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(54) Title: SYNTHESIS OF 4/5-PYRIMIDINYLMIDAZOLES VIA SEQUENTIAL FUNCTIONALIZATION OF 2,4-DICHLOROPYRIMIDINE

(57) Abstract: This invention relates to methods of making pyrimidinyl-substituted imidazole compounds by sequential substitution of the 4- and 2-chloro groups of 2,4-dichloropyrimidine, nucleophilic substitution to form pyrimidinylalkyne derivatives, oxidation to the corresponding 1,2-diketones, and cyclocondensation reactions.

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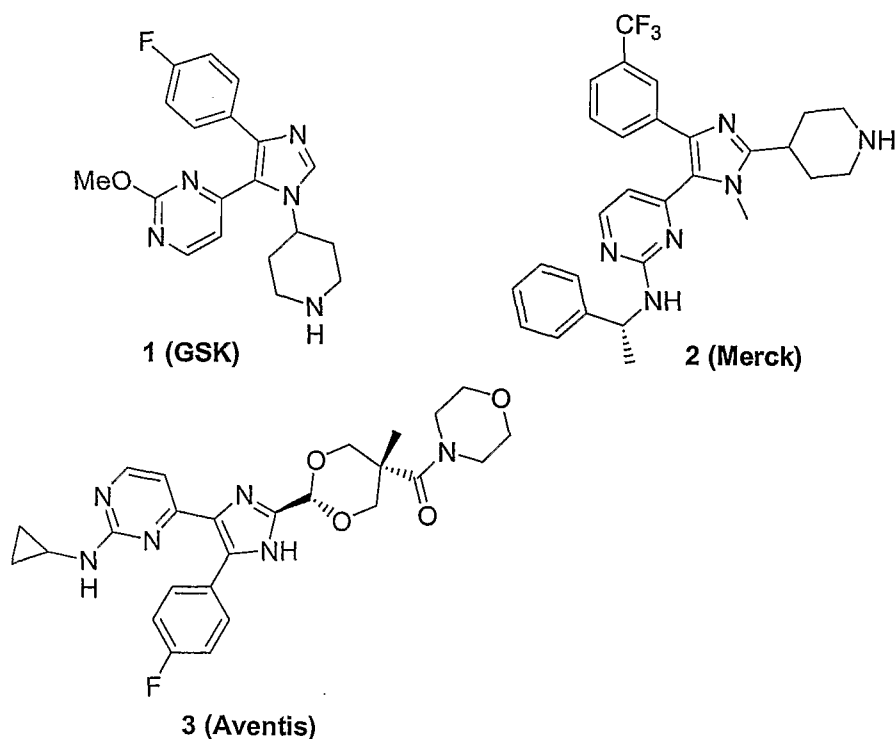
Synthesis of 4/5-Pyrimidinylimidazoles via Sequential Functionalization of 2,4-Dichloropyrimidine

FIELD OF THE INVENTION

This invention relates to methods of making pyrimidinyl-substituted imidazole compounds. More particularly, this invention relates to methods of oxidizing pyrimidinyl alkynes to pyrimidinyl diketones, which are useful in the preparation of pyrimidinyl-substituted imidazole compounds.

BACKGROUND OF THE INVENTION

4,5-Diaryl-imidazoles, in which one of the aryl substituents is a heteroaryl group such as a pyridine or pyrimidine, form an important class of p38 MAPK (mitogen-activated protein kinase) inhibitors, reportedly pursued by a number of pharmaceutical companies as anti-inflammatory drugs (Fullerton, T. et al. *Clin. Pharmacol. Ther.* 2000, 67, 114). Examples of such pyrimidinyl imidazoles include:



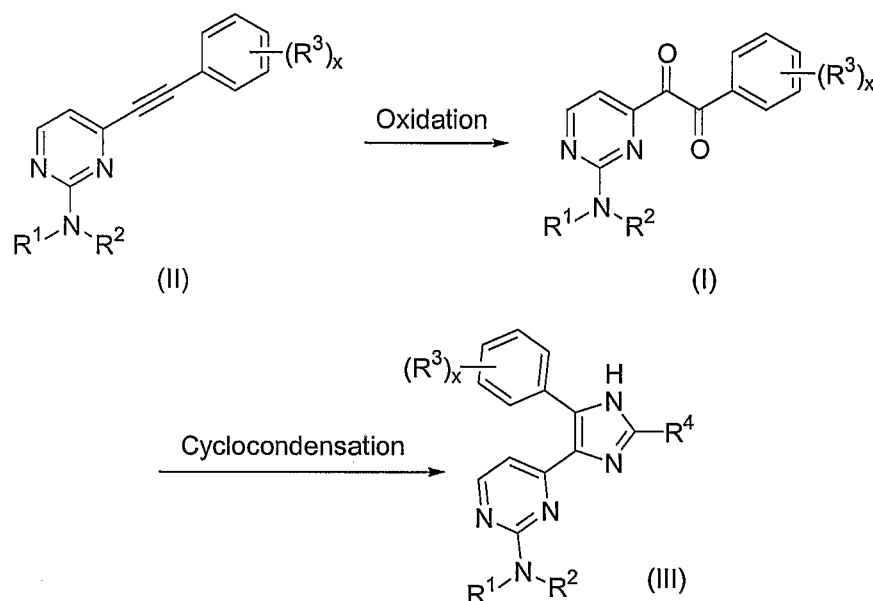
Additional examples of such compounds include inhibitors of protein tyrosine kinases such as: c-Met tyrosine kinase and src kinase (See: U.S. Pat. Appl. Publ. 2005085473; Intl. Pat. Appl. Publ. WO03/087026) for the treatment of, for example, transplant rejection, inflammatory bowel syndrome, rheumatoid arthritis, psoriasis, restenosis, allergic asthma, Alzheimer's disease, Parkinson's disease, stroke, osteoporosis, cancer, and benign hyperplasia; and inhibitors of p38 MAP kinase as anti-cancer (Intl. Pat. Appl. Publ. WO03/087026) and anti-inflammatory agents (Revesz, L. et al. *Bioorg. Med. Chem. Lett.* 2004, 14(13), 3595-3599); inhibitors of B-raf kinase (Intl. Pat. Appl. Publ. WO01/038324) for the treatment of cancer and neuronal degeneration from ischemic events.

In spite of the heightened interest, preparation of these compounds has relied largely upon two synthetic strategies. Reported methodologies (Liverton, N.J. et al. *J. Med. Chem.* 1999, 42, 2180-2190; McIntyre, C.J. et al. *Bioorg. Med. Chem. Lett.* 2002, 12, 689-692) employed the cyclocondensation of substituted 1,2-dicarbonyl compounds with ammonia and an aldehyde. Although this reaction is quite efficient, preparation of the pyrimidinyl-substituted dicarbonyl derivatives reportedly proceeds through a lengthy sequence starting from 2-mercapto-4-methylpiperidine. Another approach (Adams, J.L. et al. *Bioorg. Med. Chem. Lett.* 2001, 11, 2867-2870, and literature cited therein) involved the cycloaddition of substituted TosMIC with aldimines, originally pioneered by van Leusen (Van Leusen, A.M. et al. *J. Org. Chem.* 1977, 42, 1153-1159). More recently, Merck scientists have reported a promising one-pot synthesis of imidazoles based on the cyclocondensation of an α -ketoamide with an amine, wherein the requisite α -ketoamide was generated *in situ* by a Stetter reaction involving an α -amid sulfone (Frantz, D.E. et al. *Org. Lett.* 2004, 6, 843-846). In these cases also, access to the suitably elaborated pyrimidines required multi-step sequences.

To successfully exploit the particularly efficient condensation of 1,2-diketones bearing an electron-deficient pyrimidine moiety with an aldehyde and ammonia, a more succinct route to the requisite 1,2-diketone derivatives would clearly be advantageous.

To more readily access the desired 1,2-diketone intermediates, we considered the oxidation of disubstituted acetylene compounds, which could be derived from the readily available 2,4-dichloropyrimidine through sequential substitution reactions (Scheme 1). Cyclocondensation of the resulting
 5 diketones of Formula (I) would provide the desired pyrimidinyl imidazoles. 1,2-Diketones of Formula (I) are useful in the preparation of pharmaceutically active pyrimidinyl imidazole compounds.

Scheme 1

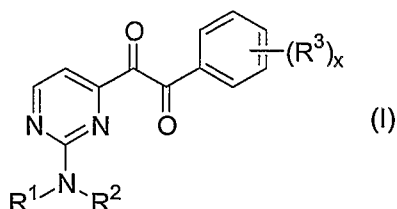


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SUMMARY OF THE INVENTION

Relative to existing methods, embodiments of the synthetic route according to this invention provide a concise methodology that is suitable for readily making a range of structurally related 1,2-diketone and imidazole
 15 analogs.

There are provided by the present invention methods of making amino substituted 1-(pyrimidin-4-yl)-2-phenyl-ethane-1,2-diones of Formula (I):



wherein:

R^1 and R^2 are each independently selected from the group consisting of -H, -C₁₋₆alkyl, -C₃₋₈cycloalkyl, benzyl, and 1-methylbenzyl;

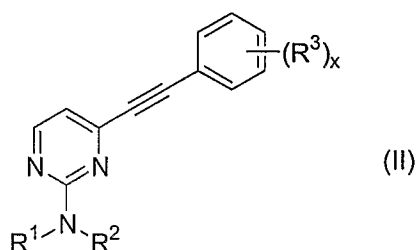
x is 0, 1, 2, or 3; and

each R^3 is independently selected from the group consisting of -OH, -Cl, -F,

- 5 -C₁₋₆alkyl, -C₃₋₈cycloalkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, phenyl, -CN, -NO₂,
 -N(R^a)R^b, -C(O)N(R^a)R^b, -N(R^c)C(O)R^d, -N(R^c)SO₂C₁₋₆alkyl, -C(O)C₁₋₆alkyl,
 -S(O)₀₋₂C₁₋₆alkyl, -SO₂N(R^a)R^b, -CO₂H, and -CO₂C₁₋₆alkyl, where R^a and R^b
 are each independently -H or -C₁₋₆alkyl, and where R^c and R^d are each
 independently -H or -C₁₋₆alkyl;

- 10 and enantiomers, diastereomers, and pharmaceutically acceptable salts and
 esters thereof;

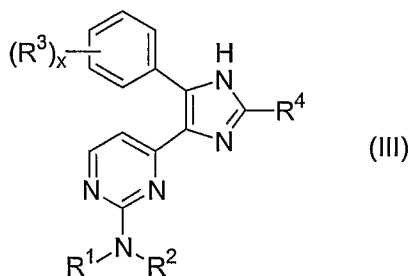
comprising oxidizing an alkyne of Formula (II):



wherein R^1 , R^2 , R^3 , and x are defined as above,

- 15 with finely powdered potassium permanganate.

The present invention further contemplates methods of making
 imidazoles of Formula (III):



and tautomers thereof, wherein R^1 , R^2 , R^3 , and x are defined as above; and

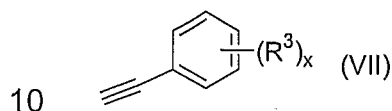
- 20 R^4 is -H, -C₁₋₈alkyl, -C₃₋₈cycloalkyl, aryl, heteroaryl, heterocycloalkyl, or
 -CH(OC₁₋₆alkyl)₂;

comprising oxidizing an alkyne of Formula (II) to a 1,2-diketone of Formula (I)
 with finely powdered potassium permanganate. Reactions such as the
 oxidation of an alkyne of Formula (II) are performed in some embodiments of

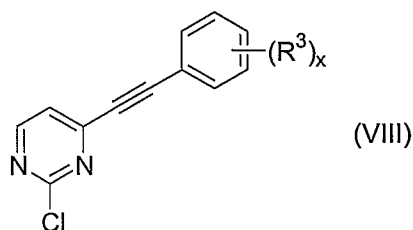
this invention in a buffered solution of suitable polarity that is chemically compatible with the reaction conditions.

The present invention further contemplates methods of making 4/5-pyrimidinylimidazoles comprising reacting 2,4-dichloropyrimidine with a nucleophilic-attack-protected-acetylene to form 2-chloro-4-(protected-ethynyl) pyrimidine.

The present invention further contemplates methods of making 4/5-pyrimidinylimidazoles comprising reacting 2,4-dichloropyrimidine with a compound of Formula (VII):



to form a compound of Formula (VIII):



An object of the present invention is to overcome or ameliorate at least one of the disadvantages of the conventional methodologies and/or prior art, or to provide a useful alternative thereto.

DETAILED DESCRIPTION OF THE INVENTION

The invention may be more fully appreciated by reference to the following description, including the following glossary of terms and the concluding examples. For the sake of brevity, the disclosures of the publications cited in this specification are herein incorporated by reference.

As used herein, the terms "including", "containing" and "comprising" are used herein in their open, non-limiting sense.

The term "alkyl" refers to a straight- or branched-chain alkyl group having from 1 to 12 carbon atoms in the chain. Examples of alkyl groups include methyl (Me, which also may be structurally depicted by /), ethyl (Et), n-propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl (tBu), pentyl, isopentyl, tert-pentyl, hexyl, isohexyl, and groups that in light of the ordinary skill in the art

and the teachings provided herein would be considered equivalent to any one of the foregoing examples.

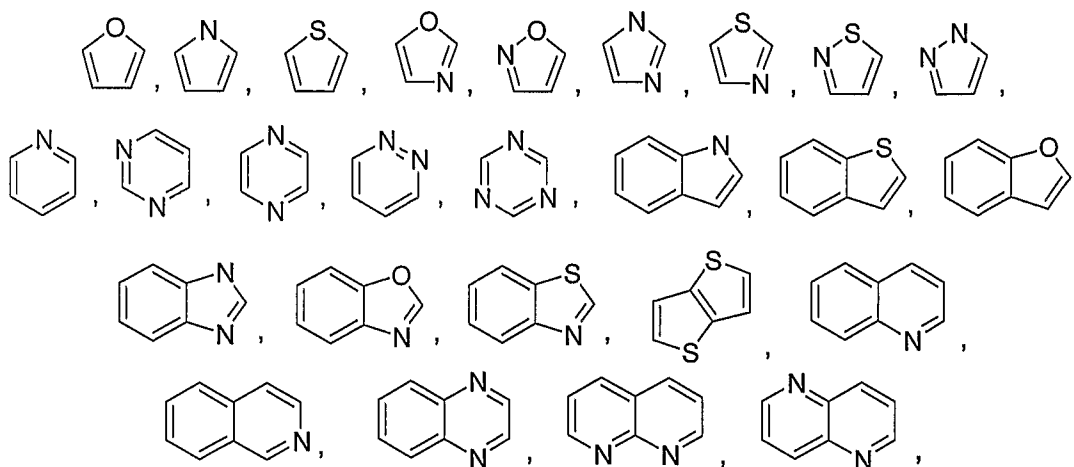
5 The term "alkylene" refers to a divalent straight- or branched-chain alkyl group having from 1 to 12 carbon atoms in the chain. Examples of alkylene groups include methylene, ethylene, propylene, and groups that in light of the ordinary skill in the art and the teachings provided herein would be considered equivalent to any one of the foregoing examples.

10 The term "alkenyl" refers to a straight- or branched-chain alkenyl group having from 2 to 12 carbon atoms in the chain. (The double bond of the alkenyl group is formed by two sp^2 hybridized carbon atoms.) Illustrative alkenyl groups include prop-2-enyl, but-2-enyl, but-3-enyl, 2-methylprop-2-enyl, hex-2-enyl, and groups that in light of the ordinary skill in the art and the teachings provided herein would be considered equivalent to any one of the foregoing examples.

15 The term "alkynyl" refers to a straight- or branched-chain alkynyl group having from 2 to 12 carbon atoms in the chain. (The triple bond of the alkynyl group is formed by two sp hybridized carbon atoms.) Illustrative alkynyl groups include prop-2-ynyl, but-2-ynyl, but-3-ynyl, 2-methylbut-2-ynyl, hex-2-ynyl, and groups that in light of the ordinary skill in the art and the teachings provided
20 herein would be considered equivalent to any one of the foregoing examples.

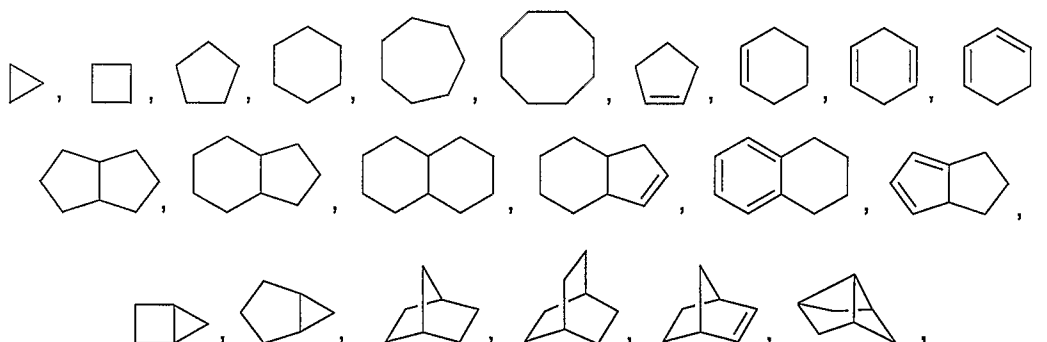
The term "aryl" refers to a monocyclic or fused polycyclic, aromatic carbocycle (ring structure having ring atoms that are all carbon) having from 3 to 12 ring atoms per carbocycle. (Carbon atoms in aryl groups are sp^2 hybridized.) Illustrative examples of aryl groups include phenyl, naphthalenyl,
25 anthracenyl, phenanthrenyl, and groups that in light of the ordinary skill in the art and the teachings provided herein would be considered equivalent to any one of the foregoing examples.

The term "heteroaryl" refers to a monocyclic, fused bicyclic, or fused polycyclic, aromatic heterocycle (ring structure having ring atoms selected from
30 carbon atoms as well as nitrogen, oxygen, and sulfur heteroatoms) having from 3 to 12 ring atoms per heterocycle. Illustrative examples of heteroaryl groups include the following entities, in the form of properly bonded moieties:



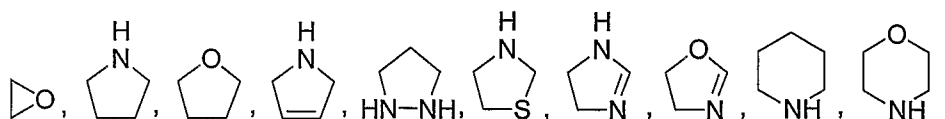
- 5 and moieties that in light of the ordinary skill in the art and the teachings provided herein would be considered equivalent to any one of the foregoing examples.

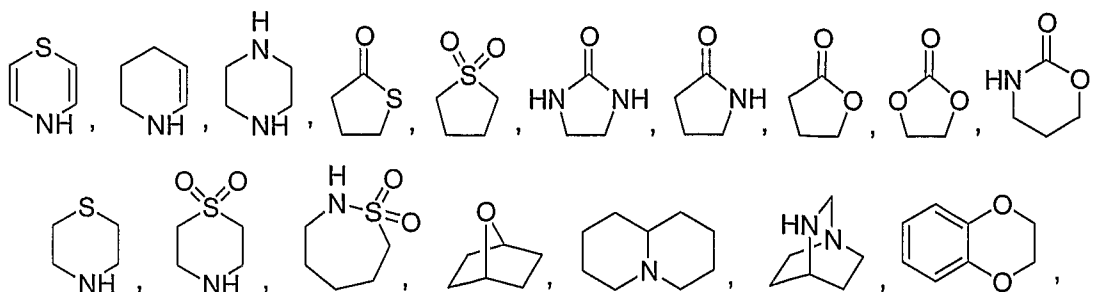
The term "cycloalkyl" refers to a saturated or partially saturated, monocyclic or fused or spiro polycyclic, carbocycle having from 3 to 12 ring atoms per carbocycle. Illustrative examples of cycloalkyl groups include the following entities, in the form of properly bonded moieties:



- 15 and moieties that in light of the ordinary skill in the art and the teachings provided herein would be considered equivalent to any one of the foregoing examples.

A "heterocycloalkyl" refers to a monocyclic, or fused or spiro polycyclic, ring structure that is saturated or partially saturated and has from 3 to 12 ring atoms per ring structure selected from C atoms and N, O, and S heteroatoms. Illustrative examples of heterocycloalkyl groups include the following entities, in the form of properly bonded moieties:





and moieties that in light of the ordinary skill in the art and the teachings provided herein would be considered equivalent to any one of the foregoing examples.

The term "halogen" represents chlorine, fluorine, bromine or iodine. The term "halo" represents chloro, fluoro, bromo or iodo.

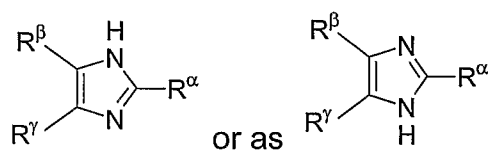
The term "substituted" means that the specified group or moiety bears one or more substituents. The term "unsubstituted" means that the specified group bears no substituents. The term "optionally substituted" means that the specified group is unsubstituted or substituted by one or more substituents. Where the term "substituted" is used to describe a structural system, the substitution is meant to occur at any valence allowed position on the system. It is understood that substitutions and combinations of substitutions recited herein, whether stated explicitly or not, refer to substitutions that are consistent with the valence of the member being substituted. Terms such as "valence allowed", "valence allowed site", "valence allowed member" and morphological variations thereof are used herein in this sense. For example, "valence allowed" when applied to a carbon member refers to the tetravalency of C; it refers to the trivalency of N when applied to a nitrogen member; and it refers to the bonding of a nitrogen member that is conventionally characterized with a positive electric charge or that is in a quaternary form. The present invention also encompasses compounds as described herein and equivalents thereof with at least one valence allowed nitrogen member, including but not limited to a quaternary nitrogen member and a nitrogen oxide. Such quaternary nitrogen member can be generated with a known agent for this purpose, such as lower alkyl halides, dialkyl sulfates, long chain halides, and aralkyl halides. Valence allowed options are part of the ordinary skill in the art.

Any formula given herein is intended to represent compounds having structures depicted by the structural formula as well as certain variations or

forms. In particular, compounds of any given formula given herein may have asymmetric centers and therefore exist in different enantiomeric forms. All optical isomers and stereoisomers of the compounds of the general formula, and mixtures thereof, are considered within the scope of the formula. Thus
5 any given formula given herein is intended to represent a racemate, one or more enantiomeric forms, one or more diastereomeric forms, one or more atropisomeric forms, and mixtures thereof.

Furthermore, certain structures may exist as geometric isomers (i.e., *cis* and *trans* isomers), as tautomers, or as atropisomers. Additionally, any
10 formula given herein is intended to represent hydrates, solvates, and polymorphs, and mixtures thereof when such forms exist in the medium.

The term "4/5-pyrimidinylimidazole" as used herein refers to an imidazole ring where the pyrimidinyl substituent is in the 4- or the 5-position in the imidazole ring, and it also refers to the pair of pyrimidinyl imidazole
15 tautomers. It is known that substituted imidazoles can interconvert due to tautomerism, and that one tautomeric form (for example the 4-substituted) may appear as the predominant form in a certain medium whereas the other tautomeric form (for example the 5-substituted) may appear as the predominant form in a different medium. It is understood that, unless specified otherwise,
20 reference to a substituted imidazole, whether referred to as 4/5 substituted imidazole or not, refers to and encompasses whichever tautomeric form is present in the medium, and if both tautomers are present in such medium, then it refers to and encompasses both tautomers. This lexicography also applies to the chemical structures given herein. Accordingly, a chemical structure that
25 displays the imidazole moiety given as



, refers to any one of the tautomers or to the tautomer pair, depending on whether one tautomer, the other tautomer or the pair is present in the medium. (R^α , R^β , and R^γ in these tautomeric structures are generic substituents that refer to any one of the imidazole
30 substituents/moieties referred to herein).

Any formula given herein is also intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. Isotopically labeled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine, chlorine, and iodine, such as ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , ^{36}Cl , and ^{125}I , respectively. Such isotopically labelled compounds are useful in metabolic studies (preferably with ^{14}C), reaction kinetic studies (with, for example ^2H or ^3H), detection or imaging techniques [such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT)] including drug or substrate tissue distribution assays, or in radioactive treatment of patients. In particular, an ^{18}F or ^{11}C labeled compound may be particularly preferred for PET or SPECT studies. Further, substitution with heavier isotopes such as deuterium (i.e., ^2H) may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements. Isotopically labeled compounds of this invention and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the schemes or in the examples and preparations described below by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

When referring to any formula given herein, the selection of a particular moiety from a list of possible species for a specified variable is not intended to define the moiety for the variable appearing elsewhere. In other words, where a variable appears more than once, the choice of the species from a specified list is independent of the choice of the species for the same variable elsewhere in the formula, unless stated otherwise.

By way of a first example on substituent terminology, if substituent $\text{S}^1_{\text{example}}$ is one of S_1 and S_2 , and substituent $\text{S}^2_{\text{example}}$ is one of S_3 and S_4 , then these assignments refer to embodiments of this invention given according to the choices $\text{S}^1_{\text{example}}$ is S_1 and $\text{S}^2_{\text{example}}$ is S_3 ; $\text{S}^1_{\text{example}}$ is S_1 and $\text{S}^2_{\text{example}}$ is S_4 ; $\text{S}^1_{\text{example}}$ is S_2 and $\text{S}^2_{\text{example}}$ is S_3 ; $\text{S}^1_{\text{example}}$ is S_2 and $\text{S}^2_{\text{example}}$ is S_4 ; and

equivalents of each one of such choices. The shorter terminology " S_{example}^1 is one of S_1 and S_2 , and S_{example}^2 is one of S_3 and S_4 " is accordingly used herein for the sake of brevity, but not by way of limitation. The foregoing first example on substituent terminology, which is stated in generic terms, is meant to

5 illustrate the various substituent assignments described herein. The foregoing convention given herein for substituents extends, when applicable, to members such as R^{1-4} , $R^{1'-4'}$ and x, and any other generic substituent symbol used herein.

Furthermore, when more than one assignment is given for any member

10 or substituent, embodiments of this invention comprise the various groupings that can be made from the listed assignments, taken independently, and equivalents thereof. By way of a second example on substituent terminology, if it is herein described that substituent S_{example} is one of S_1 , S_2 , and S_3 , this listing refers to embodiments of this invention for which S_{example} is S_1 ; S_{example} is

15 S_2 ; S_{example} is S_3 ; S_{example} is one of S_1 and S_2 ; S_{example} is one of S_1 and S_3 ; S_{example} is one of S_2 and S_3 ; S_{example} is one of S_1 , S_2 and S_3 ; and S_{example} is any equivalent of each one of these choices. The shorter terminology " S_{example} is one of S_1 , S_2 , and S_3 " is accordingly used herein for the sake of brevity, but not by way of limitation. The foregoing second example on substituent

20 terminology, which is stated in generic terms, is meant to illustrate the various substituent assignments described herein. The foregoing convention given herein for substituents extends, when applicable, to members such as R^{1-4} , $R^{1'-4'}$ and x, and any other generic substituent symbol used herein.

The nomenclature " C_{i-j} " with $j > i$, when applied herein to a class of

25 substituents, is meant to refer to embodiments of this invention for which each and every one of the number of carbon members, from i to j including i and j, is independently realized. By way of example, the term C_{1-3} refers independently to embodiments that have one carbon member (C_1), embodiments that have two carbon members (C_2), and embodiments that have three carbon members

30 (C_3).

The term $C_{n-m}\text{alkyl}$ refers to an aliphatic chain, whether straight or branched, with a total number N of carbon members in the chain that satisfies $n \leq N \leq m$, with $m > n$.

According to the foregoing interpretive considerations on assignments and nomenclature, it is understood that explicit reference herein to a set implies, where chemically meaningful and unless indicated otherwise, independent reference to embodiments of such set, and reference to each and every one of the possible embodiments of subsets of the set referred to explicitly.

"Finely powdered" potassium permanganate refers to this compound in a form that is recognized in the manufacturing and marketing of this compound with this characterization. An example of finely powdered potassium permanganate is the product Cairox M[®], marketed by Carus Chemical Company. Embodiments of finely powdered potassium permanganate include forms of this compound that have a particle size of at least 325 mesh. In one illustrative embodiment, finely powdered potassium permanganate is provided in samples that completely pass through #325 standard sieve (44 micron). Preferably, potassium permanganate is of at least 98% purity.

The terms "buffered" solution or "buffer" solution are used herein interchangeably according to their standard meaning. Buffered solutions are used to control the pH of a medium, and their choice, use, and function is known to those of ordinary skill in the art. See, for example, G.D. Considine, ed., Van Nostrand's Encyclopedia of Chemistry, p. 261, 5th ed. (2005), describing, inter alia, buffer solutions and how the concentrations of the buffer constituents relate to the pH of the buffer. See also Handbook of Chemistry and Physics, 84th ed., pp. 8-37 to 8-44. For example, a buffered solution is obtained by adding MgSO₄ and NaHCO₃ to a solution in a 10:1 w/w ratio to maintain the pH of the solution at about 7.5.

Solutions used in embodiments of this invention are exemplified by those that have one or more miscible solvents that are chemically compatible with the reaction conditions, preferably unreactive with permanganate, and that provide a medium that has a dielectric constant comparable with that of the examples given herein. For example, acetone/H₂O solutions provide examples of embodiments of solution media in embodiments of this invention. Acetone is a convenient and readily available solvent that does not interfere with the reaction conditions, and is miscible with water in the proportions desired to

achieve a suitable medium polarity for embodiments of this invention.

Dielectric constants for solvents and other liquids are readily available from standard reference materials, such as the Handbook of Chemistry and Physics. One of ordinary skill in the art should be able to replace acetone/water mixtures with other mixtures based on the teachings provided herein and available reference materials.

Embodiments of acetone/water solutions include any mixture thereof. Preferably, an acetone/H₂O solution is obtained by mixing acetone and water in a volume ratio of from about 3:1 to about 5:6, more preferably from about 8:3 to about 6:5, and more preferably about 1.75:1. Other solvents can be used instead of acetone in other embodiments of this invention, and other solvents can be used together with acetone and water in still other embodiments of this invention, provided that such media have the suitable polarity and chemical compatibility properties under the reaction conditions, as such properties are exemplified herein and equivalents thereof.

To provide a more concise description, some of the quantitative expressions given herein are not qualified with the term "about". It is understood that, whether the term "about" is used explicitly or not, every quantity given herein is meant to refer to the actual given value, and it is also meant to refer to the approximation to such given value that would reasonably be inferred based on the ordinary skill in the art, including equivalents and approximations due to the experimental and/or measurement conditions for such given value. Whenever a yield is given as a percentage, such yield refers to a mass of the entity for which the yield is given with respect to the maximum amount of the same entity that could be obtained under the particular stoichiometric conditions. Concentrations that are given as percentages refer to mass ratios, unless indicated differently.

Reference to a compound herein stands for a reference to any one of: (a) the actually recited form of such compound, and (b) any of the forms of such compound in the medium in which the compound is being considered when named. For example, reference herein to a compound such as R-COOH, encompasses reference to any one of, for example, R-COOH_(s), R-COOH_(sol), and R-COO⁻_(sol). In this example, R-COOH_(s) refers to the solid

compound, as it could be for example in a tablet or some other solid pharmaceutical composition or preparation; $R\text{-COOH}_{(\text{sol})}$ refers to the undissociated form of the compound in a solvent, such as water; and $R\text{-COO}^-_{(\text{sol})}$ refers to the dissociated form of the compound in a solvent, such as the

5 dissociated form of the compound in an aqueous environment, whether such dissociated form derives from $R\text{-COOH}$, from a salt thereof, or from any other entity that yields $R\text{-COO}^-$ upon dissociation in the medium being considered. In another example, expressions such as "exposing an entity to compound of formula $R\text{-COOH}$ ", "reacting an entity with $R\text{-COOH}$ ", and analogous

10 expressions refer to the exposure of such entity to the form, or forms, of the compound $R\text{-COOH}$ that exists, or exist, in the medium in which such exposure and/or reaction takes place. In this regard, if such entity is for example in an aqueous environment, it is understood that the compound $R\text{-COOH}$ is in such same medium, and therefore the entity is being exposed to species such as $R\text{-COOH}_{(\text{aq})}$ and/or $R\text{-COO}^-_{(\text{aq})}$, where the subscript "(aq)" stands for "aqueous" according to its conventional meaning in chemistry and biochemistry. A

15 carboxylic acid functional group has been chosen in these nomenclature examples; this choice is not intended, however, as a limitation but it is merely an illustration. It is understood that analogous examples can be provided in terms of other functional groups, including but not limited to hydroxyl, basic

20 nitrogen members, such as those in amines, ammonia and ammonium compounds, and any other group that interacts or transforms according to known manners in the medium that contains the compound. Such interactions and transformations include, but are not limited to, dissociation, association,

25 tautomerism, solvolysis, including hydrolysis, solvation, including hydration, protonation, and deprotonation. No further examples in this regard are provided herein because these interactions and transformations in a given medium are known by any one of ordinary skill in the art.

To obtain the various compounds described herein and equivalents

30 thereof, starting materials may be employed that carry the ultimately desired substituents through the reaction scheme with or without protection as appropriate. Alternatively, it may be necessary to employ, in the place of the

ultimately desired substituent, a suitable group that may be carried through the reaction scheme and replaced as appropriate with the desired substituent.

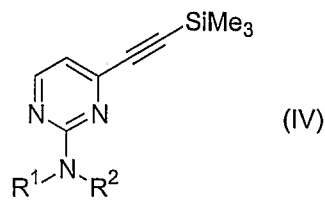
During any of the processes for preparation of the compounds of the present invention, it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. In addition, compounds of the invention may be modified by using protecting groups; such compounds, precursors, or prodrugs are also within the scope of the invention. This may be achieved by means of conventional protecting groups, such as those described in "Protective Groups in Organic Chemistry", ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, "Protective Groups in Organic Synthesis", 3rd ed., John Wiley & Sons, 1999; further examples of protecting groups are well known in organic synthesis and the peptide art, and are described by M. Bodanzsky, *Principles of Peptide Synthesis*, 1st and 2nd revised ed., Springer-Verlag, New York, 1984 and 1993; Stewart and Young, *Solid Phase Peptide Synthesis*, 2nd ed., Pierce Chemical Co, Rockford, IL 1984; L. Fieser and M. Fieser, *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley and Sons (1994); L. Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons (1995). Amino protecting groups are also given in, e.g., WO 98/07685. The protecting groups may be removed at a convenient subsequent stage by using methods known from the art. One or more than one protecting groups may often be used in a protection/deprotection operation. The choice typically intends to provide a protected group that will be stable under the conditions of subsequent reactions, and that can be removed at an appropriate step without disrupting the rest of the compound.

The methods of making imidazoles of Formula (III) may further comprise reacting, in the presence of an ammonia equivalent, a 1,2-diketone of Formula (I) with R^4CHO , where R^4 is defined as above, or with a formaldehyde equivalent.

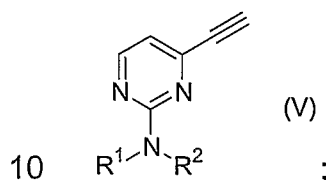
Suitable formaldehyde equivalents include hexamethylenetetramine, formaldehyde, and the like, and mixtures thereof. Suitable ammonia equivalents include ammonia, ammonium salts such as ammonium acetate and the like, and mixtures thereof.

The present invention further contemplates methods of making compounds of Formula (I), comprising at least one of:

- a) reacting 2,4-dichloropyrimidine with (trimethylsilyl)acetylene to form 2-chloro-4-trimethylsilanylethynyl-pyrimidine;
- 5 b) reacting 2-chloro-4-trimethylsilanylethynyl-pyrimidine with R^1R^2NH to form a (trimethylsilyl)alkyne of Formula (IV):

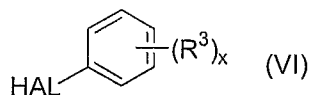


- c) deprotecting a (trimethylsilyl)alkyne of Formula (IV) to form an alkyne of Formula (V):



and

- d) reacting an alkyne of Formula (V) with a compound of Formula (VI):

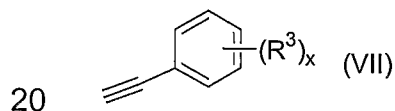


to form a compound of Formula (II);

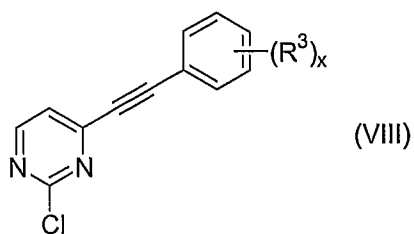
- 15 wherein R^1 , R^2 , R^3 , and x are defined as above; and
HAL is I or Br.

The present invention further contemplates methods of making compounds of Formula (I), comprising at least one of:

- a) reacting 2,4-dichloropyrimidine with a compound of Formula (VII):



to form a compound of Formula (VIII):

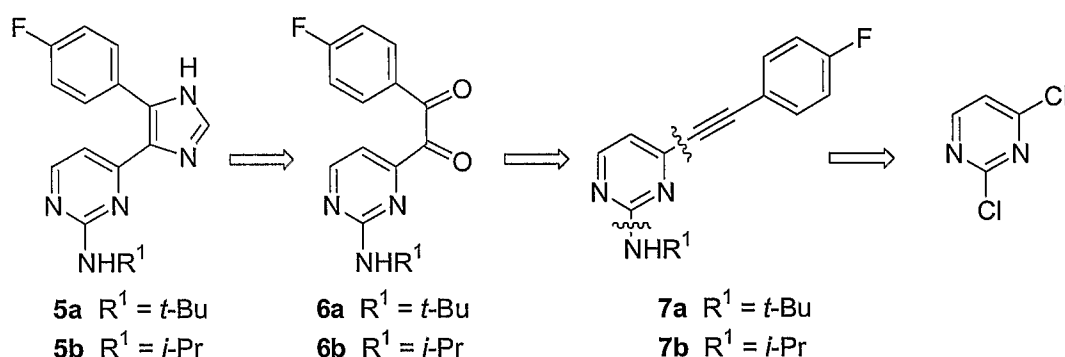


; and

b) reacting a compound of Formula (VIII) with R^1R^2NH to form a compound of Formula (II), wherein R^1 , R^2 , R^3 , and x are defined as above.

In more particular embodiments, the retrosynthetic scheme may be represented by Scheme 2.

Scheme 2

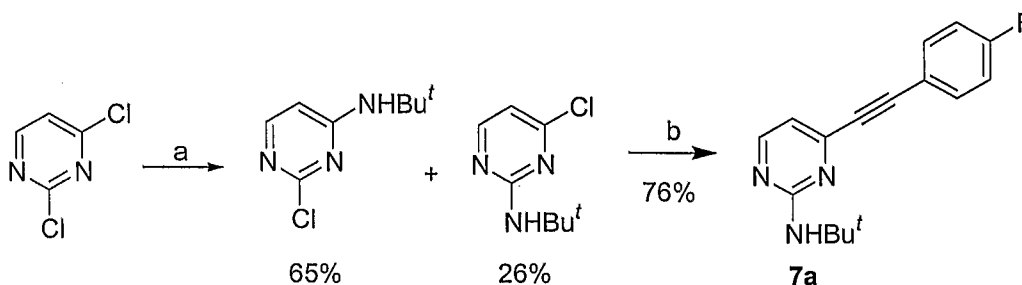


The preparation of the 1,2-diarylkynes is described in Schemes 3-5.

Initial attempts to perform selective substitution, outlined in Scheme 3, did not produce encouraging results. Reacting 2,4-dichloropyrimidine with *t*-butyl amine at 60 °C gave a mixture of 4- and 2-substitution products in 65% and 26% yield respectively. This result clearly indicated that the chloro group at the 4-position is more reactive (albeit slightly) toward substitution with amine nucleophiles than the 2-position (Mylari, B.L. et al. *J. Med. Chem.* 2001, 44, 2695-2700; Yoshida, K.; Taguchi, M. *J. Chem. Soc., Perkin Trans. 1* 1992, 7, 919-22; Chu-Moyer, M.Y. et al. *J. Med. Chem.* 2002, 45, 511-528). Although a variety of base and solvent combinations were investigated, no synthetically useful 2-position selectivity was found. On smaller scale (5-10 g), the two regioisomers can be separated by column chromatography. The 4-chloro regioisomer can then be reacted with 4-fluorophenylacetylene, under standard Sonogashira coupling conditions (Sonogashira, K. et al. *Tetrahedron Lett.* 1975, 50, 4467-4470), to furnish the desired disubstituted acetylene **7a** in 76% yield. Although we obtained diarylacetylene **7a** in two steps, the poor

regioselectivity in the nucleophilic substitution reaction rendered this approach impractical for large-scale synthesis.

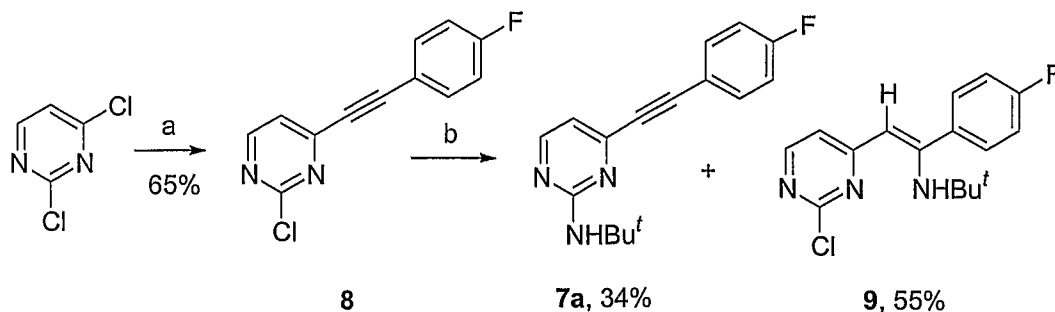
Scheme 3



5 Conditions: (a) NH_2Bu^t , neat, reflux; (b) 1-ethynyl-4-fluorobenzene, $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2/\text{CuI}$, THF/ Et_3N , reflux.

By reversing the order of the substitution steps, we overcame the regioselectivity issues. We found that a Sonogashira reaction between 2,4-dichloropyrimidine and 1-ethynyl-4-fluorobenzene smoothly afforded the desired regioisomer **8** as the major product (Scheme 4). Unfortunately, nucleophilic substitution of the 2-chloro substituent with *tert*-butylamine gave a mixture of the desired compound **7a**, along with alkyne adduct **9**. The structure of **9** was ascertained by nuclear Overhauser effect (NOE) experiments. To avoid this hydroamination reaction, a variety of conditions, such as $\text{Na}_2\text{CO}_3/\text{EtOH}$, $\text{Et}_3\text{N}/\text{THF}$, $\text{NH}_2\text{Bu}^t/\text{THF}$, and Buchwald amination, were investigated without much success. However, where amines other than *tert*-butylamine are used in this transformation, e.g. isopropylamine, yields and regioselectivity are much improved. Reactions using embodiments of amines $\text{R}^1\text{R}^2\text{NH}$ that are not *tert*-butylamine may be preferably accomplished using $\text{R}^1\text{R}^2\text{NH}$ as the solvent, or in a solvent such as THF or DMF, at temperatures between room temperature and 80 °C.

Scheme 4



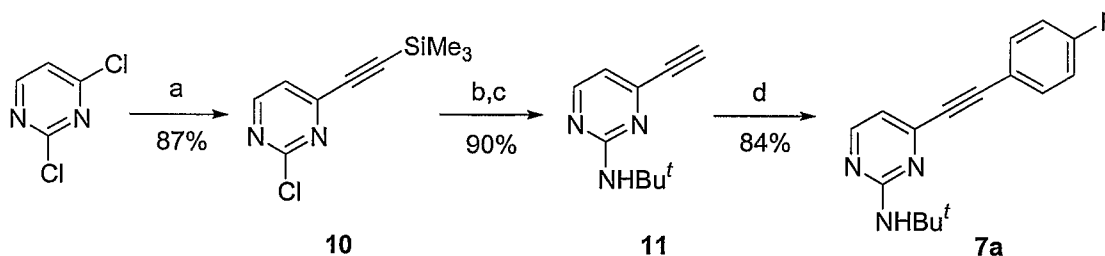
Conditions: (a) 1-ethynyl-4-fluorobenzene, $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2/\text{CuI}/\text{PPh}_3$, THF/ Et_3N , reflux, 3 h; (b) NH_2Bu^t , sealed tube, 80 °C.

5

As shown in Scheme 5, a new route was designed: Sonogashira cross-coupling reaction of a nucleophilic-attack-protected acetylene, such as [(tri-C₁₋₄alkyl)silyl]acetylene, for example (trimethylsilyl)acetylene, with 2,4-dichloropyrimidine gave good regioselectivity in excellent yield. Yields of about 87% were achieved in embodiments of this invention. Heating in neat *t*-butylamine at 80 °C gave the desired substitution product. It is understood that the SiMe₃ protection group in Scheme 5 is replaced in other embodiments of this invention by any other protection group that provides similar protective effects to a nucleophilic attack to the alkyne moiety. Such protective groups are referred to herein as “nucleophilic-attack protectors”. A nucleophilic-attack-protected acetylene is an acetylene with one of such protective groups attached to one of its ends, and a 2-chloro-4-protected-ethynyl-pyrimidine is a compound analogous to **10** with a nucleophilic-attack protector attached to the acetylenic moiety instead of the SiMe₃ given in compound **10**. Nucleophilic-attack protectors for alkyne groups are well known. See for example, Greene and Wuts, *Protective Groups in Organic Synthesis*, 3rd ed., chapter 8, which is incorporated herein by reference. Examples of such protection groups are trialkylsilanes, including, but not limited to, (tri-C₁₋₄alkyl)silanes such as SiPG¹PG²PG³, wherein each one of PG¹, PG², and PG³ is chosen independently from the other PG groups from the group of C₁₋₄alkyl, wherein “alkyl” refers to a straight- or branched-chain alkyl that has a number of carbon members ranging from one to four. Specific examples of alkyne protecting groups are provided by TMS (trimethylsilyl), TES (triethylsilyl), TBDMS (*t*-

butyldimethylsilyl), TDS (thexyldimethylsilyl), DOPS (dimethyl[1,1-dimethyl-3-(tetrahydro-2*H*-pyran-2-yloxy)propylsilyl), BDMS (biphenyldimethylsilyl), TIPS (triisopropylsilyl), biphenyldiisopropylsilyl), and Me₂C(OH) (2-(2-hydroxypropyl)). Finally, desilylation followed by another Sonogashira cross-coupling with 4-fluoro-iodobenzene afforded compound **7a** in very good overall yield. This reaction sequence was performed successfully on 20-40 g scale without the need for column chromatography. Accessing intermediate **10** as taught herein affords a more efficient route to **7a** and also allows for a point of diversification for the design of new analogues. This is a desirable feature for certain applications, such as medicinal chemistry applications and the making of libraries of compounds. In contrast, conventional methodologies direct the synthetic focus to the formation of a 1,2-diketone. It is to be noted that accessing intermediate **10** as taught herein provides a step that can be implemented in the synthesis of any 4/5-pyrimidinylimidazole, as long as basic principles of chemical compatibility are satisfied. This applicability range is due to the fact that the formation of intermediate **10** as taught herein is independent of and takes place prior to the formation of the eventual imidazole ring.

Scheme 5



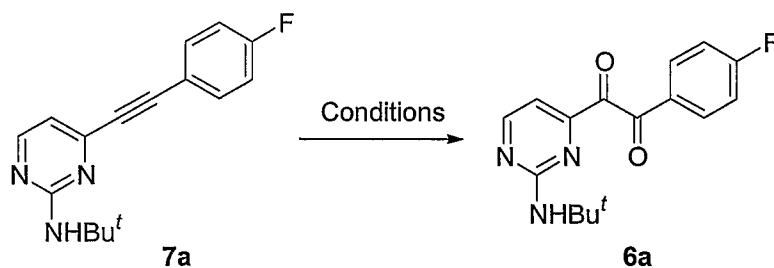
Conditions: (a) (trimethylsilyl)acetylene, 0.5% Pd(PPh₃)₂Cl₂/1% CuI/1% PPh₃, THF, Et₃N, reflux, 4.5 h; (b) NH₂Bu^t, sealed tube, 80 °C, 2 d; (c) 1% KOH, CH₃OH, rt, 2 h; (d) 4-Fluoro-iodobenzene, 0.5% Pd(PPh₃)₂Cl₂/1% CuI, THF, Et₃N, rt, 2.5 h.

The synthetic methodology developed in the context of this invention is not limited by specific theories for the underlying reaction steps. It is believed, however, that the making of the triple bond less electron deficient and more sterically encumbered are contributing factors to the results obtained in

embodiments of this invention, so that the nucleophilic substitution preferentially on the pyrimidine nucleus is effected.

With a reliable route to di-arylsubstituted acetylenes **7a** and **8** in hand, we set out to examine the oxidation reaction. Initially, we focused our attention on the oxidation of entity **8**, for it would allow the introduction of the amine substituent after imidazole formation. Oxidation of diarylsubstituted acetylene to diketone is well preceded and wide array of reagent systems have been reported (Holland, S.; Epsztein, R. *Bull. Chim. Soc. Fr.* 1971, 1694; Walsh, C.J.; Mandal, B.K. *J. Org. Chem.* 1999, 64, 6102-6105; Yusubov, M.S. et al. *Tetrahedron* 2002, 58, 1607-1610). However, oxidation of a diarylacetylene containing a pyrimidine group proved complex and difficult to achieve, as illustrated by the attempts to oxidize entity **8** by using a battery of reagent systems, attempts that resulted in no oxidation or over-oxidation (Table 1) despite the experience reported in reference teachings (Chi, K-W. et al. *Synth. Commun.* 1994, 24, 2119). In contrast, in the case of entity **7a**, oxidation using KMnO_4 or PdCl_2 went smoothly on small scale (Table 1, entries 3 and 5). The stark reactivity difference between entities **7a** and **8** could be due to the reduced electron-deficiency of the triple bond in compound **7a**.

Table 1. Oxidation of compound **7a**.



Entry	Conditions	Results
1	KMnO_4 , CH_2Cl_2 , H_2O , AcOH , Adogen 64, reflux, 3 h ¹	Over-oxidation ^a
2	KMnO_4 , CH_2Cl_2 , AcOH , Adogen 64, reflux 1.5 h ¹	30%
3	KMnO_4 , Acetone, H_2O , MgSO_4 , NaHCO_3 , rt, 45 min ²	45%
4	I_2/DMSO , 150 °C, 16 h ³	Over-oxidation ^a

5	PdCl ₂ /DMSO, 130 °C, 4 h ⁴	53%
6	NBS/DMSO, rt, 10 min ⁴	Bromination ^b
7	HBr/DMSO, 130 °C, 3 h ⁵	Bromination ^b
8	(CF ₃ COO) ₂ IPh, DMSO, 130 °C, 3 h ⁶	No reaction
9	RuCl ₃ /NaIO ₄ , H ₂ O/CH ₃ CN/CCl ₄ , reflux, 2 h ^{7,8}	SM and over-oxidation ^a
10	OsO ₄ , Me ₃ NO, <i>t</i> -BuOH, H ₂ O, reflux, 5 h ^{9,10}	No reaction

^a4-Fluorobenzoic acid was isolated. ^bBased on MS, the product was not isolated.

References for Table 1:

- ¹Lee, D.G.; Chang, V.S. *J. Org. Chem.* 1979, 44, 2726-2730.
- ²Srinivasan, N.S.; Lee, D.G. *J. Org. Chem.* 1979, 44, 1574.
- 5 ³Dötz, F.; Brand, J.D.; Ito, S.; Gherghel, L.; Müllen, K. *J. Am. Chem. Soc.* 2000, 122, 7707-7717; Ito, S.; Wehmeier, M.; Brand, J.D.; Kubel, C.; Epsch, R.; Rabe, J.P.; Mullen, K. *Chem.—Eur. J.* 2000, 6, 4327-4342.
- ⁴Chi, K-W; Yusubov, M.S.; Filimonov, V.D. *Synth. Commun.* 1994, 24, 2119.
- ⁵Yusubov, M.S.; Filimonov, V.D.; Vasilyeva, V.P.; Chi, K-W. *Synthesis* 1995, 10, 1234-1236.
- 10 ⁶Kita, Y.; Yakura, T.; Terashi, H.; Haruta, J.; Tamura, Y. *Chem. Pharm. Bull.* 1989, 37, 891-894.
- ⁷Sharpless, K.B.; Lauer, R.F.; Repic, O.; Teranishi, A.Y.; Williams, D.R. *J. Am. Chem. Soc.* 1971, 93, 3303;
- 15 ⁸Pattenden, G.; Tankard, M.; Cherry, P.C. *Tetrahedron Lett.* 1993, 34, 2677-2680.
- ⁹Minato, M.; Yamamoto, K.; Tsuji, J. *J. Org. Chem.* 1990, 55, 766-768.
- ¹⁰Page, P.C.B.; Rosenthal, S. *Tetrahedron Lett.* 1986, 27, 1947-1950.

The oxidation procedures using KMnO₄ and PdCl₂ were further investigated. In contrast with the KMnO₄ oxidation, the PdCl₂/DMSO oxidizing system exhibited drawbacks, requiring high Pd loading (~10%), prolonged reaction time, and elevated temperatures (130 °C) to achieve reasonably good conversion. Lower Pd loading caused incomplete reaction and raising the temperature caused side reactions. A Pd on C/CuCl₂/DMSO system produced similar results (Yusubov, M.S. et al. *Synthesis* 1995, 10, 1234-1236). These methods also required column chromatography to purify the final product, making them less well-suited for large-scale preparations. Although oxidation

using KMnO_4 was more promising in terms of clean reaction and easy purification, over oxidation was a major disadvantage. Preparation of 1,2-diketones by oxidizing alkynes with finely powdered potassium permanganate has been reported (Srinivasan, N.S. et al. *J. Org. Chem.* 1979, 44(9), 1574) for a small class of 1,2-diketones that are unrelated to the compounds synthesized according to the present invention. These reference teachings on the use of potassium permanganate do not teach or suggest the selection of the entities to be oxidized according to this invention, and they do not teach or suggest the specific oxidation reactions that will accomplish such oxidation with the features of the methodology according to this invention. After screening numerous conditions, it was found that the key to obtaining good yields with the chemical entities of this invention was to use finely powdered KMnO_4 and to control the reaction time while the reaction was proceeding in a buffered solution. In some embodiments the finely powdered KMnO_4 was KMnO_4 (Cairox M[®]), purchased from Carus Chemical Company. An example of such buffered solution used in embodiments of this invention is an acetone/ H_2O solution buffered with MgSO_4 and NaHCO_3 . The buffering is preferably performed in embodiments of this invention to control the pH in the range from about 7 to about 8. Some embodiments of this invention were performed with the oxidation being performed in a solution buffered at a pH of about 7.5. Under these optimized conditions, the desired diketone **6a** was obtained consistently in 65-70% yields on 5-g scale after simple aqueous workup and without column chromatography.

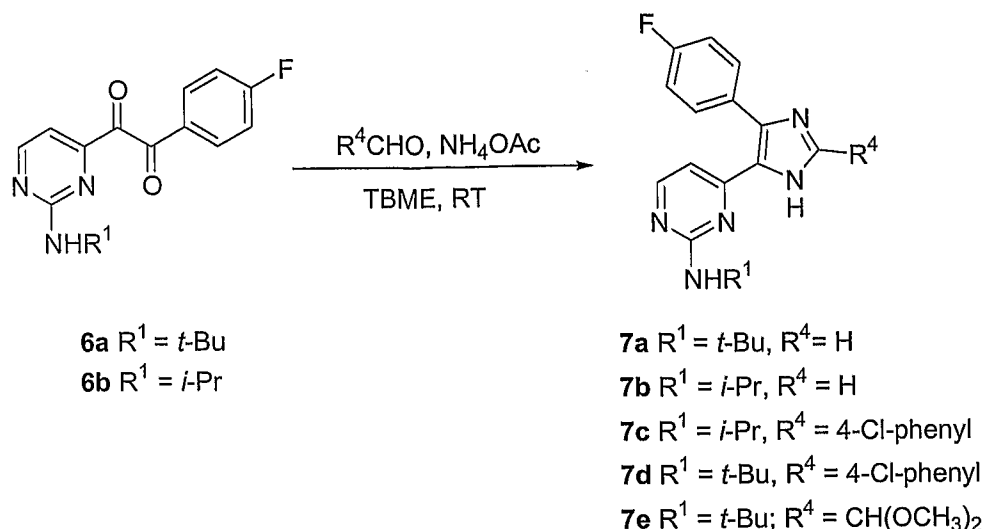
Many literature methods have been reported that efficiently oxidize simple diphenylacetylene compounds. A variety of these methods were examined to oxidize pyrimidinyl-substituted acetylene analogs, but were not successful. Therefore, based on the application of conventional methods from the literature and the poor results as applied to compounds of Formula (I), the success of the finely powdered KMnO_4 procedure was unexpected.

Reaction control was achieved by monitoring the reaction and quenching it by the addition of NaHSO_3 when complete.

Using the method described above, *iso*-propyl analog **6b** was also prepared in good yield. Cyclocondensation of the diketones with ammonium

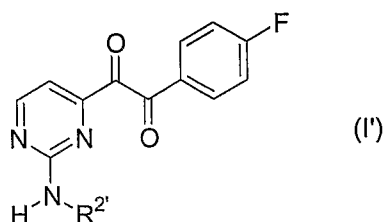
acetate and an aldehyde efficiently provided various pyrimidinyl-substituted imidazoles.

Scheme 6



Embodiments of this invention provide a concise, 6-step sequence to synthesize 4-aryl-5-pyrimidinyl imidazoles—an important scaffold useful in medicinal chemistry, such as in anticancer, antiviral, and anti-inflammatory medicinal chemistry. The methodology is well-suited to the preparation of a number of related analogs.

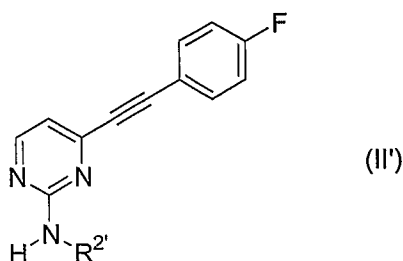
There are provided by the present invention methods of making amino substituted 1-(pyrimidin-4-yl)-2-phenyl-ethane-1,2-diones of Formula (I'):



wherein

$R^{2'}$ is isopropyl or t-butyl;

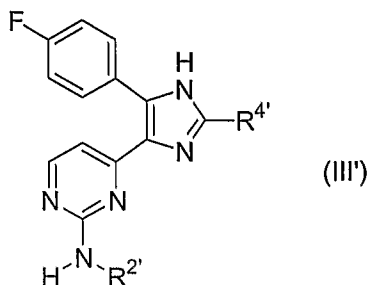
comprising oxidizing an alkyne of Formula (II'):



wherein $R^{2'}$ is defined as above,

with finely powdered potassium permanganate in a buffered acetone/H₂O solution.

The present invention further contemplates methods of making imidazoles of Formula (III'):



and tautomers thereof, wherein

R^{2'} is defined as above; and

R^{4'} is -H, 4-chlorophenyl, or -CH(OCH₃)₂;

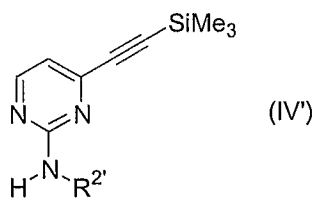
comprising oxidizing an alkyne of Formula (II') to a 1,2-diketone of Formula (I')

with finely powdered potassium permanganate in a buffered acetone/H₂O solution.

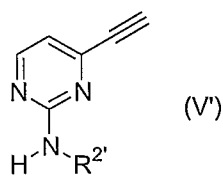
The present invention further contemplates methods of making compounds of Formula (I'), comprising at least one of:

a) reacting 2,4-dichloropyrimidine with (trimethylsilyl)acetylene to form 2-chloro-4-trimethylsilanylethynyl-pyrimidine;

b) reacting 2-chloro-4-trimethylsilanylethynyl-pyrimidine with R^{2'}NH₂ to form a (trimethylsilyl)alkyne of Formula (IV'):



c) deprotecting a (trimethylsilyl)alkyne of Formula (IV') to form an alkyne of Formula (V'):

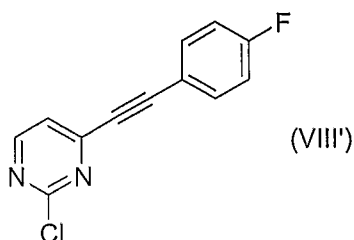


and

d) reacting an alkyne of Formula (V') with 4-iodo-fluorobenzene to form a compound of Formula (II');
wherein $R^{2'}$ is defined as above.

The present invention further contemplates methods of making
5 compounds of Formula (I'), comprising at least one of:

a) reacting 2,4-dichloropyrimidine with 1-ethynyl-4-fluorobenzene to form a compound of formula (VIII'):



; and

b) reacting a compound of formula (VIII') with $R^{2'}NH$ to form a compound of
10 Formula (II'), wherein $R^{2'}$ is defined as above.

Examples

In order to illustrate the invention, the following examples are included.
These examples do not limit the invention. They are meant to suggest a
15 method of practicing the invention. Those of ordinary skill in the art may find
other methods of practicing the invention, which are obvious to them in light of
the teachings provided herein. However, those methods are deemed to be
within the scope of this invention.

Gas chromatograph-mass spectrometry (GC-MS) was performed on
20 Shimazu GC-17A Gas Chromatograph and QP5000 Mass Spectrometer using
electrospray ionization (ESI) in either positive or negative modes as indicated.
Calculated mass corresponds to the exact mass.

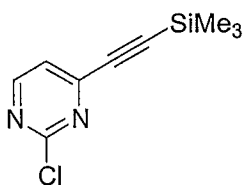
NMR spectra were obtained on an INOVA-400 NMR spectrometer (^1H ,
400 MHz; ^{13}C , 100 MHz) or Bruker 500 NMR spectrometer (^1H , 500 MHz; ^{13}C ,
25 125 MHz) as solutions in $CDCl_3$ and were internally referenced to the solvent
(^1H , 7.26 ppm; ^{13}C , 77.23 ppm). The format of the ^1H NMR data below is:
chemical shift in ppm (multiplicity, coupling constant J in Hz, integration).

Infrared (IR) Spectroscopy was performed on a Nicolet 510 FT-IR with a
resolution of 4 cm^{-1} on dry film. IR absorptions are reported in cm^{-1} .

Uncalibrated melting points were taken on a Thomas-Hoover melting point apparatus in open capillary tubes. Elemental analyses were performed by NuMega Resonance Labs, Inc., San Diego, CA.

Thin-layer chromatography was performed using Merck silica gel 60 F₂₅₄ plates, eluting with 20% EtOAc/hexanes unless otherwise specified, and visualizing with UV, I₂, or phosphomolybdic acid stain. Normal phase flash column chromatography (FCC) was typically performed using Merck silica gel 60.

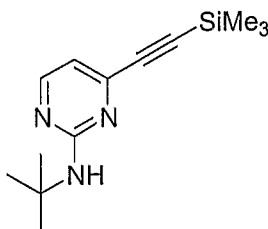
Solvents such as THF, CH₂Cl₂, and CH₃CN were dried over 4 Å molecular sieves. The water level of dried solvents was titrated with a Fisher Coulomatic K-F titrator. Other solvents were reagent grade and used as received. Unless otherwise specified, all reactions were performed under a nitrogen atmosphere. Unless otherwise specified, reactions were performed at room temperature. Solutions were concentrated under reduced pressure on a rotary evaporator.



Example 1; 2-Chloro-4-[trimethylsilyl]ethynylpyrimidine.

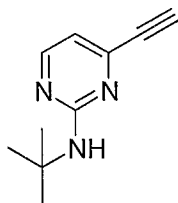
To a mixture of Pd(PPh₃)₂Cl₂ (0.9 g) and PPh₃ (0.7 g) in THF (200 mL) and Et₃N (300 mL) was added 2,4-dichloropyrimidine (40 g, 0.27 mol) under a stream of N₂. After bubbling N₂ into the solution for 15 min, CuI (0.5 g) was added, followed by (trimethylsilyl)acetylene (29 g, 0.29 mol). The mixture was heated at reflux for 4.5 h. The mixture was cooled to rt and filtered, washing with EtOAc. The filtrate was concentrated and the residue was diluted with hexanes (500 mL) and loaded directly onto a short pad of SiO₂. The product was eluted with 10% EtOAc/hexanes to provide a light orange solid (49.3 g), which was used without further purification. TLC: R_f = 0.42. mp 51-54 °C. IR: 3125 (w), 2961 (w), 1557 (s), 1523 (s). ¹H NMR: 8.58 (d, J = 5.0 Hz, 1H), 7.30 (d, J = 5.0 Hz, 1H), 0.28 (s, 9H). ¹³C NMR: 162.23, 160.16, 153.41, 122.52,

104.23, 100.75, 0.01. Anal. Calcd for $C_9H_{11}ClN_2Si$: C, 51.29; H, 5.26; N, 13.29. Found: C, 51.45; H, 5.16; N, 13.33.



5 Example 2; 2-*tert*-Butylamino-4-[trimethylsilylethynyl]pyrimidine.

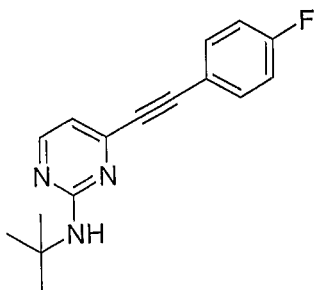
A mixture of 2-chloro-4-[trimethylsilylethynyl]pyrimidine (25 g, 0.12 mol) and *tert*-butylamine (100 mL) was heated to 80 °C for 2 d in a sealed tube. The mixture was cooled to rt and triturated with hexanes (100 mL). The resulting white precipitate was filtered and washed with hexanes. The filtrate was
10 concentrated to give the crude product as a brown oil, which was used in the following reaction without further purification. TLC: R_f = 0.40. mp 71-73 °C. IR: 3293 (br, w), 2962 (w), 1569 (s). ^1H NMR: 8.22 (d, J = 5.0 Hz, 1H), 6.57 (d, J = 5.0 Hz, 1H), 5.19 (s, 1H), 1.42 (s, 9H), 0.26 (s, 9H). ^{13}C NMR: 162.38, 158.15, 150.95, 112.94, 102.77, 97.62, 51.41, 29.25, -0.11. Anal. Calcd for
15 $C_{13}H_{21}N_3Si$: C, 63.11; H, 8.56; N, 16.98. Found: C, 63.20; H, 8.52; N, 16.70.



Example 3; *tert*-Butylamino-4-ethynylpyrimidine.

A solution of 2-*tert*-butylamino-4-[trimethylsilylethynyl]pyrimidine (from Example
20 2) in CH_3OH (150 mL) was treated with a solution of KOH (30 mg) in CH_3OH (5 mL). After 30 min, additional KOH (30 mg) in CH_3OH (5 mL) was added. After a further 30 min, the mixture was concentrated and the residue was diluted with hexanes and loaded directly onto a short pad of SiO_2 . The product was
25 eluted with 10% EtOAc in hexanes to provide the crude product as a light brown oil (18.6 g, 90% for 2 steps), which was used without further purification. TLC: R_f = 0.29. IR: 3294 (m), 2965 (m), 2114 (w), 1571 (s). ^1H NMR: 8.23 (d,

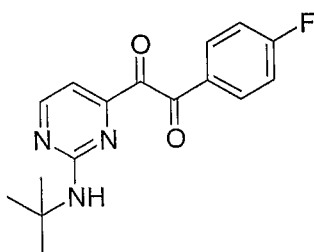
$J = 5.0$ Hz, 1H), 6.60 (d, $J = 5.0$ Hz, 1H), 5.20 (s, 1H), 3.15 (s, 1H), 1.43 (s, 9H). ^{13}C NMR: 161.97, 157.99, 149.87, 112.63, 81.71, 78.72, 51.06, 28.80.



5 Example 4; 2-*tert*-Butylamino-4-[4-fluoro-phenylethynyl]pyrimidine.

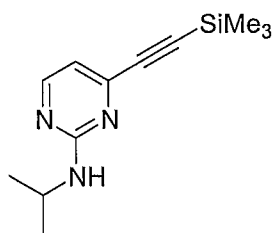
To a mixture of $\text{Pd}(\text{PPh}_3)\text{Cl}_2$ (0.4 g) in Et_3N (150 mL) and THF (150 mL) under a stream of N_2 , was added *tert*-butylamino-4-ethynylpyrimidine (18.6 g, 0.11 mol). After bubbling N_2 into the solution for 15 min, 4-iodo-fluorobenzene (23.6 g, 0.11 mol) and CuI (0.22 g) were added sequentially. The mixture was stirred
 10 at rt for 2.5 h. The precipitate was filtered and washed with EtOAc. The filtrate was concentrated and the residue was diluted with EtOAc and loaded directly onto a short pad of silica gel. The product was eluted with 10% EtOAc in hexanes to afford the crude product, which was recrystallized from EtOAc/hexanes to give the title compound as a light yellow solid (25 g, 84%).

15 TLC: $R_f = 0.30$. mp 97-99 °C. IR: 3287 (w), 2964 (w), 2222 (w), 1566 (s). ^1H NMR: 8.26 (d, $J = 4.2$ Hz, 1H), 7.60-7.55 (m, 2H), 7.10-7.00 (m, 2H), 6.65 (d, $J = 4.9$ Hz, 1H), 5.22 (s, 1H), 1.45 (s, 9H). ^{13}C NMR: 164.19, (162.19, 162.03), 157.77, 150.83, (134.35, 134.29), (117.84, 117.81), (115.94, 115.76), 112.37, 89.91, 87.24, 51.07, 28.86. Anal. Calcd for $\text{C}_{16}\text{H}_{16}\text{FN}_3$: C, 71.36; H, 5.99; N, 15.60. Found: C, 71.25; H, 5.95; N, 15.66.
 20



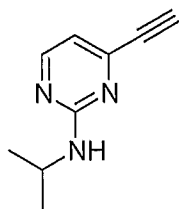
Example 5; 1-(2-*tert*-Butylamino-pyrimidin-4-yl)-2-(4-fluoro-phenyl)-ethane-1,2-dione.

To a solution of 2-*tert*-butylamino-4-[4-fluoro-phenylethynyl]pyrimidine (5.0 g, 19 mmol) in acetone (225 mL) was added a solution of NaHCO₃ (0.40 g) and MgSO₄ (4.0 g) in H₂O (120 mL). Under vigorous stirring, KMnO₄ (Cairox M from Carux Co.; 11.1 g, 70 mmol) was added at rt in one portion. After 4 min, the reaction was quenched by the addition of NaHSO₃ (15 g) in H₂O (30 mL). After stirring for 10 min, the mixture was acidified with 50% H₂SO₄ to pH < 2, and extracted with 1:1 Et₂O/hexanes (300 mL) and EtOAc (50 mL). The combined organic layers were washed with aq. K₂CO₃ (1 mol/L, saturated with NaCl; 100 mL) and brine (100 mL), dried (Na₂SO₄), and concentrated to provide the diketone as a light yellow solid (4.0 g, 71%). TLC: R_f = 0.15. mp 123-124 °C. IR: 3297 (br w), 2968 (w), 1711 (m) 1680 (m), 1596 (s), 1583 (s). ¹H NMR (95% purity): 8.54 (d, *J* = 3.4 Hz, 1H), 8.0-7.90 (m, 2H), 7.22-7.12(m, 3H), 5.29 (s, 1H), 1.18 (s, 9H). ¹³C NMR: 195.22, 167.89, 165.33, (161.80, 160.37), 157.56, (132.12, 132.02), (129.72, 129.70), (116.45, 116.23), 106.42, 51.11, 28.25. Anal. Calcd for C₁₆H₁₆FN₃O₂: C, 63.78; H, 5.35; N, 13.95. Found: C, 63.85; H, 5.22; N, 13.94.



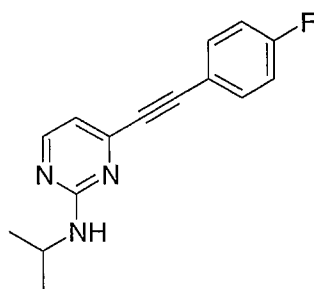
Example 6; 2-*iso*-Propylamino-4-[trimethylsilylethynyl]pyrimidine.

The title compound was prepared according to the methods described in Example 2, substituting isopropylamine for *tert*-butylamine. TLC: R_f = 0.31. mp 93-94 °C. IR: 3273 (br w), 2967 (m), 1570 (s). ¹H NMR: 8.23 (d, *J* = 5.0 Hz, 1H), 6.59 (d, *J* = 5.0 Hz, 1H), 5.02 (d, *J* = 5.5 Hz, 1H), 4.14 (sept, *J* = 6.4 Hz, 1H), 1.21 (d, *J* = 6.4 Hz, 6H), 0.25 (s, 9H). ¹³C NMR: 162.06, 158.68, 151.33, 113.21, 102.70, 98.14, 43.20, 23.28, 0.10.



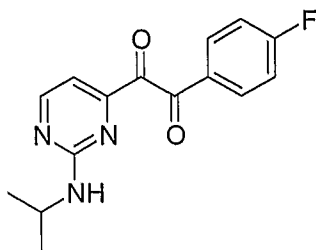
Example 7; 2-iso-Propylamino-4-ethynylpyrimidine.

The title compound was prepared according to the methods described in Example 3, substituting 2-iso-propylamino-4-[trimethylsilylethynyl]pyrimidine for *tert*-butylamino-4-ethynylpyrimidine (92% for 2 steps). TLC: R_f = 0.24. mp 84-85 °C. IR: 3256 (br, m), 2974 (w), 2113 (w), 1568 (s). ^1H NMR: 8.25 (d, J = 5.0 Hz, 1H), 6.62 (d, J = 5.0 Hz, 1H), 5.05 (s, 1H), 4.14 (sept, J = 6.5 Hz, 1H), 3.19 (s, 1H), 1.22 (d, J = 6.5 Hz, 6H). ^{13}C NMR: 162.05, 158.84, 150.66, 113.22, 81.98, 79.54, 43.19, 23.20. Anal. Calcd for $\text{C}_9\text{H}_{11}\text{N}_3$: C, 67.04; H, 6.88; N, 26.07. Found: C, 67.38; H, 6.88; N, 26.32.



Example 8; 2-iso-Propylamino-4-[4-fluorophenylethynyl]pyrimidine.

The title compound was prepared according to the methods described for Example 4 (89% yield). TLC: R_f = 0.19. mp 128-129 °C. IR: 3260 (br w), 2970 (s), 2216 (w), 1564 (s). ^1H NMR: 8.28 (d, J = 4.6 Hz, 1H), 7.60-7.50 (m, 2H), 7.10-7.00 (m, 2H), 6.66 (d, J = 4.9 Hz, 1H), 5.05 (d, J = 7.4 Hz, 1H), 4.17 (sept, J = 6.5 Hz, 1H), 1.24 (d, J = 6.5 Hz, 6H). ^{13}C NMR: 164.23, (162.23, 161.71), 158.27, 151.24, (134.39, 134.32), (117.76, 117.74), (115.96, 115.78), 112.62, 90.37, 87.18, 42.84, 22.89. Anal. Calcd for $\text{C}_{15}\text{H}_{14}\text{FN}_3$: C, 70.57; H, 5.53; N, 16.46. Found: C, 70.60; H, 5.42; N, 16.45.

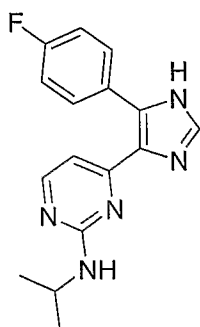


Example 9; 1-(2-*iso*-Propylamino-pyrimidin-4-yl)-2-(4-fluoro-phenyl)-ethane-1,2-dione.

The title compound was prepared according to the methods described in

- 5 Example 5 (90% yield). TLC: R_f = 0.14. mp 75-77 °C. IR: 3275 (br, w), 2971 (w), 1710 (m), 1682 (m). ^1H NMR (90% purity): 8.57 (s, 1H), 8.00-7.90 (m, 2H), 7.23-7.15 (m, 3H), 5.08 (s, 1H), 3.73 (br s, 1H), 1.09 (s, 6H). Anal. Calcd for $\text{C}_{15}\text{H}_{14}\text{FN}_3\text{O}_2$: C, 62.71; H, 4.91; N, 14.63; Found: C, 62.90; H, 4.84; N, 14.76.

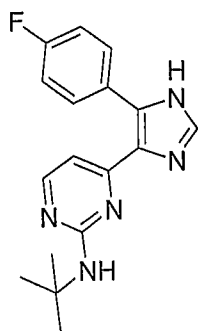
10



Example 10; tert-Butyl-{4-[5-(4-fluoro-phenyl)-1H-imidazol-4-yl]-pyrimidin-2-yl}-amine.

- A mixture of 1-(2-*iso*-propylamino-pyrimidin-4-yl)-2-(4-fluoro-phenyl)-ethane-1,2-dione (12.5 g, 43.5 mmol), hexamethylenetetramine (12.2 g, 87.1 mmol), NH_4OAc (17 g, 220 mmol), and Na_2SO_4 (12 g) in AcOH (150 mL) was heated at 65 °C. After 4 h, the mixture was cooled to rt. The mixture was filtered, washing with AcOH. The filtrate was concentrated, and the residue was dissolved in CH_2Cl_2 . The organic solution was washed with 1 N NaOH, dried (15 Na_2SO_4), and concentrated. The crude product was purified by column chromatography (MeOH/hexanes) to afford the title compound as a light yellow solid (6.8 g, 52%). TLC (10% MeOH/ CH_2Cl_2): R_f = 0.21. ^1H NMR: 8.13 (br s, 1H), 7.84 (br s, 1H), 7.61 (br s, 2H), 7.14 (t, J = 7.8 Hz, 2H), 6.87 (br s, 1H),
- 20

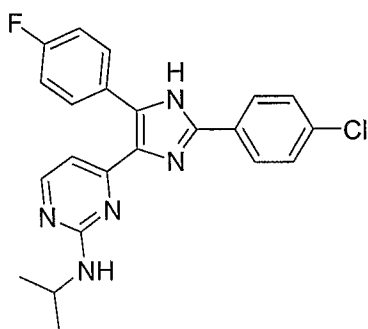
5.31 (br s, 1H), 4.14 (br s, 1H), 1.26 (d, $J = 9.8$ Hz, 6H). HRMS (ESI): $[M+H]^+$ calcd. for $C_{16}H_{17}FN_5$, 298.1463; found, 298.1461.



- 5 Example 11; tert-Butyl-{4-[5-(4-fluorophenyl)-1H-imidazol-4-yl]-pyrimidin-2-yl}-amine.

The title compound was prepared from 1-(2-*tert*-butylamino-pyrimidin-4-yl)-2-(4-fluorophenyl)-ethane-1,2-dione according to the methods described in Example 10 (56%). TLC (10% MeOH/ CH_2Cl_2): $R_f = 0.22$. ^1H NMR: 8.04 (d, $J = 5.3$ Hz, 1H), 7.75 (br s, 1H), 7.56 (dd, $J = 8.5, 5.5$ Hz, 2H), 7.12 (t, $J = 8.6$ Hz, 2H), 6.63 (d, $J = 5.3$ Hz, 1H), 5.76 (br s, 1H), 1.45 (s, 9H). ^{13}C NMR: 163.75, (161.78, 161.47), 157.33, 156.21, 140.42, 135.61, (130.97, 130.90), (130.07, 130.05), 126.13, (115.63, 115.46), 105.31, 50.86, 28.98. HRMS (ESI): $[M+H]^+$ calcd. for $C_{17}H_{19}FN_5$, 312.1619; found, 312.1631.

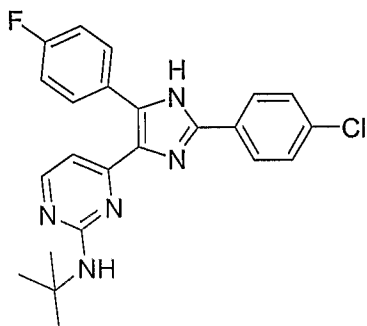
15



- Example 12; {4-[2-(4-Chlorophenyl)-5-(4-fluorophenyl)-1H-imidazol-4-yl]-pyrimidin-2-yl}-isopropyl-amine.

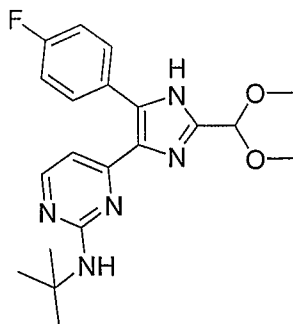
The title compound was prepared from 1-(2-*iso*-propylamino-pyrimidin-4-yl)-2-(4-fluorophenyl)-ethane-1,2-dione, 4-chlorobenzaldehyde, and NH_4OAc according to the methods described in Example 10 (62%). The reaction time was 48 h. TLC (50% EtOAc/hexanes): $R_f = 0.44$. ^1H NMR: 10.52 (br s, 1H),

8.11 (d, $J = 5.2$ Hz, 1H), 7.87 (d, $J = 8.5$ Hz, 2H), 7.61 (dd, $J = 7.6, 5.8$ Hz, 2H), 7.42 (d, $J = 8.5$ Hz, 2H), 7.13 (d, $J = 8.5$ Hz, 2H), 6.61 (br s, 1H), 5.22 (br s, 1H), 4.17 (br s, 1H), 1.25 (br s, 6H). ^{13}C NMR: 163.86, 161.88, 161.41, 158.06, 145.59, 135.41, (131.08, 131.02), 129.17, 126.84, (115.63, 115.46), 105.59, 42.83, 22.89 (weak signals for some carbon members). HRMS (ESI): $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{22}\text{H}_{20}\text{ClFN}_5$, 408.1386; found, 408.1404.



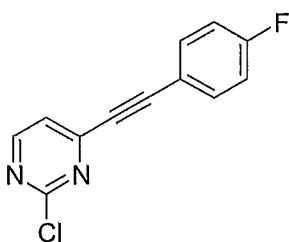
Example 13; tert-Butyl-{4-[2-(4-chloro-phenyl)-5-(4-fluoro-phenyl)-1H-imidazol-4-yl]-pyrimidin-2-yl}-amine.

The title compound was prepared from 1-(2-*tert*-butylamino-pyrimidin-4-yl)-2-(4-fluoro-phenyl)-ethane-1,2-dione, 4-chlorobenzaldehyde, and NH_4OAc according to the methods described in Example 12 (68%). TLC (50% EtOAc/hexanes): $R_f = 0.60$. ^1H NMR: 10.52 (br s, 1H), 8.10 (d, $J = 4.7$ Hz, 1H), 7.82 (d, $J = 8.5$ Hz, 2H), 7.65 (br s, 2H), 7.40 (d, $J = 8.3$ Hz, 2H), 7.12 (br s, 2H), 6.58 (br s, 1H), 5.29 (br s, 1H), 1.49 (s, 9H). ^{13}C NMR: 163.79, (161.82, 161.77), 157.86, 145.48, 135.32, (130.99, 130.93), 129.15, 127.68, 126.71, (115.63, 115.45), 105.32, 50.86, 29.02 (weak signals for some carbon members). HRMS (ESI): $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{23}\text{H}_{22}\text{ClFN}_5$, 422.1542; found, 422.1563.



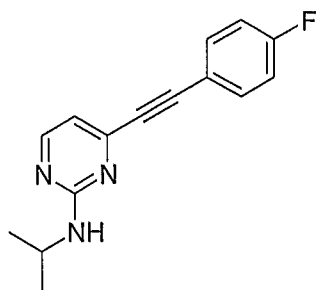
Example 14; tert-Butyl-{4-[2-dimethoxymethyl-5-(4-fluoro-phenyl)-1H-imidazol-4-yl]-pyrimidin-2-yl}-amine.

The title compound was prepared from 1-(2-*tert*-butylamino-pyrimidin-4-yl)-2-(4-fluoro-phenyl)-ethane-1,2-dione, glyoxal 1,1-dimethylacetal, and NH₄OAc, using tert-butyl methyl ether as the solvent, according to the methods described in Example 10 (20%). The reaction time was 48 h at rt. TLC (50% EtOAc/hexanes): R_f = 0.19. ¹H NMR (CDCl₃): 10.29 (br s, 1H), 8.07 (d, *J* = 5.2 Hz, 1H), 7.60 (dd, *J* = 8.0, 5.6 Hz, 2H), 7.11 (t, *J* = 8.6 Hz, 2H), 6.57 (d, *J* = 5.2 Hz, 1H), 5.55 (s, 1H), 5.23 (br s, 1H), 3.46 (s, 6H), 1.49 (s, 9H). ¹³C NMR (CDCl₃): 163.73, (161.87, 161.76), 157.88, 155.38, 145.20, 142.04, (131.03, 130.97), 130.69, 124.84, (115.50, 115.33), 105.33, 98.08, 53.60, 50.87, 29.04. MS (ESI): [M+H]⁺ calcd. for C₂₀H₂₄FN₅O₂, 385.19; found, 386.1.



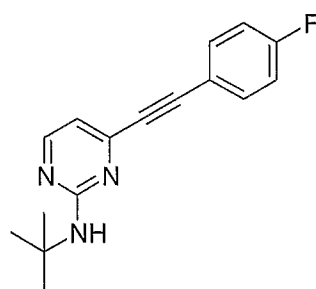
Example 15; 2-Chloro-4-(4-fluorophenylethynyl)-pyrimidine.

The title compound was prepared from 2,4-dichloropyrimidine and 1-ethynyl-4-fluorobenzene using methods analogous to those described in Example 2 (65%). TLC (25% EtOAc/hexanes): R_f = 0.21. mp 125-126 °C. IR: 3049 (w), 2210 (w), 1559 (s). ¹H NMR (CDCl₃): 8.61 (d, *J* = 5.0 Hz, 1H), 7.70-7.60 (m, 2H), 7.38 (d, *J* = 5.0 Hz, 1H), 7.13-7.06 (m, 2H). ¹³C NMR (CDCl₃): 163.99 (d, *J*_{C-F} = 252 Hz), 161.86, 159.66, 153.39, 134.96 (d, *J*_{C-F} = 8.6 Hz), 121.77, 116.96 (d, *J*_{C-F} = 3.4 Hz), 116.40 (d, *J*_{C-F} = 22 Hz), 95.27, 85.89. Anal. Calcd for C₁₂H₆ClFN₂: C, 61.95; H, 2.60; N, 12.04; Found: C, 62.15; H, 2.83; N, 12.00.



Example 16; Alternative preparation for 2-*iso*-Propylamino-4-[4-fluoro-phenylethynyl]pyrimidine.

5 A solution of 2-chloro-4-(4-fluoro-phenylethynyl)-pyrimidine (1 equiv.) in iso-propylamine (0.2 M) is heated at 35 °C for 24 h. The mixture is cooled to rt, diluted with water, and extracted with EtOAc. The organic layer is concentrated and the residue purified by column chromatography to provide the title compound.

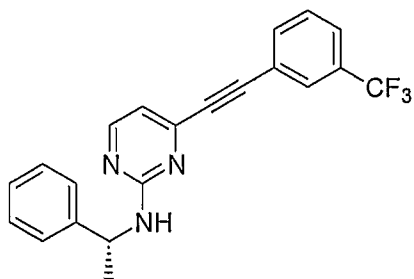


10

Example 17; Alternative preparation for 2-*tert*-Butylamino-4-[4-fluoro-phenylethynyl]pyrimidine.

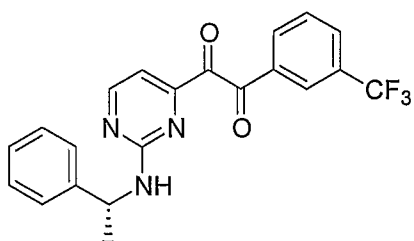
15 A solution of 2-chloro-4-(4-fluoro-phenylethynyl)-pyrimidine (1 equiv.) in *tert*-butylamine (0.2 M) is heated at 80 °C in a sealed tube for 24 h. The mixture is cooled to rt, diluted with water, and extracted with EtOAc. The organic layer is concentrated and the residue purified by column chromatography to provide the title compound.

20 The compounds in Examples 18-21 may be prepared using the methods described in the preceding examples.

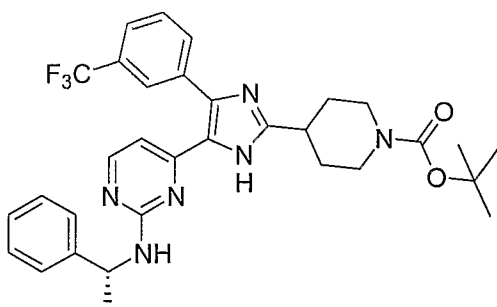


Example 18; (R)-(1-Phenyl-ethyl)-[4-(3-trifluoromethyl-phenylethynyl)-pyrimidin-2-yl]-amine.

5



Example 19; (R)-1-[2-(1-Phenyl-ethylamino)-pyrimidin-4-yl]-2-(3-trifluoromethyl-phenyl)-ethane-1,2-dione.



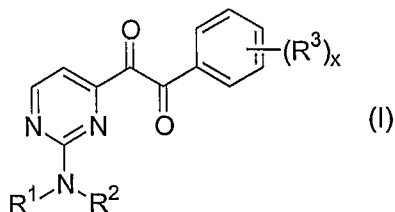
Example 20; (R)-4-[5-[2-(1-Phenyl-ethylamino)-pyrimidin-4-yl]-4-(3-trifluoromethyl-phenyl)-1H-imidazol-2-yl]-piperidine-1-carboxylic acid tert-butyl ester.

Deprotection and alkylation methods known in the art may be used to convert Example 20 into compound **2**.

15

What is claimed is:

1. A method of making amino substituted 1-(pyrimidin-4-yl)-2-phenyl-ethane-1,2-diones of Formula (I):



5

wherein:

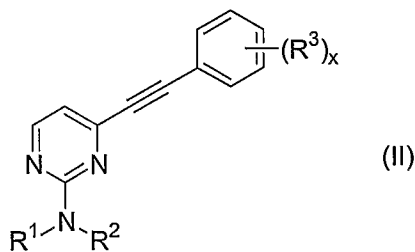
R^1 and R^2 are each independently selected from the group consisting of -H, -C₁₋₆alkyl, -C₃₋₈cycloalkyl, benzyl, and 1-methylbenzyl;

x is 0, 1, 2, or 3; and

- 10 each R^3 is independently selected from the group consisting of -OH, -Cl, -F, -C₁₋₆alkyl, -C₃₋₈cycloalkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, phenyl, -CN, -NO₂, -N(R^a) R^b , -C(O)N(R^a) R^b , -N(R^c)C(O) R^d , -N(R^c)SO₂C₁₋₆alkyl, -C(O)C₁₋₆alkyl, -S(O)₀₋₂C₁₋₆alkyl, -SO₂N(R^a) R^b , -CO₂H, and -CO₂C₁₋₆alkyl, where R^a and R^b are each independently -H or -C₁₋₆alkyl, and where R^c and R^d are each
- 15 independently -H or -C₁₋₆alkyl;

and enantiomers, diastereomers, and pharmaceutically acceptable salts and esters thereof; comprising:

oxidizing an alkyne of Formula (II):



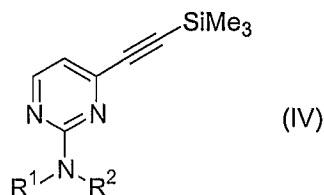
- 20 with finely powdered potassium permanganate, wherein R^1 , R^2 , R^3 , and x are defined as in compound of Formula (I).

2. A method as recited in claim 1, wherein said oxidizing is performed in a buffered acetone/H₂O solution.

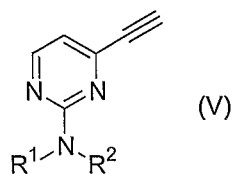
25

3. A method as recited in claim 1, further comprising: reacting 2,4-dichloropyrimidine with (trimethylsilyl)acetylene to form 2-chloro-4-trimethylsilanylethynyl-pyrimidine.

- 5 4. A method as recited in claim 1, further comprising: reacting 2-chloro-4-trimethylsilanylethynyl-pyrimidine with R^1R^2NH to form a (trimethylsilyl)alkyne of Formula (IV):



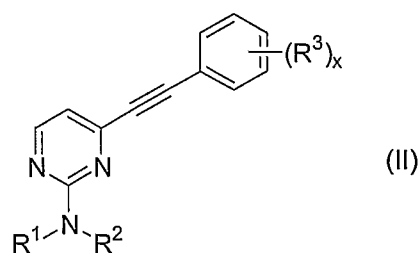
- 10 5. A method as recited in claim 4, further comprising: deprotecting a (trimethylsilyl)alkyne of Formula (IV) to form an alkyne of Formula (V):



6. A method as recited in claim 1, further comprising: reacting an alkyne of
15 Formula (V) with a compound of Formula (VI):



to form a compound of Formula (II):



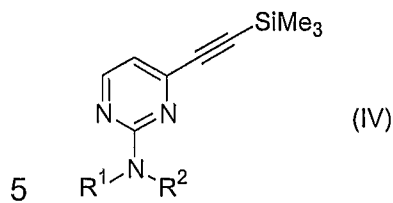
wherein HAL is I or Br.

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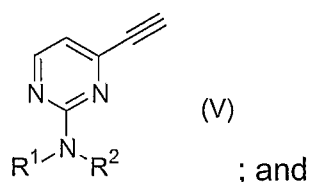
7. A method as recited in claim 1, further comprising:

reacting 2,4-dichloropyrimidine with (trimethylsilyl)acetylene to form 2-chloro-4-trimethylsilanylethynyl-pyrimidine;

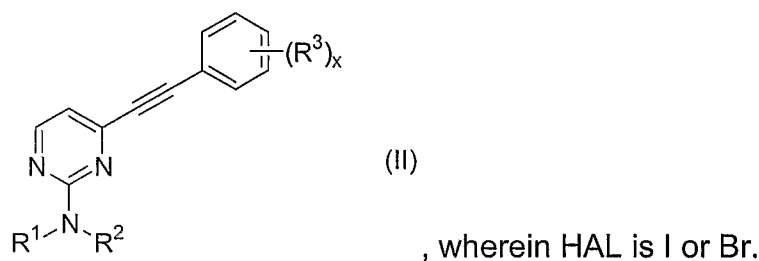
reacting 2-chloro-4-trimethylsilanylethynyl-pyrimidine with R^1R^2NH to form a (trimethylsilyl)alkyne of Formula (IV):



deprotecting the (trimethylsilyl)alkyne of Formula (IV) to form an alkyne of Formula (V):

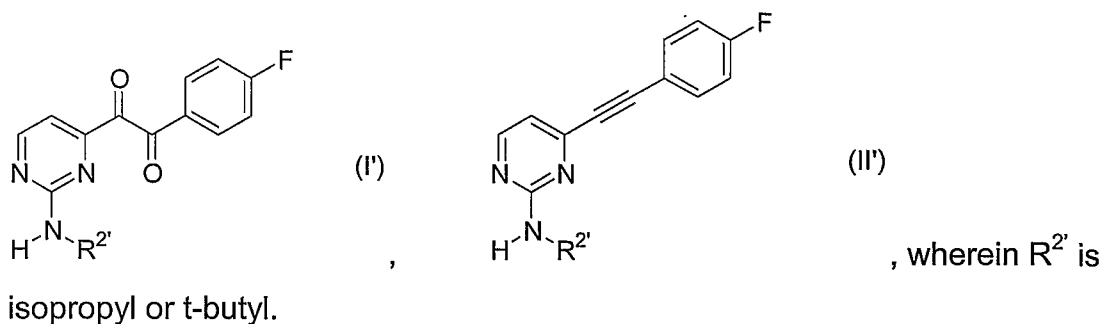


reacting the alkyne of Formula (V) with a compound of Formula (VI):



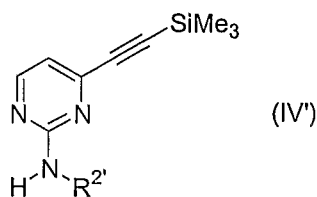
8. A method as recited in claim 1, wherein compound of Formula (I) is compound of Formula (I'), and compound of Formula (II) is compound of Formula (II'):

15

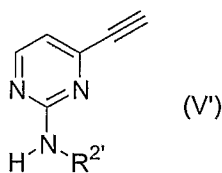


9. A method as recited in claim 8, further comprising: reacting 2,4-dichloropyrimidine with (trimethylsilyl)acetylene.

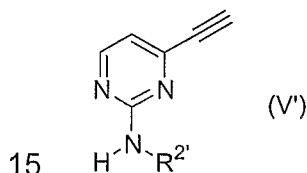
10. A method as recited in claim 8, further comprising: reacting 2-chloro-4-trimethylsilanylethynyl-pyrimidine with $R^{2'}NH_2$ to form a (trimethylsilyl)alkyne of Formula (IV'):



11. A method as recited in claim 10, further comprising: deprotecting a (trimethylsilyl)alkyne of Formula (IV') to form an alkyne of Formula (V'):

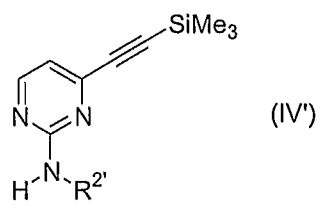


12. A method as recited in claim 8, further comprising: reacting an alkyne of Formula (V'):

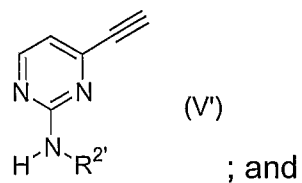


with 4-iodo-fluorobenzene to form a compound of Formula (II').

13. A method as recited in claim 8, further comprising:
 reacting 2,4-dichloropyrimidine with (trimethylsilyl)acetylene to form 2-chloro-4-trimethylsilanylethynyl-pyrimidine;
 reacting 2-chloro-4-trimethylsilanylethynyl-pyrimidine with $R^{2'}NH_2$ to form a (trimethylsilyl)alkyne of Formula (IV'):

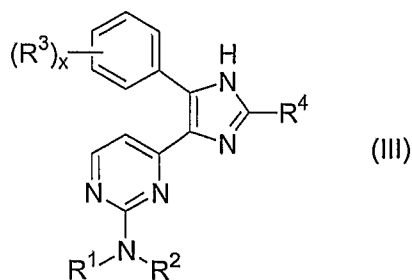


deprotecting the (trimethylsilyl)alkyne of Formula (IV') to form an alkyne of Formula (V'):



- 5 reacting the alkyne of Formula (V') with 4-iodo-fluorobenzene to form a compound of Formula (II').

14. A method of making imidazoles of Formula (III):



wherein

- 5 R¹ and R² are each independently selected from the group consisting of -H, -C₁₋₆alkyl, -C₃₋₈cycloalkyl, benzyl, and 1-methylbenzyl;

x is 0, 1, 2, or 3;

each R³ is independently selected from the group consisting of -OH, -Cl, -F,

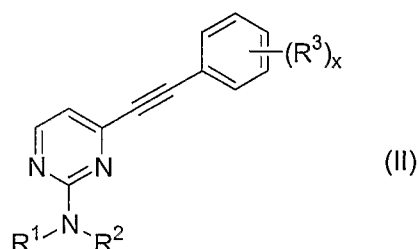
- 10 -C₁₋₆alkyl, -C₃₋₈cycloalkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, phenyl, -CN, -NO₂, -N(R^a)R^b, -C(O)N(R^a)R^b, -N(R^c)C(O)R^d, -N(R^c)SO₂C₁₋₆alkyl, -C(O)C₁₋₆alkyl, -S(O)₀₋₂C₁₋₆alkyl, -SO₂N(R^a)R^b, -CO₂H, and -CO₂C₁₋₆alkyl, where R^a and R^b are each independently -H or -C₁₋₆alkyl, and where R^c and R^d are each independently -H or -C₁₋₆alkyl; and

R⁴ is -H, -C₁₋₈alkyl, -C₃₋₈cycloalkyl, aryl, heteroaryl, heterocycloalkyl, or

- 15 -CH(OC₁₋₆alkyl)₂;

and tautomers, enantiomers, diastereomers, and pharmaceutically acceptable salts and esters thereof; comprising:

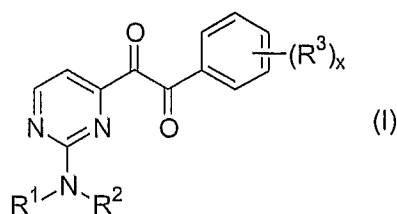
oxidizing an alkyne of Formula (II):



- 20 with finely powdered potassium permanganate, wherein R¹, R², R³, and x are defined as in compound of Formula (III).

15. A method as recited in claim 14, wherein said oxidizing is performed in a buffered acetone/H₂O solution.

16. A method as recited in claim 14, wherein said oxidizing said alkyne of Formula (II) generates a 1,2-diketone of Formula (I):



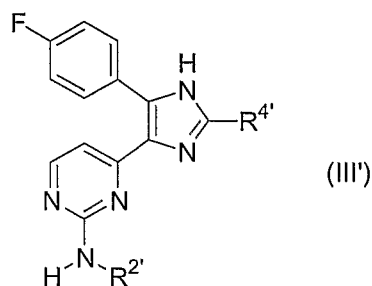
and further comprising reacting said 1,2-diketone of Formula (I) with at least one of $R^4\text{CHO}$ and a formaldehyde equivalent to generate a compound of Formula (III).

17. A method as recited in claim 16, wherein said reacting is performed in the presence of an ammonia equivalent.

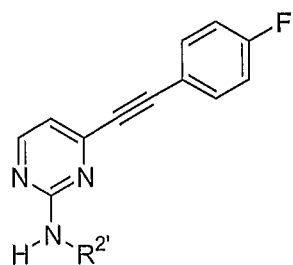
18. A method as recited in claim 17, wherein said ammonia equivalent is selected from the group consisting of ammonia, ammonium acetate, and mixtures thereof.

19. A method as recited in claim 16, wherein said formaldehyde equivalent is selected from the group consisting of hexamethylenetetramine, formaldehyde, and mixtures thereof.

20. A method as recited in claim 14, wherein said compound of Formula (III) is compound of Formula (III'):



or a tautomer thereof, and said compound of Formula (II) is compound of Formula (II'):



(II')

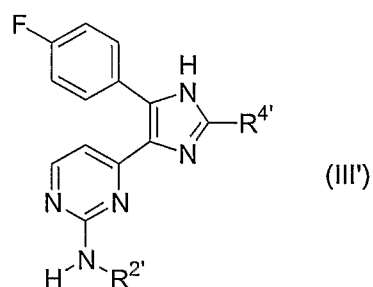
, wherein $\text{R}^{2'}$ is isopropyl or t-butyl, and $\text{R}^{4'}$ is H, 4-chlorophenyl, or $-\text{CH}(\text{OCH}_3)_2$.

21. A method of making 4/5-pyrimidinylimidazoles, comprising: reacting 2,4-dichloropyrimidine with a nucleophilic-attack-protected acetylene to form 2-chloro-4-protected-ethynyl-pyrimidine.

22. A method as recited in claim 21, wherein said nucleophilic-attack-protected acetylene is [(tri-C₁₋₄alkyl)silyl]acetylene and said 2-chloro-4-protected-ethynyl-pyrimidine is 2-chloro-4-(tri-C₁₋₄alkylsilyl)ethynylpyrimidine.

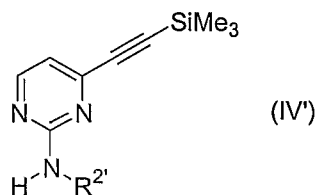
23. A method as recited in claim 22, wherein said [(tri-C₁₋₄alkyl)silyl]acetylene is (trimethylsilyl)acetylene and said 2-chloro-4-(tri-C₁₋₄alkylsilyl)ethynylpyrimidine is 2-chloro-4-trimethylsilyl)ethynylpyrimidine.

24. A method as recited in claim 23, wherein a 4/5-pyrimidinylimidazole of Formula (III') is formed:

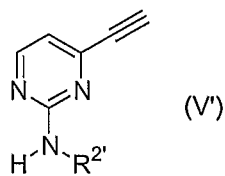


or a tautomer thereof, wherein R^{2'} is isopropyl or t-butyl, and R^{4'} is H, 4-chlorophenyl, or -CH(OCH₃)₂.

25. A method as recited in claim 24, further comprising: reacting said 2-chloro-4-trimethylsilyl)ethynylpyrimidine with R^{2'}NH₂ to form a (trimethylsilyl)alkyne of Formula (IV'):

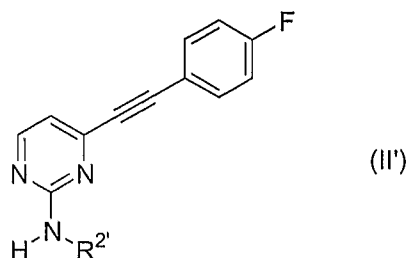


26. A method as recited in claim 25, further comprising: deprotecting the (trimethylsilyl)alkyne of Formula (IV') to form an alkyne of Formula (V'):



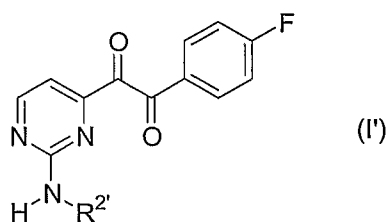
; and

reacting the alkyne of Formula (V') with 4-iodo-fluorobenzene to form an alkyne of Formula (II'):



5

27. A method as recited in claim 26, further comprising:
oxidizing the alkyne of Formula (II') with finely powdered potassium permanganate in a buffered solution to form a 1,2-diketone of Formula (I'):



10

28. A method as recited in claim 27, further comprising:
reacting said 1,2-diketone of Formula (I') in the presence of an ammonia equivalent with at least one of R⁴CHO and a formaldehyde equivalent to generate a compound of Formula (III').

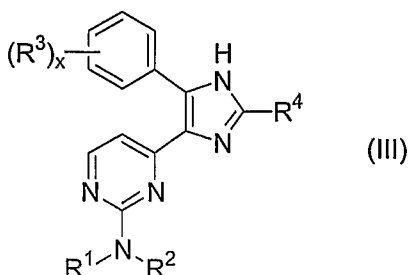
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29. A method as recited in claim 28, wherein said ammonia equivalent is selected from the group consisting of ammonia, ammonium acetate, and mixtures thereof.

20 30. A method as recited in claim 27, wherein said formaldehyde equivalent is selected from the group consisting of hexamethylenetetramine, formaldehyde, and mixtures thereof.

31. A method as recited in claim 27, wherein said buffered solution is buffered at a pH of about 7.5.

32. A method as in claim 23, wherein a 4/5-pyridinylimidazole of Formula (III) is formed:



wherein:

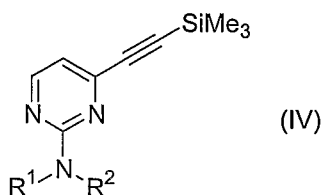
R^1 and R^2 are each independently selected from the group consisting of -H, -C₁₋₆alkyl, -C₃₋₈cycloalkyl, benzyl, and 1-methylbenzyl;

x is 0, 1, 2, or 3;

each R^3 is independently selected from the group consisting of -OH, -Cl, -F, -C₁₋₆alkyl, -C₃₋₈cycloalkyl, -OC₁₋₆alkyl, -CF₃, -OCF₃, phenyl, -CN, -NO₂, -N(R^a)R^b, -C(O)N(R^a)R^b, -N(R^c)C(O)R^d, -N(R^c)SO₂C₁₋₆alkyl, -C(O)C₁₋₆alkyl, -S(O)₀₋₂C₁₋₆alkyl, -SO₂N(R^a)R^b, -CO₂H, and -CO₂C₁₋₆alkyl, where R^a and R^b are each independently -H or -C₁₋₆alkyl, and where R^c and R^d are each independently -H or -C₁₋₆alkyl; and

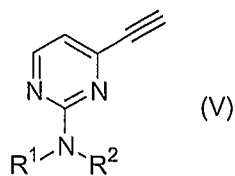
R^4 is -H, -C₁₋₈alkyl, -C₃₋₈cycloalkyl, aryl, heteroaryl, or -CH(OC₁₋₆alkyl)₂; and tautomers, enantiomers, diastereomers, and pharmaceutically acceptable salts and esters thereof.

33. A method as recited in claim 32, further comprising:
reacting 2-chloro-4-trimethylsilanylethynyl-pyrimidine with R¹R²NH to form a (trimethylsilyl)alkyne of Formula (IV):



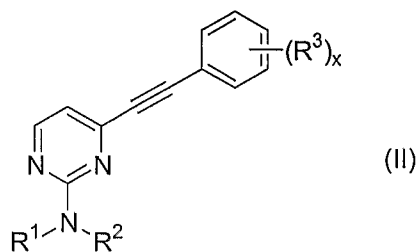
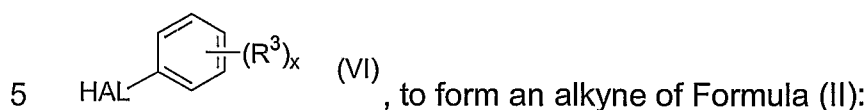
34. A method as recited in claim 33, further comprising:

deprotecting the (trimethylsilyl)alkyne of Formula (IV) to form an alkyne of Formula (V):



; and

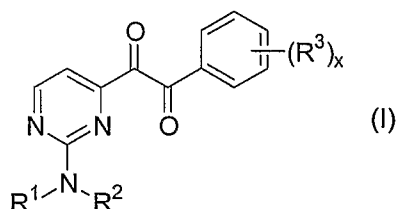
reacting the alkyne of Formula (V) with a compound of Formula (VI):



, wherein HAL is I or Br.

35. A method as recited in claim 34, further comprising:

10 oxidizing the alkyne of Formula (II) with finely powdered potassium permanganate to form a 1,2-diketone of Formula (I):



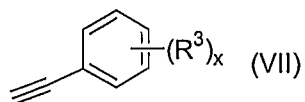
36. A method as recited in claim 35, further comprising:

15 reacting said 1,2-diketone of Formula (I) in the presence of an ammonia equivalent with at least one of R⁴CHO and a formaldehyde equivalent.

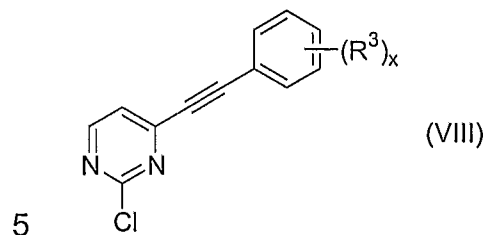
37. A method as recited in claim 36, wherein said ammonia equivalent is selected from the group consisting of ammonia, ammonium acetate, and mixtures thereof.

38. A method as recited in claim 36, wherein said formaldehyde equivalent is selected from the group consisting of hexamethylenetetramine, formaldehyde, and mixtures thereof.
- 5 39. A method as recited in claim 36, wherein said oxidizing the alkyne of Formula (II) is performed in a buffered solution, and said buffered solution is buffered at a pH in the range from about 7 to about 8.

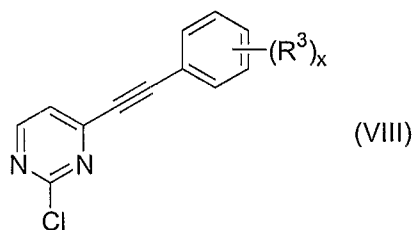
40. A method as recited in claim 1, further comprising: reacting 2,4-dichloropyrimidine with a compound of Formula (VII):



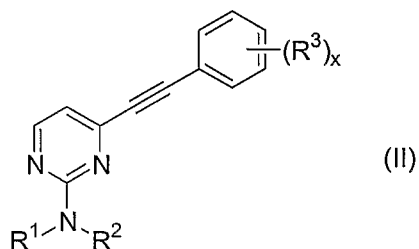
to form a compound of Formula (VIII):



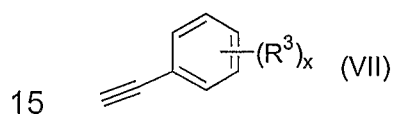
41. A method as recited in claim 1, further comprising: reacting a compound of Formula (VIII):



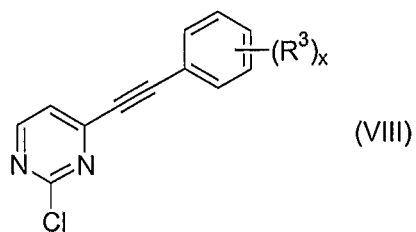
10 with R^1R^2NH to form a compound of Formula (II):



42. A method as recited in claim 1, further comprising:
reacting 2,4-dichloropyrimidine with a compound of Formula (VII):

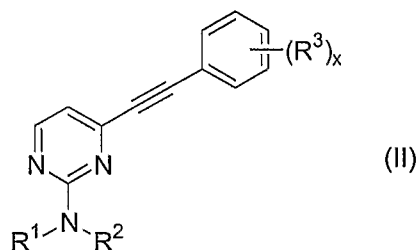


to form a compound of Formula (VIII):



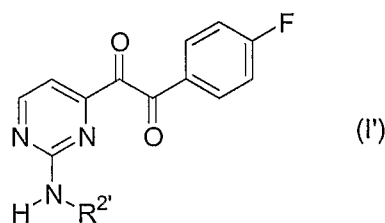
; and

reacting a compound of Formula (VIII) with R^1R^2NH to form a compound of Formula (II):

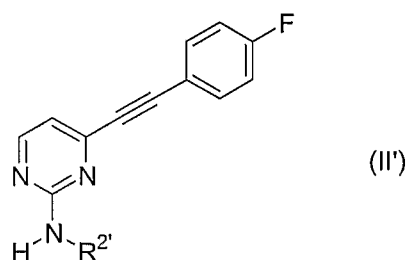


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43. A method as recited in claim 1, wherein a compound of Formula (I) is a compound of Formula (I'):



and a compound of Formula (II) is a compound of Formula (II'):

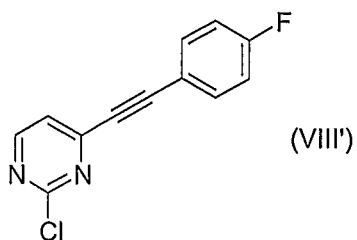


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wherein $R^{2'}$ is isopropyl or t-butyl.

44. A method as recited in claim 43, further comprising: reacting 2,4-dichloropyrimidine with 1-ethynyl-4-fluorobenzene to form a compound of formula (VIII'):

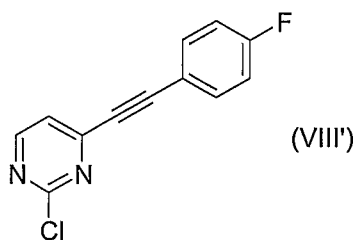
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45. A method as recited in claim 43, further comprising: reacting a compound of formula (VIII') with R^2NH to form a compound of Formula (II').

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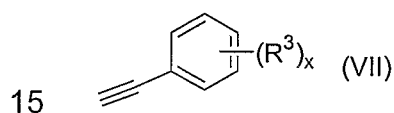
46. A method as recited in claim 43, further comprising:
reacting 2,4-dichloropyrimidine with 1-ethynyl-4-fluorobenzene to form a compound of formula (VIII'):



; and

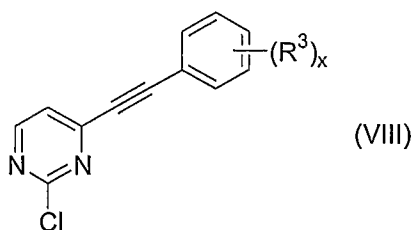
10 reacting a compound of formula (VIII') with R^2NH to form a compound of Formula (II').

47. A method as recited in claim 14, further comprising: reacting 2,4-dichloropyrimidine with a compound of Formula (VII):

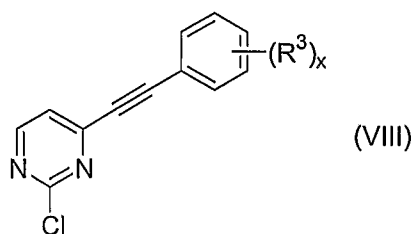


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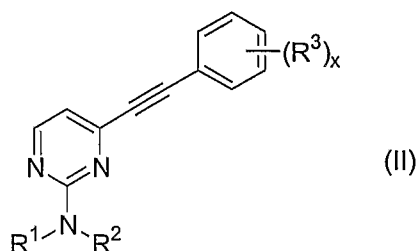
to form a compound of Formula (VIII):



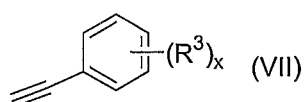
48. A method as recited in claim 14, further comprising: reacting a
20 compound of Formula (VIII):



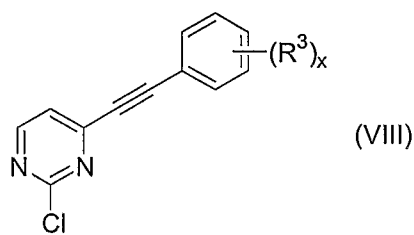
with R^1R^2NH to form a compound of Formula (II):



- 5 49. A method as recited in claim 14, further comprising:
reacting 2,4-dichloropyrimidine with a compound of Formula (VII):

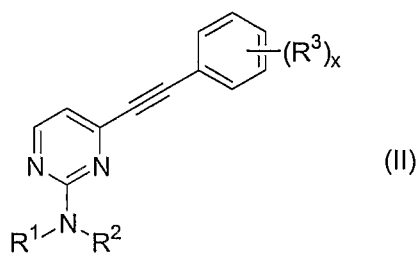


to form a compound of Formula (VIII):

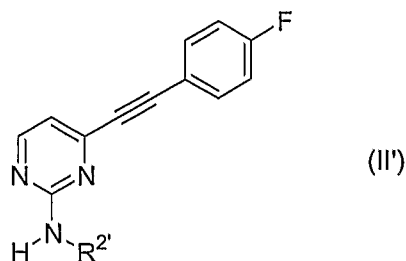


; and

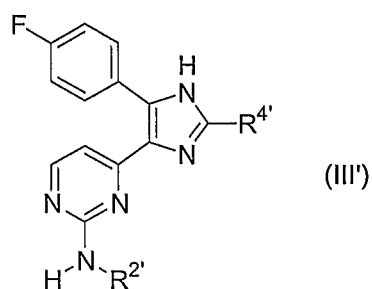
- 10 reacting a compound of Formula (VIII) with R^1R^2NH to form a compound
of Formula (II):



50. A method as recited in claim 14, wherein a compound of Formula (II) is
15 a compound of Formula (II'):



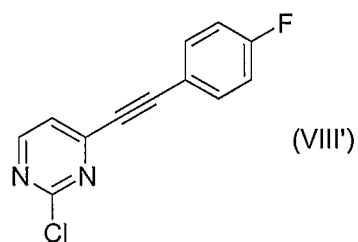
and a compound of Formula (III) is a compound of Formula (III'):



wherein $R^{2'}$ is isopropyl or t-butyl and $R^{4'}$ is -H, 4-chlorophenyl, or $-\text{CH}(\text{OCH}_3)_2$.

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51. A method as recited in claim 50, further comprising: reacting 2,4-dichloropyrimidine with 1-ethynyl-4-fluorobenzene to form a compound of formula (VIII'):

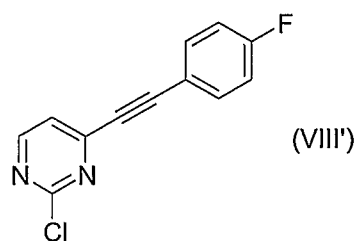


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52. A method as recited in claim 50, further comprising: reacting a compound of formula (VIII') with $R^{2'}\text{NH}$ to form a compound of Formula (II').

53. A method as recited in claim 50, further comprising:

15 reacting 2,4-dichloropyrimidine with 1-ethynyl-4-fluorobenzene to form a compound of formula (VIII'):



; and

reacting a compound of formula (VIII') with $R^{2'}NH$ to form a compound of Formula (II').

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2006/029280

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D239/42 C07D403/04

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, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01/37835 A (SMITHKLINE BEECHAM PLC) 31 May 2001 (2001-05-31) cited in the application the whole document, particularly page 13, scheme I	1, 14, 21
A	DE DIOS A ET AL: "Design of potent and selective 2-aminobenzimidazole-based p38alpha MAP kinase inhibitors with excellent in vivo efficacy" JOURNAL OF MEDICINAL CHEMISTRY, vol. 48, no. 7, 7 April 2005 (2005-04-07), pages 2270-2273, XP002407719 the whole document, particularly page 2271, second column, first paragraph ----- -/--	1, 14, 21



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

16 November 2006

Date of mailing of the international search report

29/11/2006

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INTERNATIONAL SEARCH REPORT

International application No

PCT/US2006/029280

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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A	US 3 778 441 A (BURCKHARDT U ET AL) 11 December 1973 (1973-12-11) the whole document, particularly example 20	21
A	TULLIS J S ET AL: "The development of new triazole based inhibitors of tumor necrosis factor-alpha (TNF-alpha) production" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 13, no. 10, 19 May 2003 (2003-05-19), pages 1665-1668, XP002407721 the whole document	14
P,X	DENG X ET AL: "An efficient route to 4-aryl-5-pyrimidinylimidazoles via sequential functionalization of 2,4-dichloropyrimidine" ORGANIC LETTERS, vol. 8, no. 2, 19 January 2006 (2006-01-19), pages 269-272, XP002407722 the whole document	1-53

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Information on patent family members

International application No

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