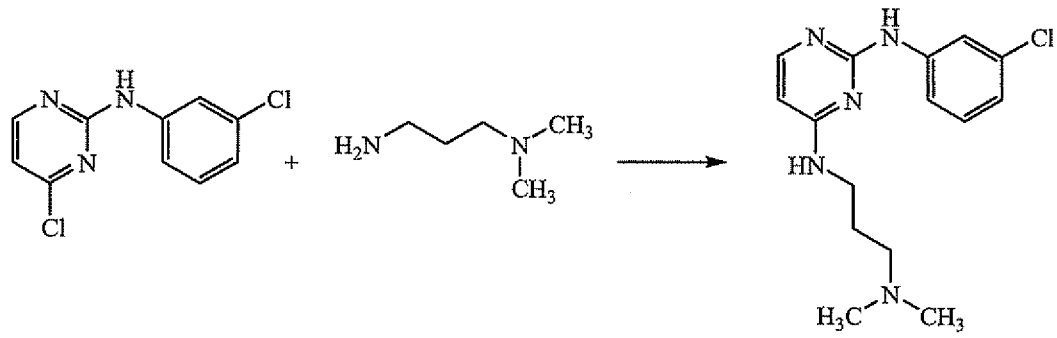
1 2

Reagents and conditions: (b) diglyme, reflux, 18 h.



2 3

Reagents and conditions (c): $POCl_3$, *N,N*-dimethylaniline, reflux, 15 min.



3 4

Reagents and conditions (d): DIPEA, THF, reflux, 18 h

EXAMPLE 1

N^2-(3-chlorophenyl)-N^4-(3-(dimethylamino)propyl)pyrimidine-2,4-diamine (4)

Preparation of 2-(methylthio)pyrimidine-4(3*H*)-one (1): To a solution of sodium hydroxide (6.24 g, 156.07 mmol) in H_2O (55 mL) at room temperature is added thiouridine (10 g, 78.03 mmol). The resulting mixture is stirred at room temperature for 20 min. Methyl iodide (5.45 mL, 87.40 mmol) in THF (10 mL) is added dropwise slowly and the mixture is stirred at room temperature for 18 hours. A white solid forms upon acidifying the mixture to pH 5 with glacial acetic acid. The mixture is allowed to stand at 0 °C (ice bath) for 2 hours and filtered to afford 7.4 g (67% yield) of the desired compound as a white solid. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.45 (s, 3H), 6.07 (d, J= 6.6 Hz, 1H), 7.85 (d, J = 6.6 Hz, 1H).

Preparation of 2-(3-chlorophenylamino)pyrimidin-4(3*H*)-one (2): To 2-(methylthio)pyrimidine-4(3*H*)-one, 1, (4.88 g, 34.37 mmol) in diglyme (20 mL) is added 3-chloroaniline (4.3 mL, 68.74 mmol). The resulting mixture is heated to reflux and stirred

for 18 hours. A solid forms upon cooling the mixture to room temperature. The solid is washed with hexanes to afford 5.0 g (66% yield) of the desired compound. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 5.91 (d, J = 5.7 Hz, 2H), 7.05 (d, J = 7.5Hz, 1H), 7.11 (br s, 1H), 7.32 (t, J = 7.8, 15.9 Hz, 1H), 7.45(d, J = 7.8 Hz, 1H), 7.86 (d, J = 4.5 Hz, 1H), 7.94 (s, 1H).

Preparation of 4-chloro-*N*-(3-chlorophenyl)pyrimidin-2-amine (3): To 2-(3-chlorophenylamino)pyrimidin-4(3*H*)-one, 2, (3.00 g, 13.5 mmol) in toluene (30 mL) is added *N,N*-dimethyl-aniline (3.57 mL, 28.4 mmol) and phosphorus oxychloride (1.24 mL, 13.5 mmol). The resulting mixture is heated to reflux for 15 minutes, cooled to room temperature and neutralized to pH 7 with 1M NaOH (aqueous). The organic layer is extracted with EtOAc (3 x 250 mL). The combined organic layers are dried ($MgSO_4$) and concentrated *in vacuo*. The residue is purified over silica (5% EtOAc in hexanes) to afford 2.0 g (61% yield) of the desired compound. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.06-7.04 (m, 2H), 7.34 (t, J = 8.1, 1H), 7.65-7.61 (m, 1H), 7.93(m, 1H), 8.50 (d, J = 5.1 Hz, 1H), 10.26 (s, 1H).

Preparation of N^2-(3-chlorophenyl)-N^4-(3-(dimethylamino)propyl)pyrimidine-2,4-diamine (4): To 4-chloro-*N*-(3-chlorophenyl)pyrimidin-2-amine, 3, (0.517 g, 2.16 mmol) in THF (10 mL) is added diisopropylethylamine (0.754 mL, 4.32 mmol) followed by 3-dimethyl-aminopropylamine (0.544 mL, 4.32 mmol). The resulting mixture is heated to reflux for 18 hours. The reaction is cooled to room temperature and concentrated *in vacuo*. The residue is diluted with 10 mL water and extracted with EtOAc (3 x 50 mL). The combined organic layers are dried ($MgSO_4$) and concentrated *in vacuo*. This residue is purified over silica (5% MeOH in CH_2Cl_2 with 0.7% Et_3N) to afford the desired compound as a yellow solid. The compound can be conveniently recrystallized from CH_2Cl_2 and MeOH to afford 0.206 g (40% yield) of a white solid. ^{1}H NMR (CD_3OD, 300 MHz): δ 1.85-1.95 (m, 2H). 2.40 (s, 6H), 2.59-2.65 (m, 2H), 3.40-3.51 (m, 2H), 5.99 (d, J = 6.3 Hz, 1H), 6.95 (d, J= 8.1 Hz, 1H), 7.24 (t, J = 8.1 Hz, 1H), 7.40 (d, J= 6.9 Hz, 1H), 7.78 (d, J = 5.7 Hz, 1H), 8.03 (s, 1H). MS (ESI, pos. ion) *m/z*: 306 (M+1).

The following are non-limiting examples of compounds which comprise Category I of the present invention, the characterization of which will assist the formulator in establishing the chemical formulae of compounds which are not specifically exemplified herein.

N^2-(3-chlorophenyl)-N^4-(3-(diethylamino)propyl)pyrimidine-2,4-diamine: ^{1}H NMR (CD_3OD, 300 MHz): δ 1.30 (t, J = 7.5 Hz, 6H), 2.15 (m, 2H), 3.18 (m, 6H), 3.60 (t, J = 5.7 Hz, 1H), 6.15 (d, J = 5.7 Hz, 1H), 6.98 (d, J = 8.1 Hz, 1H), 7.23 (dd, J = 8.1, 8.4 Hz, 1H), 7.40 (d, J = 8.4 Hz, 1H), 7.81 (br d, J = 5.7, 1H), 8.15 (s, 1H). MS (ESI, pos. ion) *m/z*: 334 (M+1).

N^4-(3-(dimethylamino)propyl)-N^2-(3-methoxyphenyl)pyrimidine-2,4-diamine hydrochloride:^{1}H NMR (CD_3OD, 300 MHz): δ 1.27 (t, J = 7.5 Hz, 6H), 2.03-2.10 (m, 2H), 2.89 (s, 3H), 3.18-3.24 (m, 2H), 3.59-3.63 (m, 2H), 3.86 (s, 3H), 6.28 (d, J = 7.5 Hz, 1H), 6.90 (d, J= 8.4 Hz, 1H), 7.05 (d, J = 8.1 Hz, 2H), 7.18 (s, 1H), 7.39 (t, J = 7.8 Hz, 1H), 7.67 (d, J= 7.2 Hz, 1H). MS (ESI, pos. ion) m/z: 302 (M+1).

N^4-(3-(dimethylamino)propyl)-N^2-(3-methylphenyl)pyrimidine-2,4-diamine hydrochloride: ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.98 (m, 2H), 2.33 (s, 3H), 2.72 (s, 6H), 3.09 (m, 2H), 3.45 (m, 2H), 6.24 (d, J = 7.5 Hz, 1H), 6.97 (d, J = 7.8 Hz, 1H), 7.29 (t, J = 7.5 Hz, 1H), 7.40-7.43, (m, 4H), 7.84 (d, J = 6.9 Hz, 1H), 9.17 (br sm 1H), 10.47 (br s, 2H). MS (ESI, pos. ion) *m/z*: 286 (M+1).

N^4-(3-(dimethylamino)propyl)-N^2-(3-(trifluoromethyl)phenyl)pyrimidine-2,4-diamine: ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.63-1.72 (m, 2H), 2.13 (s, 6H), 2.26-2.31 (m, 2H), 3.32-3.34 (m, 2H), 5.98 (d, J = 5.7 Hz, 1H), 7.17 (d, J = 7.8 Hz, 1H), 7.30 (br s, 1H), 7.43 (t, J = 7.8 Hz, 1H), 7.83 (br s, 1H), 8.48 (br s, 1H), 9.35 (br s, 1H). ^{19}F 101.76 (s, 3F). MS (ESI, pos. ion) *m/z*: 340 (M+1).

N^2-(3-chlorophenyl)-N^4-(3-(methylamino)propyl)pyrimidine-2,4-diamine: ^{1}H NMR (CD_3OD, 300 MHz): δ 2.02-2.11 (m, 2H), 2.72 (s, 3H), 3.06-3.11 (m, 2H), 3.60-3.65 (m, 2H), 6.32-6.34 (m, 1H), 7.29-7.51 (m, 3H), 7.72-7.79 (m, 2H) . MS (ESI, pos. ion) *m/z*: 292 (M+1).

N^4-(3-aminopropyl)-N^2-(3-chlorophenyl)pyrimidine-2,4-diamine: ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.90-1.97 (m, 2H), 2.89 (m, 2H), 3.46-3.52 (m, 2H), 6.35 (d, J = 7.5 Hz, 1H), 7.22 (d, J = 7.8 Hz, 1H), 7.42-7.53 (m, 2H), 7.88-7.92 (m, 2H), 8.12 (br s, 3H), 9.62 (br s, 1H), 11.15 (br s, 1H). MS (ESI, pos. ion) *m/z*: 278 (M+1).

N^2-(3,4-difluorophenyl)-N^4-(3-(dimethylamino)propyl)pyrimidine-2,4-diamine: ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.68 (m, 2H), 2.13 (s, 6H), 2.27 (m, 2H), 3.32 (m, 2H), 5.95 (d, J = 5.4 Hz, 1H), 7.20-7.29 (m, 2H), 7.37-7.41 (m, 2H), 7.79 (m, 1H), 8.07-8.14 (m, 1H), 9.18 (s, 1H). ^{19}F (DMSO-d_6, 300 MHz): δ 13.61 (m, 1F), 24.856 (m, 1F). MS (ESI, pos. ion) m/z: 308.27 (M+1).

N^2-(3-chloro-4-methylphenyl)-N^4-(3-(dimethylamino)propyl)pyrimidine-2,4-diamine: ^{1}H NMR (CD_3OD, 300 MHz): δ 1.85 (m, 2H), 2.28 (s, 6H), 2.32 (s, 3H), 2.48 (t, 2H), 3.46 (m, 2H), 5.96 (d, J = 6.3 Hz, 1H), 7.16 (d, J = 8.1Hz, 1H), 7.29 (d, J = 5.4 Hz, 1H), 7.75 (d, J = 5.1Hz, 1H), 8.00 (s, 1H). MS (ESI, pos. ion) *m/z*: 320 (M+1).

N^2-(3,4-dichlorophenyl)-N^4-(3-(dimethylamino)propyl)pyrimidine-2,4-diamine: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.85 (m, 2H), 2.34 (s, 6H), 2.52 (t, J = 6.0 Hz, 2H), 3.50 (m, 2H), 5.91 (d, J = 6.0 Hz, 1H), 6.21 (s, 1H), 7.10 (s, 1H), 7.30 (d, J = 6.0 Hz, 1H), 7.92 (d, J = 5.7 Hz, 1H), 8.13 (s, 1H). MS (ESI, pos. ion) *m/z*: 340 (M+1).

N^2-(3-chloro-4-fluorophenyl)-N^4-(3-(dimethylamino)propyl)pyrimidine-2,4-diamine: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.79-1.86 (m, 2H), 2.30 (s, 6H), 2.46 (t, J = 6.0 Hz, 2H), 3.46 (m, J = 6.0 Hz, 2H), 5.89 (d, J = 6.0 Hz, 1H), 6.13 (s, 1H), 7.06 (t, J = 6.0 Hz, 1H), 7.17 (s, 1H), 7.27 (m, 1H), 7.26 (d, J = 6.6 Hz, 1H), 7.29 (s, 1H), 7.92 (d, J = 6.0

Hz, 1H), 8.02 (d, J = 6.6 Hz, 1H). HRMS calcd for $C_{15}H_{19}ClFN_5$ 324.1391 *m/z* $(M+1)^+$; observed 324.1399 *m/z*.

N^2-(4-chloro-3-(trifluoromethyl)phenyl)-N^4-(3-(dimethylamino)propyl)pyrimidine-2,4-diamine: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.80 (m, 2H), 2.27 (s, 6H), 2.45 (t, J = 6.0 Hz, 2H), 3.49 (bs, 2H), 5.91 (d, J = 6.0 Hz, 1H), 6.37 (t, J = 4.8 Hz, 1H)), 7.37 (d, J = 8.7 Hz, 1H), 7.58 (d, J = 8.7 Hz, 1H), 7.94 (d, J = 6.0 Hz, 1H), 1H), 8.34 (bs, 2H). HRMS calcd for $C_{16}H_{19}ClF_3N_5$ 374.1359 *m/z* $(M+H)^+$; observed 374.1357 *m/z*.

N^4-(3-(dimethylamino)propyl)-N^2-(3-ethylphenyl)pyrimidine-2,4-diamine: ^{1}H NMR (CD_3OD, 300 MHz): δ 1.29 (t, J = 7.8 Hz, 3H), 2.07 (m, 2H), 2.71 (q, J = 7.8 Hz, 2H)), 2.85 (s, 6H), 3.16 (m, 2H), 3.60 (t, J = 6.6 Hz, 2H), 6.24 (d, J = 7.5 Hz, 1H), 7.16 (m, 1H), 7.34 (s, 1H), 7.38 (m, 2H), 7.65 (d, J = 7.2 Hz, 1H). HRMS calcd for $C_{17}H_{25}N_5$ 300.2188 *m/z* $(M+1)^+$; observed 300.2194 *m/z*.

N^2-(2-fluoro-3-chlorophenyl)-N^4-(3-(dimethylamino)propyl)pyrimidine-2,4-diamine ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.75-1.82 (m, 2H), 2.28 (s, 6H), 2.44 (t, J = 6.3 Hz, 2H), 3.46 (s, 2H), 5.92 (d, J = 6.0 Hz, 1H), 6.02 (bs, 1H), 6.97-7.08, (m, 3H), 7.95 (d, J = 5.1 Hz, 1H), 8.49 (t, J = 7.8 Hz, 1H). HRMS calcd for $C_{15}H_{19}N_5FCl$, 324.1391 *m/z* $(M+H)^+$; observed 324.1394 *m/z*.

Further compounds which are encompassed within Category I of the present invention but which are not fully exemplified include:

N^4-(3-(dimethylamino)propyl)-N^2-(2-fluorophenyl)pyrimidine-2,4-diamine;

N^4-(3-(dimethylamino)propyl)-N^2-(3-fluorophenyl)pyrimidine-2,4-diamine;

N^4-(3-(dimethylamino)propyl)-N^2-(4-fluorophenyl)pyrimidine-2,4-diamine;

N^4-(3-(dimethylamino)propyl)-N^2-(2,3-difluorophenyl)pyrimidine-2,4-diamine;

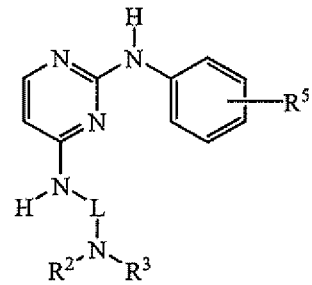
N^4-(3-(dimethylamino)propyl)-N^2-(2,4-difluorophenyl)pyrimidine-2,4-diamine;

N^4-(3-(dimethylamino)propyl)-N^2-(2,5-difluorophenyl)pyrimidine-2,4-diamine;

N^4-(3-(dimethylamino)propyl)-N^2-(2,6-difluorophenyl)pyrimidine-2,4-diamine;

N^4-(3-(dimethylamino)propyl)-N^2-(2-chlorophenyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)propyl)-N^2-(2,3-dichlorophenyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)propyl)-N^2-(2,4-dichlorophenyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)propyl)-N^2-(2,5-dichlorophenyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)propyl)-N^2-(2,6-dichlorophenyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)propyl)-N^2-(2-methylphenyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)propyl)-N^2-(4-methylphenyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)propyl)-N^2-(2,3-dimethylphenyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)propyl)-N^2-(2,4-dimethylphenyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)propyl)-N^2-(2,5-dimethylphenyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)propyl)-N^2-(2,6-dimethylphenyl)pyrimidine-2,4-diamine;
and
N^4-(3-(dimethylamino)propyl)-N^2-(3,4-dimethylphenyl)pyrimidine-2,4-diamine.

The compounds which comprise Category II of the present invention are 2-(substituted phenylamino)-4-(amino- or substituted amino-ethylene, or substituted amino-butylene)-aminopyrimidines having the formula:



wherein R^2, R^3, R^5, and L are defined herein below in Table II.

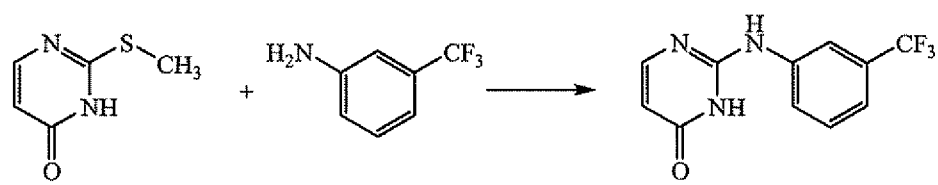
TABLE II

No.	L	R^2	R^3	R^5
61	$-CH_2-$	–H	–H	3-chloro
62	$-CH_2-$	$-CH_3$	–H	3-chloro
63	$-CH_2-$	$-CH_3$	$-CH_3$	3-chloro
64	$-CH_2-$	$-CH_2CH_3$	–H	3-chloro

65	$-CH_2-$	$-CH_2CH_3$	$-CH_3$	3-chloro
66	$-CH_2-$	$-CH_2CH_3$	$-CH_2CH_3$	3-chloro
67	$-CH_2CH_2-$	$-H$	$-H$	3-chloro
68	$-CH_2CH_2-$	$-CH_3$	$-H$	3-chloro
69	$-CH_2CH_2-$	$-CH_3$	$-CH_3$	3-chloro
70	$-CH_2CH_2-$	$-CH_2CH_3$	$-H$	3-chloro
71	$-CH_2CH_2-$	$-CH_2CH_3$	$-CH_3$	3-chloro
72	$-CH_2CH_2-$	$-CH_2CH_3$	$-CH_2CH_3$	3-chloro
73	$-CH_2C(CH_3)_2CH_2-$	$-H$	$-H$	3-trifluoromethyl
74	$-CH_2C(CH_3)_2CH_2-$	$-CH_3$	$-H$	3-trifluoromethyl
75	$-CH_2C(CH_3)_2CH_2-$	$-CH_3$	$-CH_3$	3-trifluoromethyl
76	$-CH_2C(CH_3)_2CH_2-$	$-CH_2CH_3$	$-H$	3-trifluoromethyl
77	$-CH_2C(CH_3)_2CH_2-$	$-CH_2CH_3$	$-CH_3$	3-trifluoromethyl
78	$-CH_2C(CH_3)_2CH_2-$	$-CH_2CH_3$	$-CH_2CH_3$	3-trifluoromethyl
79	$-CH_2CH_2CH_2CH_2-$	$-H$	$-H$	3-chloro
80	$-CH_2CH_2CH_2CH_2-$	$-CH_3$	$-H$	3-chloro
81	$-CH_2CH_2CH_2CH_2-$	$-CH_3$	$-CH_3$	3-chloro
82	$-CH_2CH_2CH_2CH_2-$	$-CH_2CH_3$	$-H$	3-chloro
83	$-CH_2CH_2CH_2CH_2-$	$-CH_2CH_3$	$-CH_3$	3-chloro
84	$-CH_2CH_2CH_2CH_2-$	$-CH_2CH_3$	$-CH_2CH_3$	3-chloro

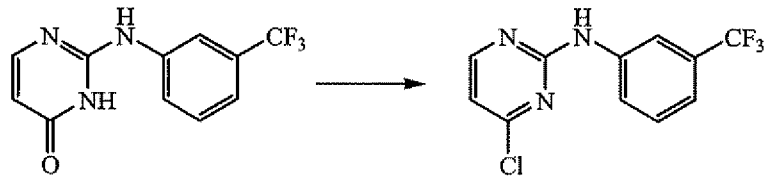
The compounds which comprise Category II of the present invention can be prepared by the procedure outlined herein below in Schemes II and III and Examples 3 and 4.

Scheme II



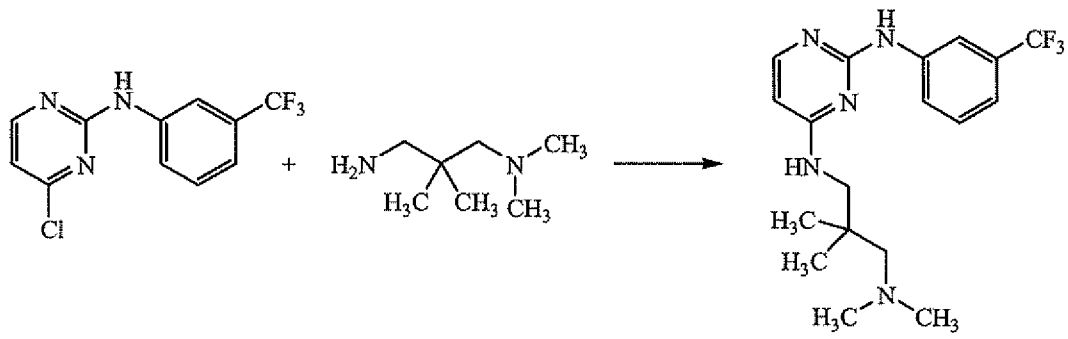
1 5

Reagents and conditions: (a) diglyme, reflux, 18 h.



5 6

Reagents and conditions (b): $POCl_3$, *N,N*-dimethylaniline, reflux, 15 min.



6 7

Reagents and conditions (c): DIPEA, THF, reflux, 20 h

EXAMPLE 2

N^4-[3-(dimethylamino)-2,2-dimethylpropyl]-N^2-[3-(trifluoromethyl)phenyl]pyrimidine-2,4-diamine hydrochloride (7)

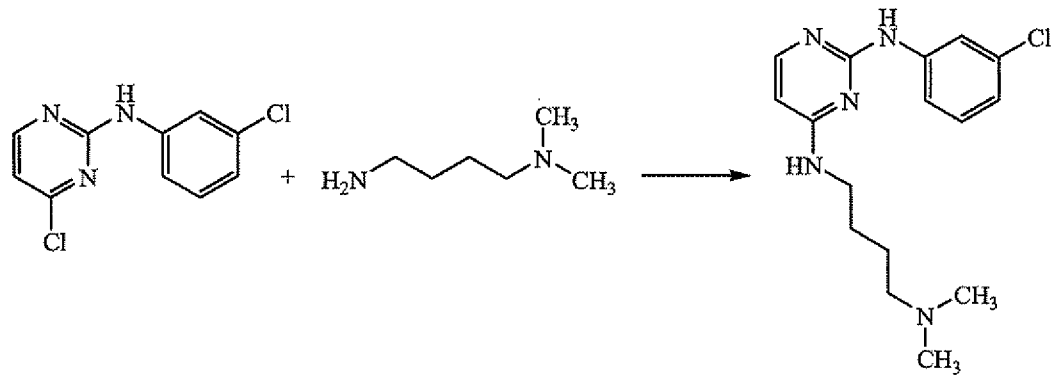
Preparation of 2-(3-trifluoromethylphenylamino)pyrimidin-4(3*H*)-one (5): To 2-(methyl-thio)pyrimidine-4(3*H*)-one, 1, (5 g, 35.21 mmol) in diglyme (25 mL) is added 3-trifluoromethylaniline (5.26 mL, 42.25 mmol). The resulting mixture is heated to reflux and stirred for 18 hours. A solid forms upon cooling the mixture to room temperature. The solid is washed with hexanes to afford 1.9 g (21 % yield) of the desired compound. MS (ESI, pos. ion) *m/z*: 256 (M+1).

Preparation of 4-chloro-*N*-(3-trifluoromethylphenyl)pyrimidin-2-amine (6): To 2-(3-chloro-phenylamino)pyrimidin-4(3*H*)-one, 5, (1.9 g, 7.4 mmol) and *N,N*-dimethyl-

aniline (2 mL) is added of phosphorus oxychloride (20 mL). The resulting mixture is heated to reflux for 15 minutes, cooled to room temperature and concentrated *in vacuo*. The residue is neutralized to pH 7 with 1M NaOH (aqueous). The organic layer is extracted with ethyl acetate (3 x 50mL). The combined organic layers are dried ($MgSO_4$) and concentrated *in vacuo*. The residue is purified over silica (5% EtOAc in hexanes) to afford 0.62 g (31 % yield) of the desired compound. ^{1}H NMR (DMSO-d_6, 300MHz): δ 7.07 (d, J = 6.3 Hz, 1H), 7.34 (d, J = 8.4 Hz, 1H), 7.55 (t, J = 8.1 Hz, 1H), 7.96 (d, J = 8.4 Hz, 1H), 8.20 (s, 1H), 8.52 (d, J = 6.0 Hz, 1H), 10.40 (s, 1H). ^{19}F NMR (DMSO-d_6, 282 MHz): δ 101.67 (s, 3F).

Preparation of N^4-[3-(dimethylamino)-2,2-dimethylpropyl]-N^2-[3-(trifluoromethyl)phenyl]pyrimidine-2,4-diamine hydrochloride (7): 4-Chloro-*N*-(3-(trifluoromethyl)phenyl)pyrimidin-2-amine, 6, (200 mg, 0.73 mmol), N^1,N^1,2,2-tetramethylpropane-1,3-diamine (0.232 mL, 1.46 mmol), and diisopropylethylamine (0.254 mL, 1.46 mmol) are dissolved in THF (5 mL) and heated to reflux for 20 hours. The reaction is cooled to room temperature and partitioned between EtOAc and water. The organic layer is dried ($MgSO_4$), concentrated *in vacuo*, and purified over silica (5% MeOH ramped to 6% MeOH in CH_2Cl_2 with 0.7% added triethylamine) to give an oil. The oil is dissolved in MeOH (0.5 mL) and Et_2O (20 mL) and cooled to 0 °C. To this solution is added a solution of 4M HCl in dioxane (0.25 mL) in one portion. The white precipitate which forms is collected by filtration and dried at reduced pressure to afford the desired compound as a white solid: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.09 (s, 6H), 2.81 (s, 3H), 2.83 (s, 3H), 3.11 (d, J = 4.2 Hz, 2H), 3.38-3.50 (m, 2H), 6.48 (d, J = 7.2 Hz, 1H), 7.51 (d, J = 7.5 Hz, 1H), 7.66 (t, J = 7.5 Hz, 1H), 7.74 (d. J = 6.6 Hz, 1H), 7.91 (d, J = 7.2 Hz, 1H), 8.20 (s, 1H), 9.67 (bs, 1H), 10.80 (bs, 1H); HRMS calcd for $C_{18}H_{24}F_3N_5$, 368.2062 *m/z* $(M+H)^+$; observed 368.2072 *m/z*.

Scheme III



3 8

Reagents and conditions (a): DIPEA, THF, reflux, 18 h

EXAMPLE 3

N^2-(3-chlorophenyl)-N^4-(4-(dimethylamino)butyl)pyrimidine-2,4-diamine (8)

Preparation of N^2-(3-chlorophenyl)-N^4-(4-(dimethylamino)butyl)pyrimidine-2,4-diamine(8): To 4-chloro-*N*-(3-chlorophenyl)pyrimidin-2-amine (0.2 g, 0.84 mmol) in THF (4 mL) is added diisopropylethylamine (0.29 mL, 1.67 mmol) followed by 4-dimethylaminobutylamine (0.2 g, 1.67 mmol). The resulting mixture is heated to reflux for 6 hours. Another 2 equivalents of 4-dimethylaminobutylamine (0.2 g, 1.67 mmol) are added and the reaction heated at reflux for 18 hours. The reaction is cooled to room temperature and concentrated *in vacuo*. The residue is diluted with water (5 mL) and extracted with EtOAc (3 x 25 mL). The combined organic layers are dried ($MgSO_4$) and concentrated *in vacuo*. This residue is purified over silica (5% MeOH in CH_2Cl_2 with 0.7% Et_3N) to afford 7 mg (3% yield) of the desired compound. ^1H NMR (CD_3OD, 300 MHz): δ 1.62-1.66 (m, 4H), 2.26 (s, 6H), 2.39-2.44 (m, 2H), 3.46-3.48 (m, 2H), 5.97 (d, *J*= 5.7 Hz, 1H), 6.93 (d, *J* = 8.1 Hz, 1H), 7.22 (t, *J*= 8.1 Hz, 1H), 7.40 (d, *J* = 8.1 Hz, 1H), 7.75 (d, *J* = 5.7 Hz, 1H), 8.06 (s, 1H). MS (ESI, pos. ion) *m/z*: 320 (M+1).

The following are non-limiting examples of compounds which comprise Category II of the present invention, the characterization of which will assist the formulator in

establishing the chemical formulae of compounds which are not specifically exemplified herein.

N^2-(3-chlorophenyl)-N^4-(2-(dimethylamino)ethyl)pyrimidine-2,4-diamine. ^{1}H NMR (CD_3OD, 300 MHz): δ 2.33 (s, 6H), 2.62 (t, J = 6.0 Hz, 2H), 3.58 (t, J = 6.0 Hz, 2H), 5.99 (d, J = 6.0 Hz, 1H), 6.95 (d, J = 8.1 Hz, 1H), 7.23 (t, J = 8.1 Hz, 1H), 7.44 (d, J = 8.1 Hz, 1H), 7.78 (d, J = 6.0 Hz, 1H), 7.95 (s, 1H). MS (ESI, pos. ion) *m/z*: 292 (M+1).

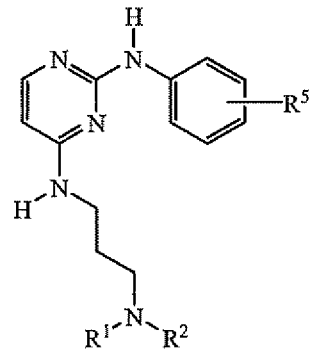
N^4-(3-aminopropyl)-N^2-(3-chlorophenyl)-N^4-methylpyrimidine-2,4-diamine: ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.88-1.92 (m, 2H), 2.78-2.84 (m, 2H), 3.13 (s, 3H), 3.62-3.68 (m, 2H), 3.43 (br s, 1H), 7.06-7.08 (m, 1H), 7.30-7.38 (m, 1H), 7.50-7.53 (m, 1H), 7.93-8.04 (m, 4H), 10.25 (br s, 1H). MS (ESI, pos. ion) *m/z*: 292 (M+1).

Further compounds which are encompassed within Category II of the present invention but which are not fully exemplified include:

N^2-(3-chlorophenyl)-N^4-(4-(dimethylamino)butyl)pyrimidine-2,4-diamine;
N^4-(2-(dimethylamino)ethyl)-N^2-(2-fluorophenyl)pyrimidine-2,4-diamine;
N^4-(2-(dimethylamino)ethyl)-N^2-(3-fluorophenyl)pyrimidine-2,4-diamine;
N^4-(2-(dimethylamino)ethyl)-N^2-(4-fluorophenyl)pyrimidine-2,4-diamine;
N^4-(2-(dimethylamino)ethyl)-N^2-(2,3-difluorophenyl)pyrimidine-2,4-diamine;
N^4-(2-(dimethylamino)ethyl)-N^2-(2,4-difluorophenyl)pyrimidine-2,4-diamine;
N^4-(2-(dimethylamino)ethyl)-N^2-(2,5-difluorophenyl)pyrimidine-2,4-diamine;
N^4-(2-(dimethylamino)ethyl)-N^2-(2,6-difluorophenyl)pyrimidine-2,4-diamine;
N^4-(2-(dimethylamino)ethyl)-N^2-(2-chlorophenyl)pyrimidine-2,4-diamine;
N^4-(2-(dimethylamino)ethyl)-N^2-(4-fluorophenyl)pyrimidine-2,4-diamine;
N^4-(2-(dimethylamino)ethyl)-N^2-(2,3-dichlorophenyl)pyrimidine-2,4-diamine;
N^4-(2-(dimethylamino)ethyl)-N^2-(2,4-dichlorophenyl)pyrimidine-2,4-diamine;
N^4-(2-(dimethylamino)ethyl)-N^2-(2,5-dichlorophenyl)pyrimidine-2,4-diamine;
N^4-(2-(dimethylamino)ethyl)-N^2-(2,6-dichlorophenyl)pyrimidine-2,4-diamine;

N^4-(2-(dimethylamino)ethyl)-N^2-(2-methylphenyl)pyrimidine-2,4-diamine;
N^4-(2-(dimethylamino)ethyl)-N^2-(3-methylphenyl)pyrimidine-2,4-diamine;
N^4-(2-(dimethylamino)ethyl)-N^2-(4-methylphenyl)pyrimidine-2,4-diamine;
N^4-(2-(dimethylamino)ethyl)-N^2-(2,3-dimethylphenyl)pyrimidine-2,4-diamine;
N^4-(2-(dimethylamino)ethyl)-N^2-(2,4-dimethylphenyl)pyrimidine-2,4-diamine;
N^4-(2-(dimethylamino)ethyl)-N^2-(2,5-dimethylphenyl)pyrimidine-2,4-diamine;
N^4-(2-(dimethylamino)ethyl)-N^2-(2,6-dimethylphenyl)pyrimidine-2,4-diamine;
N^4-(2-(dimethylamino)ethyl)-N^2-(3,4-dimethylphenyl)pyrimidine-2,4-diamine;
N^2-(3-chlorophenyl)-N^4-(4-(dimethylamino)butyl)pyrimidine-2,4-diamine;
N^4-(4-(dimethylamino)butyl)-N^2-(2-fluorophenyl)pyrimidine-2,4-diamine;
N^4-(4-(dimethylamino)butyl)-N^2-(3-fluorophenyl)pyrimidine-2,4-diamine;
N^4-(4-(dimethylamino)butyl)-N^2-(4-fluorophenyl)pyrimidine-2,4-diamine;
N^4-(4-(dimethylamino)butyl)-N^2-(2,3-difluorophenyl)pyrimidine-2,4-diamine;
N^4-(4-(dimethylamino)butyl)-N^2-(2,4-difluorophenyl)pyrimidine-2,4-diamine;
N^4-(4-(dimethylamino)butyl)-N^2-(2,5-difluorophenyl)pyrimidine-2,4-diamine;
N^4-(4-(dimethylamino)butyl)-N^2-(2,6-difluorophenyl)pyrimidine-2,4-diamine;
N^4-(4-(dimethylamino)butyl)-N^2-(2-chlorophenyl)pyrimidine-2,4-diamine;
N^4-(4-(dimethylamino)butyl)-N^2-(4-chlorophenyl)pyrimidine-2,4-diamine;
N^4-(4-(dimethylamino)butyl)-N^2-(2,3-dichlorophenyl)pyrimidine-2,4-diamine;
N^4-(4-(dimethylamino)butyl)-N^2-(2,4-dichlorophenyl)pyrimidine-2,4-diamine;
N^4-(4-(dimethylamino)butyl)-N^2-(2,5-dichlorophenyl)pyrimidine-2,4-diamine;
N^4-(4-(dimethylamino)butyl)-N^2-(2,6-dichlorophenyl)pyrimidine-2,4-diamine;
N^4-(4-(dimethylamino)butyl)-N^2-(2-methylphenyl)pyrimidine-2,4-diamine;
N^4-(4-(dimethylamino)butyl)-N^2-(4-methylphenyl)pyrimidine-2,4-diamine;
N^4-(4-(dimethylamino)butyl)-N^2-(2,3-dimethylphenyl)pyrimidine-2,4-diamine;
N^4-(4-(dimethylamino)butyl)-N^2-(2,4-dimethylphenyl)pyrimidine-2,4-diamine;
N^4-(4-(dimethylamino)butyl)-N^2-(2,5-dimethylphenyl)pyrimidine-2,4-diamine;
N^4-(4-(dimethylamino)butyl)-N^2-(2,6-dimethylphenyl)pyrimidine-2,4-diamine;
and
N^4-(4-(dimethylamino)butyl)-N^2-(3,4-dimethylphenyl)pyrimidine-2,4-diamine.

The compounds which comprise Category III of the present invention are 2-(substituted phenylamino)-4-(amino- or substituted amino-propylene)aminopyrimidines having the formula:



wherein R^5 is substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heterocyclic, and R^1, and R^2 are defined herein below in Table IIII.

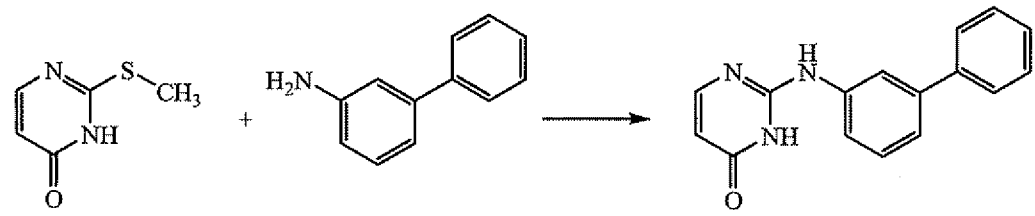
TABLE III

No	R^5	R^1	R^2
85	3-phenyl	–H	–H
86	3-phenyl	$-CH_3$	–H
87	3-phenyl	$-CH_3$	$-CH_3$
88	3-phenyl	$-CH_2CH_3$	–H
89	3-phenyl	$-CH_2CH_3$	$-CH_3$
90	3-phenyl	$-CH_2CH_3$	$-CH_2CH_3$
91	4-phenyl	–H	–H
92	4-phenyl	$-CH_3$	–H
93	4-phenyl	$-CH_3$	$-CH_3$
94	4-phenyl	$-CH_2CH_3$	–H
95	4-phenyl	$-CH_2CH_3$	$-CH_3$
96	4-phenyl	$-CH_2CH_3$	$-CH_2CH_3$
97	thiazol-4-yl	–H	–H
98	thiazol-4-yl	$-CH_3$	–H

99	thiazol-4-yl	$-CH_3$	$-CH_3$
100	thiazol-4-yl	$-CH_2CH_3$	–H
101	thiazol-4-yl	$-CH_2CH_3$	$-CH_3$
102	thiazol-4-yl	$-CH_2CH_3$	$-CH_2CH_3$
103	2-methylthiazol-4-yl	–H	–H
104	2-methylthiazol-4-yl	$-CH_3$	–H
105	2-methylthiazol-4-yl	$-CH_3$	$-CH_3$
106	2-methylthiazol-4-yl	$-CH_2CH_3$	–H
107	2-methylthiazol-4-yl	$-CH_2CH_3$	$-CH_3$
108	2-methylthiazol-4-yl	$-CH_2CH_3$	$-CH_2CH_3$
109	imidazol-2-yl	–H	–H
110	imidazol-2-yl	$-CH_3$	–H
111	imidazol-2-yl	$-CH_3$	$-CH_3$
112	imidazol-2-yl	$-CH_2CH_3$	–H
113	imidazol-2-yl	$-CH_2CH_3$	$-CH_3$
114	imidazol-2-yl	$-CH_2CH_3$	$-CH_2CH_3$
115	imidazol-4-yl	–H	–H
116	imidazol-4-yl	$-CH_3$	–H
117	imidazol-4-yl	$-CH_3$	$-CH_3$
118	imidazol-4-yl	$-CH_2CH_3$	–H
119	imidazol-4-yl	$-CH_2CH_3$	$-CH_3$
120	imidazol-4-yl	$-CH_2CH_3$	$-CH_2CH_3$
121	2-methylimidazol-4-yl	–H	–H
122	2-methylimidazol-4-yl	$-CH_3$	–H
123	2-methylimidazol-4-yl	$-CH_3$	$-CH_3$
124	2-methylimidazol-4-yl	$-CH_2CH_3$	–H
125	2-methylimidazol-4-yl	$-CH_2CH_3$	$-CH_3$
126	2-methylimidazol-4-yl	$-CH_2CH_3$	$-CH_2CH_3$

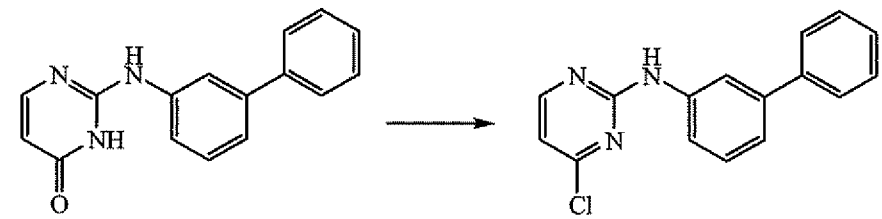
The compounds which comprise Category III of the present invention can be prepared by the following procedures outlined herein below in Scheme IV and V and Examples 4 and 5.

Scheme IV



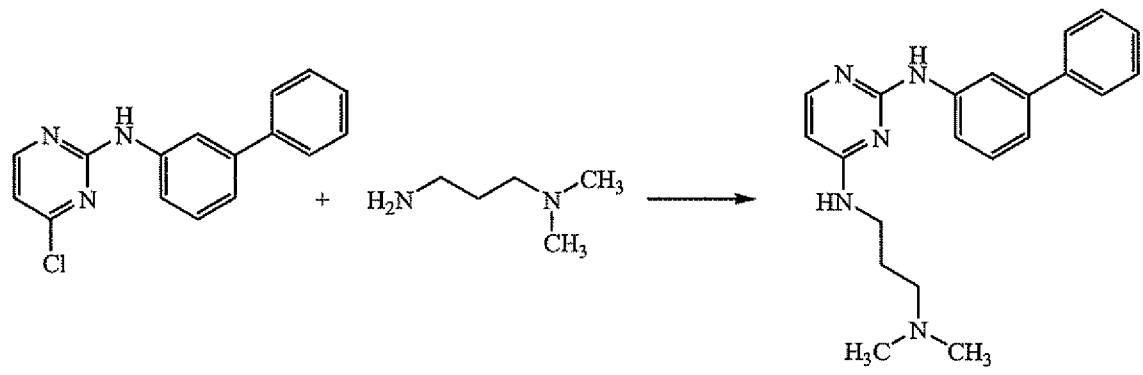
1 9

Reagents and conditions: (a) diglyme, reflux, 18 h.



9 10

Reagents and conditions (b): $POCl_3$, *N,N*-dimethylaniline, reflux, 1 hr.



10 11

Reagents and conditions (c): DIPEA, THF, reflux, 48 hr

EXAMPLE 4

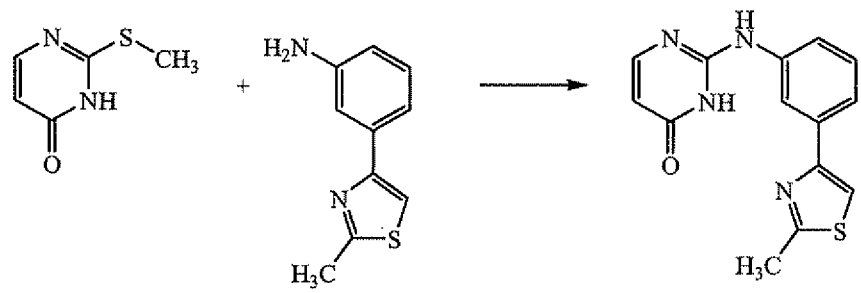
N^4-(3-(dimethylamino)propyl)-N^2-m-biphenylpyrimidine-2,4-diamine hydrochloride (11)

Preparation of 2-(3-biphenylamino)pyrimidin-4(3*H*)-one (9): To 2-(methylthio)-pyrimidine-4(3*H*)-one, 1, (790 mg, 5.5 mmol) in diglyme (5 mL) is added 3-amino-biphenyl (1.91 g, 11.2 mmol). The resulting mixture is stirred at reflux for 18 hours. The mixture is cooled to room temperature and hexane is added and a precipitate forms which is collected by filtration to afford 1.34 g (92% yield) of the desired compound which is used without further purification. MS (ESI, pos. ion) *m/z*: 264 (M+1).

Preparation of 4-chloro-*N*-(3-biphenyl)pyrimidin-2-amine (10): To 2-(3-biphenyl-amino)pyrimidin-4(3*H*)-one, 9, (1.34 g, 5.0 mmol), and *N,N*-dimethylaniline (1.5 mL) is added phosphorus oxychloride (10 mL). The resulting mixture is heated to reflux, stirred for 1 hour, cooled to room temperature and concentrated *in vacuo*. The residue is neutralized to pH 7 with 1M NaOH (aqueous). The organic layer is extracted with EtOAc (2 x 50 mL). The combined organic layers are washed once with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue is purified over silica (5% EtOAc in hexanes) to afford 780 mg (54% yield) of the desired compound. MS (ESI, pos. ion) *m/z*: 282 (M+1).

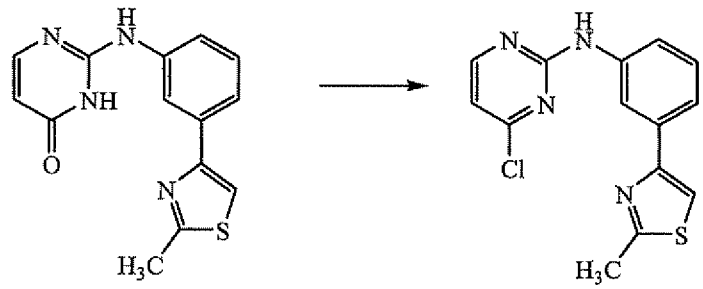
Preparation of N^2-(3-biphenyl)-N^4-(3-(dimethylamino)propyl)pyrimidine-2,4-diamine hydrochloride (11): To 4-chloro-*N*-(3-biphenyl)pyrimidin-2-amine, 10, (102 mg, 0.38 mmol) in THF (5 mL) is added N,N-diisopropylethylamine (0.15 mL, 0.84 mmol) followed by 3-(dimethylamino)propylamine (0.15 mL, 1.2 mmol). The resulting mixture is heated to reflux for 48 hours. The reaction is cooled to room temperature and concentrated *in vacuo* to afford a residue which is purified over silica (95:3:2 CH_2Cl_2/ MeOH/7N NH_3 in MeOH) to afford 61 mg (48% yield) of the desired compound. The hydrochloride salt can be formed by treatment of the neutral compound with HCl in dioxane (4M). ^{1}H NMR (CD_3OD, 300 MHz): δ(ppm) 1.74 (m, 2H), 2.15 (s, 6H), 2.27 (t, J = 6.0 Hz, 2H), 3.40 (m, 2H), 5.94 (d, J = 6.0 Hz, 1H), 7.19 (d, J = 7.2 Hz, 1H), 7.34 (m, 2H), 7.42 (m, 2H), 7.53 (d, J = 7.5 Hz, 1H), 7.61 (m, 2H), 7.76 (d, J = 5.4 Hz, 1H), 8.12 (s, 1H). MS (ESI, pos. ion) *m/z*: 348 (M+1).

Scheme V



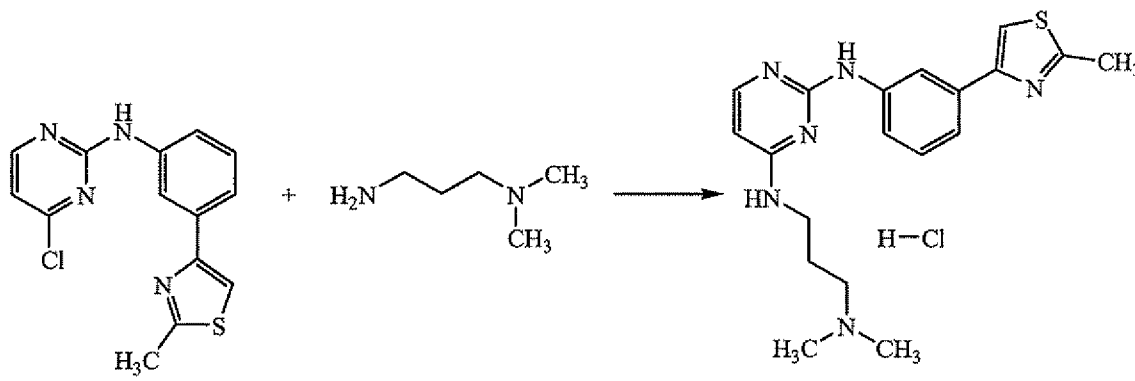
1 11

Reagents and conditions: (a) diglyme, reflux, 18 h.



11 12

Reagents and conditions (b): $POCl_3$, *N,N*-dimethylaniline, reflux, 15 min.



12 13

Reagents and conditions (c): DIPEA, THF, reflux, 20 hr.

EXAMPLE 5

N^4-(3-(dimethylamino)propyl)-N^2-(3-(2-methylthiazol-4-yl)phenyl)pyrimidine-2,4-diamine hydrochloride (13)

Preparation of 2-(3-(2-methylthiazol-4-yl)phenylamino)pyrimidin-4(3H)-one (11): To 2-(methyl-thio)pyrimidine-4(3*H*)-one, 1, (1 g, 14.08 mmol) in diglyme (9 mL) is added 3-(2-methylthiazol-4-yl)benzenamine (3.20 g, 16.90 mmol). The resulting mixture is heated to reflux and stirred for 18 hours. A solid forms upon cooling the mixture to room temperature. The solid is washed with hexanes to afford 1.0 g (25 % yield) of the desired compound. MS (ESI, pos. ion) *m/z*: 285 (M+1).

Preparation of 4-chloro-*N*-(3-(2-methylthiazol-4-yl)phenyl)pyrimidin-2-amine (12): To 2-(3-(2-methylthiazol-4-yl)phenylamino)pyrimidin-4(3H)-one, 11, (1.0 g, 3.5 mmol) and *N,N*-dimethyl-aniline (1 mL) is added phosphorus oxychloride (9.5 mL). The resulting mixture is heated to reflux for 15 minutes, cooled to room temperature and concentrated *in vacuo*. The residue is neutralized to pH 7 with 1M NaOH (aqueous). The organic layer is extracted with ethyl acetate (3 x 50mL). The combined organic layers are dried ($MgSO_4$) and concentrated *in vacuo*. The residue is purified over silica (5% EtOAc in hexanes) to afford 0.50 g (47 % yield) of the desired compound. ^{1}H NMR (DMSO-d_6, 300MHz): δ 2.73 (s, 3H), 6.98 (d, J = 5.1 Hz, 1H), 7.37 (t, J = 8.1 Hz , 1H), 7.57 (d, J = 8.1 Hz, 1H), 7.72 (d, J = 8.1 Hz, 1H), 7.83 (s, 1H), 8.25 (s, 1H), 8.46 (d, J = 5.1 Hz, 1H), 10.08 (s, 1H). MS (ESI, pos. ion) *m/z*: 303 (M+1).

Preparation of N^4-(3-(dimethylamino)propyl)-N^2-(3-(2-methylthiazol-4-yl)phenyl)pyrimidine-2,4-diamine hydrochloride (13): 4-chloro-*N*-(3-(2-methylthiazol-4-yl)phenyl)pyrimidin-2-amine, 12, (400 mg, 1.30 mmol), N^1,N^1-dimethylpropane-1,3-diamine (0.25 mL, 2.0 mmol), and diisopropylethylamine (0.46 mL, 2.6 mmol) are dissolved in THF (10 mL) and heated to reflux for 20 hours. The reaction is cooled to room temperature and partitioned between EtOAc and water. The organic layer is dried ($MgSO_4$), concentrated *in vacuo*, and purified over silica (5% MeOH ramped to 6% MeOH in CH_2Cl_2 with 0.7% added triethylamine) to give an oil. The oil is dissolved in

MeOH (0.5 mL) and Et_2O (20 mL) and cooled to 0 °C. To this solution is added a solution of 4M HCl in dioxane (0.25 mL) in one portion. The white precipitate which forms is collected by filtration and dried at reduced pressure to afford the desired compound as a white solid: ^{1}H NMR (CD_3OD, 300 MHz) δ 2.03-2.08 (m, 2H), 2.79 (s, 6H), 2.80 (s, 3H), 3.10-3.15 (m, 2H), 3.65 (t, J = 6.6 Hz, 2H), 6.30 (d, J = 7.5 Hz, 1H), 7.45 (d, J = 7.8 Hz, 1H), 7.54 (t, J = 7.8 Hz, 1H), 7.70 (d. J = 7.5 Hz, 1H), 7.77 (s, 1H), 7.82 (d, J = 7.8 Hz, 1H), 8.19 (s, 1H); HRMS calcd for $C_{19}H_{24}N_6S$, 369.1861 *m/z* $(M+H)^+$; observed 369.1855 *m/z*.

The compounds of the present invention are inhibitors of Protein Kinase C-alpha (PKC-α), therefore, they are PKC-α inhibitors which are capable of improving myocardial contraction and relaxation performance and slow the progression of heart failure. The compounds potentially inhibit additional isoforms of conventional PKC, such as PKC-β or PKc–γ. This is not undesired and can lead to increased pharmacological effects.

The level of disease, for example, the relative degree of heart failure due to PKC-α activity will vary from patient to patient and be predicated by other exacerbating circumstances, *inter alia*, presence of other disease conditions (diabetes, high blood pressure, and the like) or patients may suffer from other conditions such as obesity. Therefore, the formulator may be required to employ differing levels or amounts of the compounds described herein to obtain a therapeutic level. The formulator can determine this amount by any of the known testing procedures known to the artisan.

FORMULATIONS

The present invention also relates to compositions or formulations which comprise the PKC-α inhibitors according to the present invention. In general, the compositions of the present invention comprise:

a) an effective amount of one or more 2-arylamino-4-(aminoalkylene)amino-pyrimidines or salts thereof according to the present invention which are effective for inhibiting PKC-α; and

b) one or more excipients.

For the purposes of the present invention the term "excipient" and "carrier" are used interchangeably throughout the description of the present invention. One aspect of excipient and carrier relate to their definition in terms of a medicament, said terms are defined in that respect as, "ingredients which are used in the practice of formulating a safe and effective pharmaceutical composition."

The formulator will understand that excipients are used primarily to serve in delivering a safe, stable, and functional pharmaceutical, serving not only as part of the overall vehicle for delivery but also as a means for achieving effective absorption by the recipient of the active ingredient. An excipient may fill a role as simple and direct as being an inert filler, or an excipient as used herein may be part of a pH stabilizing system or coating to insure delivery of the ingredients safely to the stomach. The formulator can also take advantage of the fact the compounds of the present invention have improved cellular potency, pharmacokinetic properties, as well as improved oral bioavailability.

Non-limiting examples of compositions according to the present invention include:

a) from about 0.001 mg to about 1000 mg of one or more PKC-α inhibitors according to the present invention; and

b) one or more excipient.

Another embodiment according to the present invention relates to the following compositions:

a) from about 0.01 mg to about 100 mg of one or more PKC-α inhibitors according to the present invention; and

b) one or more excipient.

A further embodiment according to the present invention relates to the following compositions:

a) from about 0.1 mg to about 10 mg of one or more PKC-α inhibitors according to the present invention; and

b) one or more excipient.

The term "effective amount" as used herein means "an amount of one or more PKC-α inhibitors, effective at dosages and for periods of time necessary to achieve the desired result." An effective amount may vary according to factors known in the art, such as the disease state, age, sex, and weight of the human or animal being treated. Although particular dosage regimes may be described in examples herein, a person skilled in the art would appreciated that the dosage regime may be altered to provide optimum therapeutic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation. In addition, the compositions of the present invention can be administered as frequently as necessary to achieve a therapeutic amount.

METHOD OF USE

The present invention also relates to a method for improving cardiac contraction/relaxation parameters in heart failure patients and/or attenuating adverse cardiac remodeling and prevent or slow the progression of worsening heart failure. The present method comprises the step of administering to a human or higher mammal an effective amount of a composition comprising one or more of the PKC-α inhibitors according to the present invention.

A present invention also relates to a method of treating or preventing chronic or acute heart failure, said method comprised of the step of administering to a patient in need thereof a pharmaceutically acceptable amount of a compound according to claim 1 or a therapeutically acceptable salt thereof in combination with a drug selected that acts on the renin-angiotensin-aldosterone system, a diuretic, digoxin or a β-adrenergic receptor blockers, natriuretic peptides and inotropic agents.

The present invention also relates to the use of the 2-arylamino-4-(amino-alkylene)amino-pyrimidines or salts thereof, according to the present invention in the manufacture of a medicament for the treatment of heart disease wherein inhibition of PKC-α provides a benefit.

PROCEDURES

Assessment of PKC-α Inhibitory Activity

Measurement of PKCα enzyme activity is performed using full-length human PKCα enzyme (Upstate Biotechnology) at a final concentration of 0.12 μg/ml in a kinase assay buffer (0.09 mg/ml bovine serum albumin (BSA), 210μM ethylenediaminetetraacetic acid (EDTA), 360μM $CaCl_2$, 1mM Tris-HCl, pH=7.5, 0.5 mM $MgCl_2$, 0.015 mg/ml phosphatidylserine and 0.015 mg/ml diacylglycerol). The reaction is initiated by addition of adenosine triphosphate (ATP; final concentration 45μM) and a peptide substrate consisting of amino acids 28-43 (Ala-Ala-Lys-Ile-Gln-Ala-Ser-Phe-Arg-Gly-His-Met-Ala-Arg-Lys-Lys) of neurogranin (Promega; final concentration 22 μM). After a 30 minute incubation at 24°C the reaction is terminated by adding 5μL of the reaction mixture into 50 μL of MALDI matrix solution (5mg/ml α-cyano-4-hydroxycinnamic acid in 50% Acetonitrile/H_2O, 0.1% TFA, 5mM ammonium phosphate). Two microliters of the stopped reaction mixture is transferred onto a MALDI-TOF mass spectrometer target plate.

All spectra are collected on an Applied Biosystems 4700 Proteomics Analyzer MALDI-TOF MS equipped with a Nd:YAG laser (355 nm, 3 ns pulse width, 200 Hz repetition rate) in negative ion reflector mode. The system is operated with 4700 Explorer software, version 3.0. Automated acquisition parameters are adjusted to capture and average only those individual spectra within defined success criteria. Specifically, signal intensities for the substrate peptide are set to a minimum threshold of 3000 counts and a maximum intensity of 65,000 counts. This ensured that neither null spectra nor saturated spectra are averaged into the final readout. Between 1000 and 1500 laser shots are averaged for each sample. Data are collected in triplicate from 3 successive days to capture the maximum variability related to preparation of enzyme reaction, transfer of samples to MALDI target plates, data collection, and data extraction.

The isotope cluster areas for each peptide substrate and product peaks are extracted into a Microsoft Excel worksheet from the 10 x 10 array of spectral data simultaneously using the automated analysis function provided within the 4700 Explore

software. The isotope cluster area is defined by the software algorithm based on the molecular weight and the general elemental composition of the peptides. The percent conversion (%C) of substrate to product is calculated as the cluster area of the product (P) divided by the sum of the cluster areas of the substrate (S) and the product multiplied by 100 as represented by the following equation:

$$\%\,C = \frac{P}{P+S} \times 100$$

For dose-dependent inhibition studies, the inhibition is plotted as a % Maximal Activity (%MA). Equation one is a measure of the ratio of product to substrate then solving for the %C. However, to measure inhibition of the enzyme activity, one must measure the degree to which that activity (%C) is curtailed. Thus the dose-dependant inhibition data is plotted as %MA where the maximal activity is the %C measured in control reactions with no inhibitor as represented by the following equation:

$$\%\,MA = \frac{\%\,C \text{ with inhibitor}}{\%\,C \text{ with no inhibitor}} \times 100$$

Evaluation of PKCα Inhibitors in Cardiomyocytes.

Determination of PKCα activity in cells is determined using murine HL-1 atrial cardiac muscle cells. On day 1, HL-1 cells are plated at 18,000 cells/well in a 96-well tissue culture plate. Cells are cultured in 0.1 ml Claycomb growth medium (without norepinephrine) supplemented with 10% fetal bovine serum, 200mM glutamine and 1% antibiotic/antimycotic. On day 2, cells are washed 1x with 100µl of phosphate buffered saline (PBS) and the medium is replaced with 100µl serum free Claycomb medium supplemented with 200mM glutamine. For compound testing, the medium is removed and replaced with serum free Claycomb medium supplemented with 200mM glutamine containing different concentrations of compound at a final volume of 50µl. Compounds are dissolved in 100% dimethylsulfoxide (DMSO) and final DMSO concentrations are maintained at 0.5%. Plates are then incubated for 30 minutes at 37°C in a 5%CO_2 incubator. The medium is then removed and the plates are rinsed 1x with ice-cold 100 µl PBS. The PBS is removed and replaced with 10µl of ice-cold lysis buffer consisting of B-PERII detergent (Pierce) diluted 1:1 in distilled water and including a final concentration

of 0.3% β-mercaptoethanol, 50μg/ml phenylmethylsulfonylfluoride (PMSF) 10mM benzamidine, 10nM okadaic acid, 20μg/ml leupeptin and 20μg/ml soybean trypsin inhibitor. The plates are gently mixed for 10-20 minutes at 4°C. Next, 90μl of coactivation buffer, consisting of 0.1mg/ml BSA, 250μM EDTA, 400μM $CaCl_2$, is added to each well. Twenty-five microliters of the cell lysate/coactivation buffer solution is removed from each well and the enzyme activity measured by addition of 25μl of substrate solution, consisting of 0.1 mg/ml bovine serum albumin, 235μM EDTA, 400μM $CaCl_2$, 1mM Tris-HCl, pH=7.5, 0.5 mM $MgCl_2$, 0.015 mg/ml phosphatidylserine and 0.015 mg/ml diacylglycerol, 20μM ATP and 2μM of an octapeptide fragment of the EGF receptor (Arg-Lys-Arg-Thr-Leu-Arg-Arg-Leu). After a 30 minute incubation at 24°C the reaction is terminated by adding 5μL of the reaction mixture into 50 μL of MALDI matrix solution (5mg/ml α-cyano-4-hydroxycinnamic acid in 50% Acetonitrile/H_2O, 0.1% TFA, 5mM ammonium phosphate). Two microliters of the stopped reaction mixture is transferred onto a MALDI-TOF mass spectrometer target plate. Dose-dependent inhibition is measured by mass spectrometry as % maximal activity as described above for the isolated PKCα inhibition assays.

In Vivo Evaluation of PKCα Inhibitors in the Anesthetized Rat.

Selected PKCα inhibitors are evaluated in rats with acute heart failure (HF) after myocardial infarction (MI) for effects on cardiac contractility and hemodynamics. Male, Sprague-Dawley rats are anesthetized with isoflurane, intubated, placed on ventilators and maintained at a surgical plane of anesthesia during the course of the experiment. The animals are instrumented, for the measurement of left ventricular function (+dP/dt, LVDP), arterial blood pressure, and the ECG is monitored for the incidence of arrhythmias. A thoracotomy is performed at the fourth intercostal space to visualize the heart, the pericardium is opened and a suture is placed around the left anterior descending (LAD) coronary artery approximately 3-4 mm from its origin. When hemodynamic values are stabilized, the LAD is permanently ligated to induce a myocardial infarction. Severe arrhythmia are treated with the administration of lidocaine. Typically, cardiac function stabilized approximately 40-60 min after ligation and baseline hemodynamic

values are measured. N^2-(3-chlorophenyl)-N^4-(3-(dimethylamino)propyl)pyrimidine-2,4-diamine, 100 and 300 nmol/kg/min for 10 min each dose, and hemodynamic parameters are measured after each dose. The effects of treatment are normalized to pre-treatment baseline values and expressed as a percentage. Statistical significance ($p<0.05$) is evaluated using one-way ANOVA and Dunnett's multiple comparison test.

In Vivo Evaluation of PKCα Inhibitors in the Anesthetized Rat.

Selected PKCα inhibitors are evaluated in rats with myocardial infarction (MI) for effects on cardiac contractility and hemodynamics.

Male, Sprague-Dawley or Lewis rats weighing between 225-500 gm are anesthetized with isoflurane and an MI is induced as follows. A thoracotomy is performed at the fourth intercostal space to visualize the heart, the pericardium is opened and a suture is placed around the left anterior descending (LAD) coronary artery approximately 3-4 mm from its origin. When hemodynamic values are stabilized, the LAD is permanently ligated to induce a myocardial infarction. Severe arrhythmias are treated with the administration of lidocaine. Typically, cardiac function stabilized approximately 40-60 min after ligation and baseline hemodynamic values are measured.

The effects of inhibitors on cardiac contractility and hemodynamics are evaluated in MI rats as follows. The animals are anesthetized with isoflurane. A femoral artery is isolated and cannulated for the measurement of systemic blood pressure. A jugular vein is isolated and cannulated for the intravenous infusion of inhibitor. The right carotid artery is isolated and a Millar conductance catheter is inserted to the left ventricle (LV) of the heart. The LV systolic pressure, end-diastolic pressure, + dP/dt_{max}, - dP/dt_{min}, and heart rate are derived from the LV pressure waveform. Mean arterial blood pressure is derived from the systemic blood pressure waveform. Data are recorded continuously and derived using computerized data acquisition software (Notocord or Powerlab).

After a period of stabilization, PKC-α inhibitors are infused at the following infusion doses in MI rats: 10, 30, 100, 300 and 1000 nmol/kg/min. The infusion of each dose is allowed to run for at least five minutes. At the end of the test infusions, 5.0 μg/kg/min of dobutamine is infused. The effects of treatment are normalized to

pretreatment baseline values and expressed as a percentage. Statistical significance ($p<0.05$) is evaluated using a one-way ANOVA and Dunnett's multiple comparison test.

Table IV provides non-limiting examples of PKC-α IC_{50} values for representative compounds of the present invention.

TABLE IV

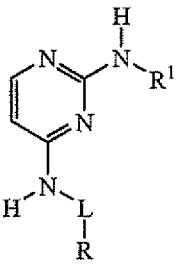
No.	Compound	PKC-α IC_{50} (nM)
1	N^2-(3-chlorophenyl)-N^4-(3-aminopropyl)pyrimidine-2,4-diamine	312
2	N^2-(3-chlorophenyl)-N^4-[3-(methylamino)propyl]pyrimidine-2,4-diamine	4
3	N^2-(3-chlorophenyl)-N^4-[3-(dimethylamino)propyl]pyrimidine-2,4-diamine	0.8
6	N^2-(3-chlorophenyl)-N^4-[3-(diethylamino)propyl]pyrimidine-2,4-diamine	1
15	N^2-(3,4-dichlorophenyl)-N^4-[3-(dimethylamino)propyl]pyrimidine-2,4-diamine	15
21	N^2-(3-chloro-4-methylphenyl)-N^4-[3-(dimethylamino)propyl]-pyrimidine-2,4-diamine	3
25	N^2-(3-chloro-2-fluorophenyl)-N^4-[3-(dimethylamino)propyl]-pyrimidine-2,4-diamine	23
27	N^2-(3-chloro-4-fluorophenyl)-N^4-[3-(dimethylamino)propyl]-pyrimidine-2,4-diamine	8
33	N^2-(3,4-difluorophenyl)-N^4-[3-(dimethylamino)propyl]-pyrimidine-2,4-diamine	65
39	N^2-(3-trifluoromethylphenyl)-N^4-[3-(dimethylamino)propyl]-pyrimidine-2,4-diamine	0.5
45	N^2-(3-trifluoromethyl-4-chlorophenyl)-N^4-[3-(dimethylamino)-propyl]pyrimidine-2,4-diamine	3

51	N^2-(3-methoxyphenyl)-N^4-[3-(dimethylamino)propyl]pyrimidine-2,4-diamine	14
55	N^2-(3-methylphenyl)-N^4-[3-(dimethylamino)propyl]pyrimidine-2,4-diamine	40
58	N^2-(3-methylphenyl)-N^4-[3-(dimethylamino)propyl]pyrimidine-2,4-diamine	93
69	N^2-(3-chlorophenyl)-N^4-[2-(dimethylamino)ethyl]pyrimidine-2,4-diamine	83
81	N^2-(3-chlorophenyl)-N^4-[4-(dimethylamino)butyl]pyrimidine-2,4-diamine	12
87	N^2-(biphenyl-3-yl)-N^4-[3-(dimethylamino)propyl]pyrimidine-2,4-diamine	0.4
105	N^2-[3-(2-methyl-thiazol-4-yl)phenyl]-N^4-[3-(dimethylamino)-propyl]pyrimidine-2,4-diamine	48

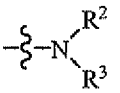
While particular embodiments of the present invention have been illustrated and described, it would be obvious to those skilled in the art that various other changes and modifications can be made without departing from the spirit and scope of the invention. It is therefore intended to cover in the appended claims all such changes and modifications that are within the scope of this invention.

WHAT IS CLAIMED IS:

1. A compound having the formula:



wherein **R** is a unit having the formula:



$\mathbf{R^2}$ and $\mathbf{R^3}$ are each independently chosen from:

i) hydrogen; or

ii) C_1-C_4 substituted or unsubstituted linear, branched, or cyclic alkyl;

L is a linking unit having the formula:

$$-[C(R^{4a}R^{4b})]_n-$$

each $\mathbf{R^{4a}}$ and $\mathbf{R^{4b}}$ is independently chosen from:

i) hydrogen; or

ii) C_1-C_4 linear, branched, or cyclic alkyl;

the index n is from 1 to 4; and

$\mathbf{R^1}$ is substituted or unsubstituted aryl;

excluding the compounds N^2-(4-chlorophenyl)-N^4-[(2-diethylamino)ethyl]-pyrimidine-2,4-diamine, N^2-(4-chlorophenyl)-N^4-[(3-diethylamino)propyl]-pyrimidine-2,4-diamine, and N^2-(4-methylphenyl)-N^4-[(2-diethylamino)ethyl]-pyrimidine-2,4-diamine.

2. A compound according to Claim 1 wherein $\mathbf{R^2}$ and $\mathbf{R^3}$ are each independently chosen from hydrogen, methyl, ethyl, n-propyl, *iso*-propyl, cyclopropyl, n-butyl, *iso*-butyl, *sec*-butyl, and *tert*-butyl.

3. A compound according to Claim 1 wherein R is a unit chosen from $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NH(CH_2CH_3)$, $-N(CH_2CH_3)_2$, $-N(CH_3)(CH_2CH_3)$, $-NH(CH_2CH_2CH_3)$, $-N(CH_3)(CH_2CH_2CH_3)$, $-N(CH_2CH_3)(CH_2CH_2CH_3)$, and $-N(CH_2CH_2CH_3)_2$.

4. A compound according to Claim 3 wherein **R** is a unit chosen from $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NH(CH_2CH_3)$, and $-N(CH_2CH_3)_2$.

5. A compound according to Claim 1 wherein $\mathbf{R^1}$ is a phenyl unit substituted with one or more units chosen from:

i) C_1-C_4 linear, branched, or cyclic alkyl;

ii) halogen;

iii) $-OR^6$;

iv) $-SO_2N(R^6)_2$;

v) $-CH_mX_n$; wherein each X is independently F, Cl, Br, or I, m is from 0 to 2, m+n =3; and

vi) $-NO_2$;

each $\mathbf{R^6}$ is independently hydrogen, C_1-C_4 linear, branched, or cyclic alkyl, or phenyl.

6. A compound according to Claim 5 wherein $\mathbf{R^1}$ is chosen from 3-chlorophenyl, 4-chlorophenyl, 3,4-dichlorophenyl, 3-chloro-4-methylphenyl, 3-chloro-4-fluorophenyl, 3,4-difluorophenyl, 3-trifluoromethylphenyl, 3-trifluoromethyl-4-chlorophenyl, 3-methoxyphenyl, 3-methylphenyl, 3-ethylphenyl, and 3-isopropylphenyl.

7. A compound according to Claim 5 wherein $\mathbf{R^1}$ is chosen from 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,3-difluorophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, 2,3,4-trifluorophenyl, 2,3,5-trifluorophenyl, 2,3,6-trifluorophenyl, 2,4,5-trifluorophenyl, 2,4,6-trifluorophenyl, 2-chlorophenyl,

2,3-dichlorophenyl, 2,4-dichlorophenyl, 2,5-dichlorophenyl, 2,6-dichlorophenyl, 2,3,4-trichlorophenyl, 2,3,5-trichlorophenyl, 2,3,6-trichlorophenyl, 2,4,5-trichlorophenyl, and 2,4,6-trichlorophenyl.

8. A compound according to Claim 5 wherein $\mathbf{R^1}$ is chosen from 2-methylphenyl, 4-methylphenyl, 2,3-dimethylphenyl, 2,4-dimethylphenyl, 2,5-dimethyl-phenyl, 2,6-dimethylphenyl, 3,4-dimethyl-phenyl, 2,3,4-trimethylphenyl, 2,3,5-trimethyl-phenyl, 2,3,6-trimethylphenyl, 2,4,5-trimethylphenyl, 2,4,6-trimethylphenyl, 2-ethylphenyl, 4-ethylphenyl, 2,3-diethylphenyl, 2,4-diethylphenyl, 2,5-diethylphenyl, 2,6-diethylphenyl, 3,4-diethylphenyl, 2,3,4-triethylphenyl, 2,3,5-triethylphenyl, 2,3,6-triethylphenyl, 2,4,5-triethylphenyl, and 2,4,6-triethylphenyl.

9. A compound according to Claim 5 wherein $\mathbf{R^1}$ is chosen from 2-methoxyphenyl, 4-methoxyphenyl, 2,3-dimethoxyphenyl, 2,4-dimethoxyphenyl, 2,5-dimethoxyphenyl, 2,6-dimethoxyphenyl, 3,4-dimethoxyphenyl, 2,3,4-trimethoxyphenyl, 2,3,5-trimethoxyphenyl, 2,3,6-trimethoxy-phenyl, 2,4,5-trimethoxyphenyl, 2,4,6-trimethoxyphenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 2,3-dihydroxyphenyl, 2,4-dihydroxyphenyl, 2,5-dihydroxyphenyl, 2,6-dihydroxyphenyl, 3,4-dihydroxy-phenyl, 2,3,4-trihydroxyphenyl, 2,3,5-trihydroxy-phenyl, 2,3,6-trihydroxyphenyl, 2,4,5-trihydroxyphenyl, and 2,4,6-trihydroxyphenyl.

10. A compound chosen from:

N^2-(3-chlorophenyl)-N^4-(3-(dimethylamino)propyl)pyrimidine-2,4-diamine;

N^2-(3-chlorophenyl)-N^4-(3-(diethylamino)propyl)pyrimidine-2,4-diamine;

N^4-(3-(dimethylamino)propyl)-N^2-(3-methoxyphenyl)pyrimidine-2,4-diamine;

N^4-(3-(dimethylamino)propyl)-N^2--(3-methylphenyl)pyrimidine-2,4-diamine;

N^4-(3-(dimethylamino)propyl)-N^2-(3-(trifluoromethyl)phenyl)pyrimidine-2,4-diamine;

N^2-(3-chlorophenyl)-N^4-(3-(methylamino)propyl)pyrimidine-2,4-diamine;

N^4-(3-aminopropyl)-N^2-(3-chlorophenyl)pyrimidine-2,4-diamine;
N^2-(3, 4-difluorophenyl)-N^4-(3-(dimethylamino)propyl)pyrimidine-2,4-diamine;
N^2-(3-chloro-4-methylphenyl)-N^4-(3-(dimethylamino)propyl)pyrimidine-2,4-diamine;
N^2-(3,4-dichlorophenyl)-N^4-(3-(dimethylamino)propyl)pyrimidine-2,4-diamine;
N^2-(3-chloro-4-fluorophenyl)-N^4-(3-(dimethylamino)propyl)pyrimidine-2,4-diamine;
N^2-(4-chloro-3-(trifluoromethyl)phenyl)-N^4-(3-(dimethylamino)propyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)propyl)-N^2-(3-ethylphenyl)pyrimidine-2,4-diamine;
N^4-[3-(dimethylamino)-2,2-dimethylpropyl]-N^2-[3-(trifluoromethyl)phenyl]-pyrimidine-2,4-diamine;
N^2-(3-chlorophenyl)-N^4-(3-(dimethylamino)butyl)pyrimidine-2,4-diamine;
N^2-(3-chlorophenyl)-N^4-(2-(dimethylamino)ethyl)pyrimidine-2,4-diamine; and
N^4-(3-aminopropyl)-N^2-(3-chlorophenyl)-N^4-methylpyrimidine-2,4-diamine.

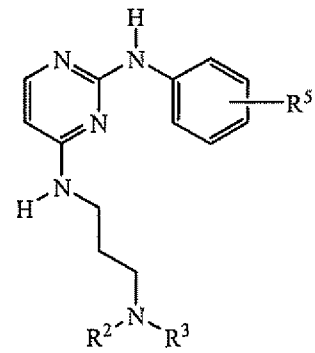
11. A compound chosen from:
N^4-(3-(dimethylamino)propyl)-N^2-(2-fluorophenyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)propyl)-N^2-(3-fluorophenyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)propyl)-N^2-(4-fluorophenyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)propyl)-N^2-(2,3-difluorophenyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)propyl)-N^2-(2,4-difluorophenyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)propyl)-N^2-(2,5-difluorophenyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)propyl)-N^2-(2,6-difluorophenyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)propyl)-N^2-(2-chlorophenyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)propyl)-N^2-(2,3-dichlorophenyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)propyl)-N^2-(2,4-dichlorophenyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)propyl)-N^2-(2,5-dichlorophenyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)propyl)-N^2-(2,6-dichlorophenyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)propyl)-N^2-(2-methylphenyl)pyrimidine-2,4-diamine;

N^4-(3-(dimethylamino)propyl)-N^2-(4-methylphenyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)propyl)-N^2-(2,3-dimethylphenyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)propyl)-N^2-(2,4-dimethylphenyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)propyl)-N^2-(2,5-dimethylphenyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)propyl)-N^2-(2,6-dimethylphenyl)pyrimidine-2,4-diamine; and
N^4-(3-(dimethylamino)propyl)-N^2-(3,4-dimethylphenyl)pyrimidine-2,4-diamine.

12. A compound chosen from:
N^2-(3-chlorophenyl)-N^4-(3-(dimethylamino)butyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)ethyl)-N^2-(2-fluorophenyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)ethyl)-N^2-(3-fluorophenyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)ethyl)-N^2-(4-fluorophenyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)ethyl)-N^2-(2,3-difluorophenyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)ethyl)-N^2-(2,4-difluorophenyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)ethyl)-N^2-(2,5-difluorophenyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)ethyl)-N^2-(2,6-difluorophenyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)ethyl)-N^2-(2-chlorophenyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)ethyl)-N^2-(4-fluorophenyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)ethyl)-N^2-(2,3-dichlorophenyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)ethyl)-N^2-(2,4-dichlorophenyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)ethyl)-N^2-(2,5-dichlorophenyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)ethyl)-N^2-(2,6-dichlorophenyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)ethyl)-N^2-(2-methylphenyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)ethyl)-N^2-(3-methylphenyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)ethyl)-N^2-(4-methylphenyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)ethyl)-N^2-(2,3-dimethylphenyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)ethyl)-N^2-(2,4-dimethylphenyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)ethyl)-N^2-(2,5-dimethylphenyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)ethyl)-N^2-(2,6-dimethylphenyl)pyrimidine-2,4-diamine;

N^4-(3-(dimethylamino)ethyl)-N^2-(3,4-dimethylphenyl)pyrimidine-2,4-diamine;
N^2-(3-chlorophenyl)-N^4-(3-(dimethylamino)butyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)butyl)-N^2-(2-fluorophenyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)butyl)-N^2-(3-fluorophenyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)butyl)-N^2-(4-fluorophenyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)butyl)-N^2-(2,3-difluorophenyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)butyl)-N^2-(2,4-difluorophenyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)butyl)-N^2-(2,5-difluorophenyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)butyl)-N^2-(2,6-difluorophenyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)butyl)-N^2-(2-chlorophenyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)butyl)-N^2-(4-chlorophenyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)butyl)-N^2-(2,3-dichlorophenyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)butyl)-N^2-(2,4-dichlorophenyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)butyl)-N^2-(2,5-dichlorophenyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)butyl)-N^2-(2,6-dichlorophenyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)butyl)-N^2-(2-methylphenyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)butyl)-N^2-(4-methylphenyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)butyl)-N^2-(2,3-dimethylphenyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)butyl)-N^2-(2,4-dimethylphenyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)butyl)-N^2-(2,5-dimethylphenyl)pyrimidine-2,4-diamine;
N^4-(3-(dimethylamino)butyl)-N^2-(2,6-dimethylphenyl)pyrimidine-2,4-diamine;
and
N^4-(3-(dimethylamino)butyl)-N^2-(3,4-dimethylphenyl)pyrimidine-2,4-diamine.

13. A compound having the formula:



R^2 and R^3 are each independently chosen from:

i) hydrogen; or

ii) C_1-C_4 linear or branched alkyl; and

R^5 is chosen from:

i) C_1-C_4 linear, branched, or cyclic alkyl;

ii) halogen;

iii) $-OR^6$;

iv) $-SO_2N(R^6)_2$;

v) $-CH_mX_n$; wherein each X is independently F, Cl, Br, or I, m is from 0 to 2, m+n =3;

vi) $-NO_2$; and

vii) phenyl;

each R^6 is independently hydrogen, or C_1-C_4 linear, branched, or cyclic alkyl; excluding N^2-(4-chlorophenyl)-N^4-[(3-diethylamino)propyl]-pyrimidine-2,4-diamine.

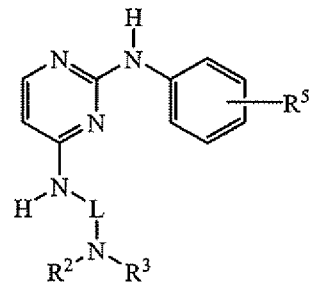
14. A compound according to Claim 13 wherein $\mathbf{R^2}$ and $\mathbf{R^3}$ are each independently hydrogen, methyl, and ethyl.

15. A compound according to Claim 13 wherein $\mathbf{R^5}$ is chosen from 3-chloro, 4-chloro, 3,4-dichloro, 3-chloro-4-methyl-, 3-chloro-4-fluoro, 3,4-difluoro, 3-trifluoro-methyl, 3-trifluoromethyl-4-chloro, 3-methoxy, 3-methyl, 3-ethyl, and 3-iso-propyl.

16. A compound according to Claim 13 wherein $\mathbf{R^5}$ is chosen from 2-fluoro, 3-fluoro, 4-fluoro, 2,3-difluoro, 2,4-difluoro, 2,5-difluoro, 2,6-difluoro, 2-chloro, 2,3-dichloro, 2,4-dichloro, 2,5-dichloro and, 2,6-dichloro.

17. A compound according to Claim 13 wherein $\mathbf{R^5}$ is chosen from 2-methoxy, 4-methoxy, 2,3-dimethoxy, 2,4-dimethoxy, 2,5-dimethoxy, 2,6-dimethoxy, 3,4-dimethoxy, 2-hydroxy, 3-hydroxy, 4-hydroxy, 2,3-dihydroxy, 2,4-dihydroxy, 2,5-dihydroxy, 2,6-dihydroxy, and 3,4-dihydroxy.

18. A compound having the formula:



$\mathbf{R^2}$ and $\mathbf{R^3}$ are each independently chosen from:

i) hydrogen; or

ii) C_1-C_4 linear or branched alkyl; and

$\mathbf{R^5}$ is chosen from:

i) C_1-C_4 linear, branched, or cyclic alkyl;

ii) halogen;

iii) $-OR^6$;

iv) $-SO_2N(R^6)_2$;

v) $-CH_mX_n$; wherein each X is independently F, Cl, Br, or I, m is from 0 to 2, m+n =3;

vi) $-NO_2$; and

vii) phenyl;

each $\mathbf{R^6}$ is independently hydrogen, or C_1-C_4 linear, branched, or cyclic alkyl; and

L is chosen from:

i) $-CH_2-$, methylene;

ii) $-CH_2CH_2-$, ethylene;

iii) $-CH(CH_3)CH_2-$, 1-propylene;

iv) $-CH_2CH(CH_3)-$, 2-propylene;

v) $-CH_2CH_2CH_2CH_2-$, butylene.

vi) $-CH(CH_3)CH_2CH_2-$, 1-butylene;

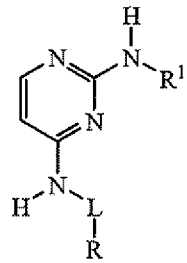
vii) $-CH_2CH(CH_3)CH_2-$, 2-butylene; and

viii) $-CH_2C(CH_3)_2CH_2-$, 2,2-dimethylpropylene;

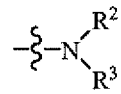
excluding N^2-(4-chlorophenyl)-N^4-[(2-diethylamino)ethyl]-pyrimidine-2,4-diamine and N^2-(4-methylphenyl)-N^4-[(2-diethylamino)ethyl]-pyrimidine-2,4-diamine.

19. A composition comprising:

A) a compound having the formula:



wherein **R** is a unit having the formula:



$\mathbf{R^2}$ and $\mathbf{R^3}$ are each independently chosen from:

i) hydrogen; or

ii) C_1-C_4 linear, branched, or cyclic alkyl;

L is a linking unit having the formula:

$$-[C(R^{4a}R^{4b})]_n-$$

each $\mathbf{R^{4a}}$ and $\mathbf{R^{4b}}$ is independently chosen from:

i) hydrogen; or

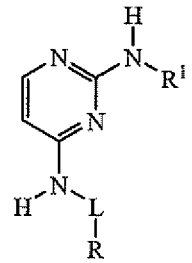
ii) C_1-C_4 linear, branched, or cyclic alkyl;

the index n is from 1 to 4; and

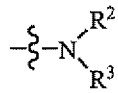
$\mathbf{R^1}$ is aryl; and

B) the balance carriers and excipients.

20. A method for improving cardiac contraction/relaxation parameters in heart failure patients comprising administering to a human suffering from acute heart failure a composition comprising a compound having the formula:



wherein R is a unit having the formula:



$\mathbf{R^2}$ and $\mathbf{R^3}$ are each independently chosen from:

i) hydrogen; or

ii) C_1-C_4 linear, branched, or cyclic alkyl;

L is a linking unit having the formula:

$$-[C(\mathbf{R^{4a}R^{4b}})]_n-$$

each $\mathbf{R^{4a}}$ and $\mathbf{R^{4b}}$ is independently chosen from:

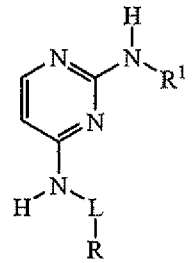
i) hydrogen; or

ii) C_1-C_4 linear, branched, or cyclic alkyl;

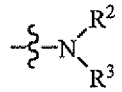
the index n is from 1 to 4; and

$\mathbf{R^1}$ is aryl.

21. A method for treating chronic or acute heart failure comprising administering to a human an effective amount of a composition comprising one or more of the PKC-α inhibitors having the formula:



wherein **R** is a unit having the formula:



$\mathbf{R^2}$ and $\mathbf{R^3}$ are each independently chosen from:

i) hydrogen; or

ii) C_1-C_4 linear, branched, or cyclic alkyl;

L is a linking unit having the formula:

$$-[C(R^{4a}R^{4b})]_n-$$

each $\mathbf{R^{4a}}$ and $\mathbf{R^{4b}}$ is independently chosen from:

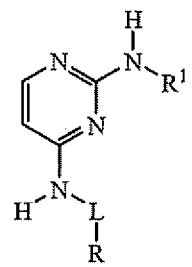
i) hydrogen; or

ii) C_1-C_4 linear, branched, or cyclic alkyl;

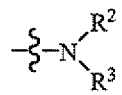
the index n is from 1 to 4; and

$\mathbf{R^1}$ is aryl.

22. The use of a compound in the manufacture of a medicament, said compound having the formula:



wherein **R** is a unit having the formula:



$\mathbf{R^2}$ and $\mathbf{R^3}$ are each independently chosen from:

i) hydrogen; or

ii) C_1-C_4 linear, branched, or cyclic alkyl;

L is a linking unit having the formula:

$$-[C(R^{4a}R^{4b})]_n-$$

each $\mathbf{R^{4a}}$ and $\mathbf{R^{4b}}$ is independently chosen from:

i) hydrogen; or

ii) C_1-C_4 linear, branched, or cyclic alkyl;

the index n is from 1 to 4; and

$\mathbf{R^1}$ is aryl.

23. A method for treating or preventing a disease or medical condition selected from diabetes, numerous forms of cancer, microalbinuria, endothelial dysfunction, cerebrovascular disease, stroke, coronary heart disease, cardiovascular disease and sequela (e.g. arrhythmia, sudden death, increased infarct size, congestive heart failure, angina), myocardial ischemic states, hypertension, lipid disorders, ischemia-reperfusion injury, atherosclerosis, peripheral artery/vascular disease, microvascular complications of diabetes (neuropathy, nephropathy, retinopathy), restenosis, renal disease, blood coagulation disorders, inflammatory diseases, cardiac hypertrophy, dilated cardiomyopathy, ischemic injury and suboptimal mitogen stimulation said method comprised of the steps of administering to a patient in need thereof a therapeutic amount of a compound according to claim 1.

24. A method for treating acute heart failure comprising administering to a human an effective amount of a composition comprising one or more of the PKC-α inhibitors according to Claim 1.

25. A method for chronic heart failure comprising administering to a human an effective amount of a composition comprising one or more of the PKC-α inhibitors according to Claim 1.

26. A method of treating or preventing chronic or acute heart failure, said method comprised of the step of administering to a patient in need thereof a pharmaceutically acceptable amount of a compound according to claim 1 or a therapeutically acceptable salt thereof in combination with a drug selected that acts on the renin-angiotensin-aldosterone system, a diuretic, digoxin or a β-adrenergic receptor blockers, natriuretic peptides and inotropic agents.

27. The method of claim 26 wherein the drug used in combination with a compound according to claim 1 is a renin-angiotensin-aldosterone system selected from an ACEI, ARB, or aldosterone inhibitor.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/071073

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D239/48 C07D401/12 C07D403/12 C07D417/12 A61K31/506
A61K31/425 A61K31/4178 A61P29/00

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

B. FIELDS SEARCHED

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 1 092 571 A (CIBA LTD) 29 November 1967 (1967-11-29) page 2, lines 28-32; claim 41; examples 19,23	1-4, 19-27
A	EP 1 571 146 A (ONO PHARMACEUTICAL CO [JP]) 7 September 2005 (2005-09-07) examples 15-42, 15-43, 15-46; claims 10,25	1

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

☒ See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 November 2007	14/11/2007

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2007/071073

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

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

Although claims 20, 21, 23-27 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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

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

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.

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

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

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

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2007/071073

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB 1092571 A	29-11-1967	AT 260253 B	26-02-1968
		AT 260267 B	26-02-1968
		BE 664381 A	24-11-1965
		DE 1545677 A1	07-08-1969
		FR 4723 M	
		NL 6506572 A	26-11-1965
		US 3445467 A	20-05-1969
EP 1571146 A	07-09-2005	AU 2003288994 A1	30-06-2004
		WO 2004052862 A1	24-06-2004
		US 2007167459 A1	19-07-2007