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(19) **United States**(12) **Patent Application Publication****McDonald et al.**(10) **Pub. No.: US 2009/0156601 A1**(43) **Pub. Date: Jun. 18, 2009**(54) **PYRIMIDINE DERIVATIVES FOR THE TREATMENT OF CANCER**

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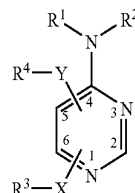
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The invention provides compounds which are pyrimidines of formula (I): wherein —XR³ is bonded at ring position 2 and —YR⁴ is bonded at ring position 5 or 6; R¹ and R² form, together with the N atom to which they are attached, a mor-

phorine ring which is unsubstituted or substituted; X is a direct bond; R³ is selected from (i) a group of the following formula (1): wherein B is a phenyl ring which is unsubstituted or substituted and Z is selected from —OR, CH₂OR and —NRS(O) mR, wherein each R is independently selected from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl and a 5- to 12-membered aryl or heteroaryl group, the group being unsubstituted or substituted, and m is 2; and (ii) an indazole group which is unsubstituted or substituted; and Y is selected from —O—(CH₂)_n—, —NH—(CH₂)_n—, —NHC(O)—(CH₂)_n— and —C(O)NH—(CH₂)_n— wherein n is 0 or an integer of 1 to 3, and R⁴ is selected from an unsaturated 5- to 12-membered carbocyclic or heterocyclic group which is unsubstituted or substituted and a group —NR⁵R⁶ wherein R⁵ and R⁶, which are the same or different, are each independently selected from H, C₁-C₆ alkyl which is unsubstituted or substituted, C₃-C₁₀ cycloalkyl which is unsubstituted or substituted, —C(O)R, —C(O)N(R)₂ and —S(O)_mR wherein R and m are as defined above, or R⁵ and R⁶ together form, with the nitrogen atom to which they are attached, a saturated 5-, 6- or 7-membered N-containing heterocyclic group which is unsubstituted or substituted; and the pharmaceutically acceptable salts thereof. These compounds are inhibitors of PI3K and may thus be used to treat diseases and disorders arising from abnormal cell growth, function or behaviour associated with PI3 kinase such as cancer, immune disorders, cardiovascular disease, viral infection, inflammation, metabolism/endocrine function disorders and neurological disorders.



(I)

PYRIMIDINE DERIVATIVES FOR THE TREATMENT OF CANCER

FIELD OF THE INVENTION

[0001] The present invention relates to pyrimidine compounds and to their use as inhibitors of phosphatidylinositol 3-kinase (PI3K).

BACKGROUND TO THE INVENTION

[0002] Phosphatidylinositol (hereinafter abbreviated as "PI") is one of a number of phospholipids found in cell membranes. In recent years it has become clear that PI plays an important role in intracellular signal transduction. In the late 1980s, a PI3 kinase (PI3K) was found to be an enzyme which phosphorylates the 3-position of the inositol ring of phosphatidylinositol (D. Whitman et al, 1988, Nature, 332, 664).

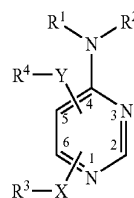
[0003] PI3K was originally considered to be a single enzyme, but it has now been clarified that a plurality of subtypes are present in PI3K. Each subtype has its own mechanism for regulating activity. Three major classes of PI3Ks have been identified on the basis of their in vitro substrate specificity (B. Vanhaesebroeck, 1997, Trend in Biol. Sci, 22, 267). Substrates for class I PI3Ks are PI, PI 4-phosphate (PI4P) and PI 4,5-biphosphate (PI (4,5)P2). Class I PI3Ks are further divided into two groups, class Ia and class Ib, in terms of their activation mechanism. Class Ia PI3Ks include PI3K p110 α , p110 β and p110 δ subtypes, which transmit signals from tyrosine kinase-coupled receptors. Class Ib PI3K includes a p110 γ subtype activated by a G protein-coupled receptor. PI and PI(4)P are known as substrates for class II PI3Ks. Class II PI3Ks include PI3K C2 α , C2 β and C2 γ subtypes, which are characterized by containing C2 domains at the C terminus. The substrate for class III PI3Ks is PI only.

[0004] In the PI3K subtypes, the class Ia subtype has been most extensively investigated to date. The three subtypes of class Ia are heterodimers of a catalytic 110 kDa subunit and regulatory subunits of 85 kDa or 55 kDa. The regulatory subunits contain SH2 domains and bind to tyrosine residues phosphorylated by growth factor receptors with a tyrosine kinase activity or oncogene products, thereby inducing the PI3K activity of the p110 catalytic subunit which phosphorylates its lipid substrate. Thus, the class Ia subtypes are considered to be associated with cell proliferation and carcinogenesis.

[0005] WO 01/083456 describes a series of condensed heteroaryl derivatives which have activity as inhibitors of PI3K and which suppress cancer cell growth.

SUMMARY OF THE INVENTION

[0006] It has now been found that a series of novel pyrimidine compounds have activity as inhibitors of PI3K. The compounds exhibit selectivity for class Ia PI3Ks over class Ib. Accordingly, the present invention provides a compound which is a pyrimidine of formula (I):



(I)

wherein

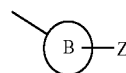
[0007] —XR³ is bonded at ring position 2 and —YR⁴ is bonded at ring position 5 or 6;

[0008] R¹ and R² form, together with the N atom to which they are attached, a morpholine ring which is unsubstituted or substituted;

[0009] X is a direct bond;

[0010] R³ is selected from:

[0011] (i) a group of the following formula:



wherein:

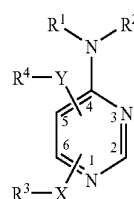
[0012] B is a phenyl ring which is unsubstituted or substituted and Z is selected from —OR, CH₂OR and —NRS(O)_mR, wherein each R is independently selected from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl and a 5- to 12-membered aryl or heteroaryl group, the group being unsubstituted or substituted, and m is 2; and

[0013] (ii) an indazole group which is unsubstituted or substituted; and

[0014] Y is selected from —O—(CH₂)_n—, —NH—(CH₂)_n—, —NHC(O)—(CH₂)_n— and —C(O)NH—(CH₂)_n— wherein n is 0 or an integer of 1 to 3, and R⁴ is selected from an unsaturated 5- to 12-membered carbocyclic or heterocyclic group which is unsubstituted or substituted, and a group —NR⁵R⁶ wherein R⁵ and R⁶, which are the same or different, are each independently selected from H, C₁-C₆ alkyl which is unsubstituted or substituted, C₃-C₁₀ cycloalkyl which is unsubstituted or substituted, —C(O)R, —C(O)N(R)₂ and —S(O)_mR wherein R and m are as defined above, or R⁵ and R⁶ together form, with the nitrogen atom to which they are attached, a saturated 5-, 6- or 7-membered N-containing heterocyclic group which is unsubstituted or substituted;

[0015] or a pharmaceutically acceptable salt thereof.

[0016] The invention also provides a pyrimidine of formula (I')



(I')

wherein

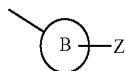
—XR³ is bonded at ring position 2 and —YR⁴ is bonded at ring position 5 or 6, or —YR⁴ is bonded at ring position 2 and —XR³ is bonded at ring position 6;

R¹ and R², which are the same or different, are each independently selected from H, C₁-C₆ alkyl which is unsubstituted or substituted, C₃-C₁₀ cycloalkyl which is unsubstituted or substituted, and C₁-C₆ alkoxy which is unsubstituted or substituted, or R¹ and R² form, together with the N atom to which they are attached, a saturated 5-, 6- or 7-membered N-containing heterocyclic ring which includes 0, 1 or 2 additional heteroatoms selected from O, N and S and which is unsubstituted or substituted;

X is selected from a direct bond, —O—, —CR'R"— and —NR'— wherein R' and R" are each, independently, H or C₁-C₆ alkyl;

R³ is selected from:

[0017] (i) a group of the following formula:



[0018] wherein B is a phenyl ring which is unsubstituted or substituted and Z is selected from H, —OR, —SR, CH₂OR, —CO₂R, CF₂OH, CH(CF₃)OH, C(CF₃)₂OH, —(CH₂)_qOR, —(CH₂)_qNR₂, —C(O)N(R)₂, —NR₂, —NRC(O)R, —S(O)_mN(R)₂, —OC(O)R, OC(O)N(R)₂, —NRS(O)_mR, —NRC(O)N(R)₂, CN, halogen and —NO₂, wherein each R is independently selected from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl and a 5- to 12-membered aryl or heteroaryl group, the group being unsubstituted or substituted, m is 1 or 2 and q is 0, 1 or 2;

[0019] (ii) a heteroaryl group which contains 1, 2, 3 or 4 ring nitrogen atoms and 0, 1 or 2 additional heteroatoms selected from O and S, which group is monocyclic or bicyclic and which is unsubstituted or substituted; and

[0020] (iii) a group comprising a benzene ring which is unsubstituted or substituted and which is fused to a heteroaryl group as defined above; and either:

[0021] (a) Y is selected from —O—(CH₂)_n—, —NH—(CH₂)_n—, —NHC(O)—(CH₂)_n— and —C(O)NH—(CH₂)_n— wherein n is 0 or an integer of 1 to 3, and R⁴ is selected from an unsaturated 5- to 12-membered carbocyclic or heterocyclic group which is unsubstituted or substituted and a group —NR⁵R⁶ wherein R⁵ and R⁶, which are the same or different, are each independently selected from H, C₁-C₆ alkyl which is unsubstituted or substituted, C₃-C₁₀ cycloalkyl which is unsubstituted or substituted, —C(O)R, —C(O)N(R)₂ and —S(O)_mR wherein R and m are as defined above, or R⁵ and R⁶ together form, with the nitrogen atom to which they are attached, a saturated 5-, 6- or 7-membered N-containing heterocyclic group which is unsubstituted or substituted;

[0022] (b) Y is a direct bond and R⁴ is selected from an unsaturated 5- to 12-membered carbocyclic or heterocyclic group which is unsubstituted or substituted, and a group —NR⁵R⁶ wherein R⁵ and R⁶, which are the same or different, are each independently selected from H, C₁-C₆ alkyl which is unsubstituted or substituted, C₃-C₁₀ cycloalkyl which is unsubstituted or substituted, —C(O)R, —C(O)N(R)₂ and —S(O)_mR wherein R and m are as defined above;

or a pharmaceutically acceptable salt thereof.

DETAILED DESCRIPTION OF THE INVENTION

[0023] A C₁-C₆ alkyl group is linear or branched. A C₁-C₆ alkyl group is typically a C₁-C₄ alkyl group, for example a methyl, ethyl, propyl, n-butyl, sec-butyl or tert-butyl group. A C₁-C₆ alkyl group is unsubstituted or substituted, typically by one or more groups Z as defined above, or by one or more groups Z as defined above or R⁷ as defined below. Typically it is C₁-C₄ alkyl, for example methyl, ethyl, i-propyl, n-propyl, t-butyl, s-butyl or n-butyl.

[0024] R⁷ is selected from C₁-C₆ alkoxy, OR⁸, SR⁸, S(O)_mR⁸, nitro, CN, halogen, —C(O)R⁸, —CO₂R⁸, —C(O)N(R⁸)₂ and —N(R⁸)₂, wherein each R⁸, which are the same or different when more than one is present in a given substituent, is selected from H, C₁-C₆ alkyl and C₃-C₁₀ cycloalkyl, and m is 1 or 2.

[0025] A halogen is F, Cl, Br or I. Preferably it is F, Cl or Br. A C₁-C₆ alkyl group substituted by halogen may be denoted by the term "halo-C₁-C₆ alkyl", which means an alkyl group in which one or more hydrogens is replaced by halo. A halo-C₁-C₆ alkyl group preferably contains one, two or three halo groups. A preferred example of such a group is trifluoromethyl.

[0026] A C₁-C₆ alkoxy group is linear or branched. It is typically a C₁-C₄ alkoxy group, for example a methoxy, ethoxy, propoxy, i-propoxy, n-propoxy, n-butoxy, sec-butoxy or tert-butoxy group. A C₁-C₆ alkoxy group is unsubstituted or substituted, typically by one or more groups Z or R⁷ as defined above.

[0027] A C₃-C₁₀ cycloalkyl group may be, for instance, C₃-C₈ cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl. Typically it is C₃-C₆ cycloalkyl. A C₃-C₁₀ cycloalkyl group is unsubstituted or substituted, typically by one or more groups Z or R⁷ as defined above.

[0028] A C₁-C₆ acyl group is a group —C(O)Alk in which Alk is C₁-C₆ alkyl as defined above. It is, for instance, formyl, acetyl or propionyl.

[0029] A saturated 5-, 6-, or 7-membered N-containing heterocyclic ring may be, for example, piperidine, piperazine, morpholine or pyrrolidine. The ring typically contains one nitrogen atom and either an additional N atom or an O atom, or no additional heteroatoms. The ring is unsubstituted or substituted on one or more ring carbon atoms and/or on any additional N atom present in the ring. Examples of suitable substituents include one or more groups Z or R⁷ as defined above, and a C₁-C₆ alkyl group which is unsubstituted or substituted by a group Z or R⁷ as defined above. When the ring is piperazine it is typically unsubstituted or substituted, typically on the second ring nitrogen atom, by —C(O)R⁸, —C(O)N(R⁸)₂ or —S(O)_mR⁸, or by C₁-C₆ alkyl which is unsubstituted or substituted by C₁-C₆ alkoxy or OH.

[0030] An unsaturated 5- to 12-membered carbocyclic group is a 5-, 6-, 7-, 8-, 9-, 10, 11- or 12-membered carbocyclic ring containing at least one unsaturated bond. It is a monocyclic or fused bicyclic ring system. The group is aromatic or non-aromatic, for instance a 5- to 12-membered aryl group. Examples include phenyl, naphthyl, indanyl, indenyl and tetrahydronaphthyl groups. The group is unsubstituted or substituted, typically by one or more groups Z or R⁷ as defined above.

[0031] An aryl group is a 5- to 12-membered aromatic carbocyclic group. It is monocyclic or bicyclic. Examples

include phenyl and naphthyl groups. The group is unsubstituted or substituted, for instance by a group Z or R⁷ as defined above.

[0032] An unsaturated 5- to 12-membered heterocyclic group is typically heteroaryl. Heteroaryl is a 5- to 12-membered heteroaryl group which contains 1, 2, 3, or 4 heteroatoms selected from O, N and S. Typically it contains one N atom and 0, 1, 2 or 3 additional heteroatoms selected from O, S and N. It may be, for example, furan, thiophene, pyrrole, indole, isoindole, pyrazole, imidazole, benzothiophene, benzothiazole, benzofuran, isoxazole, oxazole, oxadiazole, thiazole, isothiazole, thiadiazole, dihydroimidazole, pyridine, pyridine, quinoline, isoquinoline, quinoxaline, thenopyrazine, pyran, pyrimidine, pyridazine, pyrazine, triazine, triazole or tetrazole. The group is unsubstituted or substituted, typically by one or more groups Z or R⁷ as defined above.

[0033] In the definition of R⁴ this heteroaryl group is typically selected from pyridine, thiophene and pyrrole. Most typically it is pyridine, for instance a pyrid-2-yl, pyrid-3-yl or pyrid-4-yl group. In formula (I) R¹ and R² typically form, together with the N atom to which they are attached, a secondary or tertiary amine, most typically a tertiary amine. The amine is acyclic or cyclic. Thus, one or both of R¹ and R² is typically a C₁-C₆ alkyl group which is unsubstituted or substituted. If the alkyl group is substituted it is typically substituted by Z or R⁷ as defined above. When R¹ or R² is a C₁-C₆ alkyl group which is unsubstituted it is typically a methyl or ethyl group. When R¹ or R² is a C₁-C₆ alkyl group which is substituted it is typically C₁-C₆ alkyl substituted by a group selected from C₁-C₆ alkoxy and —NR² as defined above, for instance C₁-C₆ alkyl substituted by —OCH₃ or by —NH₂, —NHCH₃ or —N(CH₃)₂. Thus one or both of R¹ and R² may be —(CH₂)_r—OR¹³ wherein r is 0 or an integer of 1 to 6, for instance 1 to 4, such as 1, 2, 3 or 4, and R¹³ is C₁-C₆ alkyl. Alternatively one or both of R¹ and R² may be —(CH₂)_r—NR² wherein r and R are as defined above. Typically one or each of R¹ and R² is selected from —(CH₂)₂OCH₃, —(CH₂)₂NH₂, —(CH₂)₂NHCH₃ and —(CH₂)₂N(CH₃)₂.

[0034] In formula (I), R¹ and R² form, together with the N-atom to which they are attached, a morpholine ring. The ring is unsubstituted or substituted, either on a ring carbon atom or (if present) on a second heteroatom, for instance by a group Z or R⁷ as defined above.

[0035] In formula (I), in the definition (i) for R³, the phenyl ring B is unsubstituted (apart from group Z) or substituted. When it is unsubstituted the group Z is the sole substituent. When it is substituted it typically comprises, in addition to group Z, one or more substituents selected from halo, alkyl, alkenyl, alkynyl, CN, NO₂, OR', SR', NR'₂, C(O)R', SOR', SO₂R', SO₂NR'₂, NC(O)R' and CO₂R', wherein each R' is independently H or C₁-C₆ alkyl. Group Z is bonded to any available ring position on the phenyl ring B. Typically the phenyl ring, which is otherwise unsubstituted or substituted, for instance as specified above, is meta-substituted or para-substituted by Z. Thus it may be situated at the 2-, 3-, 4-, 5- or 6-position of the phenyl ring. Typically it is bonded at position 3 or 4. Z is other than H, such that moiety —BZ is a substituted phenyl ring. A typical example of Z is a group OR as defined above, in particular OH. In this embodiment the OR group, or OH group, is typically bonded at ring position 3 or 4 of phenyl ring B. Typically —BZ is a 3-hydroxyphenyl or 4-hydroxyphenyl group.

[0036] In formula (I), in definition (ii) for R³, the indazole group is linked to the pyrimidine ring via any available ring C

or N atom. For instance, it is an indazol-4-yl, indazol-5-yl or indazol-6-yl group. Typically it is an indazol-4-yl group.

[0037] In formula (I), in definition (ii) for R³, the heteroaryl group is unsubstituted or substituted. If it is substituted it may be substituted by one or more substituents selected from a group Z or R⁷ as defined above, any group specified above as an additional substituent on the phenyl ring B, and an oxo group (=O). Typically, if substituted, the heteroaryl group is substituted by OH, NH₂ or an oxo group. In one embodiment the heteroaryl group is unsubstituted.

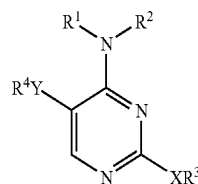
[0038] In formula (I), in definition (iii) for R³, the benzene ring is unsubstituted or substituted. If it is substituted it may be substituted by a group Z or R⁷ as defined above or by any of the groups specified above as options an additional substituent on the phenyl ring B. The heteroaryl group to which the benzene ring is fused is itself unsubstituted or substituted, for instance by a group Z or R⁷ as defined above, by any group specified above as an option for an additional substituent on the phenyl ring B, or by an oxo group (=O). In one embodiment both the benzene ring and the heteroaryl group are unsubstituted.

[0039] Examples of the groups included in definitions (ii) and (iii) for R³ in formula (I) include pyrrole, pyrazole, triazole, tetrazole, indazole, thiazole, isothiazole, oxazole, isooxazole, indole, isoindole, 1,3-dihydro-indol-2-one, pyridine-2-one, pyridine, pyridin-3-ol, imidazole, 1,3-dihydro-benzimidazolone, benzimidazole, benzothiazole, benzothiadiazole, quinoline, isoquinoline, quinoxaline, pyrazolopyridine, aminopyrazolinone, imidazopyridine, pyrimidine, pyridazine, pyrazine and isatin groups. Preferred examples include indazole, indole, pyrazole and tetrazole groups. These groups may be unsubstituted or substituted, for instance as specified above.

[0040] When R⁴ is an unsaturated 5- to 12-membered carbocyclic group it is typically an aromatic carbocyclic group such as phenyl or naphthyl. When R⁴ is an unsaturated 5- to 12-membered heterocyclic group it is typically pyridyl, for instance a pyrid-2-yl, pyrid-3-yl or pyrid-4-yl group. When R⁴ is a saturated 5-, 6- or 7-membered N-containing heterocyclic group it is typically a 6-membered such heterocyclic group, for instance piperidyl or morpholinyl. The group R⁴ is unsubstituted or substituted, for instance by a group Z or R⁷ as defined above.

[0041] The linker group X in formula (I) is typically a direct bond, —O—, —CH₂—, —CHR¹³—, —NH— or —NR¹³ wherein R¹³ is C₁-C₆ alkyl. Most typically it is a direct bond.

[0042] In one embodiment the pyrimidine is of formula (Ia):



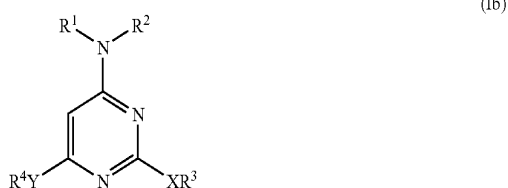
(Ia)

wherein R¹, R², R³, R⁴, X and Y are as defined above for formula (I).

[0043] In formula (Ia) Y is typically —NH—C(O)— or C(O)—NH—; R⁴ is typically an aromatic unsaturated 5- to 12-membered carbocyclic or heterocyclic group which is unsubstituted or substituted, for instance a phenyl or pyridyl

group. The pyridyl group may be a pyrid-2-yl, pyrid-3-yl or pyrid-4-yl group. XR^3 is typically a group $-\text{BZ}$ as defined above in which the group Z is typically bonded at position 3 or 4 of the phenyl ring. Typically $-\text{BZ}$ is a 3-hydroxyphenyl or 4-hydroxyphenyl group. R^1 and R^2 form, together with the N atom to which they are attached, a morpholino group.

[0044] In a second embodiment the pyrimidine is of formula (Ib):



wherein R^1 , R^2 , R^3 , R^4 , Y and X are as defined above for formula (I).

[0045] In formula (Ib), Y is typically a group $-\text{O}-(\text{CH}_2)_n-$ in which n is 0, 1 or 2 and R^4 is an aromatic unsaturated 5- to 12-membered carbocyclic or heterocyclic group which is unsubstituted or substituted, for instance a phenyl or pyridyl group. The phenyl group is unsubstituted or substituted, for instance by a group Z or a group R^7 as defined above, for example by a halogen such as Cl or Br. The pyridyl group is unsubstituted or substituted by a group Z or R^7 as defined above. Alternatively Y may be a group $-\text{NH}-(\text{CH}_2)_n-$ in which n is 0, 1 or 2 and R^4 may be an aromatic unsaturated 5- to 12-membered carbocyclic or heterocyclic group or a group $-\text{NR}^5\text{R}^6$ as defined above, for instance a group $-\text{NR}^5\text{R}^6$ wherein R^5 and R^6 form, together with the nitrogen atom to which they are attached, or a saturated 5-, 6- or 7-membered N-containing heterocyclic group. Typically R^4 is an unsubstituted pyrid-2-yl, pyrid-3-yl or pyrid-4-yl group, a piperidine or morpholine group, or a phenyl group which is unsubstituted or substituted. R^1 and R^2 form, together with the N atom to which they are attached, a morpholino group.

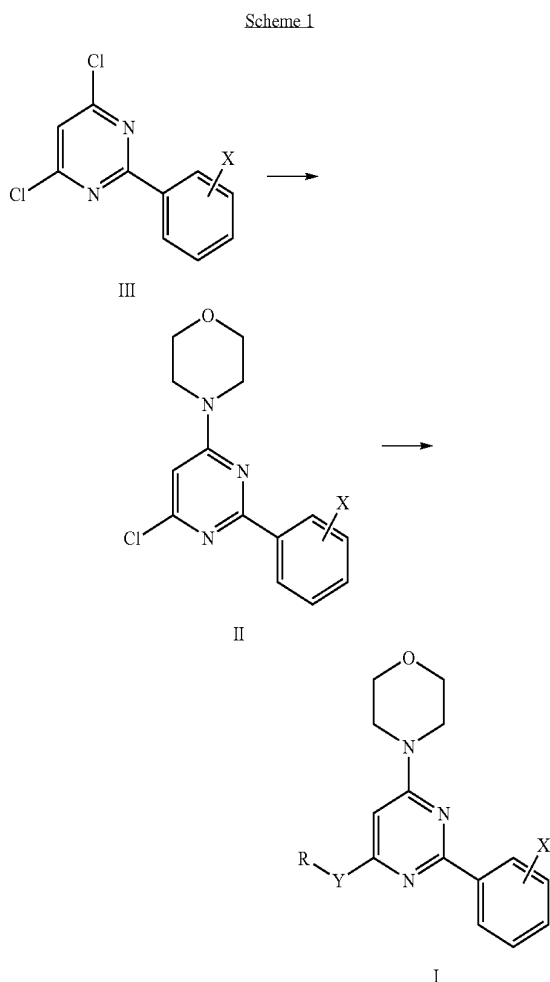
[0046] Specific examples of compounds of the invention include:

- [0047]** 2-(3-hydroxyphenyl)-4-(morpholin-4-yl)-6-(pyridin-3-ylmethylamino) pyrimidine;
- [0048]** 2-(3-hydroxyphenyl)-4-(morpholin-4-yl)-6-(pyridin-2-ylmethylamino) pyrimidine;
- [0049]** 2-(3-hydroxyphenyl)-4-(morpholin-4-yl)-6-(pyridin-4-ylmethylamino) pyrimidine;
- [0050]** 2-(3-hydroxyphenyl)-4-(morpholin-4-yl)-6-[(2-(pyridin-2-yl)ethylamino)] pyrimidine;
- [0051]** 2-(3-hydroxyphenyl)-4-(morpholin-4-yl)-6-[(2-(pyridin-3-yl)ethylamino)] pyrimidine;
- [0052]** 2-(3-hydroxyphenyl)-4-(morpholin-4-yl)-6-[(2-(pyridin-4-yl)ethylamino)] pyrimidine;
- [0053]** 2-(3-hydroxyphenyl)-4-(morpholin-4-yl)-6-(pyridin-2-ylmethoxy) pyrimidine;
- [0054]** 2-(3-hydroxyphenyl)-4-(morpholin-4-yl)-6-[2-(morpholin-4-yl)ethylamino] pyrimidine;
- [0055]** 2-(3-methoxyphenyl)-4-(morpholin-4-yl)-5-[(pyridin-4-yl)carbonylamino] pyrimidine;
- [0056]** 2-(3-methoxyphenyl)-4-(morpholin-4-yl)-5-[(pyridin-3-yl)carbonylamino] pyrimidine;
- [0057]** 2-(3-methoxyphenyl)-4-(morpholin-4-yl)-5-[(pyridin-3-yl)carbonylamino] pyrimidine;

- [0058]** 2-[3-(methanesulfonylamino)phenyl]-4-(morpholin-4-yl)-2-[(2-(pyridin-2-yl)ethylamino)]pyrimidine;
 - [0059]** 2-[3-(methanesulfonylamino)phenyl]-4-(morpholin-4-yl)-6-[(2-(pyridin-3-yl)ethylamino)]pyrimidine;
 - [0060]** 2-[3-(methanesulfonylamino)phenyl]-4-(morpholin-4-yl)-6-[(2-(pyridin-4-yl)ethylamino)]pyrimidine;
 - [0061]** 2-[3-(methanesulfonylamino)phenyl]-4-(morpholin-4-yl)-6-(pyridin-2-ylmethoxy)pyrimidine;
 - [0062]** 3-(4-Benzylamino-6-morpholin-4-yl-pyrimidin-2-yl)-phenol;
 - [0063]** 3-(4-Morpholin-4-yl-6-phenylamino-pyrimidin-2-yl)-phenol;
 - [0064]** 3-(4-Morpholin-4-yl-6-p-tolylamino-pyrimidin-2-yl)-phenol;
 - [0065]** 3-(4-Morpholin-4-yl-6-m-tolylamino-pyrimidin-2-yl)-phenol;
 - [0066]** 3-[4-(3-Fluoro-phenylamino)-6-morpholin-4-yl-pyrimidin-2-yl]-phenol;
 - [0067]** 3-[4-(4-Fluoro-phenylamino)-6-morpholin-4-yl-pyrimidin-2-yl]-phenol;
 - [0068]** 3-(4-Morpholin-4-yl-6-o-tolylamino-pyrimidin-2-yl)-phenol;
 - [0069]** 3-[4-(2-Fluoro-phenylamino)-6-morpholin-4-yl-pyrimidin-2-yl]-phenol;
 - [0070]** 3-[4-(2-Methoxy-phenylamino)-6-morpholin-4-yl-pyrimidin-2-yl]-phenol;
 - [0071]** 3-[4-(3-Methoxy-phenylamino)-6-morpholin-4-yl-pyrimidin-2-yl]-phenol;
 - [0072]** 3-[4-(4-Methoxy-phenylamino)-6-morpholin-4-yl-pyrimidin-2-yl]-phenol;
 - [0073]** 3-[2-(3-Hydroxy-phenyl)-6-morpholin-4-yl-pyrimidin-4-ylamino]-benzonitrile;
 - [0074]** 4-[2-(3-Hydroxy-phenyl)-6-morpholin-4-yl-pyrimidin-4-ylamino]-benzonitrile;
 - [0075]** 3-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-ylamino)-6-morpholin-4-yl-pyrimidin-2-yl]-phenol;
 - [0076]** 3-[4-(2-Methanesulfonyl-1,2,3,4-tetrahydro-isoquinolin-7-ylamino)-6-morpholin-4-yl-pyrimidin-2-yl]-phenol;
 - [0077]** 3-[4-(3-Methanesulfonyl-phenylamino)-6-morpholin-4-yl-pyrimidin-2-yl]-phenol;
 - [0078]** 3-(4-Morpholin-4-yl-6-phenoxy-pyrimidin-2-yl)-phenol;
 - [0079]** 2-(indazol-4-yl)-4-(morpholin-4-yl)-6-[(2-(pyridin-2-yl)ethylamino)]pyrimidine;
 - [0080]** 2-(indazol-4-yl)-4-(morpholin-4-yl)-6-[(2-(pyridin-3-yl)ethylamino)]pyrimidine;
 - [0081]** 2-(indazol-4-yl)-4-(morpholin-4-yl)-6-[(2-(pyridin-4-yl)ethylamino)]pyrimidine; and
 - [0082]** 2-(indazol-4-yl)-4-(morpholin-4-yl)-6-(pyridin-2-ylmethoxy)pyrimidine;
- and the pharmaceutically acceptable salts thereof
- [0083]** Pyrimidines of formula (I) may be converted into pharmaceutically acceptable salts, and salts may be converted into the free compound, by conventional methods. Pharmaceutically acceptable salts include salts of inorganic acids such as hydrochloric acid, hydrobromic acid and sulfuric acid, and salts of organic acids such as acetic acid, oxalic acid, malic acid, methanesulfonic acid, trifluoroacetic acid, benzoic acid, citric acid and tartaric acid. In the case of compounds of the invention bearing a free carboxy substituent, the salts include both the above-mentioned acid addition salts and the salts of sodium, potassium, calcium and ammonium. The latter are prepared by treating the free pyrimidine of

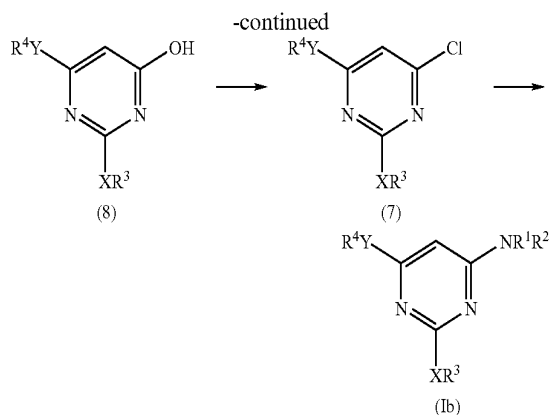
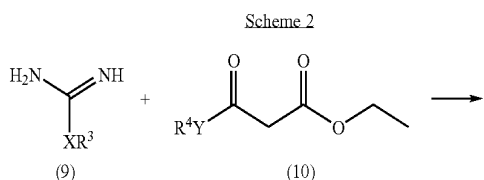
formula (I), or the acid addition salt thereof, with the corresponding metal base or ammonia.

[0084] The pyrimidines of formula (I) may be prepared by any suitable synthetic route, for instance selected from those set out in any of schemes 1 to 8 below.



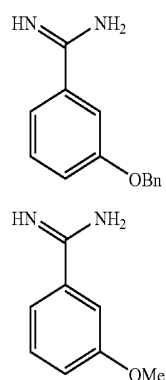
[0085] A compound of formula III, which is a known compound or is prepared by methods known in the literature, is converted into a compound of formula II by treatment with morpholine. This reaction may take place in an aprotic or protic solvent, optionally in the presence of a base. Typically the solvent is acetonitrile or an alcohol such as methanol. The base is typically sodium carbonate or potassium carbonate.

[0086] A compound of formula I is prepared by treatment of the compound of formula II with a compound RYH, where R and Y are as defined above. The reaction may take place with or without a solvent, and optionally in the presence of a base. It is typically performed at a temperature from room temperature to 150° C.



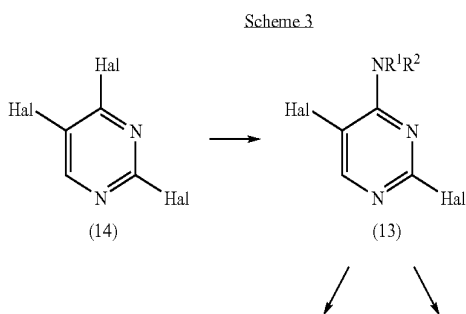
[0087] In scheme 2, R¹, R², R³, R⁴, X and Y are as defined above for formula (I). Compounds of formula (Ib) may be prepared by treating compounds of formula (7) with an amine of formula HNR¹R² in an inert solvent in the presence of a base. Compounds of formula (7) may be prepared by treating compounds of formula (8) with phosphorous oxychloride in the presence of an N,N-dialkylaniline. Compounds of formula (8) may be prepared by reacting together compounds of formula (9) and (10) in an inert solvent.

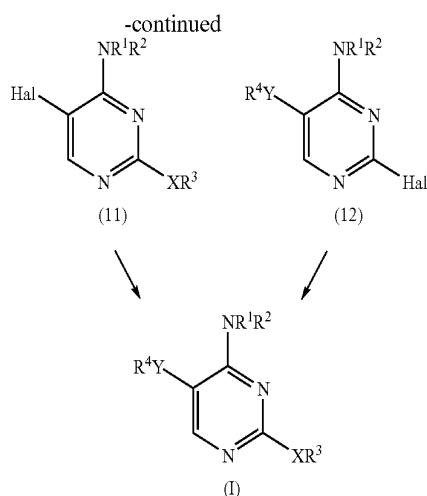
[0088] Compounds of formula (10) were prepared according to the method in *Tetrahedron*, 1991, 47, 975. Compounds of formula (9) were prepared according to *J. Med. Chem.*, 1995, 38, 2251. Examples of compounds of formula (9) include the following:



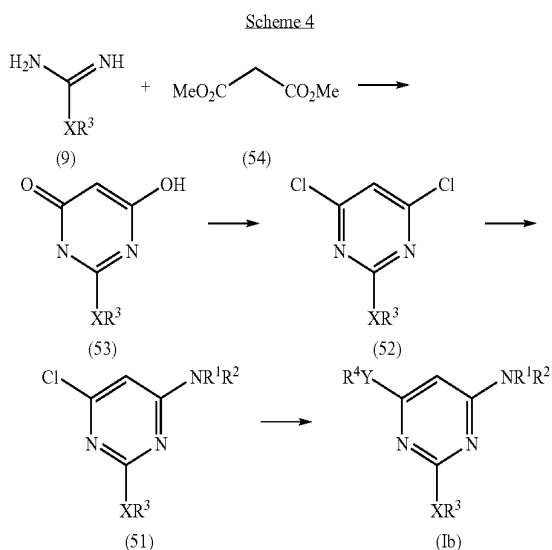
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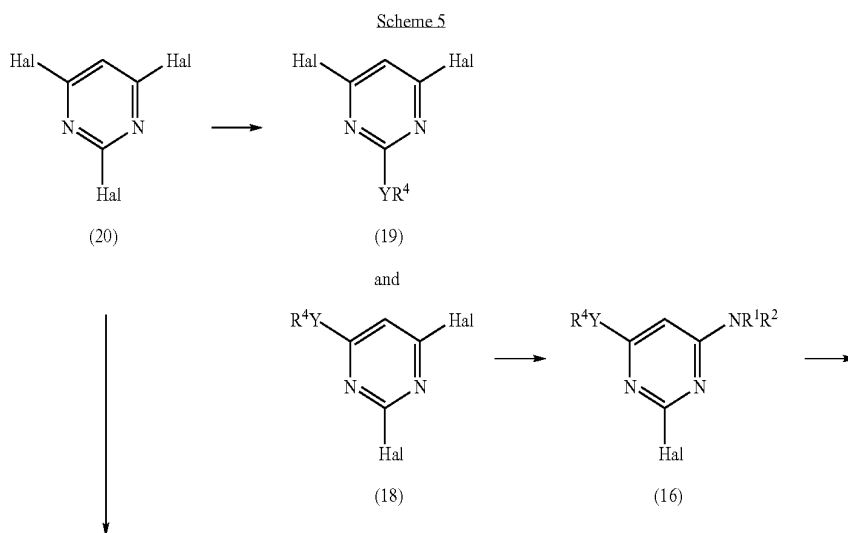


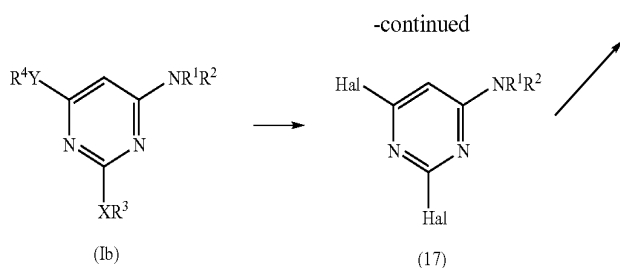


[0089] In scheme 3, R^1 , R^2 , R^3 , R^4 , X and Y are as defined above for formula (I). Compounds of formula (I) may be prepared by the Suzuki coupling of either a compound of formula (12) with a boronic acid of formula $R^3X-B(OH)_2$, or a compound of formula (II) with a boronic acid of formula $R^4Y-B(OH)_2$, in the presence of Pd and a base. Compounds of formulae (II) and (12) may be prepared by the Suzuki coupling of a compound of formula (13) with, respectively, a boronic acid of formula $R^3X-B(OH)_2$ or a boronic acid of formula $R^4Y-B(OH)_2$, in each case in the presence of Pd and a base. A compound of formula (13) may be prepared by treating a solution of a compound of formula (14) with an amine of formula HNR^1R^2 in the presence of a base. The trihalopyrimidines of formula (14) are known compounds and may be obtained commercially or synthesized by known methods.



[0090] In Scheme 4, R^1 , R^2 , R^3 , R^4 and X are as defined above for formula (I). Treatment of (51) with either a boronic acid $R^4-B(OH)_2$ (Y is a direct bond), a suitable alcohol R^4-OH (Y is $-O-(CH_2)_n-$ wherein n is 0) or an amine R^4-NH_2 (Y is $-NH-(CH_2)_n-$ wherein n is 0) gives compounds of formula (Ib). Compounds of formula (II) may be prepared by treating compounds of formula (52) with one molar equivalent of an amine of formula HNR^1R^2 in an inert solvent in the presence of a base. Compounds of formula (52) may be prepared by treating compounds of formula (53) with phosphorous oxychloride in the presence of an N,N -dialkylaniline. Compounds of formula (53) may be prepared by reacting together compounds of formula (9) and (54) in an inert solvent in the presence of a base.



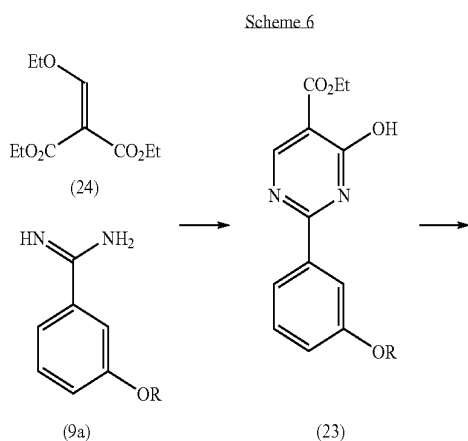
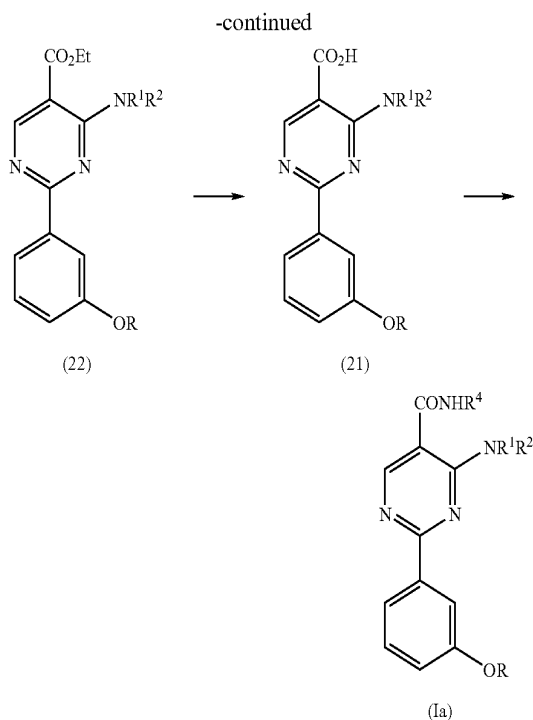


[0091] In Scheme 5, R^1 , R^2 , R^3 , R^4 , Y and X are as defined above for formula (I), and Hal is a halogen. Compounds of formula (Ib) may be prepared by Suzuki coupling of compounds of formula (16) with a boronic acid $R^3X-B(OH)_2$ in the presence of $Pd(0)$ and a base, for instance using the general procedure described in Reference Example 15. A compound of formula (16) may be obtained by treatment of a compound of formula (18) with two molar equivalents of an amine of formula HNR^1R^2 in an inert solvent at elevated temperature (for example $80^\circ C.$).

[0092] The isomeric compounds (18) and (19) can both be prepared by treating a compound of formula (20) with either a boronic acid $R^4-B(OH)_2$ (Y is a direct bond), a suitable alcohol R^4-OH (Y is $-O-(CH_2)_n-$ wherein n is 0) or an amine R^4-NH_2 (Y is $-NH-(CH_2)_n-$ wherein n is 0) and separating the two products.

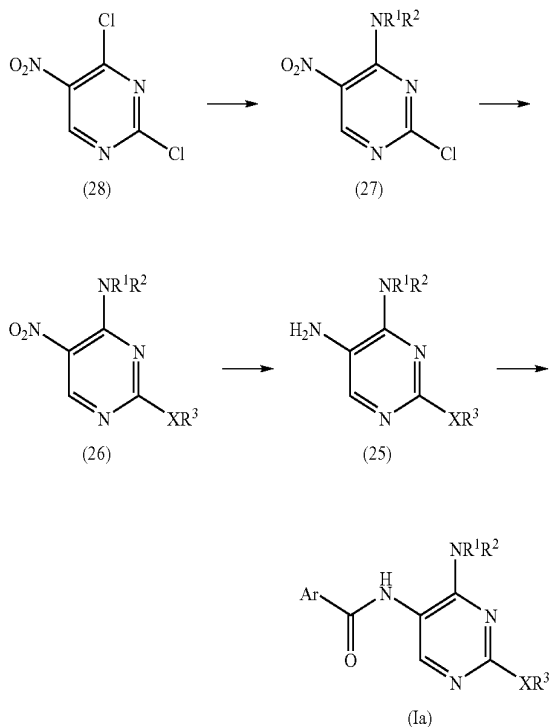
[0093] Alternatively a compound of formula (16) may be prepared by treatment of a compound of formula (17) with either, a suitable alcohol R^4-OH (Y is $-O-(CH_2)_n-$ wherein n is 0) or an amine R^4-NH_2 (Y is $-NH-(CH_2)_n-$ wherein n is 0). A compound of formula (17) may be prepared by treatment of a compound of formula (20) with one molar equivalent of an amine of formula HNR^1R^2 in an inert solvent in the presence of a base. Compounds of formulae (19) and (18) were prepared as described in Reference Example 3.

[0094] A compound (1b) in which X is other than a direct bond may be prepared by treating the intermediate (16) with a suitable amine, alcohol or thiol nucleophile under neutral or basic conditions.



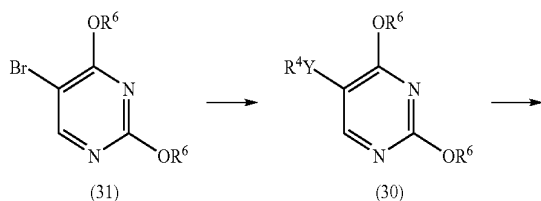
[0095] In Scheme 6, R^1 , R^2 , R^4 and OR are as defined above for formula (I) OR being one option for R^3 in formula (I). Compounds of formula (1a) can be prepared by coupling of an acid of structure (21) with an amine by one of the standard methods of amide bond formation. Compounds like (21) can be obtained by hydrolysis of esters of type (22). Structures like (22) can be obtained from compounds of formula (23) by treatment with phosphorous oxychloride in the presence of an N,N -dialkylaniline, followed by treatment with an amine of formula NHR^1R^2 in an inert solvent in the presence of a base. Compounds like (23) can be obtained by reacting together compounds of formula (9a) with commercially available compound (24) in an inert solvent. Compounds (23), (22) and (21) can be prepared as described in Reference Examples 7 to 9 which follow.

Scheme 7

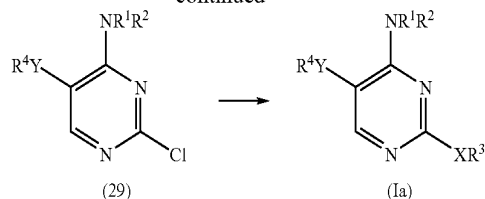


[0096] In scheme 7, R^1 , R^2 , R^3 and X are as defined for formula (I) and Ar is an unsaturated 5- to 12-membered carbocyclic or heterocyclic group which is unsubstituted or substituted, as defined above within the definition of R^4 in formula (I). Compounds of formula (I) can be prepared by the reaction of a compound of formula (25) with an acid chloride in the presence of a base in an inert solvent. A compound of formula (25) can be prepared by reduction of a compound of formula (26), using for example catalytic hydrogenation over a suitable metal catalyst. A compound of formula (26) may be prepared by Suzuki coupling of compounds of formula (27) with a boronic acid $\text{R}^3\text{X}-\text{B}(\text{OH})_2$ in the presence of Pd (0) and a base, for instance using the general procedure described in Reference Example 15. Compounds of formula (27) can be prepared by treatment of compound (28) with an amine of formula NHR^1R^2 in an inert solvent in the presence of a base. Compound (28) can be prepared by treatment of commercially available 5-nitouracil with phosphorous oxychloride in the presence of an N,N-dialkylaniline.

Scheme 8

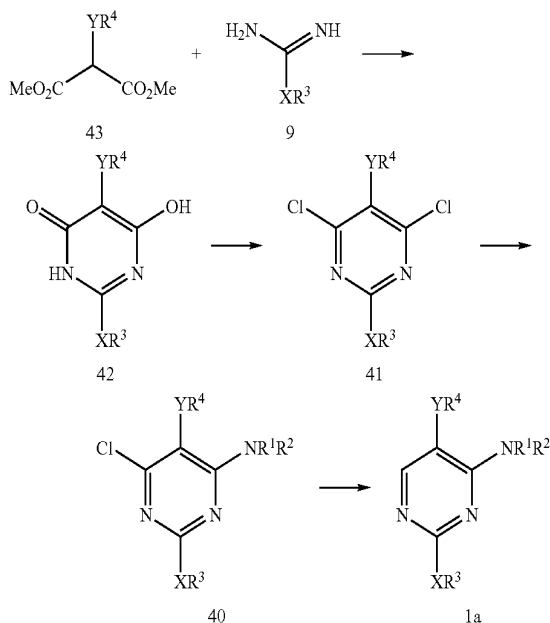


-continued



[0097] In scheme 8, R^1 , R^2 , R^3 , R^4 , X and Y are as defined above for formula (I) and R^6 is linear or branched C_1 - C_4 alkyl or $\text{SiR}^7\text{R}^8\text{R}^9$ wherein each of R^7 , R^8 and R^9 , which are the same or different, is linear or branched C_1 - C_4 alkyl, or phenyl. Compounds of formula (Ia) may be prepared by Suzuki coupling of compounds of formula (29) with a boronic acid $\text{R}^3\text{X}-\text{B}(\text{OH})_2$ in the presence of Pd (0) and a base, for instance using the general procedure described in Reference Example 15. A compound of formula (29) may be prepared by treatment of a compound of formula (30) with phosphorous oxychloride in the presence of an N,N-dialkylaniline, followed by treatment with an amine of formula NHR^1R^2 in an inert solvent in the presence of a base. Compounds like (30) could be prepared by coupling of compounds of type (31) with for example a boronic acid $\text{R}^3\text{X}-\text{B}(\text{OH})_2$.

Scheme 9



[0098] In scheme 9, R^1 , R^2 , R^3 , R^4 , X and Y are as defined above for formula (I). Compounds of formula Ia may be prepared by treatment of a compound of formula 40 with a suitable reducing agent (eg. hydrogen). A compound of formula 40 may be prepared by treatment of a compound of formula 41 with an amine of formula NHR^1R^2 in an inert solvent in the presence of a base. A compound of formula 41 may be prepared from a compound of formula 42 by treatment with phosphorous oxychloride in the presence of an N,N-dialkylaniline. Compounds of formula 42 may be prepared by reacting together compounds of formula 9 and 43 in

an inert solvent in the presence of a base. Compounds of formula 43 may be prepared from commercially available dimethyl halomalonate compounds (where halo refers to chloro, bromo or iodo) by means of suitable nucleophilic displacement reactions.

[0099] Compounds of the present invention have been found in biological tests to be inhibitors of PI3 kinase. The compounds are selective for class Ia PI3 kinases over class Ib and typically exhibit selectivity for class Ia over class Ib PI3 kinases. In general the compounds are selective for the p110 α isoform over p110 γ .

[0100] A compound of the present invention may thus be used as an inhibitor of PI3 kinase, in particular of a class Ia PI3 kinase. Accordingly, a compound of the present invention can be used to treat a disease or disorder arising from abnormal cell growth, function or behaviour associated with PI3 kinase. Examples of such diseases and disorders are discussed by Drees et al in Expert Opin. Ther. Patents (2004) 14(5):703-732. These include proliferative disorders such as cancer, immune disorders, cardiovascular disease, viral infection, inflammation, metabolism/endocrine disorders and neurological disorders. Examples of metabolism/endocrine disorders include diabetes and obesity. Examples of cancers which the present compounds can be used to treat include leukaemia, brain tumours, renal cancer, gastric cancer and cancer of the skin, bladder, breast, uterus, lung, colon, prostate, ovary and pancreas.

[0101] A compound of the present invention may be used as an inhibitor of PI3 kinase. A human or animal patient suffering from a disease or disorder arising from abnormal cell growth, function or behaviour associated with PI3 kinase, such as an immune disorder, cancer, cardiovascular disease, viral infection, inflammation, a metabolism/endocrine disorder or a neurological disorder, may thus be treated by a method comprising the administration thereto of a compound of the present invention as defined above. The condition of the patient may thereby be improved or ameliorated.

[0102] A compound of the present invention can be administered in a variety of dosage forms, for example orally such as in the form of tablets, capsules, sugar- or film-coated tablets, liquid solutions or suspensions or parenterally, for example intramuscularly, intravenously or subcutaneously. The compound may therefore be given by injection or infusion.

[0103] The dosage depends on a variety of factors including the age, weight and condition of the patient and the route of administration. Daily dosages can vary within wide limits and will be adjusted to the individual requirements in each particular case. Typically, however, the dosage adopted for each route of administration when a compound is administered alone to adult humans is 0.0001 to 50 mg/kg, most commonly in the range of 0.001 to 10 mg/kg, body weight, for instance 0.01 to 1 mg/kg. Such a dosage may be given, for example, from 1 to 5 times daily. For intravenous injection a suitable daily dose is from 0.0001 to 1 mg/kg body weight, preferably from 0.0001 to 0.1 mg/kg body weight. A daily dosage can be administered as a single dosage or according to a divided dose schedule.

[0104] A compound of the invention is formulated for use as a pharmaceutical or veterinary composition also comprising a pharmaceutically or veterinarily acceptable carrier or diluent. The compositions are typically prepared following conventional methods and are administered in a pharmaceu-

tically or veterinarily suitable form. The compound may be administered in any conventional form, for instance as follows:

[0105] A) Orally, for example, as tablets, coated tablets, dragees, troches, lozenges, aqueous or oily suspensions, liquid solutions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known in the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavouring agents, colouring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations.

[0106] Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, dextrose, saccharose, cellulose, corn starch, potato starch, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, maize starch, alginic acid, alginates or sodium starch glycolate; binding agents, for example starch, gelatin or acacia; lubricating agents, for example silica, magnesium or calcium stearate, stearic acid or talc; effervescing mixtures; dyestuffs, sweeteners, wetting agents such as lecithin, polysorbates or lauryl sulphate. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. Such preparations may be manufactured in a known manner, for example by means of mixing, granulating, tableting, sugar coating or film coating processes.

[0107] Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is present as such, or mixed with water or an oil medium, for example, peanut oil, liquid paraffin, or olive oil.

[0108] Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone gum tragacanth and gum acacia; dispersing or wetting agents may be naturally-occurring phosphatides, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides for example polyoxyethylene sorbitan monooleate.

[0109] The said aqueous suspensions may also contain one or more preservatives, for example, ethyl or n-propyl p-hydroxybenzoate, one or more colouring agents, such as sucrose or saccharin.

[0110] Oily suspension may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol.

[0111] Sweetening agents, such as those set forth above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by this addition of an antioxidant such as ascorbic acid. Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavouring and colouring agents, may also be present.

[0112] The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oils, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally occurring phosphatides, for example soy bean lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan mono-oleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsion may also contain sweetening and flavouring agents. Syrups and elixirs may be formulated with sweetening agents, for example glycerol, sorbitol or sucrose. In particular a syrup for diabetic patients can contain as carriers only products, for example sorbitol, which do not metabolise to glucose or which only metabolise a very small amount to glucose.

[0113] Such formulations may also contain a demulcent, a preservative and flavouring and coloring agents;

[0114] B) Parenterally, either subcutaneously, or intravenously, or intramuscularly, or intrasternally, or by infusion techniques, in the form of sterile injectable aqueous or oleaginous suspensions. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic pharmaceutically-acceptable diluent or solvent, for example as a solution in 1,3-butane diol.

[0115] Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition fatty acids such as oleic acid find use in the preparation of injectables;

[0116] C) By inhalation, in the form of aerosols or solutions for nebulizers;

[0117] D) Rectally, in the form of suppositories prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperature but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and poly-ethylene glycols;

[0118] E) Topically, in the form of creams, ointments, jellies, collyriums, solutions or suspensions.

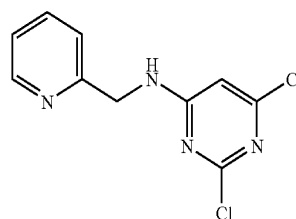
[0119] The invention will be further described in the Examples which follow:

REFERENCE EXAMPLE 1

Preparation of intermediates (18) in scheme 5

2,4-dichloro-6-(pyridin-2-ylmethylamino)pyrimidine (L1)

[0120]



L1

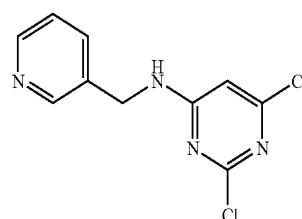
[0121] A solution of 2,4,6-trichloropyrimidine (1.00 g, 5.45 mmol) in dioxane (15 ml) at room temperature was treated with diisopropylethylamine (1.1 eq, 6.00 mmol, 1.04 ml) and dropwise with 2-aminomethylpyridine (1.1 eq, 6.00 mmol, 0.62 ml) and stirred for 2 h. tlc analysis (EtOAc-hexane, 3:1) showed conversion to 2 products. The dioxane was evaporated in vacuo, and the residue partitioned between H₂O (15 ml) and CHCl₃ (15 ml). The organic layer was separated and the aqueous layer further extracted with CHCl₃ (2×10 ml). The combined extracts were dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography (same eluent) gave the product L1 (575 mg, 41%) and its 2-isomer (280 mg, 20%) as pale yellow solids.

[0122] L1: δ_H (250 MHz, CDCl₃) 8.49 (1H, d, J 4.5, pyridine Ar), 7.66 (1H, td, J 7.5, 1.5, pyridine Ar), 7.25-7.17 (2H, m, 2× pyridine Ar), 6.85 (1H, br, NH), 6.36 (1H, s, br, pyrimidine Ar), 4.66 (2H, br, CH₂).

[0123] Examples of further compounds of formula (18) that were prepared using this method are as follows:

2,4-dichloro-6-(pyridin-3-ylmethylamino)pyrimidine (N1)

[0124]

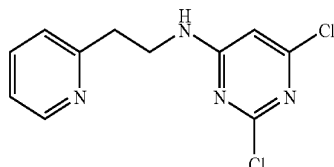


N1

[0125] δ_H (250 MHz, CDCl₃) 8.50 (2H, m, 2× pyridine Ar), 7.62 (1H, d, J 7.5, pyridine Ar), 7.28-7.25 (1H, m, pyridine Ar), 6.26 (1H, s, pyrimidine Ar), 5.95 (1H, br, NH), 4.58 (2H, br, CH₂).

2,4-dichloro-6-[(2-(pyridin-2-yl)ethylamino)pyrimidine (O1)

[0126]

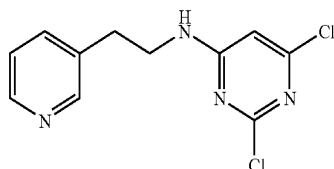


O1

[0127] δ_H (250 MHz, $CDCl_3$) 8.55 (1H, d, J 4.0, pyridine Ar), 7.66 (1H, td, J 7.5, 2.0, pyridine Ar), 7.23-7.19 (2H, m, 2 \times pyridine Ar), 6.66 (1H, br, NH), 6.31 (1H, s, pyrimidine Ar), 3.92-3.85 (2H, m, $NHCH_2$), 3.12 (2H, t, 16.0, $ArCH_2$).

2,4-dichloro-6-[2-(pyridin-3-yl)ethylamino]pyrimidine (P1)

[0128]

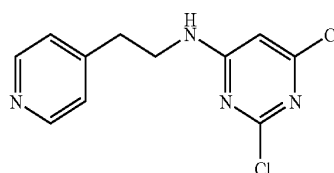


P1

[0129] δ_H (250 MHz, $CDCl_3$) 8.41-8.37 (1H, m, pyridine Ar), 7.48 (2H, d, J 8.0, pyridine Ar), 7.20 (1H, t, J 6.0, pyridine Ar), 6.20 (1H, s, pyrimidine Ar), 5.75 (1H, br, NH), 3.63-3.61 (2H, m, $NHCH_2$), 2.88 (2H, t, J 7.0, $ArCH_2$).

2,4-dichloro-6-[2-(pyridin-4-yl)ethylamino]pyrimidine (Q1)

[0130]

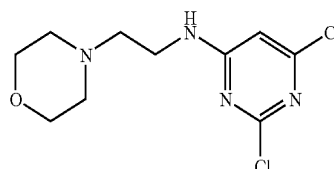


Q1

[0131] δ_H (250 MHz, $CDCl_3$) 8.47 (2H, d, J 6.0, 2 \times pyridine Ar), 7.08 (2H, d, J 6.0, 2 \times pyridine Ar), 6.20 (1H, s, pyrimidine Ar), 5.28 (1H, br, NH), 3.62 (2H, s, br, $NHCH_2$), 2.87 (2H, t, J 7.0, $ArCH_2$).

2,4-dichloro-6-[2-(morpholin-4-yl)ethylamino]pyrimidine (R1)

[0132]

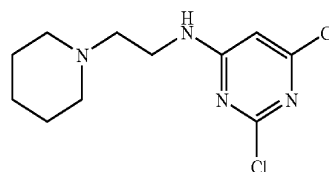


R1

[0133] δ_H (250 MHz, $CDCl_3$) 6.21 (1H, br s, pyrimidine Ar), 5.97 (1H, br, NH), 3.63-3.60 (4H, m, 2 \times morpholine CH_2), 3.41-3.31 (2H, m, br, $NHCH_2$), 2.51 (2H, t, J 6.0, $ArCH_2$), 2.40-2.37 (4H, m, 2 \times morpholine CH_2).

2,4-dichloro-6-[2-piperidin-1-yl)ethylamino]pyrimidine (S1)

[0134]



S1

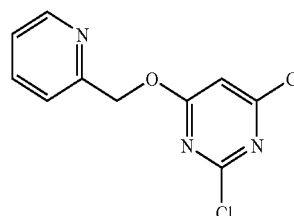
[0135] δ_H (250 MHz, $CDCl_3$) 6.21 (1H, br s, pyrimidine Ar), 6.05 (1H, br, NH), 3.39 (1H, br, q, J 5.0, $NHCH_2H_B$), 3.15 (1H, br, $NHCH_2H_B$), 2.47 (2H, t, J 6.0, NCH_2), 2.32-2.30 (4H, br, 2 \times piperidine CH_2), 1.55-1.48 (4H, m, 2 \times piperidine CH_2), 1.40-1.38 (2H, m, piperidine CH_2).

REFERENCE EXAMPLE 2

Preparation of Further Intermediates (18) in Scheme 5

2,4-Dichloro-6-(pyridin-2-ylmethoxy)pyrimidine (B2)

[0136]



B2

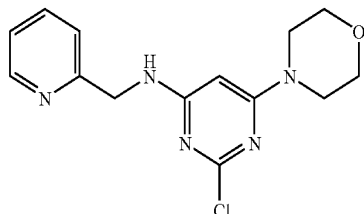
[0137] Compound B2 was prepared according to the method described in WO 99/65881, as follows:

[0138] 248 mg of NaH (60% in mineral oil, 10.36 mmol) was added to a solution of 2-pyridinemethanol (0.90 eq, 9.81 mmol, 0.95 ml) in THF (20 ml) at room temperature and stirred for 30 minutes. After cooling to $-78^\circ C$, 2,4,6-trichloropyrimidine (2 g, 10.90 mmol) was added dropwise and the reaction allowed to warm to room temperature and stirred for 3 h. Saturated aqueous NH_4Cl (20 ml) was added and the mixture extracted with EtOAc (20 ml). The organic phase was dried ($MgSO_4$) and evaporated in vacuo. Column chromatography (EtOAc-DCM, 1:1) gave a mixture of the two products (491 mg, 18%) as a pale yellow solid and in a ratio of 2.4:1, with compound B2 tentatively assigned as the major isomer; δ_H (250 MHz, $CDCl_3$) 8.66-8.61 (2H, m, 1 \times pyridine Ar major, 1 \times pyridine Ar minor), 7.75 (1H, td, J 8.0, 2.0, 1 \times pyridine Ar major), 7.74 (1H, td, J 8.0, 2.0, 1 \times pyridine Ar minor), 7.53 (1H, d, J 8.0, 1 \times pyridine Ar minor), 7.44 (1H, d, J 8.0, 1 \times pyridine Ar major), 7.32-7.24 (1H, 2H, m, 1 \times pyridine Ar major, 1 \times pyridine Ar minor), 7.09 (1H, s, pyridine Ar minor), 6.84 (1H, s, pyrimidine Ar major), 5.59 (2H, s, CH_2 minor), 5.58 (2H, s, CH_2 major).

REFERENCE EXAMPLE 3

Preparation of Intermediates (16) in Scheme 5
2-chloro-4-(morpholin-4-yl)-6-(pyridin-2-ylmethylamino)pyrimidine (K2)

[0139]



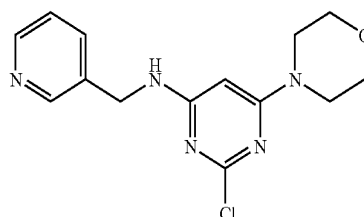
K2

[0140] A solution of compound L₁ (100 mg, 0.39 mmol) in dioxane (1 ml) was treated with diisopropylethylamine (1.5 eq, 0.59 mmol, 0.10 ml) and morpholine (1.8 eq, 0.70 mmol, 0.06 ml) and heated to 70° C. for 8 hours. tlc analysis (CHCl₃-MeOH, 9:1) showed complete conversion. The dioxane was evaporated in vacuo, and the residue partitioned between H₂O (5 ml) and CHCl₃ (5 ml). The organic layer was separated and the aqueous layer further extracted with CHCl₃ (2×2 ml). The combined extracts were dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography (same eluent) gave the product (91 mg, 76%) as a colourless solid; δ_H (250 MHz, CDCl₃) 8.49 (1H, d, J 4.5, pyridine Ar), 7.60 (1H, td, J 8.0, 2.0, pyridine Ar), 7.22-7.12 (2H, m, 2× pyridine Ar), 5.85 (1H, br, NH), 5.75 (1H, s, pyrimidine Ar), 4.56 (2H, d, J 5.0, NHCH₂), 3.68-3.60 (8H, m, 4× morpholine CH₂).

[0141] Using an analogous method the following further compounds (16) were prepared:

2-chloro-4-(morpholin-4-yl)-6-(pyridin-3-ylmethylamino)pyrimidine (L2)

[0142]

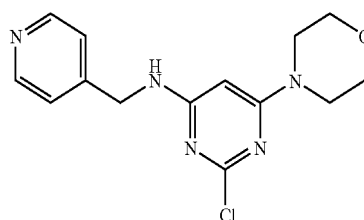


L2

[0143] δ_H (250 MHz, CDCl₃) 8.51 (1H, d, J 2.0, pyridine Ar), 8.46 (1H, dd, J 5.0, 1.5, pyridine Ar), 7.57 (1H, dd, J 8.0, 2.0, pyridine Ar), 7.23-7.18 (1H, m, pyridine Ar), 5.68 (1H, s, pyrimidine Ar), 5.03 (1H, br, NH), 4.49 (2H, d, J 6.0, NHCH₂), 3.68-3.60 (8H, m, 4× morpholine CH₂).

2-chloro-4-(morpholin-4-yl)-6-(pyridin-4-ylmethylamino)pyrimidine (M2)

[0144]

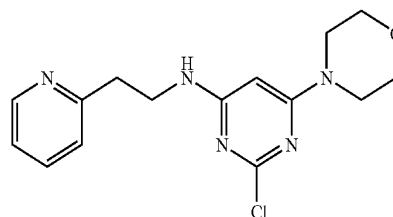


M2

[0145] δ_H (250 MHz, CDCl₃) 8.52 (2H, d, J 6.0, 2× pyridine Ar), 7.33 (2H, d, J 6.0, 2× pyridine Ar), 5.72 (1H, s, pyrimidine Ar), 5.36 (1H, br, NH), 4.57 (2H, d, J 6.0, NHCH₂), 3.65-3.55 (8H, m, 4× morpholine CH₂).

2-chloro-4-(morpholin-4-yl)-6-[(2-(pyridin-2-yl)ethylamino)pyrimidine (N2)

[0146]

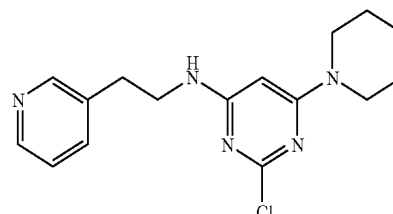


N2

[0147] δ_H (250 MHz, CDCl₃) 8.48 (1H, dt, J 5.0, 1.5 pyridine Ar), 7.55 (1H, td, J 7.5, 2.0, pyridine Ar), 7.12-7.07 (2H, m, 2× pyridine Ar), 5.64 (1H, s, pyrimidine Ar), 5.39 (1H, br, NH), 3.65-3.62 (10H, m, 4× morpholine CH₂, NHCH₂), 2.98 (2H, t, J 6.5, ArCH₂).

2-chloro-4-(morpholin-4-yl)-6-[(2-(pyridin-3-yl)ethylamino)pyrimidine (O2)

[0148]

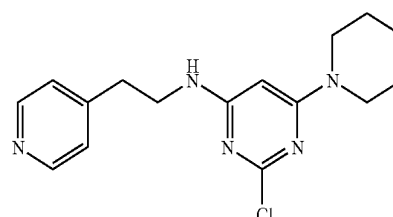


O2

[0149] δ_H (250 MHz, CDCl₃) 8.44-8.39 (2H, m, 2× pyridine Ar), 7.45 (1H, dt, J 8.0, 2.0, pyridine Ar), 7.20-7.16 (1H, m, pyridine Ar), 5.62 (1H, s, pyrimidine Ar), 4.73 (1H, br, NH), 3.66 (8H, br s, 4× morpholine CH₂), 3.52 (2H, br q J 6.5, NHCH₂), 2.83 (2H, t J 7.0, ArCH₂).

2-chloro-4-(morpholin-4-yl)-6-[(2-(pyridin-4-yl)ethylamino)pyrimidine (P2)

[0150]

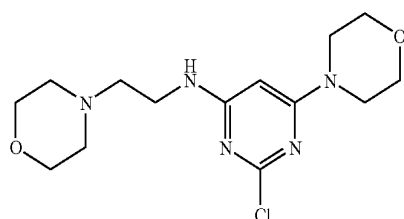


P2

[0151] δ_H (250 MHz, CDCl₃) 8.58 (2H, d, J 6.0, 2× pyridine Ar), 7.24 (2H, d, J 6.0, 2× pyridine Ar), 5.74 (1H, s, pyrimidine Ar), 4.88 (1H, br, NH), 3.80-3.63 (10H, m, 4× morpholine CH₂, NHCH₂), 2.98 (2H, t, J 7.0, ArCH₂).

2-chloro-4-(morpholin-4-yl)-6-[2-(morpholin-4-yl)ethylamino]pyrimidine (Q2)

[0152]

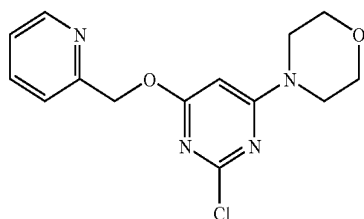


Q2

[0153] δ_H (250 MHz, $CDCl_3$) 5.67 (1H, s, pyrimidine Ar), 5.22 (1H, br, NH), 3.70-3.62 (12H, m, 6 \times morpholine CH_2), 3.30 (2H, br, $NHCH_2$), 2.50 (2H, t, J 6.0, NCH_2), 2.40 (4H, t, J 4.5, 1 \times morpholine CH_2).

2-chloro-4-(morpholin-4-yl)-6-(pyridin-2-ylmethoxy)pyrimidine (R2)

[0154]



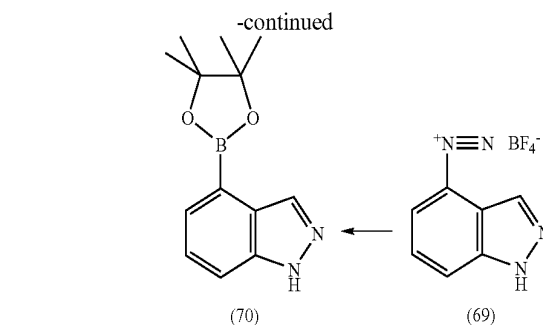
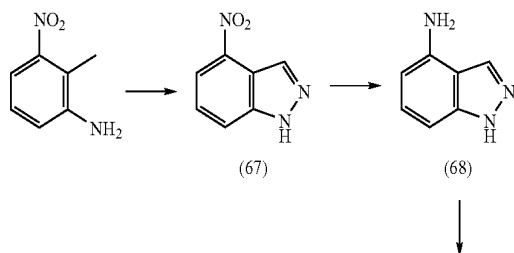
R2

[0155] δ_H (250 MHz, $CDCl_3$) 8.51 (1H, d, J 4.5, 1 \times pyridine Ar), 7.63 (1H, td, J 8.0, 2.0, 1 \times pyridine Ar), 7.31 (1H, d, J 8.0, 1 \times pyridine Ar), 7.16 (1H, dd, J 7.0, 5.5, 1 \times pyridine Ar), 6.08 (1H, s, pyrimidine Ar), 5.40 (2H, s, OCH_2), 3.68-3.59 (8H, m, 4 \times morpholine CH_2).

REFERENCE EXAMPLE 4

Indazole-4-Boronate Ester: (Route 1)

[0156]



[0157] To a solution of 2-methyl-3-nitroaniline (2.27 g, 14.91 mmol) in acetic acid (60 mL) was added a solution of sodium nitrite (1.13 g, 1.1 eq.) in water (5 mL). After 2 h, the deep red solution was poured onto ice/water and the resulting precipitate collected by filtration to yield 4-nitro-1H-indazole (67) (1.98 g, 81%).

[0158] A mixture of 4-nitro-1H-indazole (760 mg, 4.68 mmol), palladium on charcoal (10%, cat.) and ethanol (30 mL) was stirred under a balloon of hydrogen for 4 h. The reaction mixture was then filtered through celite, and the solvent removed in vacuo to yield 1H-indazole-4-ylamine (68) (631 mg, 100%).

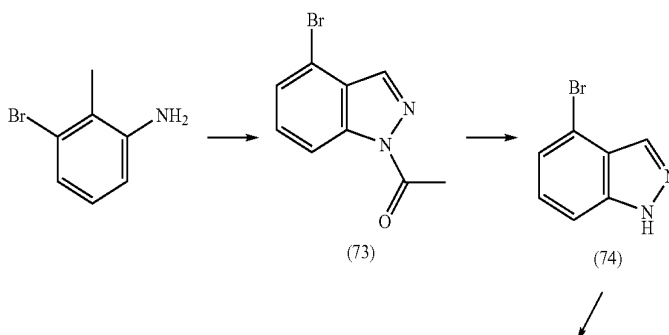
[0159] An aqueous solution of sodium nitrite (337 mg, 4.89 mmol) in water (2 mL) was added dropwise to a suspension of 1H-indazole-4-ylamine (631 mg, 4.74 mmol) in 6M hydrochloric acid (7.2 mL) at below 0° C. After stirring for 30 minutes, sodium tetrafluoroborate (724 mg) was added to the reaction mixture. A viscous solution resulted, which was filtered and washed briefly with water to yield 1H-indazole-4-diazonium tetrafluoroborate salt (69) (218 mg, 20%) as a deep red solid.

[0160] Dry MeOH (4 mL) was purged with argon for 5 minutes. To this was added 1H-indazole-4-diazonium tetrafluoroborate salt (218 mg, 0.94 mmol), bis-pinacolato diboron (239 mg, 1.0 eq.) and [1,1'-bis(diphenylphosphino)ferrocene]palladium (II) chloride (20 mg). The reaction mixture was stirred for 5 h and then filtered through celite. The residue was purified using flash chromatography to yield the desired title compound (70), (117 mg).

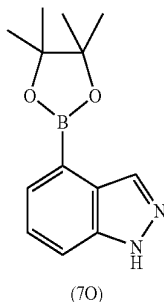
REFERENCE EXAMPLE 5

Indazole-4-Boronate Ester: (Route 2)

[0161]



-continued



[0162] To a solution of 3-bromo-2-methyl aniline (5.0 g, 26.9 mmol) in chloroform (50 mL) was added potassium acetate (1.05 eq., 28.2 mmol, 2.77 g). Acetic anhydride (2.0 eq., 53.7 mmol, 5.07 mL) was added with concurrent cooling in ice-water. The mixture was then stirred at room temperature for 10 minutes after which time a white gelatinous solid formed. 18-Crown-6 (0.2 eq., 5.37 mmol, 1.42 g) was then added followed by iso-amyl nitrite (2.2 eq., 59.1 mmol, 7.94 mL) and the mixture was heated under reflux for 18 h. The reaction mixture was allowed to cool, was partitioned between chloroform (3×100 mL) and saturated aqueous sodium hydrogen carbonate (100 mL). The combined organic extracts were washed with brine (100 mL), separated and dried (MgSO₄).

[0163] The crude product was evaporated onto silica and purified by chromatography eluting with 20%→40% EtOAc-petrol to give the N-acetyl indazole (73) (3.14 g, 49%) as an orange solid followed by the indazole (74) (2.13 g, 40%) as a pale orange solid.

[0164] 73: ¹H NMR (400 MHz, CDCl₃) 2.80 (3H, s), 7.41 (1H, t, J=7.8 Hz), 7.50 (1H, d, J=7.8 Hz), 8.15 (1H, s), 8.40 (1H, d, J=7.8 Hz).

[0165] 74: ¹H NMR (400 MHz, CDCl₃) 7.25 (1H, t, J=7.3 Hz), 7.33 (1H, d, J=7.3 Hz), 7.46 (1H, d, J=7.3 Hz), 8.11 (1H, s), 10.20 (1H, br s),

[0166] To a solution of the N-acetyl indazole (3.09 g, 12.9 mmol) in MeOH (50 mL) was added 6N aqueous HCl (30 mL) and the mixture was stirred at room temperature for 7 h. The MeOH was evaporated and the mixture partitioned between EtOAc (2×50 mL) and water (50 mL). The combined organic layers were washed with brine (50 mL), separated and dried (MgSO₄). The solvent was removed by evaporation under reduced pressure to give an orange solid (2.36 g, 93%).

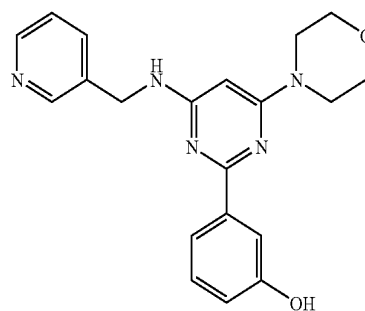
[0167] To a solution of the 4-bromoindazole (500 mg, 2.54 mmol) and bis(pinacolato)diboron (1.5 eq., 3.81 mmol) in DMSO (20 mL) was added potassium acetate (3.0 eq., 7.61 mmol, 747 mg; dried in drying pistol) and PdCl₂(dppf)₂ (3 mol %, 0.076 mmol, 62 mg). The mixture was degassed with argon and heated at 80° C. for 40 h. The reaction mixture was allowed to cool and partitioned between water (50 mL) and ether (3×50 mL). The combined organic layers were washed with brine (50 mL), separated and dried (MgSO₄). The crude material was purified by chromatography eluting with 30%→40% EtOAc-petrol to give an inseparable 3:1 mixture of the boronate ester (369 mg, 60%) and indazole (60 mg, 20%); this was isolated as a yellow gum which solidified upon standing to furnish (70) as an off-white solid.

[0168] ¹H NMR (400 MHz, d₆-DMSO) (70) 1.41 (12H, s), 7.40 (1H, dd, J=8.4 Hz, 6.9 Hz), 7.59 (1H, d, J=8.4 Hz), 7.67 (1H, d, J=6.9 Hz), 10.00 (1H, br s), 8.45 (1H, s), and indazole: 7.40 (1H, t), 7.18 (1H, t, J=7.9 Hz), 7.50 (1H, d, J=9.1 Hz), 7.77 (1H, d, J=7.9 Hz), 8.09 (1H, s). Impurity at 1.25.

EXAMPLE 1

Preparation of Compounds of Formula (Ib) in Scheme 5

2-(3-hydroxyphenyl)-4-(morpholin-4-yl)-6-(pyridin-3-ylmethylamino)pyrimidine (S2)

[0169]

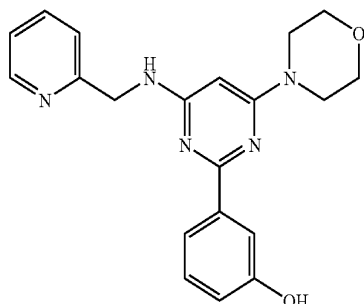
S2

[0170] A mixture of compound L2 (58 mg, 0.19 mmol) and PdCl₂(dppf) (5 mol %, 8 mg) in DME (1 mL) was stirred at room temperature for 15 minutes. 3-hydroxyphenylboronic acid (3 eq, 0.57 mmol, 78 mg), Na₂CO₃ (2 eq, 0.38 mmol, 40 mg) and 5 drops of water were added and the mixture heated at 80° C. for 18 h. The solvents were then removed in vacuo and the residue partition between water and chloroform. The organic phase was dried (Na₂SO₄) and concentrated in vacuo. Purification by preparative tlc (CHCl₃-MeOH, 95:5) gave the product (17 mg, 25%) as an off-white solid; δ_H (250 MHz, CD₃OD) 8.45 (1H, s, pyridine Ar), 8.30 (1H, d, J 4.0, pyridine Ar), 7.74 (1H, d, J 8.0, pyridine Ar), 7.32-7.26 (3H, m, 1× pyridine Ar, 2× Ar), 7.12 (1H, t, J 8.0, Ar), 6.73 (1H, ddd, J 8.0, 2.5, 1.0, Ar), 6.18 (1H, s, pyrimidine Ar), 4.53 (2H, s, NHCH₂), 3.67 (4H, m, 2× morpholine CH₂), 3.60-3.57 (4H, m, 2× morpholine CH₂).

[0171] Using an analogous method, the following further compounds of formulae (Ib) were prepared:

2-(3-hydroxyphenyl)-4-(morpholin-4-yl)-6-(pyridin-2-ylmethylamino)pyrimidine (T2)

[0172]

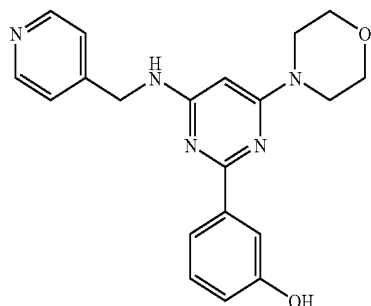


T2

[0173] δ_H (250 MHz, $CDCl_3$) 8.50 (1H, d, J 4.5, pyridine Ar), 7.62 (1H, td, J 8.0, 2.0, pyridine Ar), 7.35-7.29 (3H, m, 2 \times pyridine Ar, 1 \times Ar), 7.20-7.15 (2H, m, 2 \times Ar), 6.83 (1H, br d, J 8.0, Ar), 5.94 (1H, s, pyrimidine Ar), 5.74 (1H, br, NH), 4.64 (2H, d, J 5.5, $NHCH_2$), 3.66-3.62 (8H, m, 4 \times morpholine CH_2).

2-(3-hydroxyphenyl)-4-(morpholin-4-yl)-6-(pyridin-4-ylmethylamino)pyrimidine (U2)

[0174]

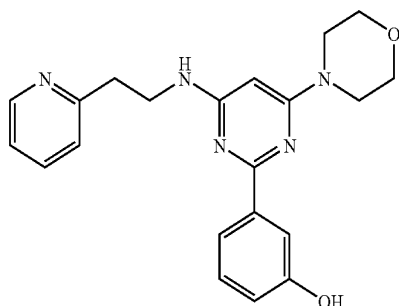


U2

[0175] δ_H (250 MHz, $CDCl_3$) 8.49 (2H, d, J 5.0, 2 \times pyridine Ar), 6.82 (1H, ddd, J 8.0, 2.5, 1.0, Ar), 7.40-7.36 and 7.23-7.18 (total 5H 2 \times m, 2 \times pyridine Ar, 3 \times Ar), 6.06 (1H, s, pyrimidine Ar), 5.07 (1H, br t, J 6.0, NH), 4.56 (2H, d, J 6.0, $NHCH_2$), 3.71-3.69 (4H, m, 2 \times morpholine CH_2), 3.67-3.62 (4H, m, 2 \times morpholine CH_2).

2-(3-hydroxyphenyl)-4-(morpholin-4-yl)-6-[(2-(pyridin-2-yl)ethylamino)pyrimidine (V2)

[0176]

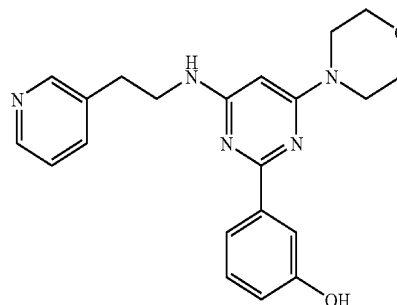


V2

[0177] δ_H (250 MHz, $CDCl_3$) 8.61 (1H, dq, J 5.0, 1.0, pyridine Ar), 7.67 (1H, td, J 8.0, 2.0, pyridine Ar), 7.46 (1H, app t, J 8.0, 1 \times pyridine Ar, 1 \times Ar), 7.30-7.19 (3H, m, 1 \times pyridine Ar, 2 \times Ar), 6.91 (1H, ddd, J 8.0, 2.0, 1.0, Ar), 6.00 (1H, s, pyrimidine Ar), 5.25 (1H, br t, J 5.5, NH), 3.84-3.72 (10H, m, 4 \times morpholine CH_2 , $NHCH_2$), 3.14 (2H, t, J 6.5, $ArCH_2$).

2-(3-hydroxyphenyl)-4-(morpholin-4-yl)-6-[(2-(pyridin-3-yl)ethylamino)pyrimidine (W2)

[0178]

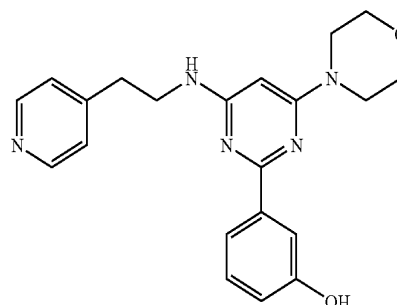


W2

[0179] δ_H (250 MHz, $CDCl_3$) 8.42-8.40 (2H, m, 2 \times pyridine Ar), 7.48 (1H, br d, J 8.0, pyridine Ar), 7.39-7.34 (2H, m, 1 \times pyridine Ar, 1 \times Ar), 7.21-7.14 (2H, m, 2 \times Ar), 6.82 (1H, br dd, J 7.0, 1.5, Ar), 5.92 (1H, s, pyrimidine Ar), 4.75 (1H, br t, J 6.0, NH), 3.75-3.65 (8H, m, 4 \times morpholine CH_2), 3.55 (2H, q, J 6.5, $NHCH_2$), 2.81 (2H, t, J 6.5, $ArCH_2$).

2-(3-hydroxyphenyl)-4-(morpholin-4-yl)-6-[(2-(pyridin-4-yl)ethylamino)pyrimidine (X2)

[0180]

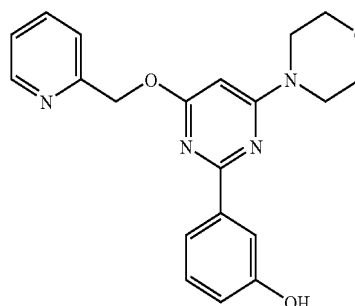


X2

[0181] δ_H (250 MHz, $CDCl_3$) 8.45 (2H, d, J 4.5, 2 \times pyridine Ar), 7.39-7.37 (2H, m, 2 \times pyridine Ar), 7.19 (1H, t, J 8.0, Ar), 7.09 (2H, app d, J 6.0, 2 \times Ar), 6.83 (1H, ddd, J 8.0, 2.0, 1.0, Ar), 5.96 (1H, s, pyrimidine Ar), 4.70 (1H, t, J 6.0, NH), 3.78-3.74 (4H, m, 2 \times morpholine CH_2), 3.70-3.67 (4H, m, 2 \times morpholine CH_2), 3.56 (2H, q, J 6.5, $NHCH_2$), 2.86 (2H, t, J 6.5, $ArCH_2$).

2-(3-hydroxyphenyl)-4-(morpholin-4-yl)-6-(pyridin-2-ylmethoxy)pyrimidine (Y2)

[0182]

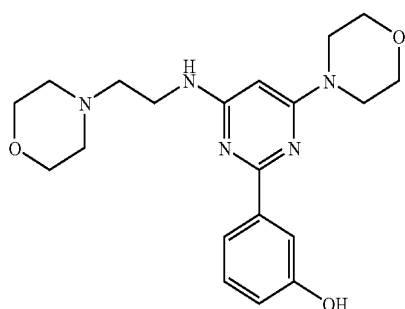


Y2

[0183] δ_H (250 MHz, $CDCl_3$) 8.54 (1H, d, J 4.5, pyridine Ar), 7.67 (1H, td, J 7.5, 2.0, pyridine Ar), 7.42-7.38 (3H, m, 2 \times pyridine Ar, 1 \times Ar), 7.24-7.17 (2H, m, 2 \times Ar), 6.85 (1H, ddd, J 8.0, 2.5, 1.0, Ar), 6.39 (1H, s, pyrimidine Ar), 5.45 (2H, s, OCH_2), 3.70-3.61 (8H, m, 4 \times morpholine CH_2).

2-(3-hydroxyphenyl)-4-(morpholin-4-yl)-6-[2-(morpholin-4-yl)ethylamino]pyrimidine (Z2)

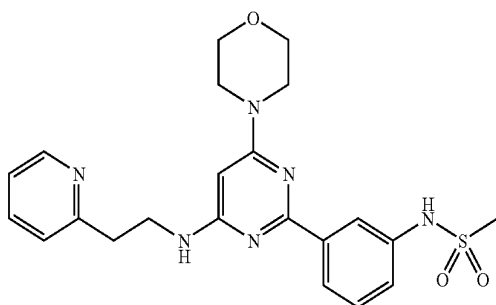
[0184]



Z2

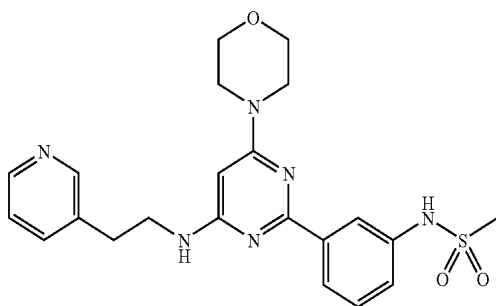
[0185] δ_H (250 MHz, $CDCl_3$) 7.41-7.36 (2H, m, 2 \times Ar), 7.23-7.16 (1H, m, Ar), 6.83-6.78 (1H, m, Ar), 5.99 (1H, s, pyrimidine Ar), 5.21 (1H, br, NH), 3.79-3.67 (12H, m, 6 \times morpholine CH_2), 3.42 (2H, q, J 5.5, $NHCH_2$), 2.57 (2H, t, J 6.0, $NHCH_2CH_2$), 2.47 (4H, t, J 4.5, 2 \times morpholine CH_2).

B4



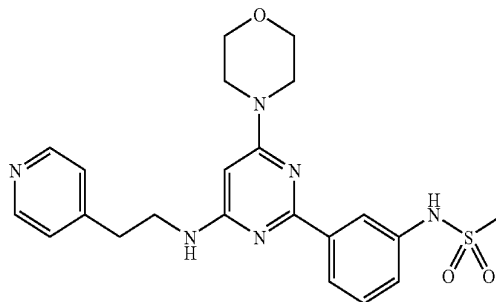
[0186] δ_H (500 MHz, CD_3OD) 8.46 (1H, d, J 4.2, pyridine Ar), 7.90 (1H, t, J 1.9, Ar), 7.74 (1H, td, J 7.7, 1.8, pyridine Ar), 7.70 (1H, d, J 7.8, Ar), 7.38 (1H, t, J 7.9, Ar), 7.33-7.29 (2H, m, 1 \times pyridine Ar, 1 \times Ar), 7.25 (1H, dd, J 7.5, 1.5 pyridine Ar), 6.22 (1H, s, pyrimidine Ar), 3.81-3.73 (10H, m, 4 \times morpholine CH_2 , $NHCH_2$), 3.09 (2H, t, J 7.0, $ArCH_2$), 2.97 (3H, s, CH_3).

D4



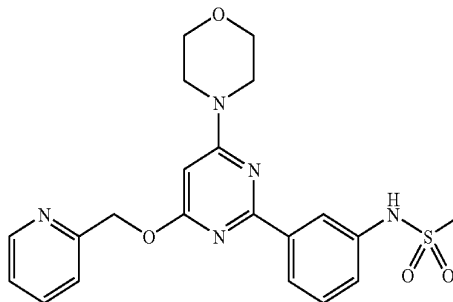
[0187] δ_H (500 MHz, $CDCl_3$) 8.51 (1H, d, J 1.8, pyridine Ar), 8.50 (1H, dd, J 4.9, 1.8, pyridine Ar), 7.81 (1H, br t, J 1.9, Ar), 7.77 (1H, dt, J 7.9, 1.9, pyridine Ar), 7.55 (1H, dt, J 7.9, 1.9, Ar), 7.41 (1H, t, J 7.9, Ar), 7.33 (1H, ddd, J 7.9, 1.9, 0.9, Ar), 7.26 (1H, dd, J 7.6, 4.9, pyridine Ar), 6.11 (1H, s, pyrimidine Ar), 4.79 (1H, br t, J 6.3, NH), 3.86-3.84 (4H, m, 2 \times morpholine CH_2), 3.79-3.77 (4H, m, 2 \times morpholine CH_2), 3.68 (2H, dt, J 6.9, 6.3, $NHCH_2$), 3.01 (1H, s, CH_3), 2.95 (2H, t, J 6.9, $ArCH_2$).

F4



[0188] δ_H (500 MHz, $CDCl_3$) 8.57 (2H, d, J 5.0, 2 \times pyridine Ar), 7.81 (1H, s, Ar), 7.77 (1H, d, J 7.8, Ar), 7.43 (1H, t, J 7.8, Ar), 7.32 (1H, d, J 7.8, Ar), 7.18 (2H, d, J 5.0, 2 \times pyridine Ar), 6.09 (1H, s, pyrimidine Ar), 3.89-3.87 (4H, m, 2 \times morpholine CH_2), 3.81-3.80 (4H, m, 2 \times morpholine CH_2), 3.73 (2H, dt, J 6.9, 6.3, $NHCH_2$), 3.04 (3H, s, CH_3), 2.27 (2H, t, J 7.0, $ArCH_2$).

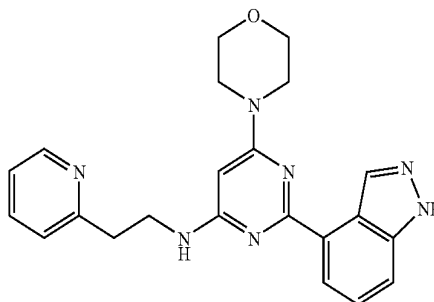
G4



[0189] δ_H (500 MHz, $DMSO-d_6$) 9.87 (1H, br s, NH), 8.56 (1H, d, J 4.8, pyridine Ar), 7.96 (1H, t, J 1.8, Ar), 7.82 (1H, td, J 7.7, 1.8, pyridine Ar), 7.78 (1H, d, J 7.9, Ar), 7.48 (1H, d, J 7.8, Ar), 7.43 (1H, t, J 7.9, Ar), 7.35-7.32 (2H, m, 2 \times pyridine Ar), 6.69 (1H, s, pyrimidine Ar), 5.47 (2H, s, OCH_2), 3.74-3.72 (4H, m, 2 \times morpholine CH_2), 3.65-3.63 (4H, m, 2 \times morpholine CH_2), 3.01 (3H, s, CH_3).

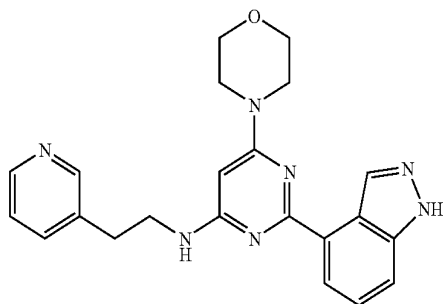
[0190] Using an analogous method, in which the boronic acid Suzuki reagent was replaced by the indazole 4-pinacol boronate ester described in Reference Examples 4 and 5, the following further compounds were prepared:

B5



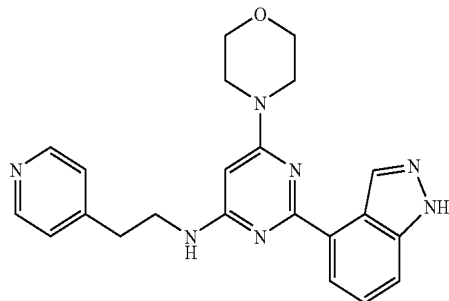
[0191] δ_H (500 MHz, $CDCl_3$) 8.65 (1H, s, indazole Ar), 8.58 (1H, d, J 5.0, pyridine Ar), 7.62 (1H, td, J 7.5, 1.6, pyridine Ar), 7.59 (1H, d, J 7.5, indazole Ar), 7.53 (1H, d, J 7.5 indazole Ar), 7.43 (1H, t, J 7.5, indazole Ar), 7.19 (1H, d, J 7.5, pyridine Ar), 7.16 (1H, dd, J 7.3, 5.0, pyridine Ar), 6.23 (1H, s, pyrimidine Ar), 5.39 (1H, br t, J 5.1, NH), 3.90-3.83 (6H, m, 2 \times morpholine CH_2 , $NHCH_2$), 3.81-3.79 (4H, m, 2 \times morpholine CH_2), 3.13 (2H, t, J 6.5, $ArCH_2$).

C5



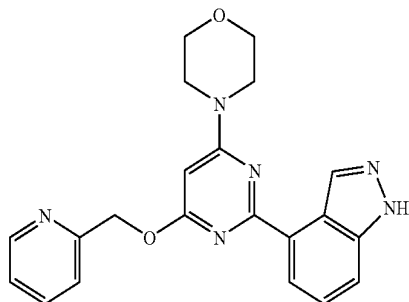
[0192] δ_H (500 MHz, $CDCl_3$) 8.65 (1H, s, indazole Ar), 8.54 (1H, d, J 1.5, pyridine Ar), 8.52 (1H, dd, J 5.0, 1.5, pyridine Ar), 7.58-7.54 (2H, m, 1 \times pyridine Ar, 1 \times indazole Ar), 7.53 (1H, d, J 8.3, indazole Ar), 7.41 (1H, dd, J 7.3, 8.2, indazole Ar), 7.25 (1H, dd, J 7.5, 5.0, pyridine Ar), 6.20 (1H, s, pyrimidine Ar), 4.87 (1H, t, J 5.5, NH), 3.90-3.88 (4H, m, 2 \times morpholine CH_2), 3.81-3.79 (4H, m, 2 \times morpholine CH_2), 3.71-3.67 (2H, m, $NHCH_2$), 2.97 (t, J 7.0, $ArCH_2$).

D5



[0193] δ_H (500 MHz, CD_3OD) 8.65 (1H, s, br, indazole Ar), 8.55 (2H, d, J 6.0, 2 \times pyridine Ar), 7.58 (1H, d, J 7.5, indazole Ar), 7.55 (1H, d, J 8.3, indazole Ar), 7.49 (1H, dd, J 8.3, 7.5, indazole Ar), 7.17 (2H, d, J 6.0, 2 \times pyridine Ar), 6.21 (1H, s, br, pyrimidine Ar), 4.69 (1H, s, br, NH), 3.83-3.82 (4H, t, J 4.8, 2 \times morpholine CH_2), 3.76-3.75 (4H, t, J 4.8, 2 \times morpholine CH_2), 3.70 (2H, dt, J 7.0, 6.5, $NHCH_2$), 2.95 (2H, t, J 7.0, $ArCH_2$).

E5



[0194] δ_H (500 MHz $CDCl_3$) 10.20 (1H, br, NH), 8.67 (1H, s, br, indazole Ar), 8.62 (1H, d, J 4.0, pyridine Ar), 7.73 (1H, td, J 7.7, 1.7, pyridine Ar), 7.68 (1H, dd, J 7.2, 0.5, indazole Ar), 7.60 (1H, d, J 8.4, indazole Ar), 7.50-7.46 (2H, m, 1 \times pyridine Ar, 1 \times indazole Ar), 7.25 (1H, dd, J 7.2, 5.1, pyridine Ar), 6.69 (1H, s, pyrimidine Ar), 5.59 (2H, s, OCH_2), 3.90-3.88 (4H, t, J 4.7, 2 \times morpholine CH_2), 3.79-3.78 (4H, t, J 4.8, 2 \times morpholine CH_2).

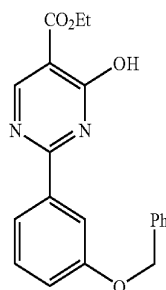
REFERENCE EXAMPLE 6

Preparation of Intermediates (23) in Scheme 6

Ethyl 2-(3-benzyloxyphenyl)-4-hydroxypyrimidine Carboxylate (H3)

[0195]

H3



[0196] To a solution of the malonate derivative (24) 1.5 g, 6.95 mmol) and the amidine S (1.1 eq, 7.65 mmol, 1.73 g) in ethanol (20 ml) was added sodium ethoxide (1.1 eq, 7.65 mmol, 520 mg) and the mixture stirred at room temperature for 4 h. After this time, the solid product was filtered off and allowed to dry in air, affording 1.56 g (64%) as a pale yellow solid; δ_H (250 MHz, $DMSO-d_6$) 8.54 (1H, br, pyrimidine Ar), 7.96-7.90 (2H, br, 2 \times Ar), 7.48-7.32 (6H, br, 6 \times Ar), 7.06 (1H, br d, J 7.0, Ar), 5.17 (2H, br, s, OCH_2), 4.17 (2H, br q, J 6.5, CO_2CH_2), 1.27 (3H, br, t, J 6.5, $CO_2CH_2CH_3$).

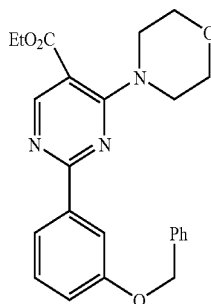
REFERENCE EXAMPLE 7

Preparation of Intermediates (22) in Scheme 6

Ethyl 2-(3-benzyloxyphenyl)-4-(morpholin-4-yl)pyrimidine Carboxylate (I3)

[0197]

I3



[0198] A solution of compound H3 (225 mg, 0.64 mmol) in $POCl_3$ (2 ml) containing N,N-dimethylaniline (1.1 eq, 0.71 mmol, 0.09 ml) was stirred at 110 $^\circ$ C. for 18 h. The $POCl_3$ was removed in vacuo and the residue azeotroped with toluene (5 ml), re-dissolved in $CHCl_3$ (5 ml) and poured into ice. The organic layer was separated, washed with water, dried

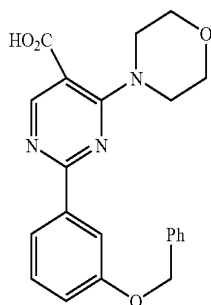
(MgSO₄) and concentrated in vacuo. The crude product was dissolved in dioxane (2 ml) and treated with DIPEA (2 eq, 1.28 mmol, 0.22 ml) and morpholine (5 eq, 3.21 mmol, 0.28 ml) and heated at 80° C. for 4 h. The dioxane was evaporated in vacuo, and the residue partitioned between H₂O (5 ml) and CHCl₃ (5 ml). The organic layer was separated and the aqueous layer further extracted with CHCl₃ (2×2 ml). The combined extracts were dried (Na₂SO₄) and concentrated in vacuo. Purification by column chromatography (hexane-EtOAc, 3:1) gave the product (196 mg, 73% for two steps) as a colourless solid; δ_H (250 MHz, CDCl₃) 8.79 (1H, s, pyrimidine Ar), 7.96-7.92 (2H, m, 2×Ar), 7.42-7.23 (6H, m, 6×Ar), 7.06-7.02 (1H, m, Ar), 5.09 (2H, s, OCH₂), 4.30 (2H, q, J 7.0, CO₂CH₂), 3.76-3.72 (4H, m, 2× morpholine CH₂), 3.65-3.60 (4H, m, 2× morpholine CH₂), 1.32 (3H, t, J 7.0, CO₂CH₂CH₃).

REFERENCE EXAMPLE 8

Preparation of Intermediates (21) in Scheme 6

2-(3-benzyloxyphenyl)-4-(morpholin-4-yl)pyrimidine Carboxylic Acid (J3)

[0199]



J3

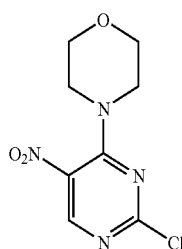
[0200] A solution of compound 13 (94 mg) in THF-MeOH-water (5:2:2, 1.5 ml) was treated with lithium hydroxide (5 eq, 1.79 mmol, 75 mg) and stirred at 100° C. for 1.5 h. After this time it was cooled and carefully acidified with 2M HCl, causing precipitation of the product (51 mg) as a yellow solid; δ_H (250 MHz, DMSO-d₆) 8.63 (1H, s, pyrimidine Ar), 7.97-7.93 (2H, s, 2×Ar), 7.55-7.30 (6H, m, 6×Ar), 7.19-7.15 (1H, m, Ar), 5.20 (2H, s, OCH₂), 3.68-3.65 (8H, m, 4× morpholine CH₂).

REFERENCE EXAMPLE 9

Preparation of Intermediates (27) in Scheme 7

2-chloro-4-(morpholin-4-yl)-5-nitropyrimidine (K3)

[0201]



K3

[0202] A solution of the dichloropyrimidine (1.00 g, 5.16 mmol) in acetone (10 ml) at 0° C. containing Na₂CO₃ (1.0 eq, 5.16 mmol, 546 mg) was treated dropwise with a solution of morpholine (1.0 eq, 5.16 mmol, 0.45 ml) in acetone (3 ml) and stirred for 1 h at 0° C. Tlc (DCM-hexane, 4:2) showed completion of the reaction to give two products. The acetone was removed in vacuo and the residue partitioned between water and EtOAc, the organic layer dried (MgSO₄) and evaporated in vacuo. Column chromatography (DCM-EtOAc, 9:1) gave the product (560 mg, 45%) as a pale yellow solid, together with 260 mg (17%) of the disubstituted product also as a yellow solid.

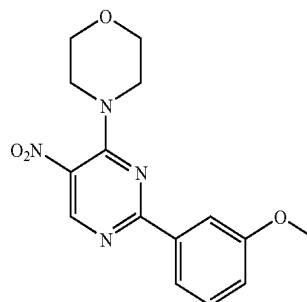
[0203] K3: δ_H (250 MHz, CDCl₃) 8.68 (1H, s, pyrimidine Ar), 3.75-3.71 (4H, m, 2× morpholine CH₂), 3.57-3.53 (4H, m, 2× morpholine CH₂).

REFERENCE EXAMPLE 10

Preparation of Intermediate of Formula (26) in Scheme 7

2-(3-methoxyphenyl)-4-(morpholin-4-yl)-5-nitropyrimidine (L3)

[0204]



L3

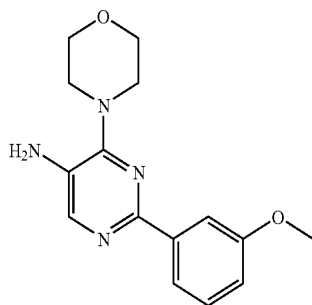
[0205] A solution of compound K3 (100 mg, 0.41 mmol) in DME-H₂O-EtOH (7:3:2, 2.5 ml) in a sealable tube was treated with PdCl₂(dppf) (5 mol %, 17 mg), 3-methoxyphenylboronic acid (2.2 eq, 0.90 mmol, 136 mg) and Na₂CO₃ (2.0 eq, 0.82 mmol, 88 mg), sealed and heated at 150° C. in a microwave apparatus for 10 minutes. The solvents were then removed in vacuo and the residue was partitioned between water and CHCl₃, the organic phase separated and dried (MgSO₄) and concentrated in vacuo. Column chromatography (DMC-EtOAc, 95:5) gave the product (50 mg, 39%) as a yellow solid; δ_H (250 MHz, CDCl₃) 9.07 (1H, s, pyrimidine Ar), 8.04-8.00 (2H, m, 2×Ar), 7.44 (1H, t, J 8.0, Ar), 7.13 (1H, ddd, J 8.0, 2.5, 1.0, Ar), 3.94 (3H, s, OCH₃), 3.90-3.87 (4H, m, 2× morpholine CH₂), 3.77-3.74 (4H, m, 2× morpholine CH₂).

REFERENCE EXAMPLE 11

Preparation of Intermediate (25) in Scheme 7

5-amino-2-(3-methoxyphenyl)-4-(morpholin-4-yl)pyrimidine (M3)

[0206]



M3

[0207] A solution of the nitro compound L3 (31 mg, 0.099 mmol) in EtOH-EtOAc (1:1, 2 ml) containing 10% Pd on carbon (5 mg) was stirred under a balloon of hydrogen gas for 1.5 hours. tlc (DCM-EtOAc, 9:1) then showed completion of the reaction. The mixture was diluted with EtOAc and filtered through a short pad of celite and the solvents evaporated in vacuo to give the amine (25 mg, 89%) as an oil;

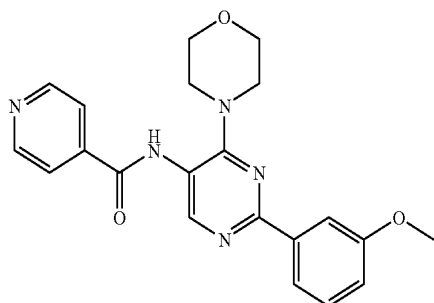
[0208] δ_H (250 MHz, $CDCl_3$) 8.03 (1H, s, pyrimidine Ar), 7.87-7.83 (2H, m, Ar), 7.28 (1H, t, J 8.0, Ar), 6.89 (1H, ddd, J 8.0, 2.5, 1.0 Ar), 3.83 (3H, s, OCH_3), 3.80-3.75 (4H, m, 2 \times morpholine CH_2), 3.64 (2H, br, NH_2), 3.47-3.43 (4H, m, 2 \times morpholine CH_2).

EXAMPLE 2

Preparation of Compounds of Formula (Ia) in Scheme 7

2-(3-methoxyphenyl)-4-(morpholin-4-yl)-5-[(pyridin-4-yl)carbonylamino]pyrimidine (N3)

[0209]



N3

[0210] A solution of the amine M3 (25 mg, 0.087 mmol) in $CHCl_3$ (1 ml) at room temperature was treated with diisopropylethylamine (2.5 eq, 0.21 mmol, 0.03 ml) and the acid chloride (2.2 eq, 0.196 mmol, 34 mg) and stirred at room temp for 1 h. tlc (DCM-EtOAc, 9:1) showed incomplete reaction. Further base (0.03 ml) and acid chloride (34 mg) were added and the reaction stirred at room temperature for 18 h. tlc then

showed complete conversion. A standard aqueous work up and column chromatography (same eluent) gave the product (16 mg, 47%) as a colourless solid;

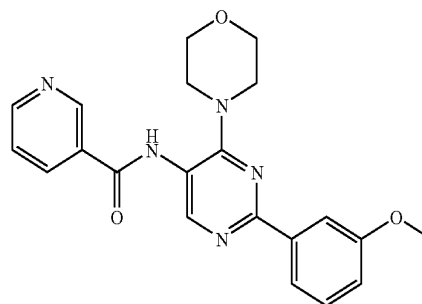
[0211] δ_H (250 MHz, $CDCl_3$) 9.03 (1H, s, pyrimidine Ar), 8.79-8.61 (3H, m, 2 \times pyridine Ar, NH), 7.94-7.89 (2H, m, Ar), 7.76 (2H, d, J 5.0, pyridine Ar), 7.34 (1H, t, J 8.0, Ar), 6.99 (1H, ddd, J 8.0, 2.5, 1.0, Ar), 3.85 (3H, s, OCH_3), 3.81-3.72 (4H, m, 2 \times morpholine CH_2), 3.57-3.53 (4H, m, 2 \times morpholine CH_2).

[0212] Using an analogous method, the following further compounds of formula (Ia) were prepared:

2-(3-methoxyphenyl)-4-(morpholin-4-yl)-5-[(pyridin-3-yl)carbonylamino]pyrimidine (O3)

[0213]

O3

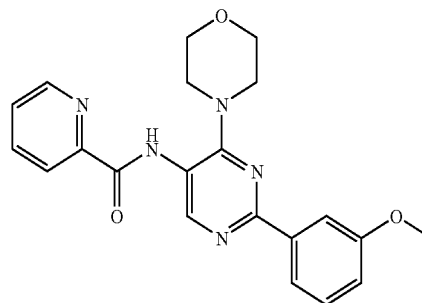


[0214] δ_H (250 MHz, $CDCl_3$) 9.17 (1H, br, NH), 9.05 (1H, d, J 2.0, pyrimidine Ar), 8.77 (1H, dd, J 5.0, 1.5, pyridine Ar), 8.21 (1H, dt, J 8.0, 2.0, pyridine Ar), 7.96-7.87 (3H, m, 2 \times pyridine Ar, 1 \times Ar), 7.44 (1H, dd, J 8.0, 5.5, Ar), 7.32 (1H, t, J 8.0, Ar), 6.95 (1H, ddd, J 8.0, 2.5, 1.0, Ar), 3.84 (3H, s, OCH_3), 3.83-3.79 (4H, m, 2 \times morpholine CH_2), 3.45-3.41 (4H, m, 2 \times morpholine CH_2).

2-(3-methoxyphenyl)-4-(morpholin-4-yl)-5-[(pyridin-3-yl)carbonylamino]pyrimidine (P3)

[0215]

P3

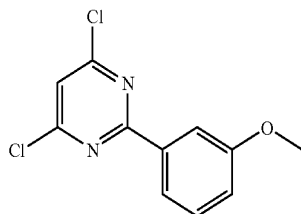


[0216] δ_H (250 MHz, $CDCl_3$) 9.96 (1H, br, NH), 9.40 (1H, s, pyrimidine Ar), 8.58 (1H, dq, J 4.5, 1.0, pyridine Ar), 8.24 (1H, dt, J 8.0, 1.0, pyridine Ar), 7.97-7.85 (3H, m, 2 \times pyridine Ar, 1 \times Ar), 7.47 (1H, ddd, J 8.0, 5.0, 1.0, Ar), 7.31 (1H, t, J 8.0, Ar), 6.94 (1H, ddd, J 8.0, 2.5, 1.0, Ar), 3.90-3.87 (4H, m, 2 \times morpholine CH_2), 3.85 (3H, s, OCH_3), 3.46-3.43 (4H, m, 2 \times morpholine CH_2).

REFERENCE EXAMPLE 12

Preparation of 4,6-Dichloro-2-(3-methoxy-phenyl)-pyrimidine

[0217]

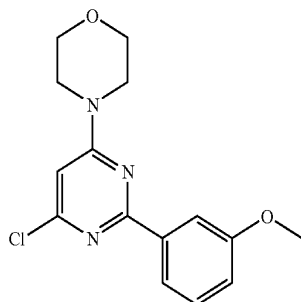


[0218] 2-(3-Methoxy-phenyl)-1H-pyrimidine-4,6-dione (2 g) [prepared according to *Helv. Chin. Acta.* 2003, 86(5), pp 1598-1624] was refluxed in POCl_3 (20 mL). After 3 h the mixture was cooled and poured onto ice/water. Precipitate was collected, washed with water and air dried to give product (70%).

REFERENCE EXAMPLE 13

Preparation of 4-[6-Chloro-2-(3-methoxy-phenyl)-pyrimidin-4-yl]-morpholine

[0219]

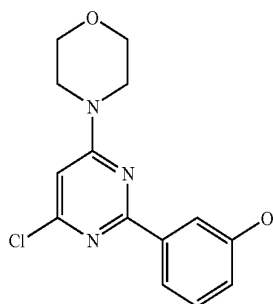


[0220] A mixture of 4,6-dichloro-2-(3-methoxy-phenyl)-pyrimidine (1.64 g), K_2CO_3 (1.07 g) and morpholine (0.56 mL) in dry MeCN was stirred together at R.T. for 3 h. An aqueous work-up followed by purification on silica gave product (1.14 g).

REFERENCE EXAMPLE 14

Preparation of 3-(4-Chloro-6-morpholin-4-yl-pyrimidin-2-yl)-phenol

[0221]

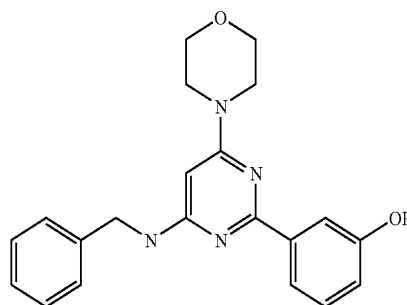


[0222] A solution of 4-[6-chloro-2-(3-methoxy-phenyl)-pyrimidin-4-yl]-morpholine (1.85 g) in dry CH_2Cl_2 (15 mL) was added to a suspension of AlCl_3 (4.5 g) in dry CH_2Cl_2 (70 mL) at $<10^\circ\text{C}$. The resultant mixture was heated at 50°C overnight. An aqueous work-up followed by purification on silica gave product (1.33 g).

EXAMPLE 3

Preparation of 3-(4-Benzylamino-6-morpholin-4-yl-pyrimidin-2-yl)-phenol

[0223]



[0224] 3-(4-Chloro-6-morpholin-4-yl-pyrimidin-2-yl)-phenol (100 mg, 0.343 mmol) was heated in neat benzylamine (1 mL) at 100°C . O/N. The reaction mixture was cooled to room temperature, diluted with dichloromethane and washed with brine. Organic layer was dried over magnesium sulphate, volatiles removed in vacuo and the residue purified by flash chromatography. Trituration with diethyl ethyl afforded the title compound as a cream-coloured solid (105 mg).

[0225] NMR (CDCl_3): 3.59-3.62 (4H, m), 3.79-3.82 (4H, m), 4.55 (2H, d, $J=5.8$), 4.80 (1H, br), 5.10 (1H, br), 5.40 (1H, s), 6.90 (1H, dd), 7.26-7.38 (6H, m), 7.83 (1H, s), 7.94 (1H, d, $J=7.8$)

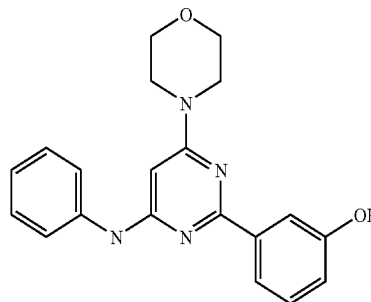
[0226] MS (ESI+): MH^+ 363 (100%)

EXAMPLE 4

Preparation of Further Compounds of Formula (I)

3-(4-Morpholin-4-yl-6-phenylamino-pyrimidin-2-yl)-phenol

[0227]



[0228] 3-(4-Chloro-6-morpholin-4-yl-pyrimidin-2-yl)-phenol (100 mg, 0.343 mmol) was heated in neat aniline (1

ml) at 100° C. O/N. The reaction mixture was cooled to room temperature, diluted with dichloromethane and washed with brine. Organic layer was dried over magnesium sulphate, volatiles removed in vacuo and the residue purified by flash chromatography. Recrystallisation from hot dichloromethane/hexane gave the title compound as a beige solid (82 mg).

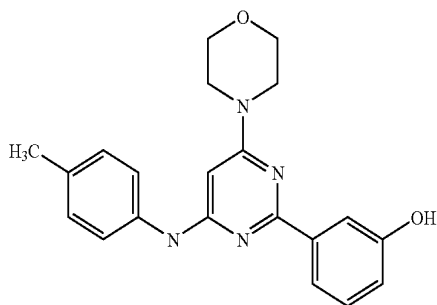
[0229] NMR (DMSO): 3.52-3.58 (4H, m), 3.72-3.76 (4H, m), 5.92 (1H, s), 6.84 (1H, d, J=9.3), 6.95 (1H, t, J=7.4), 7.26 (1H, t, J=8.2), 7.32 (2H, t, J=8.3), 7.70 (2H, d, J=7.6), 7.74-7.76 (2H, m), 9.10 (1H, s), 9.45 (1H, s)

[0230] MS (ESI+): MH+ 349 (100%)

[0231] The following compounds were prepared in an analogous manner, using the appropriately substituted aniline.

3-(4-Morpholin-4-yl-6-p-tolylamino-pyrimidin-2-yl)-phenol was Prepared from p-toluidine

[0232]

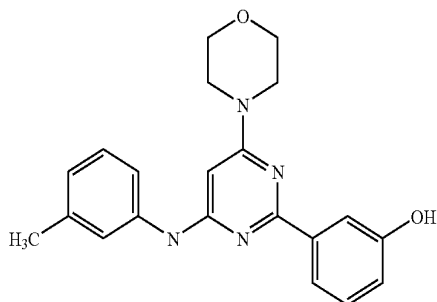


[0233] MS (ESI+): MH+ 363 (100%)

[0234] NMR (CDCl₃): 2.31 (3H, s), 3.52-3.58 (4H, m), 3.72-3.76 (4H, m), 5.02 (1H, s, br.), 5.75 (1H, s), 6.55 (1H, s, br.), 6.91-6.93 (1H, m), 7.15-7.32 (5H, m), 7.81 (1H, s), 7.95 (1H, d)

3-(4-Morpholin-4-yl-6-m-tolylamino-pyrimidin-2-yl)-phenol was Prepared from m-toluidine

[0235]

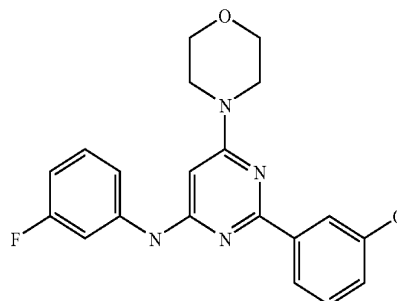


[0236] MS (ESI+): MH+ 363 (100%)

[0237] NMR (CDCl₃): 2.41 (3H, s), 3.59-3.65 (4H, m), 3.72-3.76 (4H, m), 4.80 (1H, s, br.), 5.82 (1H, s), 6.55 (1H, s, br.), 6.96-6.99 (2H, m), 7.12-7.18 (2H, m), 7.28-7.35 (2H, m), 7.81 (1H, s), 7.95 (1H, d)

3-[4-(3-Fluoro-phenylamino)-6-morpholin-4-yl-pyrimidin-2-yl]-phenol was Prepared from 3-fluoroaniline

[0238]

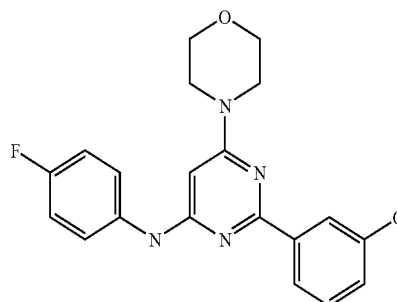


[0239] NMR: (CDCl₃): 3.63-3.66 (m, 4H, 2×CH₂), 3.79-3.82 (m, 4H, 2×CH₂), 5.85 (s, H, ArH), 6.69 (s, br, H, NH), 6.78-6.82 (m, H, ArH), 6.93-6.95 (m, H, ArH), 7.07-7.09 (m, H, ArH), 7.23-7.34 (m, 3H, 3×ArH), 7.85 (m, H, ArH), 7.93-7.96 (m, H, ArH).

[0240] MS: (ESI+) MH+=367.18

3-[4-(4-Fluoro-phenylamino)-6-morpholin-4-yl-pyrimidin-2-yl]-phenol was Prepared from 4-fluoroaniline

[0241]

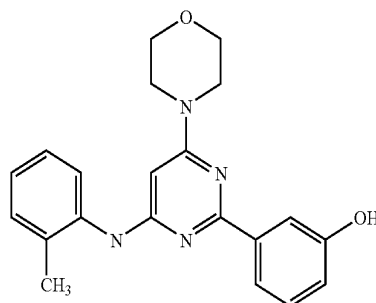


[0242] NMR: (CDCl₃): 3.59-3.62 (m, 4H, 2×CH₂), 3.77-3.80 (m, 4H, 2×CH₂), 4.93 (s, br, H, OH), 5.66 (s, H, ArH), 6.49 (s, br, H, NH), 6.90-6.93 (m, H, ArH), 7.05-7.09 (m, 2H, 2×ArH), 7.28-7.32 (m, 3H, 3×ArH), 7.82-7.83 (m, H, ArH), 7.92-7.94 (m, H, ArH).

[0243] MS: (ESI+) MH+=367.16

3-(4-Morpholin-4-yl-6-o-tolylamino-pyrimidin-2-yl)-phenol was Prepared from o-toluidine

[0244]

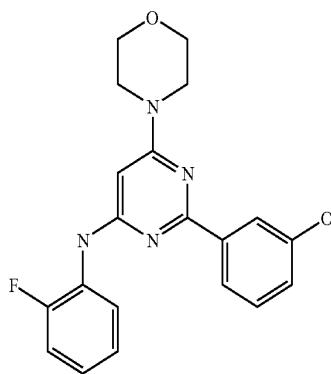


[0245] MS (ESI+): MH+ 363 (60%)

[0246] NMR (CDCl₃): 2.37 (3H, s), 3.59-3.65 (4H, m), 3.72-3.76 (4H, m), 5.05 (1H, s, br.), 5.50 (1H, s), 6.45 (1H, s, br.), 6.96-6.99 (1H, m), 7.15-7.35 (5H, m), 7.84 (1H, s), 7.95 (1H, d)

3-[4-(2-Fluoro-phenylamino)-6-morpholin-4-yl-pyrimidin-2-yl]-phenol was Prepared from 2-fluoroaniline

[0247]

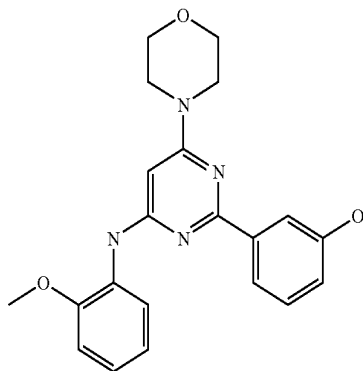


[0248] NMR: (CDCl₃): 3.63-3.66 (m, 4H, 2×CH₂), 3.80-3.82 (m, 4H, 2×CH₂), 4.77 (s, br, H, OH), 5.77 (s, H, ArH), 6.58 (s, br, H, NH), 6.91-6.94 (m, H, ArH), 7.04-7.07 (m, H, ArH), 7.12-7.19 (m, 2H, 2×ArH), 7.32 (m, H, ArH), 7.85 (m, H, ArH), 7.96-8.00 (m, 2H, 2×ArH).

[0249] MS: (ESI+) MH+=367.14

3-[4-(2-Methoxy-phenylamino)-6-morpholin-4-yl-pyrimidin-2-yl]-phenol was Prepared from o-anisidine

[0250]

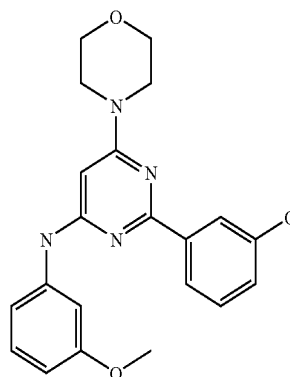


[0251] NMR: (CDCl₃): 3.63-3.65 (m, 4H, 2×CH₂), 3.79-3.81 (m, 4H, 2×CH₂), 3.89 (s, 3H, CH₃), 4.85 (s, br, H, OH), 5.87 (s, H, ArH), 6.90-6.94 (m, 2H, 2×ArH), 6.98-7.05 (m, 3H, 3×ArH), 7.31 (t, H, ArH, J=7.89 Hz), 7.86 (m, H, ArH), 7.99 (m, H, ArH).

[0252] MS: (ESI+) MH+=379.17

3-[4-(3-Methoxy-phenylamino)-6-morpholin-4-yl-pyrimidin-2-yl]-phenol was Prepared from m-anisidine

[0253]

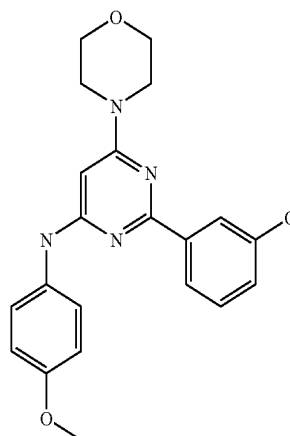


[0254] NMR: (CDCl₃): 3.61-3.64 (m, 4H, 2×CH₂), 3.78-3.81 (m, 4H, 2×CH₂), 3.82 (s, 2H, CH₂), 5.04 (s, br, H, OH), 5.88 (s, H, ArH), 6.63 (s, br, H, NH), 6.66-6.69 (m, H, ArH), 6.88-6.93 (m, 2H, 2×ArH), 7.85 (m, H, ArH), 7.95 (m, H, ArH).

[0255] MS: (ESI+) MH+=379.16

3-[4-(4-Methoxy-phenylamino)-6-morpholin-4-yl-pyrimidin-2-yl]-phenol was Prepared from p-anisidine

[0256]

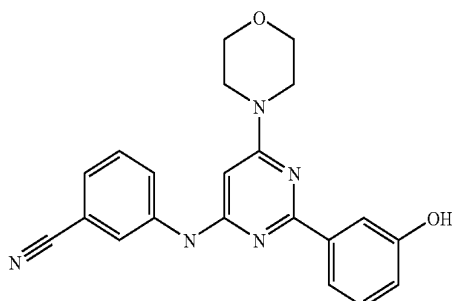


[0257] NMR: (CDCl₃): 3.57-3.60 (m, 4H, 2×CH₂), 3.76-3.78 (m, 4H, 2×CH₂), 3.82 (s, 3H, CH₃), 4.84 (s, br, H, OH), 5.62 (s, H, ArH), 6.44 (s, br, H, ArH), 6.90-6.93 (m, 3H, 3×ArH), 7.22-7.25 (m, 2H, 2×CH₂), 7.30 (t, H, ArH, J=7.9 Hz), 7.83 (m, H, ArH), 7.94 (m, H, ArH).

[0258] MS: (ESI+) MH+=379.15

3-[2-(3-Hydroxy-phenyl)-6-morpholin-4-yl-pyrimidin-4-ylamino]-benzonitrile was Prepared from 3-aminobenzonitrile

[0259]

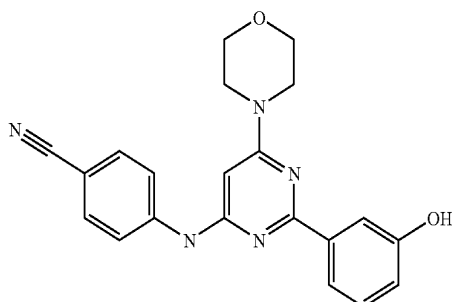


[0260] MS (ESI+): MH+ 374 (100%)

[0261] NMR: (DMSO): 3.57-3.65 (4H, m), 3.72-3.76 (4H, m), 5.95 (1H, s), 6.82 (1H, d), 7.21-7.23 (1H, m), 7.31 (1H, d), 7.51-7.52 (1H, m), 7.71-7.73 (2H, m), 7.95 (1H, d), 8.15 (1H, s), 9.45 (1H, s), 9.50 (1H, s).

4-[2-(3-Hydroxy-phenyl)-6-morpholin-4-yl-pyrimidin-4-ylamino]-benzonitrile was Prepared from 4-aminobenzonitrile

[0262]

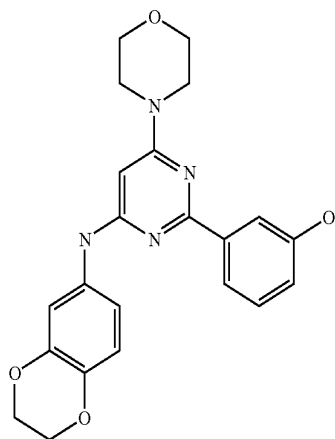


[0263] MS (ESI+): MH+ 374 (100%)

[0264] NMR: (MeOD/CDCl₃): 3.70-3.75 (4H, m), 3.89-3.95 (4H, m), 6.00 (1H, s), 6.99 (1H, d), 7.31-7.33 (1H, m), 7.70 (2H, d), 7.91-7.93 (2H, m), 7.98 (2H, d).

3-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-ylamino)-6-morpholin-4-yl-pyrimidin-2-yl]-phenol was Prepared from O-3,4-ethylenedioxyaniline

[0265]

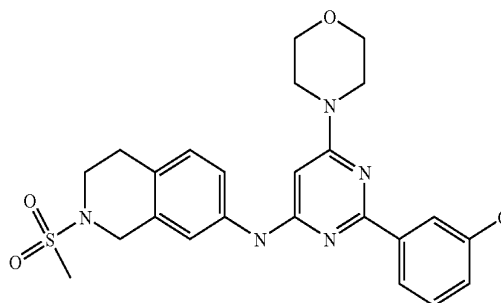


[0266] NMR: (CDCl₃): 3.59-3.61 (m, 4H, 2×CH₂O), 3.77-3.79 (m, 4H, 2×CH₂), 4.28 (s, 4H, 2×CH₂), 4.91 (s, br, H, OH), 5.79 (s, H, ArH), 6.43 (s, br, H, NH), 6.78 (m, H, ArH), 6.86 (m, 2H, 2×ArH), 6.91 (m, H, ArH), 7.30 (t, H, ArH, J=7.9 Hz), 7.83 (m, H, ArH), 7.93 (d, H, ArH, J=7.79 Hz).

[0267] MS: (ESI+) MH+=407.16

3-[4-(2-Methanesulfonyl-1,2,3,4-tetrahydro-isoquinolin-7-ylamino)-6-morpholin-4-yl-pyrimidin-2-yl]-phenol was Prepared from 2-methanesulfonyl-1,2,3,4-tetrahydro-isoquinolin-7-ylamine

[0268]



[0269] NMR: (CDCl₃): 2.86 (s, 3H, CH₃), 2.98 (t, 2H, CH₂, J=5.99 Hz), 3.59-3.61 (m, 4H, 2×CH₂), 3.77-3.79 (m, 4H, 2×CH₂), 4.28 (s, 4H, 2×CH₂), 3.79-3.81 (m, 4H, 2×CH₂), 4.47 (s, 2H, CH₂), 5.01 (s, br, H, OH), 5.74 (s, H, ArH), 6.50 (s, br, H, NH), 6.93 (m, H, ArH), 7.16 (m, 2H, 2×ArH), 7.17 (s, H, ArH), 7.31 (t, H, ArH, J=7.9 Hz), 7.83 (m, H, ArH), 7.94 (d, H, ArH, J=7.81 Hz).

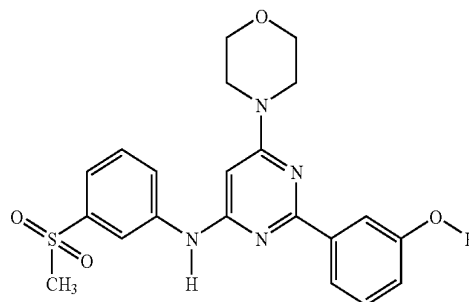
[0270] MS: (ESI+) MH+=482.17

[0271] 2-Methanesulfonyl-1,2,3,4-tetrahydro-isoquinolin-7-ylamine was prepared as follows: A solution of 1,2,3,4-tetrahydro-isoquinolin-7-ylamine (1.255 g)[prepared from 1,2,3,4-tetrahydroisoquinoline according to *J. Med. Chem.*, 2003, 46(5), pp 831-7.], NEt₃ (1.1 mL) and methanesulfonylchloride (0.6 mL) in dry CH₂Cl₂ (20 mL) was stirred at R.T. overnight. Aqueous work-up followed by purification on silica gave 2-methanesulfonyl-7-nitro-1,2,3,4-tetrahydro-isoquinoline (1.435 g).

[0272] A solution of 2-methanesulfonyl-7-nitro-1,2,3,4-tetrahydro-isoquinoline (1.33 g) in EtOH (30 mL) and MeOH (20 mL) with 10% Pd/C (300 mg) was stirred under positive hydrogen pressure overnight. Filtration and concentration in vacuo gave 2-methanesulfonyl-1,2,3,4-tetrahydro-isoquinolin-7-ylamine

3-[4-(3-Methanesulfonyl-phenylamino)-6-morpholin-4-yl-pyrimidin-2-yl]-phenol was Prepared from 3-methylsulphonylaniline

[0273]

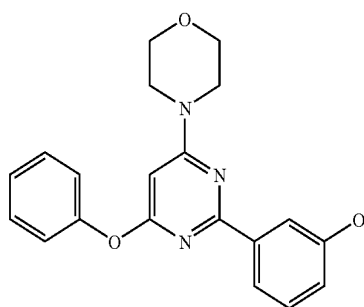


[0274] (400 MHz, DMSO): 3.21 (3H, s, CH₃), 3.58-3.59 (4H, m, CH₂), 3.72-3.74 (4H, m, CH₂), 5.93 (1H, s, OH), 6.86 (1H, d, J 9.92, ar), 7.24 (1H, t, J 7.88, ar), 7.47 (1H, d, J 8.10, ar), 7.58 (1H, t, J 7.94, ar), 7.76 (1H, s, ar), 7.84 (1H, d, J 7.82, ar), 7.94 (1H, d, J 8.71, ar), 8.52 (1H, s, ar), 9.40 (1H, s, ar), 9.59 (1H, s, NH)

[0275] (M+H)⁺ 427.18

3-(4-Morpholin-4-yl-6-phenoxy-pyrimidin-2-yl)-phenol

[0276]



[0277] 3-(4-Chloro-6-morpholin-4-yl-pyrimidin-2-yl)-phenol (100 mg) was heated with sodium phenoxide (2973 mg) at 100° C. overnight. Purification on silica followed by trituration gave the desired product (56 mg).

[0278] NMR: (CDCl₃): 3.64-3.67 (m, 4H, 2×CH₂), 3.79-3.81 (m, 4H, 2×CH₂), 4.73 (s, H, OH), 5.77 (s, H, ArH), 6.90 (m, H, ArH), 7.18-7.28 (m, 4H, 4×ArH), 7.39-7.43 (m, 2H, 2×ArH), 7.75 (s, H, ArH), 7.87 (d, H, ArH, J=7.77 Hz).

[0279] MS: (ESI⁺) MH⁺=350.14

EXAMPLE 5

Biological Testing

[0280] Compounds of the invention, prepared as described in the preceding Examples, were submitted to the following series of biological assays

(i) PI3K Biochemical Screening

[0281] Compound inhibition of PI3K was determined in a radiometric assay using purified, recombinant enzyme and ATP at a concentration of 1 μM. All compounds were serially diluted in 100% DMSO. The kinase reaction was incubated for 1 hour at room temperature, and the reaction was terminated by the addition of PBS. IC₅₀ values were subsequently determined using sigmoidal dose-response curve fit (variable slope). All of the compounds tested had an IC₅₀ against PI3K of 50 μM or less. Typically the IC₅₀ against PI3K was 5-500 nM.

(ii) Cellular Proliferation Inhibition

[0282] Cells were seeded at optimal density in a 96 well plate and incubated for 4 days in the presence of test compound. Alamar Blue™ was subsequently added to the assay medium, and cells were incubated for 6 hours before reading at 544 nm excitation, 590 nm emission. EC₅₀ values were

calculated using a sigmoidal dose response curve fit. All the compounds tested had an EC₅₀s of 50 μM or less in the range of cell lines utilized.

EXAMPLE 6

Tablet Composition

[0283] Tablets, each weighing 0.15 g and containing 25 mg of a compound of the invention were manufactured as follows:

Composition for 10,000 tablets

Compound of the invention (250 g)

Lactose (800 g)

[0284] Corn starch (415 g)

Talc powder (30 g)

Magnesium stearate (5 g)

[0285] The compound of the invention, lactose and half of the corn starch were mixed. The mixture was then forced through a sieve 0.5 mm mesh size. Corn starch (10 g) is suspended in warm water (90 ml). The resulting paste was used to granulate the powder. The granulate was dried and broken up into small fragments on a sieve of 1.4 mm mesh size. The remaining quantity of starch, talc and magnesium was added, carefully mixed and processed into tablets.

EXAMPLE 7

Injectable Formulation

[0286]

Compound of the invention	200 mg
Hydrochloric Acid Solution 0.1M or	4.0 to 7.0
Sodium Hydroxide Solution 0.1M q.s. to pH	
Sterile water q.s. to	10 ml

[0287] The compound of the invention was dissolved in most of the water (35° 40° C.) and the pH adjusted to between 4.0 and 7.0 with the hydrochloric acid or the sodium hydroxide as appropriate. The batch was then made up to volume with water and filtered through a sterile micropore filter into a sterile 10 ml amber glass vial (type 1) and sealed with sterile closures and oversells.

EXAMPLE 8

Intramuscular Injection

[0288]

Compound of the invention	200 mg
Benzyl Alcohol	0.10 g
Glycofurol 75	1.45 g
Water for injection q.s to	3.00 ml

[0289] The compound of the invention was dissolved in the glycofurol. The benzyl alcohol was then added and dissolved,

and water added to 3 ml. The mixture was then filtered through a sterile micropore filter and sealed in sterile 3 ml glass vials (type 1).

EXAMPLE 9

Syrup Formulation

[0290]

Compound of invention	250 mg
Sorbitol Solution	1.50 g
Glycerol	2.00 g
Sodium benzoate	0.005 g
Flavour	0.0125 ml
Purified Water q.s. to	5.00 ml

[0291] The compound of the invention was dissolved in a mixture of the glycerol and most of the purified water. An aqueous solution of the sodium benzoate was then added to the solution, followed by addition of the sorbital solution and finally the flavour. The volume was made up with purified water and mixed well.

1. A compound which is a pyrimidine of formula (I):



wherein

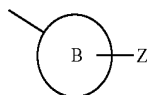
—XR³ is bonded at ring position 2 and —YR⁴ is bonded at ring position 5 or 6;

R¹ and R² form, together with the N atom to which they are attached, a morpholine ring which is unsubstituted or substituted;

X is a direct bond;

R³ is selected from:

(i) a group of the following formula:



wherein B is a phenyl ring which is unsubstituted or substituted and Z is selected from —OR, CH₂OR and —NRS(O)_mR, wherein each R is independently selected from HC₁-C₆ alkyl, C₃-C₁₀ cycloalkyl and a 5- to 12-membered aryl or heteroaryl group, the group being unsubstituted or substituted, and m is 2; and

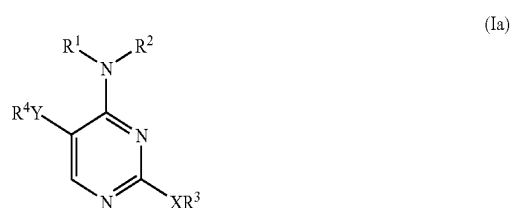
(ii) an indazole group which is unsubstituted or substituted; and

Y is selected from —O—(CH₂)_n—, —NH—(CH₂)_n—, —NHC(O)—(CH₂)_n— and —C(O)NH—(CH₂)_n— wherein n is 0 or an integer of 1 to 3, and R⁴ is selected from an unsaturated 5- to 12-membered carbocyclic or heterocyclic group which is unsubstituted or substituted,

and a group —NR⁵R⁶ wherein R⁵ and R⁶, which are the same or different, are each independently selected from H, C₁-C₆ alkyl which is unsubstituted or substituted, C₃-C₁₀ cycloalkyl which is unsubstituted or substituted, —C(O)R, —C(O)N(R)₂ and —S(O)_mR wherein R and m are as defined above, or R⁵ and R⁶ together form, with the nitrogen atom to which they are attached, a saturated 5-, 6- or 7-membered N-containing heterocyclic group which is unsubstituted or substituted;

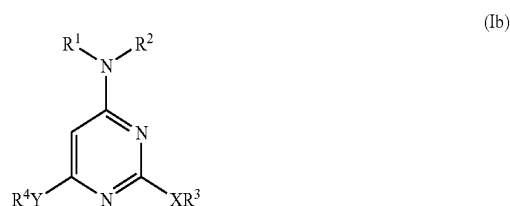
or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein the pyrimidine is of formula (Ia):



in which R¹, R², R³, R⁵, Y and X are as defined in claim 1.

3. A compound according to claim 1 wherein the pyrimidine is of formula (Ib):



in which R¹, R², R³, R⁴, Y and X are as defined in claim 1.

4. A compound according to claim 1 wherein R³ is an indazol-4-yl group.

5. A compound according to claim 1 which is selected from:

2-(3-hydroxyphenyl)-4-(morpholin-4-yl)-6-(pyridin-3-yl-methylamino) pyrimidine;

2-(3-hydroxyphenyl)-4-(morpholin-4-yl)-6-(pyridin-2-yl-methylamino) pyrimidine;

2-(3-hydroxyphenyl)-4-(morpholin-4-yl)-6-(pyridin-4-yl-methylamino) pyrimidine;

2-(3-hydroxyphenyl)-4-(morpholin-4-yl)-6-[(2-(pyridin-2-yl)ethylamino)] pyrimidine;

2-(3-hydroxyphenyl)-4-(morpholin-4-yl)-6-[(2-(pyridin-3-yl)ethylamino)] pyrimidine;

2-(3-hydroxyphenyl)-4-(morpholin-4-yl)-6-[(2-(pyridin-4-yl)ethylamino)] pyrimidine;

2-(3-hydroxyphenyl)-4-(morpholin-4-yl)-6-(pyridin-2-yl-methoxy) pyrimidine;

2-(3-hydroxyphenyl)-4-(morpholin-4-yl)-6-[2-(morpholin-4-yl)ethylamino] pyrimidine;

2-(3-methoxyphenyl)-4-(morpholin-4-yl)-5-[(pyridin-4-yl)carbonylamino] pyrimidine;

2-(3-methoxyphenyl)-4-(morpholin-4-yl)-5-[(pyridin-3-yl)carbonylamino] pyrimidine;

2-(3-methoxyphenyl)-4-(morpholin-4-yl)-5-[(pyridin-3-yl)carbonylamino] pyrimidine;

2-[3-(methanesulfonylamino)phenyl]-4-(morpholin-4-yl)-2-[(2-(pyridin-2-yl)ethylamino)pyrimidine];
 2-[3-(methanesulfonylamino)phenyl]-4-(morpholin-4-yl)-6-[(2-(pyridin-3-yl)ethylamino)pyrimidine];
 2-[3-(methanesulfonylamino)phenyl]-4-(morpholin-4-yl)-6-[(2-(pyridin-4-yl)ethylamino)pyrimidine];
 2-[3-(methanesulfonylamino)phenyl]-4-(morpholin-4-yl)-6-(pyridin-2-ylmethoxy)pyrimidine;
 3-(4-Benzylamino-6-morpholin-4-yl-pyrimidin-2-yl)-phenol;
 3-(4-Morpholin-4-yl-6-phenylamino-pyrimidin-2-yl)-phenol;
 3-(4-Morpholin-4-yl-6-p-tolylamino-pyrimidin-2-yl)-phenol;
 3-(4-Morpholin-4-yl-6-m-tolylamino-pyrimidin-2-yl)-phenol;
 3-[4-(3-Fluoro-phenylamino)-6-morpholin-4-yl-pyrimidin-2-yl]-phenol;
 3-[4-(4-Fluoro-phenylamino)-6-morpholin-4-yl-pyrimidin-2-yl]-phenol;
 3-(4-Morpholin-4-yl-6-o-tolylamino-pyrimidin-2-yl)-phenol;
 3-[4-(2-Fluoro-phenylamino)-6-morpholin-4-yl-pyrimidin-2-yl]-phenol;
 3-[4-(2-Methoxy-phenylamino)-6-morpholin-4-yl-pyrimidin-2-yl]-phenol;
 3-[4-(3-Methoxy-phenylamino)-6-morpholin-4-yl-pyrimidin-2-yl]-phenol;
 3-[4-(4-Methoxy-phenylamino)-6-morpholin-4-yl-pyrimidin-2-yl]-phenol;
 3-[2-(3-Hydroxy-phenyl)-6-morpholin-4-yl-pyrimidin-4-ylamino]-benzonitrile;

4-[2-(3-Hydroxy-phenyl)-6-morpholin-4-yl-pyrimidin-4-ylamino]-benzonitrile;
 3-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-ylamino)-6-morpholin-4-yl-pyrimidin-2-yl]-phenol;
 3-[4-(2-Methanesulfonyl-1,2,3,4-tetrahydro-isoquinolin-7-ylamino)-6-morpholin-4-yl-pyrimidin-2-yl]-phenol;
 3-[4-(3-Methanesulfonyl-phenylamino)-6-morpholin-4-yl-pyrimidin-2-yl]-phenol;
 3-(4-Morpholin-4-yl-6-phenoxy-pyrimidin-2-yl)-phenol;
 2-(indazol-4-yl)-4-(morpholin-4-yl)-6-[(2-(pyridin-2-yl)ethylamino)pyrimidine];
 2-(indazol-4-yl)-4-(morpholin-4-yl)-6-[(2-(pyridin-3-yl)ethylamino)pyrimidine];
 2-(indazol-4-yl)-4-(morpholin-4-yl)-6-[(2-(pyridin-4-yl)ethylamino)pyrimidine]; and
 2-(indazol-4-yl)-4-(morpholin-4-yl)-6-(pyridin-2-ylmethoxy)pyrimidine;
 and the pharmaceutically acceptable salts thereof.

6. A pharmaceutical composition which comprises a pharmaceutically acceptable carrier or diluent and, as an active ingredient, a compound as defined in claim 1.

7-10. (canceled)

11. A method of treating a disease or disorder arising from abnormal cell growth, function or behaviour associated with PI3 kinase, which method comprises administering to a patient in need thereof a compound as defined in claim 1.

12. A method according to claim 11 wherein the disease or disorder is selected from cancer, immune disorders, cardiovascular disease, viral infection, inflammation, metabolism/endocrine function disorders and neurological disorders.

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