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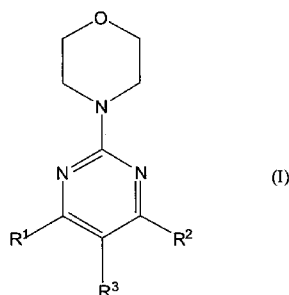
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(54) Title: 2-MORPHOLINOPYRIMIDINES AND THEIR USE AS PI3 KINASE INHIBITORS



(57) Abstract: Morpholino pyrimidines of formula (I): wherein R^1 is selected from $-Y-R^6$ and $-NR^{10}$; R^2 is a N-containing monocyclic heteroaryl group which is selected from pyridyl, isoxazolyl, imidazolyl, pyrazolyl, pyrrolyl, thiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, oxazolyl, furanyl, thienyl, triazolyl and tetrazolyl and which is unsubstituted or substituted by halo, $-CN$, $-NR^{10}$, $-OR^{10}$, $-C(O)R^{10}$, $-NR^{10}C(O)R^{11}$, $-N(C(O)R^{11})_2$

$-NR^{10}C(O)NR^{10}R^{11}$, $-SO_2R^{10}R^{11}$, $-SO_2NR^{10}R^{11}$, $-C(=O)OR^{10}$, $-C(=O)NR^{10}R^{11}$, halo- C_1-C_6 alkyl and unsubstituted C_1-C_{12} alkyl; R^3 is selected from H, C_1-C_6 alkyl and C_1-C_6 alkoxy; Y is selected from a direct bond, $-(CR_2)_m$, C_2-C_6 alkenylene, C_2-C_6 alkynylene, $-(CR_2)_p-O-(CR_2)_t$, $-(CR_2)_p-NR-(CR_2)_t$, $-(CR_2)_p-NR-(CR_2)_n-C(O)-$, $-(CR_2)_p-NR-C(O)-(CR_2)_n$, $-(CR_2)_p-C(O)-NR-(CR_2)_t$, $-(CR_2)_p-C(O)-(CR_2)_n-NR-(CR_2)_t$ and $-(CR_2)_p-C(O)-(CR_2)_n$; R_6 is selected from an unsaturated 5- to 12-membered carbocyclic or heterocyclic ring, a saturated 5-, 6- or 7- membered N-containing heterocyclic group which is unsubstituted or substituted, C_1-C_6 alkyl, $-NR_2$, $-OR$, $-NR(CO)R$ and $-C(O)NR_2$; R^4 and R^5 , which are the same or different, are both C_1-C_6 alkyl which is unsubstituted or substituted, or R_4 and R_5 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; each R, which are the same or different when more than one is present in a given group, is independently H, C_1-C_6 alkyl which is unsubstituted or substituted or a 5- to 12-membered aryl or heteroaryl group which is unsubstituted or substituted; R^{10} and R^{11} , which are the same or different, are independently selected from H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl and C_3-C_8 cycloalkyl; n is 0 or an integer of 1 to 6; m is an integer of 1 to 6; p is 0 or an integer of 1 to 6; and t is 0 or an integer of 1 to 6, with the proviso that t is an integer of 2 to 6 when R^6 is linked to Y through a constituent O or N atom of R^6 ; and the pharmaceutically acceptable salts thereof, subject to various provisos, have activity as inhibitors of PI3K and may thus be used to treat diseases and disorders arising from abnormal cell growth, function or behaviour, particularly that associated with PI3 kinase such as cancer, immune disorders, cardiovascular disease, viral infection, inflammation, metabolism/endocrine disorders and neurological disorders. Processes for synthesizing the compounds are also described.

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2 -MORPHOLINOPYRIMIDINES AND THEIR USE AS PI3 KINASE INHIBITORS

Field of the Invention

The present invention relates to pyrimidine derivatives and their use as inhibitors
5 of phosphatidylinositol 3-kinase (PI3K).

Background to the Invention

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
10 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 (M. Whitman *et al.*, 1988, Nature, 332, 644-646).

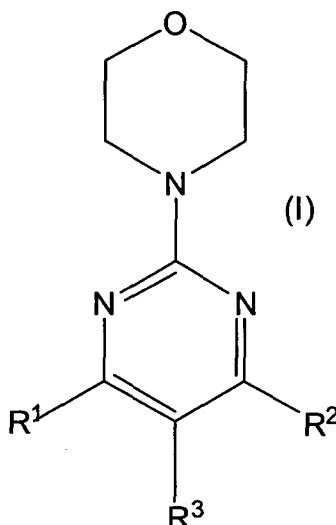
PI3K was originally considered to be a single enzyme, but it has now been
clarified that a plurality of subtypes are present in PI3K. Each subtype has its own
15 mechanism for regulating activity. Three major classes of PI3Ks have been identified on
the basis of their *in vitro* substrate specificity (B. Vanhaesebroeck *et al.*, 1997, Trends in
Biochemical Sciences, 22, 267-272). 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
20 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.

25 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
30 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.

Summary of the Invention

It has now been found that a series of pyrimidine derivatives are potent inhibitors of PI3K, in particular for the p110 α subtype.

- 5 Accordingly, the present invention provides a compound which is a morpholino pyrimidine of formula (I):



wherein

- 10 R^1 is selected from $-Y-R^6$ and $-NR^4R^5$;

R^2 is a N-containing monocyclic heteroaryl group which is selected from pyridyl, isoxazolyl, imidazolyl, pyrazolyl, pyrrolyl, thiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, oxazolyl, furanyl, thienyl, triazolyl and tetrazolyl and which is unsubstituted or substituted by $-CN$, $-NR^{10}R^{11}$, $-OR^{10}$, $-C(O)R^{10}$, $-NR^{10}C(O)R^{11}$, $-N(C(O)R^{11})_2$, $-NR^{10}C(O)NR^{10}R^{11}$, $-SO_2R^{10}R^{11}$, $-SO_2NR^{10}R^{11}$, $-C(=O)OR^{10}$, $-C(=O)NR^{10}R^{11}$, halo-
15 C_1-C_6 alkyl and and unsubstituted C_1-C_{12} alkyl;

R^3 is selected from H, C_1-C_6 alkyl and C_1-C_6 alkoxy;

Y is selected from a direct bond, $-(CR_2)_m-$, C_2-C_6 alkenylene, C_2-C_6 alkynylene, $-(CR_2)_p-O-(CR_2)_t-$, $-(CR_2)_p-NR-(CR_2)_t-$, $-(CR_2)_p-NR-(CR_2)_n-C(O)-$, $-(CR_2)_p-NR-C(O)-$
20 $(CR_2)_n-$, $-(CR_2)_p-C(O)-NR-(CR_2)_t-$, $-(CR_2)_p-C(O)-(CR_2)_n-NR-(CR_2)_t-$ and $-(CR_2)_p-C(O)-(CR_2)_n-$;

R^6 is selected from an unsaturated 5- to 12-membered carbocyclic or heterocyclic ring, a saturated 5-, 6- or 7- membered N-containing heterocyclic group

which is unsubstituted or substituted, C₁-C₆ alkyl, -NR₂, -OR, -NR(CO)R and -C(O)NR₂;

R⁴ and R⁵, which are the same or different, are both C₁-C₆ alkyl which is unsubstituted or substituted, or R⁴ and R⁵ 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;

each R, which are the same or different when more than one is present in a given group, is independently H, C₁-C₆ alkyl which is unsubstituted or substituted or a 5- to 12-membered aryl or heteroaryl group which is unsubstituted or substituted;

R¹⁰ and R¹¹, which are the same or different, are independently selected from H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl and C₃-C₈ cycloalkyl;

n is 0 or an integer of 1 to 6;

m is an integer of 1 to 6;

p is 0 or an integer of 1 to 6; and

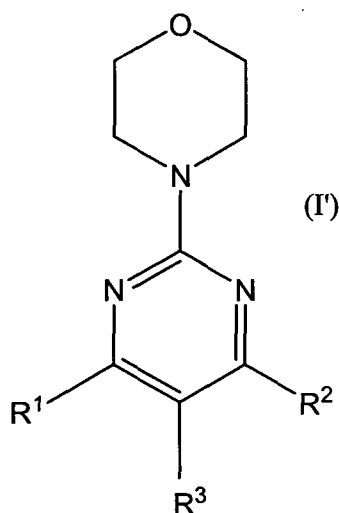
t is 0 or an integer of 1 to 6, with the proviso that t is an integer of 2 to 6 when R⁶ is linked to Y through a constituent O or N atom of R⁶;

or a pharmaceutically acceptable salt thereof;

with the provisos that:

- (i) when R² is a 4-pyridyl group and R³ is H then R¹ is other than a phenyl group which is unsubstituted or substituted;
- (ii) when R² is a pyridyl group and R³ is H then R¹ is other than a dimethylamino group, a morpholine group or a piperazinyl group which is unsubstituted or substituted by C₁-C₆ alkyl, phenyl or heteroaryl;
- (iii) when R² is a thiazole group, R¹ is -Y-R⁶ in which Y is a direct bond and R³ is H, then R⁶ is other than a 5 – 12 membered aryl group; and
- (iv) when R¹ is -Y-R⁶ in which Y is a group -C(O)-NH-, R³ is H and R⁶ is an a 5 – 12 membered aryl group, then R² is other than an unsubstituted pyrazole ring.

In one aspect, the invention provides a compound which is a morpholino pyrimidine of formula (I'):



wherein

R^1 is selected from $-Y-R^6$ and $-NR^4R^5$;

R^2 is a N-containing monocyclic heteroaryl group which is selected from
 5 pyridyl, isoxazolyl, imidazolyl, pyrazolyl, pyrrolyl, thiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, oxazolyl, furanyl, thienyl, triazolyl and tetrazolyl and which is substituted by $-NR^{10}R^{11}$, $-OR^{10}$, $-C(O)R^{10}$, $-NR^{10}C(O)R^{11}$, $-N(C(O)R^{11})_2$, $-NR^{10}C(O)NR^{10}R^{11}$, $-SO_2R^{10}R^{11}$, $-SO_2NR^{10}R^{11}$, $-C(=O)OR^{10}$, $-C(=O)NR^{10}R^{11}$, halo- C_1-C_6 alkyl and unsubstituted C_1-C_{12} alkyl;

10 R^3 is selected from H, C_1-C_6 alkyl and C_1-C_6 alkoxy;

Y is selected from a direct bond, $-(CR_2)_m-$, C_2-C_6 alkenylene, C_2-C_6 alkynylene, $-(CR_2)_p-O-(CR_2)_t-$, $-(CR_2)_p-NR-(CR_2)_t-$, $-(CR_2)_p-NR-(CR_2)_n-C(O)-$, $-(CR_2)_p-NR-C(O)-(CR_2)_n-$, $-(CR_2)_p-C(O)-NR-(CR_2)_t-$, $-(CR_2)_p-C(O)-(CR_2)_n-NR-(CR_2)_t-$ and $-(CR_2)_p-C(O)-(CR_2)_n-$;

15 R^6 is selected from C_1-C_6 alkyl, $-NR_2$, $-OR$, $-NR(CO)R$, $-C(O)NR_2$, an unsaturated 5- to 12-membered carbocyclic or heterocyclic ring which is unsubstituted or substituted and a saturated 5-, 6- or 7- membered N-containing heterocyclic group which is unsubstituted or substituted by a group Z' ;

R^4 and R^5 , which are the same or different, are both C_1-C_6 alkyl which is
 20 unsubstituted or substituted, or R^4 and R^5 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 by a group Z' ;

each R, which are the same or different when more than one is present in a given group, is independently H or C₁-C₆ alkyl which is unsubstituted or substituted;

R¹⁰ and R¹¹, which are the same or different, are independently selected from H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl and C₃-C₈ cycloalkyl;

5 Z' is selected from unsubstituted C₁-C₆ alkyl, -(alk)_v-OR, -(alk)_v-NR₂, -(alk)_v-C(O)NR₂, -(alk)_v-C(O)NR^{4a}R^{5a}, -(alk)_v-C(O)R, -(alk)_v-C(O)Ar, -(alk)_v-C(O)Het, -SO₂R, -SO₂Ar, -SO₂Het and =O, wherein alk is C₁-C₈ alkylene, v is 0 or 1, R is selected from H, C₁-C₆ alkyl and Ar, Ar is 5- to 12-membered aryl as defined above, Het is 5- to 12-membered heteroaryl as defined above, and R^{4a} and R^{5a} form together, 10 with the N atom to which they are attached, a saturated 5-, 6-, or 7-membered N-containing heterocyclic group which is unsubstituted or substituted;

n is 0 or an integer of 1 to 6;

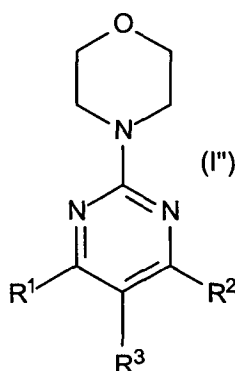
m is an integer of 1 to 6;

p is 0 or an integer of 1 to 6; and

15 t is 0 or an integer of 1 to 6, with the proviso that t is an integer of 2 to 6 when R⁶ is linked to Y through a constituent O or N atom of R⁶;
or a pharmaceutically acceptable salt thereof.

In a yet further aspect the invention provides a compound which is a morpholino pyrimidine of formula (I''):

20



wherein

R¹ is -Y-R⁶;

25 R² is a N-containing monocyclic heteroaryl group which is selected from pyridyl, isoxazolyl, imidazolyl, pyrazolyl, pyrrolyl, thiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, oxazolyl, furanyl, thienyl, triazolyl and tetrazolyl and which is substituted by

$-\text{NR}^{10}\text{R}^{11}$, $-\text{OR}^{10}$, $-\text{C}(\text{O})\text{R}^{10}$, $-\text{NR}^{10}\text{C}(\text{O})\text{R}^{11}$, $-\text{N}(\text{C}(\text{O})\text{R}^{11})_2$, $-\text{NR}^{10}\text{C}(\text{O})\text{NR}^{10}\text{R}^{11}$, $-\text{SO}_2\text{R}^{10}\text{R}^{11}$, $-\text{SO}_2\text{NR}^{10}\text{R}^{11}$, $-\text{C}(=\text{O})\text{OR}^{10}$, $-\text{C}(=\text{O})\text{NR}^{10}\text{R}^{11}$, halo- C_1-C_6 alkyl and unsubstituted C_1-C_{12} alkyl;

R^3 is selected from H, C_1-C_6 alkyl and C_1-C_6 alkoxy;

5 Y is C_2-C_6 alkynylene or $-\text{O}-(\text{CR}_2)_t-$;

R^6 is selected from C_1-C_6 alkyl, $-\text{NR}_2$, $-\text{OR}$, $-\text{NR}(\text{CO})\text{R}$, $-\text{C}(\text{O})\text{NR}_2$, an unsaturated 5- to 12-membered carbocyclic or heterocyclic ring which is unsubstituted or substituted and a saturated 5-, 6- or 7- membered N-containing heterocyclic group which is unsubstituted or substituted, said saturated N-containing heterocyclic group
10 being C-linked to Y when Y is $-\text{O}-(\text{CR}_2)_t-$;

R^4 and R^5 , which are the same or different, are both C_1-C_6 alkyl which is unsubstituted or substituted, or R^4 and R^5 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;

15 each R, which are the same or different when more than one is present in a given group, is independently H or C_1-C_6 alkyl which is unsubstituted or substituted;

R^{10} and R^{11} , which are the same or different, are independently selected from H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl and C_3-C_8 cycloalkyl; and

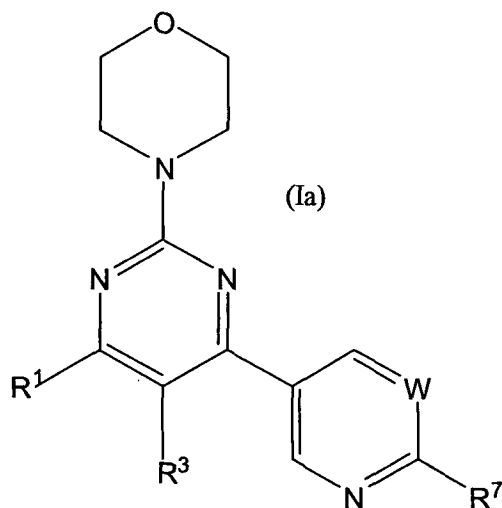
t is 0 or an integer of 1 to 6;

20 or a pharmaceutically acceptable salt thereof.

In one embodiment of formula (I''), when t is 0 then R^6 is not an unsubstituted 5- to 12-membered heterocyclic ring which is unsubstituted or substituted or a saturated 5-, 6- or 7-membered N-containing heterocyclic group which is unsubstituted or substituted.

25 When, in formula (I'') an atom or group is substituted, it is typically substituted by a group Z' as defined above.

In a further aspect the invention provides a compound which is a morpholino pyrimidine of formula (Ia):



wherein

R^1 and R^3 are as defined above for formula (I), (I') or (I'');

5 W is CR or N;

R is H or C_1-C_6 alkyl which is unsubstituted or substituted; and

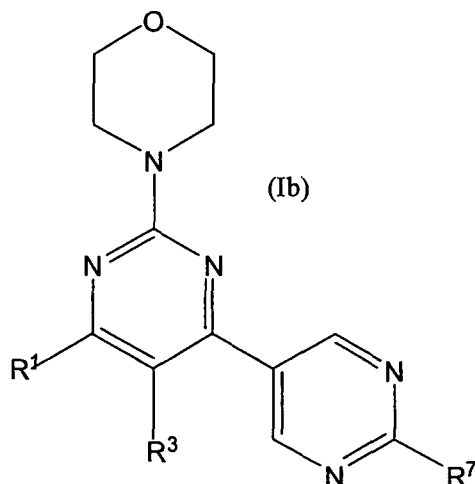
R^7 is selected from $-NR^{10}R^{11}$, $-OR^{10}$, $-C(O)R^{10}$, $-NR^{10}C(O)R^{11}$, $-N(C(O)R^{11})_2$, $-NR^{10}C(O)NR^{10}R^{11}$, $SO_2R^{10}R^{11}$, $-SO_2NR^{10}R^{11}$, $-C(=O)OR^{10}$, $-C(=O)NR^{10}R^{11}$, halo- C_1-C_6 alkyl and unsubstituted C_1-C_{12} alkyl, wherein R^{10} and R^{11} are as defined above;

10 or a pharmaceutically acceptable salt thereof;

with the proviso that, when W is CR, R^1 is other than a piperazinyl group which is substituted by a phenyl or heteroaryl group.

When W in formula (Ia) is CR, R is typically H or unsubstituted C_1-C_6 alkyl. More typically W is CH.

In yet a further aspect the invention provides a compound which is a morpholino pyrimidine of formula (Ib):



wherein

5 R^1 and R^3 are as defined above for formula (I), (I') or (I'');

R^7 is selected from halo, $-CN$, $-NR^{10}R^{11}$, $-OR^{10}$, $-C(O)R^{10}$, $-NR^{10}C(O)R^{11}$, $-N(C(O)R^{11})_2$, $-NR^{10}C(O)NR^{10}R^{11}$, $-SO_2R^{10}R^{11}$, $-SO_2NR^{10}R^{11}$, $-C(=O)OR^{10}$, $-C(=O)NR^{10}R^{11}$, halo- C_1 - C_6 alkyl and unsubstituted C_1 - C_{12} alkyl, wherein R^{10} and R^{11} are as defined above;

10 or a pharmaceutically acceptable salt thereof.

Detailed description of the Invention

As specified herein, an alkyl group is a straight or branched chain saturated hydrocarbon radical which is unsubstituted or substituted. Typically it is C_1 - C_{20} alkyl, for instance C_1 - C_{10} alkyl, such as C_1 - C_6 alkyl group. C_1 - C_6 alkyl is typically C_1 - C_4 alkyl. It may be, for example, methyl (Me, $-CH_3$), ethyl (Et, $-CH_2CH_3$), 1-propyl (n-Pr, n-propyl, $-CH_2CH_2CH_3$), 2-propyl (i-Pr, i-propyl, $-CH(CH_3)_2$), 1-butyl (n-Bu, n-butyl, $-CH_2CH_2CH_2CH_3$), 2-methyl-1-propyl (i-Bu, i-butyl, $-CH_2CH(CH_3)_2$), 2-butyl (s-Bu, s-butyl, $-CH(CH_3)CH_2CH_3$), 2-methyl-2-propyl (t-Bu, t-butyl, $-C(CH_3)_3$), 1-pentyl (n-pentyl, $-CH_2CH_2CH_2CH_2CH_3$), 2-pentyl ($-CH(CH_3)CH_2CH_2CH_3$), 3-pentyl ($-CH(CH_2CH_3)_2$), 2-methyl-2-butyl ($-C(CH_3)_2CH_2CH_3$), 3-methyl-2-butyl ($-CH(CH_3)CH(CH_3)_2$), 3-methyl-1-butyl ($-CH_2CH_2CH(CH_3)_2$), 2-methyl-1-butyl ($-CH_2CH(CH_3)CH_2CH_3$), 1-hexyl ($-CH_2CH_2CH_2CH_2CH_2CH_3$), 2-hexyl ($-CH(CH_3)CH_2CH_2CH_2CH_3$), 3-hexyl ($-CH(CH_2CH_3)(CH_2CH_2CH_3)$), 2-methyl-2-pentyl

(-C(CH₃)₂CH₂CH₂CH₃), 3-methyl-2-pentyl (-CH(CH₃)CH(CH₃)CH₂CH₃), 4-methyl-2-pentyl (-CH(CH₃)CH₂CH(CH₃)₂), 3-methyl-3-pentyl (-C(CH₃)(CH₂CH₃)₂), 2-methyl-3-pentyl (-CH(CH₂CH₃)CH(CH₃)₂), 2,3-dimethyl-2-butyl (-C(CH₃)₂CH(CH₃)₂), or 3,3-dimethyl-2-butyl (-CH(CH₃)C(CH₃)₃). An alkyl group is unsubstituted or substituted,
 5 typically by one or more groups Z or R⁹ as defined below. Typically it is C₁-C₄ alkyl, for example methyl, ethyl, i-propyl, n-propyl, t-butyl, s-butyl or n-butyl

Z is selected from H, unsubstituted C₁-C₆ alkyl, halo, -OR', -SR', CH₂OR', -CF₃, -(halo)-C₁-C₆ alkyl, -(CR⁸)_qO-(halo)-C₁-C₆ alkyl, -CO₂R', -(CR⁸)_qCO₂R', -(CR⁸)_qCOR', -CF₂OH, -CH(CF₃)OH, -C(CF₃)₂OH, -(CH₂)_qOR', -(CR⁸)_qOR',
 10 -(CH₂)_qNR'₂, -(CR⁸)_qNR'₂, -(CR⁸)_s-NR'-(CR⁸)₂-R', -C(O)NR'₂, -C(O)NR'-(CR'₂)_s-NR'₂, -(CR⁸)_qCONR'₂, -NR'₂, -(CR⁸)_qNR'₂, -NR'C(O)R', -(CR⁸)_qNR'C(O)OR', -S(O)_rR', -S(O)_rN(R')₂, -(CR⁸)_qS(O)_rNR'₂, -OC(O)R', -(CR⁸)_qOC(O)R', -OC(O)NR'₂, -(CR⁸)_qOC(O)NR'₂, -NRS(O)_rR', -(CR⁸)_qNR'S(O)_rR', -NR'C(O)N(R')₂, -(CR⁸)_qNR'C(O)NR'₂, CN, -NO₂ and a 5- to

15 12-membered aryl or heteroaryl group, which group is unsubstituted or substituted; wherein each R' is independently selected from H, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, a saturated 5-, 6- or 7-membered N-containing heterocyclic group which is unsubstituted or substituted and a 5- to 12-membered aryl or heteroaryl group which is unsubstituted or substituted; or two groups R' present on a N atom together form, with said N atom, a
 20 saturated 5-, 6- or 7-membered N-containing heterocyclic group which is unsubstituted or substituted; q is 0 or an integer of 1 to 4; r is 1 or 2; and s is an integer of 1 to 4.

R⁹ 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.

R⁸, each of which is the same or different when more than one is present in a
 25 given substituent, is selected from H, C₁-C₆ alkyl and C₃-C₁₀ cycloalkyl, and m is 1 or 2.

A halogen or halo group 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
 30 halo-C₁-C₆ alkyl group preferably contains one, two or three halo groups. A preferred example of such a group is trifluoromethyl.

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 R⁹ as defined above.

5 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 R⁹ as defined above.

10 An alkylene group is unsubstituted or substituted, straight or branched chain saturated divalent hydrocarbon group. The term "alk" as used herein denotes such an alkylene group. Typically alkylene (or "alk") is C₁-C₈ alkylene, for instance C₁-C₆ alkylene. Preferably it is C₁-C₄ alkylene, for example C₂-C₄ alkylene, such as methylene, ethylene, i-propylene, n-propylene, t-butylene, s-butylene or n-butylene. It may also be pentylene, hexylene, heptylene, octylene and the various branched chain
15 isomers thereof. When the alkylene group is substituted it is typically substituted by a group R²⁰ as defined above.

In an alkylene chain -(CR₂)_m-, -(CR₂)_n-, -(CR₂)_p-, -(CR₂)_t-, or -(CR⁸₂)_q- each of the constituent units CR₂ or CR⁸₂ may be the same or different when m, n, p, q or t is greater than 1.

20 An alkenyl group is an unsubstituted or substituted, straight or branched chain hydrocarbon radical having one or more double bonds. Typically it is C₂-C₈ alkenyl, for instance C₂-C₆ alkenyl, such as allyl, butenyl, butadienyl, pentenyl or hexenyl. When the alkenyl group is substituted it is typically substituted by a group Z or R⁹ as defined above or by alkyl which is unsubstituted or substituted by a group Z or R⁹ as
25 defined above.

An alkenylene group is a divalent alkenyl group as defined above.

An alkynyl group is an unsubstituted or substituted, straight or branched chain hydrocarbon radical having one or more triple bonds. Typically it is C₂-C₈ alkynyl, for instance C₂-C₆ alkynyl, such as ethynyl, propynyl or butynyl. When the alkynyl group
30 is substituted it is typically substituted by a group R²⁰ as defined above or by alkyl which is unsubstituted or substituted by a group R²⁰ as defined above..

An alkynylene group is a divalent alkynyl group as defined above.

A saturated 5-, 6-, or 7-membered N-containing heterocyclic group typically contains one nitrogen atom and either an additional N atom or an O or S atom, or no additional heteroatoms. It may be C-linked or N-linked. It may alternatively be O- or S- linked when an additional O or S atom is present. The group may be, for example,
 5 piperidine, piperazine, morpholine, thiomorpholine, pyrrolidine or homopiperazine.

The saturated 5-, 6-, or 7-membered N-containing heterocyclic group 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 R⁹ as defined above, and a C₁-C₆ alkyl group which is unsubstituted or
 10 substituted by a group Z or R⁹ 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.

An unsaturated 5- to 12-membered carbocyclic group is a 5-, 6-, 7-, 8-, 9-, 10,
 15 11- or 12-membered carbocyclic ring containing at least one unsaturated bond. It is a monocyclic or fused bicyclic ring system. The group is non-aromatic or 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 R⁹ as defined above.

20 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 R⁹ as defined above.

An unsaturated 5- to 12-membered heterocyclic group is a 5-, 6-, 7-, 8-, 9-, 10,
 11- or 12-membered heterocyclic ring containing at least one unsaturated bond and at
 25 least one heteroatom selected from O, N and S. It is C-linked or heteroatom-linked. It is a monocyclic or fused bicyclic ring system. The group is non-aromatic or aromatic, for instance heteroaryl. The group may be, for example, furan, thiophene, pyrrole, pyrrolopyrazine, pyrrolopyrimidine, pyrrolopyridine, pyrrolopyridazine, indole, isoindole, pyrazole, pyrazolopyrazine, pyrazolopyrimidine, pyrazolopyridine,
 30 pyrazolopyridazine, imidazole, imidazopyrazine, imidazopyrimidine, imidazopyridine, imidazopyridazine, benzimidazole, benzodioxole, benzodioxine, benzoxazole, benzothiophene, benzothiazole, benzofuran, indole, indoliziny, isoxazole, oxazole,

oxadiazole, thiazole, isothiazole, thiadiazole, dihydroimidazole, dihydrobenzofuran, dihydrodioxinopyridine, dihydropyrrolopyridine, dihydrofuranopyridine, dioxolopyridine, pyridine, quinoline, isoquinoline, quinazoline, quinoxaline, tetrahydrobenzofuran, tetrahydroquinoline, tetrahydroisoquinoline, 5,6,7,8-tetrahydro-
 5 imidazo[1,5-a]pyrazine, 5,6,7,8-tetrahydro-imidazo[1,2-a]pyrazine, thienopyrazine, pyrimidine, pyridazine, pyrazine, triazine, triazole or tetrazole. The group is unsubstituted or substituted, typically by one or more groups Z or R⁹ as defined above.

Heteroaryl is a 5- to 12-membered aromatic heterocyclic group which contains 1, 2, 3, or 4 heteroatoms selected from O, N and S. It is monocyclic or bicyclic.

10 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, selected from the heteroaryl groups in the above list of options for a 5 to 12-membered heterocyclic group. In particular heteroaryl is selected from pyridyl, isoxazolyl, imidazolyl, pyrazolyl, pyrrolyl, thiazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, oxazolyl, furanyl, thienyl, triazolyl, tetrazolyl,
 15 indolyl, quinolinyl, isoquinolinyl, quinazolinyl and indazolyl.

When R⁶ is an unsaturated 5- to 12-membered carbocyclic ring, for instance an aryl group as defined above, it is unsubstituted or substituted by a group Z or R⁹ as defined above. When it is substituted it is typically substituted by one or more, typically 1 or 2, substituents selected from -(alk)_v-OR, -SO₂R, -SO₂NR₂,
 20 -SO₂NR^{4a}R^{5a}, -NRSO₂R, -(alk)_v-NRC(O)R, -(alk)_v-C(O)NR₂, -CO₂R, halo, unsubstituted C₁-C₆ alkyl, -(alk)_v-NR₂, -C(O)-NR-alk-NR₂, -(alk)_v-C(O)NR^{4a}R^{5a}, -alk-NR^{4a}R^{5a}, -alk-NR-R¹¹, -alk-NR-alk-Het and -CN, wherein R is H, C₁-C₆ alkyl or aryl as defined above; alk is alkylene as defined above; R^{4a} and R^{5a} form together, with the N atom to which they are attached, a saturated 5-, 6-, or 7-membered N-containing
 25 heterocyclic group which is unsubstituted or substituted, typically by a group Z or R⁹ as defined above and more typically by a group selected from unsubstituted C₁-C₆ alkyl, -SO₂R, -SO₂NR₂, Ar and Het wherein R is as defined above, Ar is 5- to 12-membered aryl as defined above, Het is 5- to 12-membered heteroaryl as defined above; R¹¹ is a saturated 5-, 6- or 7- membered N-containing heterocyclic group which is unsubstituted
 30 or substituted; and v is 0 or 1.

When R⁶ is a saturated 5-, 6- or 7- membered N-containing heterocyclic group which is unsubstituted or substituted, it is unsubstituted or substituted by a group Z or

R^9 as defined above. When it is substituted it is typically substituted by one or more, typically 1 or 2, groups selected from unsubstituted C_1 - C_6 alkyl, Ar, Het, $-(alk)_v-OR$, $-(alk)_v-NR_2$, $-(alk)_v-C(O)NR_2$, $-(alk)_v-C(O)NR^{4a}R^{5a}$, $-(alk)_v-C(O)R$, $-(alk)_v-C(O)Ar$, $-(alk)_v-C(O)Het$, $-SO_2R$, $-SO_2Ar$, $-SO_2Het$ and $=O$, wherein alk, Ar, Het, R, R^{4a} , R^5 and v are as defined above.

When R^4 and R^5 together form, with the nitrogen atom to which they are attached, a saturated 5-, 6- or 7- membered N-containing heterocyclic group which is substituted, it is typically substituted one or more, typically 1 or 2, groups selected from unsubstituted C_1 - C_6 alkyl, Ar, Het, $-(alk)_v-OR$, $-(alk)_v-NR_2$, $-(alk)_v-C(O)NR_2$, $-(alk)_v-C(O)NR^{4a}R^{5a}$, $-(alk)_v-C(O)R$, $-(alk)_v-C(O)Ar$, $-(alk)_v-C(O)Het$, $-SO_2R$, $-SO_2Ar$, $-SO_2Het$ and $=O$, wherein alk, Ar, Het, R, R^{4a} , R^5 and v are as defined above.

When linker Y is $-(CR_2)_p-O-(CR_2)_t$, it may, for example, be selected from $-O-$, $-alk-O-alk-$, $-alk-O-$ and $-O-alk-$ wherein alk is alkylene as defined above. In one embodiment $-(CR_2)_p-O-(CR_2)_t$ is $-O-(CR_2)_t$, of which $-O-alk-$ is an example. Examples of $-O-alk-$ include $-O-(CH_2)-$, $-O-(CHMe)-$, $-O-(CMe_2)-$, $-O-(CH_2)_2-$ and $-O-(CH_2)_3-$. Examples of $-alk-O-$ include $-(CH_2)-O-$, $-(CHMe)-O-$, $-(CMe_2)-O-$, $-(CH_2)_2-O-$ and $-(CH_2)_3-O-$. When linker Y is $-(CR_2)_p-NR-(CR_2)_t$ it may, for example, be selected from $-NR-$, $alk-NR-alk$, $-alk-NR-$ and $-NR-alk$ wherein alk is alkylene as defined above. Examples of $-alk-NR-$ include $-(CH_2)-NH-$, $-(CH_2)-NMe-$, $-(CHMe)-NH-$, $-(CHMe)-NMe-$, $-(CMe_2)-NH-$, $-(CMe_2)-NMe-$, $-(CH_2)_2-NH-$, $-(CH_2)_2-NMe-$, $-(CH_2)_3-NH-$ and $-(CH_2)_3-NMe-$. Examples of $-NR-alk$ include $-NH-(CH_2)-$, $-NMe-(CH_2)-$, $-NH-(CHMe)-$, $-NMe-(CHMe)-$, $-NH-(CMe_2)-$, $-NMe-(CMe_2)-$, $-NH-(CH_2)_2-$, $-NMe-(CH_2)_2-$, $-NH-(CH_2)_3-$ and $-NMe-(CH_2)_3-$.

When linker Y is $-(CR_2)_p-NR-(CR_2)_n-C(O)-$ it may, for example, be selected from $-NR-C(O)-$, $alk-NR-alk-C(O)-$, $alk-NR-C(O)-$ and $-NR-alk-C(O)-$ wherein alk is alkylene as defined above.

Examples of $-NR-C(O)-$ include $-NH-C(O)-$ and $-NMe-C(O)-$.

Examples of $alk-NR-alk-C(O)-$ include $-(CH_2)-NH-(CH_2)-C(O)-$, $-(CH_2)-NMe-(CH_2)-C(O)-$, $-(CHMe)-NH-(CH_2)-C(O)-$, $-(CHMe)-NMe-(CH_2)-C(O)-$, $-(CH_2)-NH-(CHMe)-C(O)-$, $-(CH_2)-NMe-(CHMe)-C(O)-$, $-(CMe_2)-NH-(CH_2)-C(O)-$, $-(CMe_2)-NMe-(CH_2)-C(O)-$, $-(CH_2)-NH-(CMe_2)-C(O)-$, $-(CH_2)-NMe-(CMe_2)-C(O)-$ and $-(CMe_2)-NMe-(CMe_2)-C(O)-$.

Examples of -alk-NR-C(O)- include $-(CH_2)-NH-C(O)-$, $-(CH_2)-NMe-C(O)-$, $-(CHMe)-NH-C(O)-$, $-(CHMe)-NMe-C(O)-$, $-(CMe_2)-NH-C(O)-$, $-(CMe_2)-NMe-C(O)-$, $-(CH_2)_2-NH-C(O)-$, $-(CH_2)_2-NMe-C(O)-$, $-(CH_2)_3-NH-C(O)-$ and $-(CH_2)_3-NMe-C(O)-$.

- 5 Examples of -NR-alk-C(O)- include $-NH-(CH_2)-C(O)-$, $-NMe-(CH_2)-C(O)-$, $-NH-(CHMe)-C(O)-$, $-NMe-(CHMe)-C(O)-$, $-NH-(CMe_2)-C(O)-$, $-NMe-(CMe_2)-C(O)-$, $-NH-(CH_2)_2-C(O)-$, $-NMe-(CH_2)_2-C(O)-$, $-NH-(CH_2)_3-C(O)-$ and $-NMe-(CH_2)_3-C(O)-$.

When linker Y is $-(CR_2)_p-NR-C(O)-(CR_2)_n-$ it may, for example, be selected from -alk-NR-C(O)-alk-, -alk-NR-C(O)- and -NR-C(O)-alk-.

- 10 Examples of -alk-NR-C(O)-alk- include $-(CH_2)-NH-C(O)-(CR''_2)-$, $-(CH_2)-NMe-C(O)-(CR''_2)-$, $-(CHMe)-NH-C(O)-(CR''_2)-$, $-(CHMe)-NMe-C(O)-(CR''_2)-$, $-(CMe_2)-NH-C(O)-(CR''_2)-$, $-(CMe_2)-NMe-C(O)-(CR''_2)-$, $-(CH_2)_2-NH-C(O)-(CR''_2)-$, $-(CH_2)_2-NMe-C(O)-(CR''_2)-$, $-(CH_2)_3-NH-C(O)-(CR''_2)-$ and $-(CH_2)_3-NMe-C(O)-(CR''_2)-$ wherein R'' is H or Me.

- 15 Examples of -alk-NR-C(O)- include those given above.

Examples of -NR-C(O)-alk- include $-NH-C(O)-(CH_2)-$, $-NMe-C(O)-(CH_2)-$, $-NH-C(O)-(CHMe)-$, $-NMe-C(O)-(CHMe)-$, $-NH-C(O)-(CMe_2)-$, $-NMe-C(O)-(CMe_2)-$, $-NH-C(O)-(CH_2)_2-$, $-NMe-C(O)-(CH_2)_2-$, $-NH-C(O)-(CH_2)_3-$ and $-NMe-C(O)-(CH_2)_3-$.

- 20 When linker Y is $-(CR_2)_p-C(O)-NR-(CR_2)_t-$ it may, for example, be selected from -alk-C(O)-NR-alk-, -alk-C(O)-NR- and -C(O)-NR-alk-.

- Examples of alk-C(O)-NR-alk- include $-(CH_2)-C(O)-NH-(CR''_2)-$, $-(CH_2)-C(O)-NMe-(CR''_2)-$, $-(CHMe)-C(O)-NH-(CR''_2)-$, $-(CHMe)-C(O)-NMe-(CR''_2)-$, $-(CMe_2)-C(O)-NH-(CR''_2)-$, $-(CMe_2)-C(O)-NMe-(CR''_2)-$, $-(CH_2)_2-C(O)-NH-(CR''_2)-$, $-(CH_2)_2-C(O)-NMe-(CR''_2)-$, $-(CH_2)_3-C(O)-NH-(CR''_2)-$ and $-(CH_2)_3-C(O)-NMe-(CR''_2)-$ wherein R'' is H or Me.
- 25

Examples of -alk-C(O)-NR- include $-(CH_2)-C(O)-NH-$, $-(CH_2)-C(O)-NMe-$, $-(CHMe)-C(O)-NH-$, $-(CHMe)-C(O)-NMe-$, $-(CMe_2)-C(O)-NH-$, $-(CMe_2)-C(O)-NMe-$, $-(CH_2)_2-C(O)-NH-$, $-(CH_2)_2-C(O)-NMe-$, $-(CH_2)_3-C(O)-NH-$ and $-(CH_2)_3-C(O)-NMe-$.

30

When linker Y is $-(CR_2)_p-C(O)-(CR_2)_n-NR-(CR_2)_t-$ it may, for example, be -alk-C(O)-alk-NR-, -C(O)-alk-NR-, -alk-C(O)-NR- or -alk-C(O)-NR-alk-.

Examples of $-\text{alk}-\text{C}(\text{O})-\text{alk}-\text{NR}-$ include include $-(\text{CH}_2)-\text{C}(\text{O})-(\text{CR}'')_2-\text{NH}-$, $-(\text{CH}_2)-\text{C}(\text{O})-(\text{CR}'')_2-\text{NMe}-$, $-(\text{CHMe})-\text{C}(\text{O})-(\text{CR}'')_2-\text{NH}-$, $-(\text{CHMe})-\text{C}(\text{O})-(\text{CR}'')_2-\text{NMe}$, $-(\text{CMe}_2)-\text{C}(\text{O})-(\text{CR}'')_2-\text{NH}-$, $-(\text{CMe}_2)-\text{C}(\text{O})-(\text{CR}'')_2-\text{NMe}-$, $-(\text{CH}_2)_2-\text{C}(\text{O})-(\text{CR}'')_2-\text{NH}$, $-(\text{CH}_2)_2-\text{C}(\text{O})-(\text{CR}'')_2-\text{NMe}-$, $-(\text{CH}_2)_3-\text{C}(\text{O})-(\text{CR}'')_2-\text{NH}-$ and $-(\text{CH}_2)_3-\text{C}(\text{O})-(\text{CR}'')_2-\text{NMe}-$ wherein R'' is H or Me.

Examples of $-\text{C}(\text{O})-\text{alk}-\text{NR}-$ include $-\text{C}(\text{O})-(\text{CH}_2)-\text{NH}-$, $-\text{C}(\text{O})-(\text{CH}_2)-\text{NMe}-$, $-\text{C}(\text{O})-(\text{CHMe})-\text{NH}-$, $-\text{C}(\text{O})-(\text{CHMe})-\text{NMe}-$, $-\text{C}(\text{O})-(\text{CMe}_2)-\text{NH}-$, $-\text{C}(\text{O})-(\text{CMe}_2)-\text{NMe}$, $-\text{C}(\text{O})-(\text{CH}_2)_2-\text{NH}$, $-\text{C}(\text{O})-(\text{CH}_2)_2-\text{NMe}-$, $-\text{C}(\text{O})-(\text{CH}_2)_3-\text{NH}-$ and $-\text{C}(\text{O})-(\text{CH}_2)_3-\text{NMe}-$

Examples of $-\text{alk}-\text{C}(\text{O})-\text{NR}-$ are those given above.

Examples of $\text{alk}-\text{C}(\text{O})-\text{NR}-\text{alk}-$ include $-(\text{CH}_2)-\text{C}(\text{O})-\text{NH}-(\text{CH}_2)-$, $-(\text{CH}_2)-\text{C}(\text{O})-\text{NH}-(\text{CH}_2)_2-$, $-(\text{CH}_2)-\text{C}(\text{O})-\text{NH}-(\text{CH}_2)_3-$, $-(\text{CH}_2)-\text{C}(\text{O})-\text{NMe}-(\text{CH}_2)-$, $-(\text{CH}_2)-\text{C}(\text{O})-\text{NMe}-(\text{CH}_2)_2-$, $-(\text{CHMe})-\text{C}(\text{O})-\text{NH}-(\text{CH}_2)-$, $-(\text{CHMe})-\text{C}(\text{O})-\text{NMe}-(\text{CH}_2)$, $-(\text{CMe}_2)-\text{C}(\text{O})-\text{NH}-(\text{CH}_2)_2-$, $-(\text{CMe}_2)-\text{C}(\text{O})-\text{NMe}-(\text{CH}_2)_2-$, $-(\text{CH}_2)_2-\text{C}(\text{O})-\text{NH}-(\text{CH}_2)_2-$, $-(\text{CH}_2)_2-\text{C}(\text{O})-\text{NMe}-(\text{CH}_2)_2-$, $-(\text{CH}_2)_3-\text{C}(\text{O})-\text{NH}-(\text{CH}_2)_2-$, and $-(\text{CH}_2)_3-\text{C}(\text{O})-\text{NMe}-(\text{CH}_2)_2-$.

When linker Y is $-(\text{CR}_2)_p-\text{C}(\text{O})-(\text{CR}_2)_n-$ it may, for example, be $-\text{C}(\text{O})-$, $-\text{alk}-\text{C}(\text{O})-$, $-\text{C}(\text{O})-\text{alk}-$ or $\text{alk}-\text{C}(\text{O})-\text{alk}-$.

Examples of $\text{alk}-\text{C}(\text{O})-$ include $-(\text{CH}_2)-\text{C}(\text{O})-$, $-(\text{CH}_2)_2-\text{C}(\text{O})-$, $-(\text{CHMe})-\text{C}(\text{O})-$ and $-(\text{CMe}_2)-\text{C}(\text{O})-$.

Examples of $-\text{C}(\text{O})-\text{alk}-$ include $-\text{C}(\text{O})-(\text{CH}_2)-$, $-\text{C}(\text{O})-(\text{CH}_2)_2-$, $-\text{C}(\text{O})-(\text{CHMe})-$ and $-\text{C}(\text{O})-(\text{CMe}_2)-$. Examples of $\text{alk}-\text{C}(\text{O})-\text{alk}-$ include $-(\text{CH}_2)-\text{C}(\text{O})-(\text{CH}_2)-$, $-(\text{CHMe})-\text{C}(\text{O})-(\text{CH}_2)-$, $-(\text{CMe}_2)-\text{C}(\text{O})-(\text{CH}_2)-$, $-(\text{CH}_2)-\text{C}(\text{O})-(\text{CHMe})-$ and $-(\text{CH}_2)-\text{C}(\text{O})-(\text{CMe}_2)-$.

The monocyclic heteroaryl group R^2 in formulae (I) and (I') as defined above is typically a C-linked monocyclic heteroaryl group. When it is substituted, it is typically substituted by $-\text{NR}^{10}\text{R}^{11}$, $-\text{OR}^{10}$ or C_1-C_6 alkyl. Likewise, R^7 in formulae (Ia) and (Ib) as defined above is typically selected from $-\text{NR}^{10}\text{R}^{11}$, $-\text{OR}^{10}$ and C_1-C_6 alkyl.

In compounds of formulae (I), (I'), (I''), (Ia) or (Ib), Y is typically C_2-C_6 alkynylene or $-\text{O}-(\text{CR}_2)_t-$ wherein t is as defined above. R^6 is typically selected from OR, $-\text{NR}_2$, an unsaturated 5- to 12-membered carbocyclic or heterocyclic ring which is unsubstituted or substituted and a saturated 5-, 6- or 7- membered N-containing heterocyclic group which is unsubstituted or substituted, said saturated N-containing

heterocyclic group being C-linked to Y when Y is $-O-(CR_2)_t$. For instance, R^6 is selected from $-NR_2$, $-OR$, an aryl group as defined above, a heteroaryl group as defined above and a C-linked saturated 5-, 6- or 7- membered N-containing heterocyclic group, each said group being unsubstituted or substituted, for instance by a group Z or R^9 as

5 defined above.

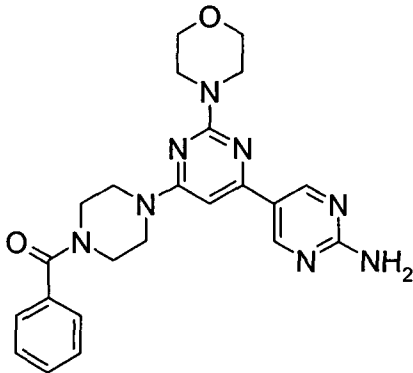
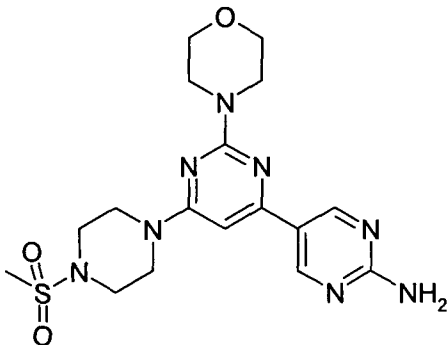
In one embodiment of formulae (I), (I'), (I''), (Ia) or (Ib) Y is C_2-C_6 alkynylene or $-O-(CR_2)_t$ wherein t is as defined above and R^6 is selected from $-NR_2$, $-OR$, an aryl group as defined above and a heteroaryl group as defined above. The aryl or heteroaryl group is unsubstituted or substituted by a group Z or R^9 as defined above, for instance

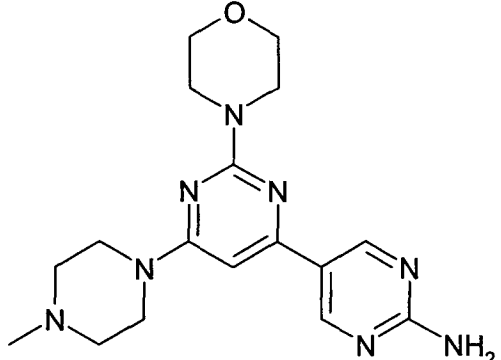
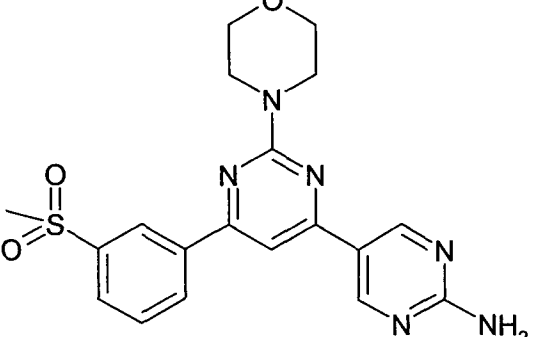
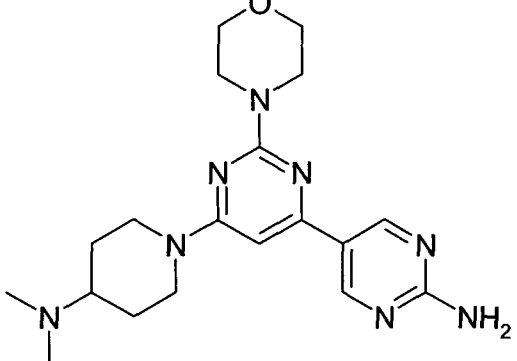
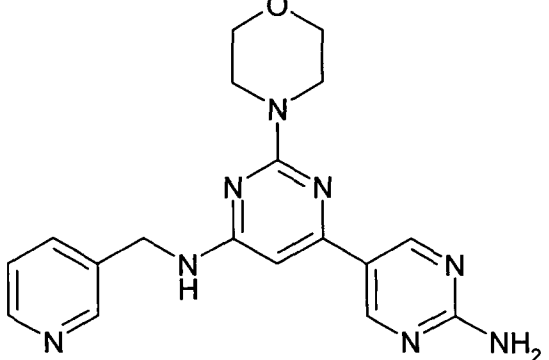
10 by a group $-SO_2R$, $-COR$, $-CONR_2$ or $-CN$ wherein each R is, independently, H or C_1-C_6 alkyl. In this embodiment the aryl group is typically phenyl and the heteroaryl group is typically pyridyl, imidazolyl or quinolinyl.

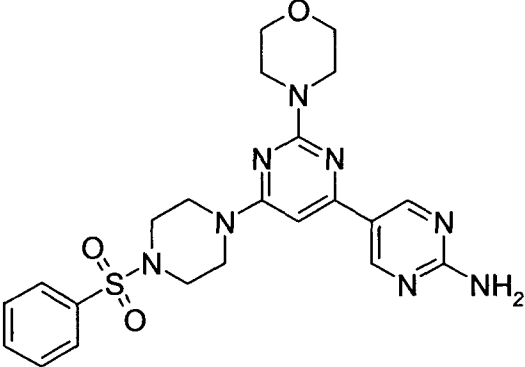
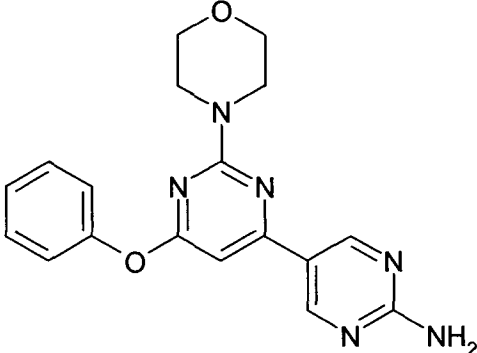
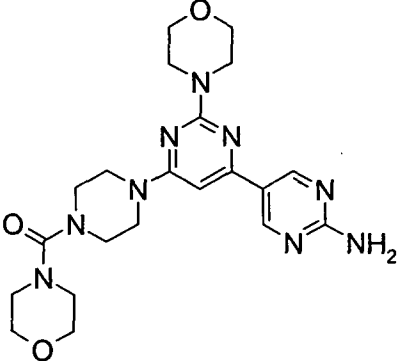
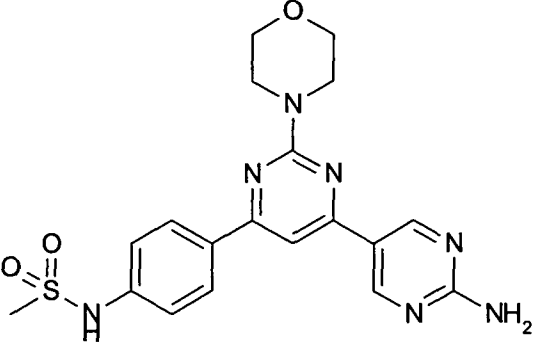
Specific examples of compounds of the invention include those listed in the table 1 which follows:

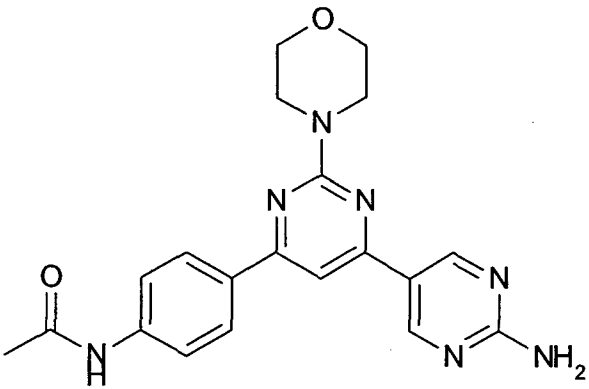
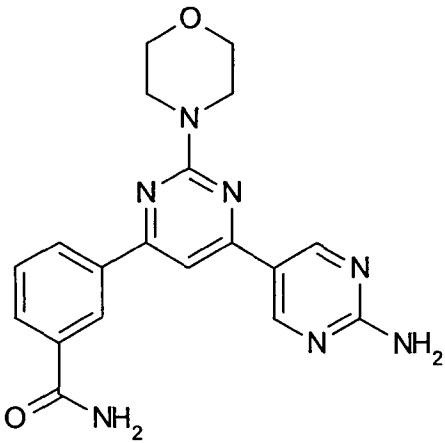
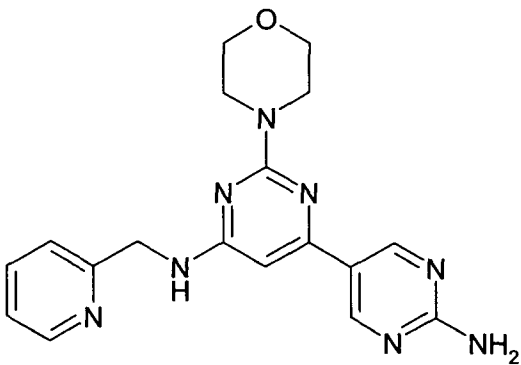
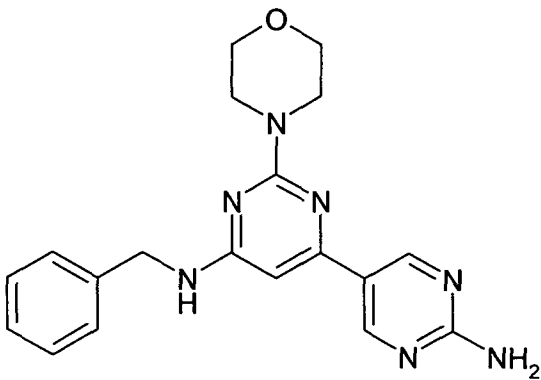
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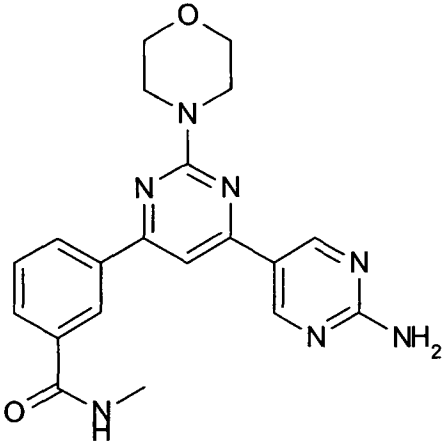
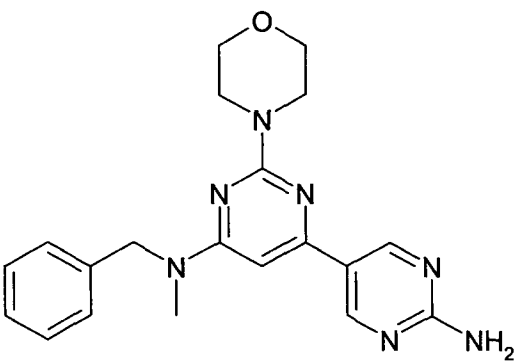
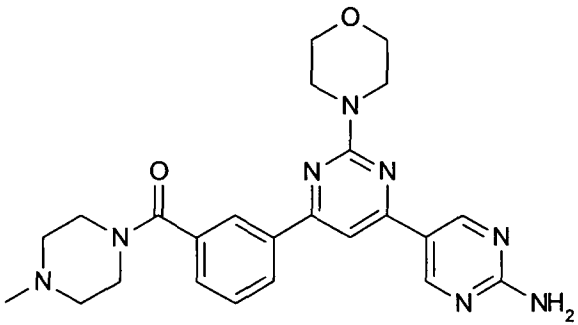
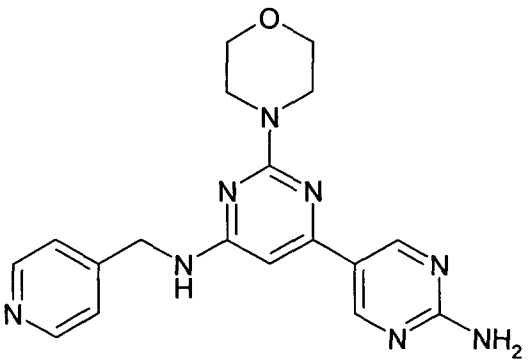
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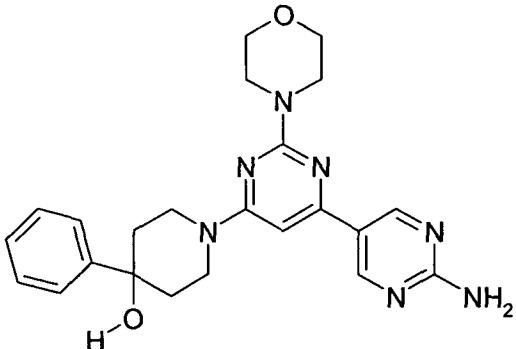
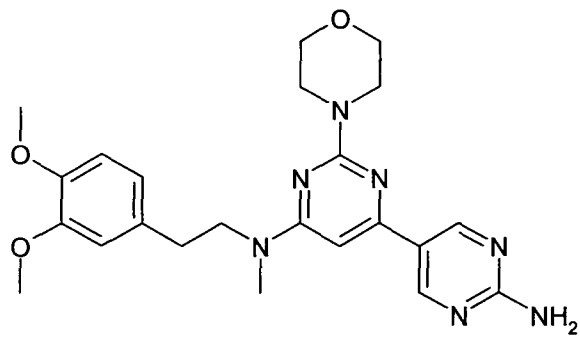
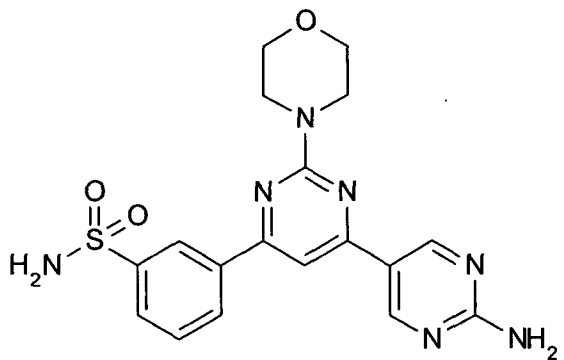
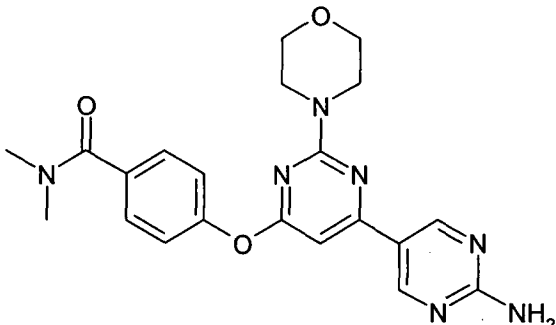
Number	Structure	Name
3		[4-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrin-6-yl)-piperazin-1-yl]-phenyl-methanone
4		6-(4-Methanesulfonyl-piperazin-1-yl)-2-morpholin-4-yl-[4,5']bipyrin-2'-ylamine

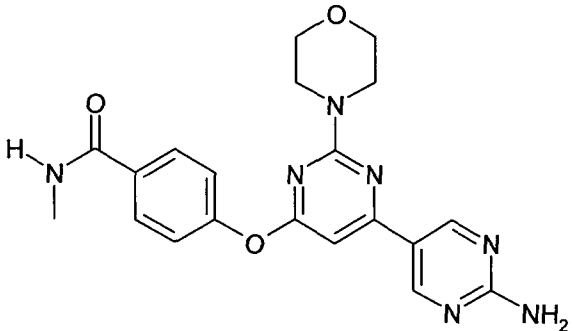
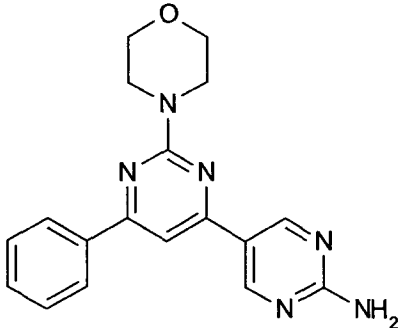
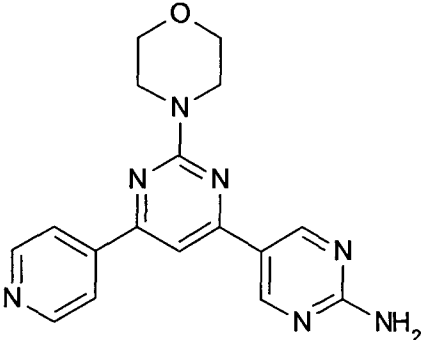
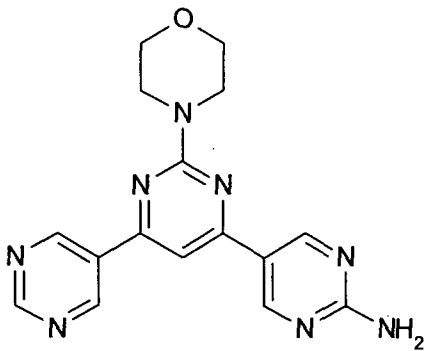
5		6-(4-Methyl-piperazin-1-yl)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine
6		6-(3-Methanesulfonyl-phenyl)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine
7		6-(4-Dimethylamino-piperidin-1-yl)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine
8		2-Morpholin-4-yl-N-6-pyridin-3-ylmethyl-[4,5']bipyrimidinyl-6,2'-diamine

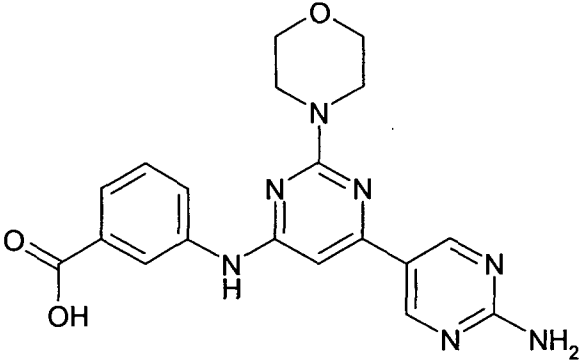
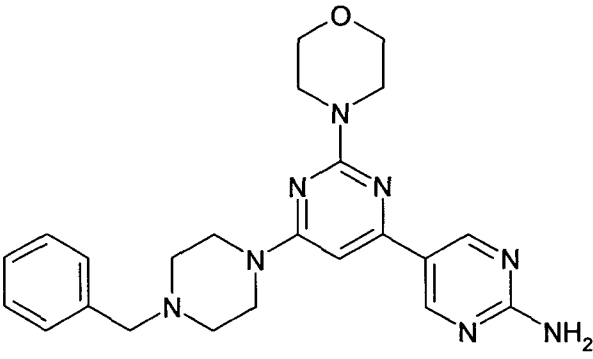
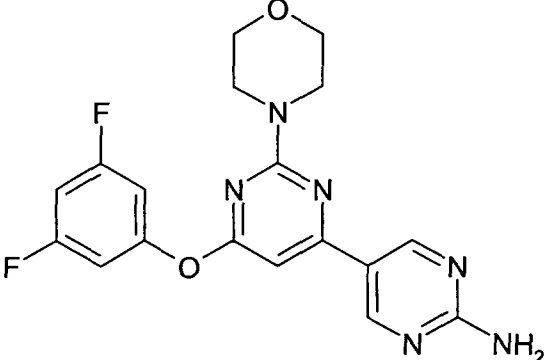
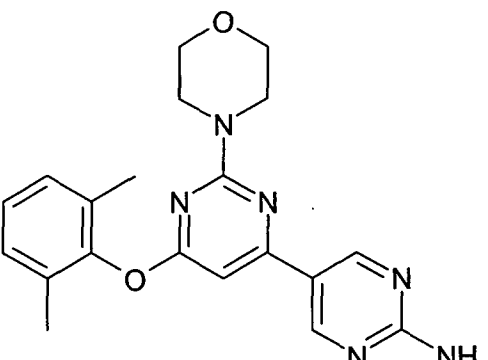
9		6-(4-Benzenesulfonyl-piperazin-1-yl)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine
10		2-Morpholin-4-yl-6-phenoxy-[4,5']bipyrimidinyl-2'-ylamine
11		[4-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-piperazin-1-yl]-morpholin-4-yl-methanone
12		N-[4-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-phenyl]-methanesulfonamide

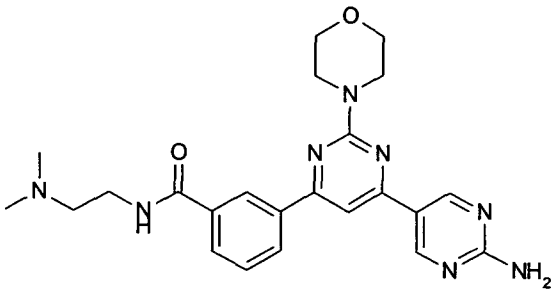
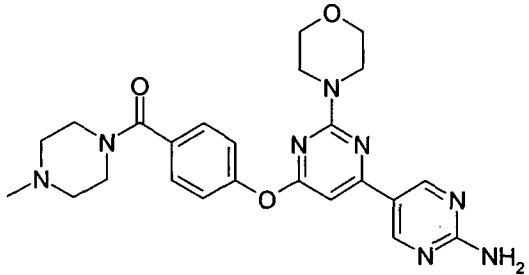
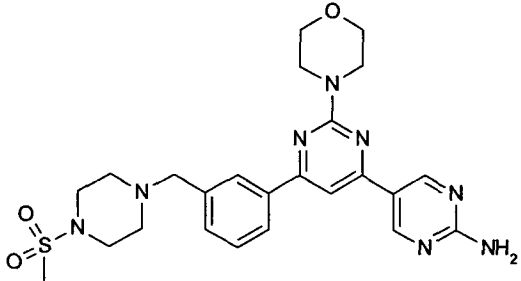
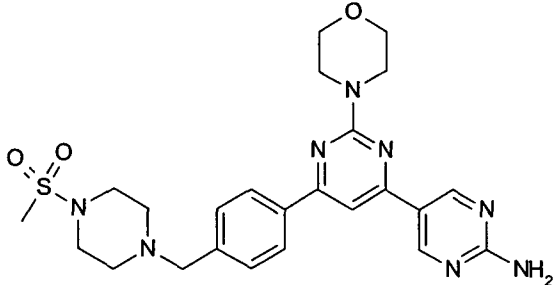
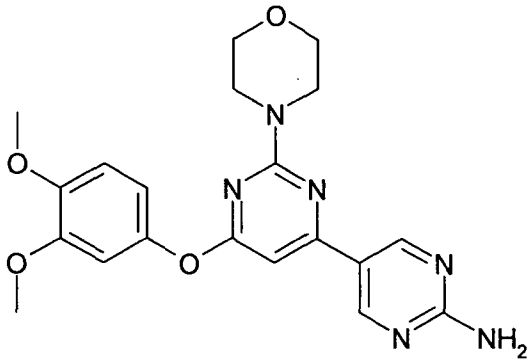
13		N-[4-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidin-6-yl)-phenyl]-acetamide
14		3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidin-6-yl)-benzamide
15		2-Morpholin-4-yl-N-6-pyridin-2-ylmethyl-[4,5']bipyrimidin-6,2'-diamine
16		N-6-Benzyl-2-morpholin-4-yl-[4,5']bipyrimidin-6,2'-diamine

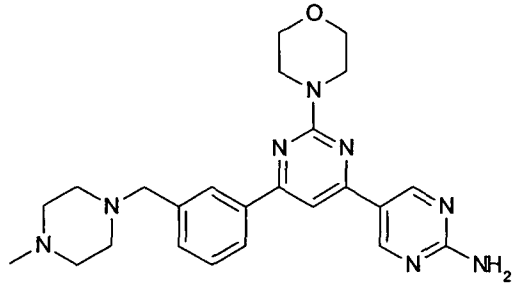
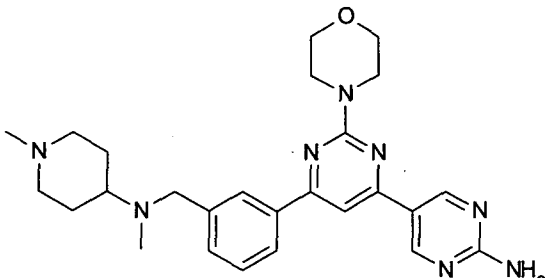
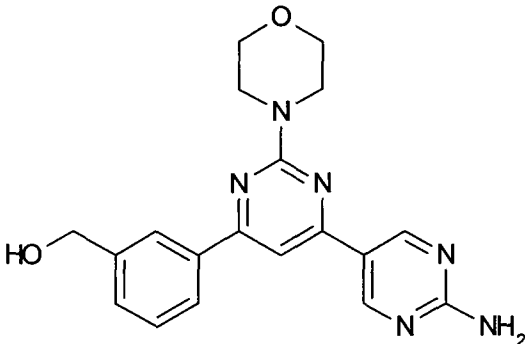
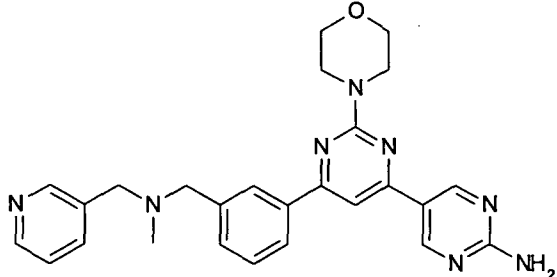
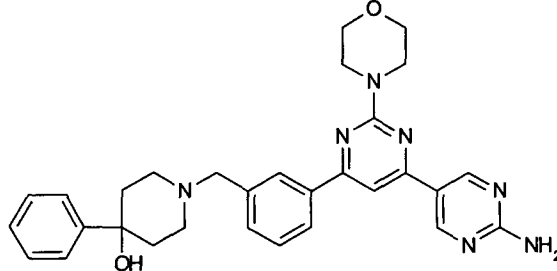
17		3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-N-methyl-benzamide
18		N-6-Benzyl-N-6-methyl-2-morpholin-4-yl-[4,5']bipyrimidinyl-6,2'-diamine
19		[3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-phenyl]-(4-methyl-piperazin-1-yl)-methanone
20		2-Morpholin-4-yl-N-6-pyridin-4-ylmethyl-[4,5']bipyrimidinyl-6,2'-diamine

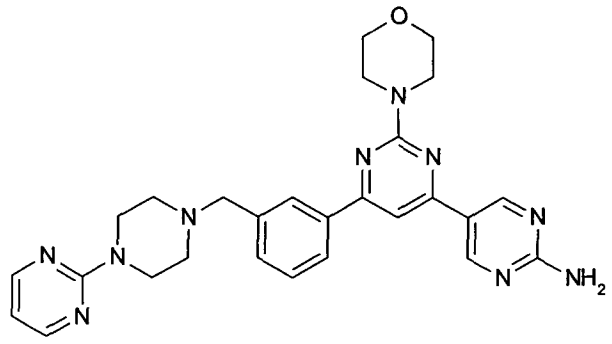
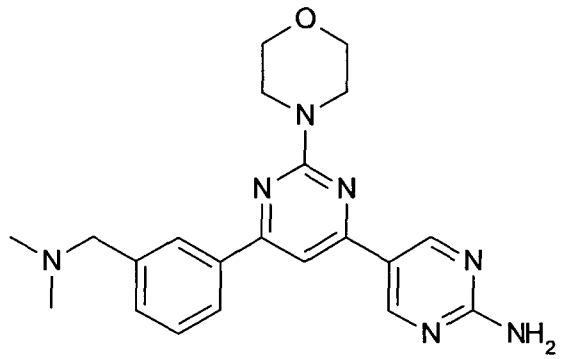
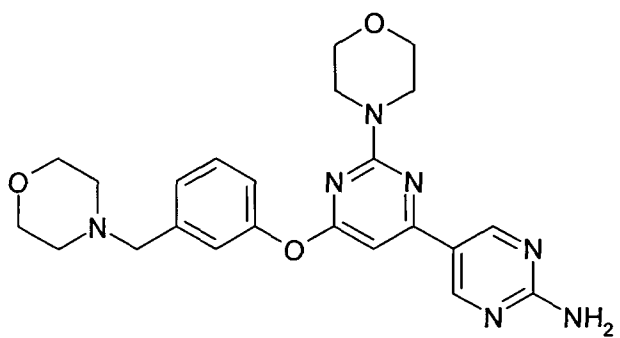
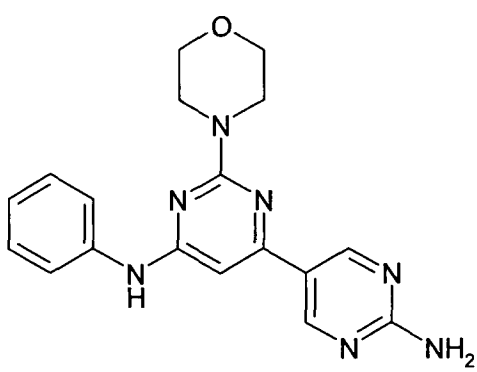
21		1-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-4-phenyl-piperidin-4-ol
23		N-6-[2-(3,4-Dimethoxyphenyl)-ethyl]-N-6-methyl-2-morpholin-4-yl-[4,5']bipyrimidinyl-6,2'-diamine
24		3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-benzenesulfonamide
26		4-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yloxy)-N,N-dimethylbenzamide

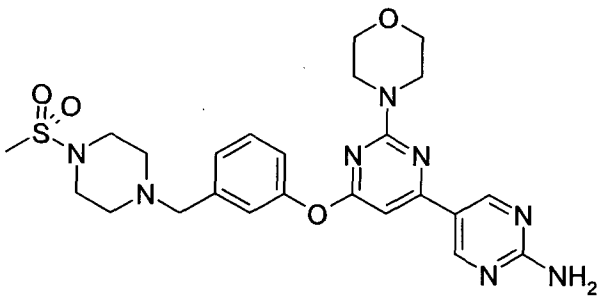
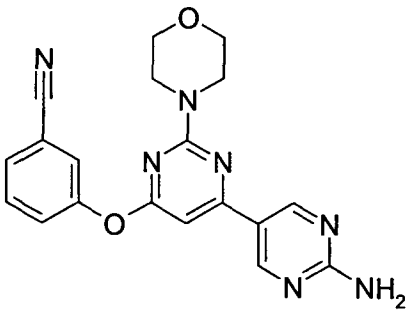
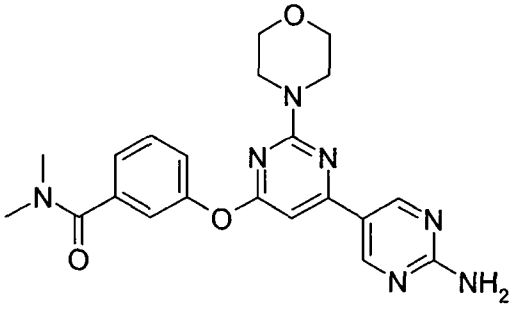
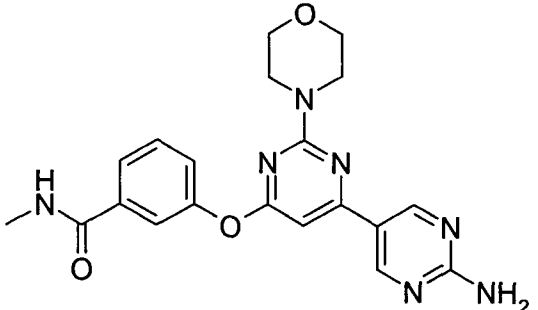
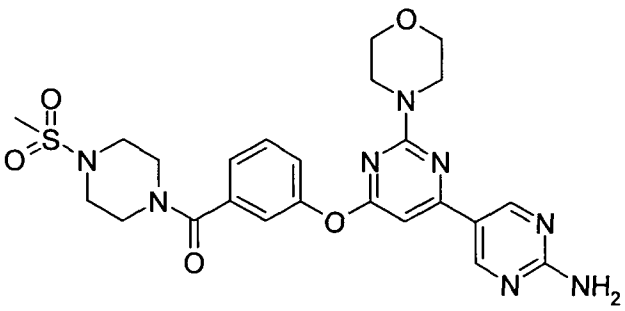
27		4-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yloxy)-N-methyl-benzamide
28		2-Morpholin-4-yl-6-phenyl-[4,5']bipyrimidinyl-2'-ylamine
30		2-Morpholin-4-yl-6-pyridin-4-yl-[4,5']bipyrimidinyl-2'-ylamine
31		2'-Morpholin-4-yl-[5,4';6',5'']terpyrimidin-2-ylamine

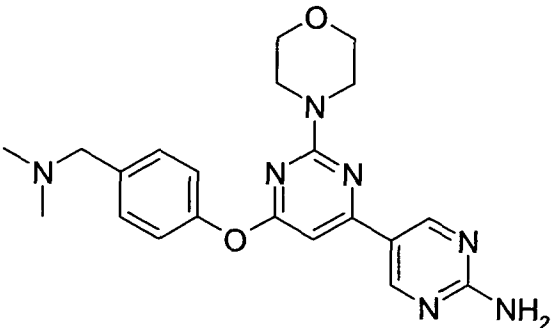
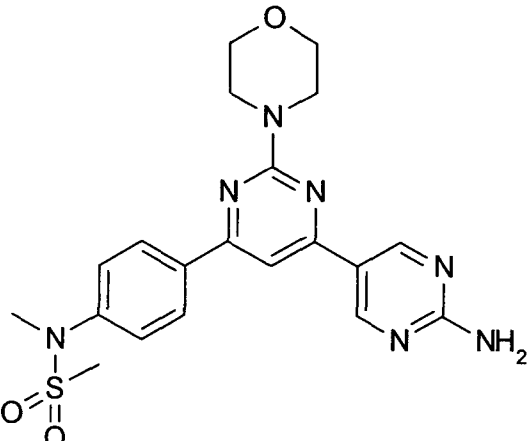
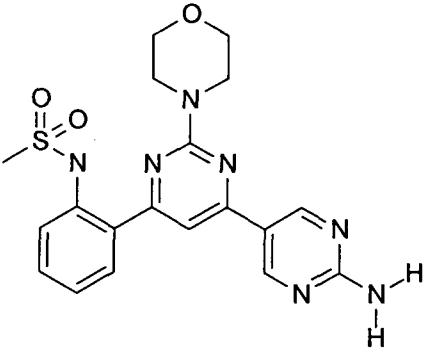
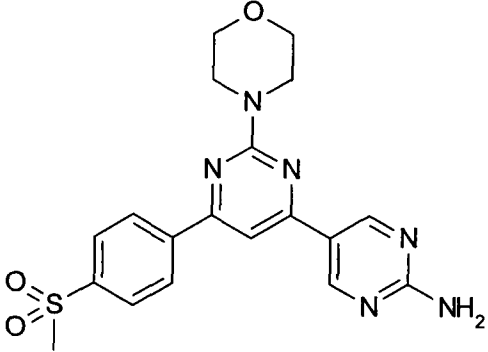
32		3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-ylamino)-benzoic acid
33		6-(4-Benzyl-piperazin-1-yl)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine
34		6-(3,5-Difluoro-phenoxy)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine
35		6-(2,6-Dimethyl-phenoxy)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine

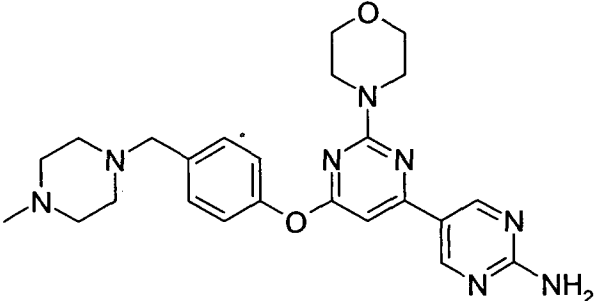
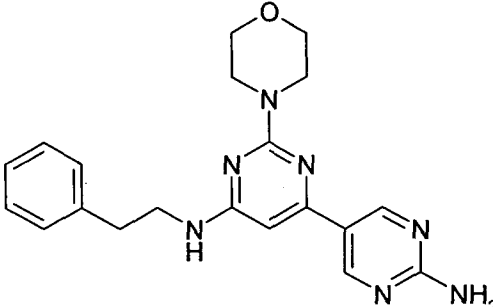
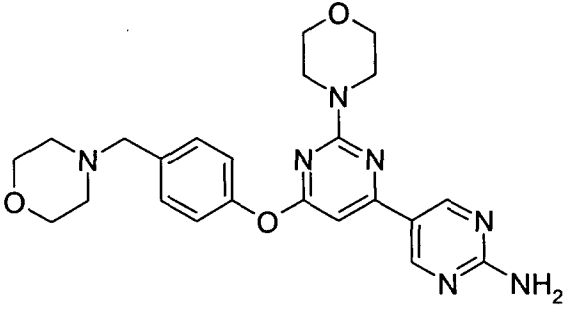
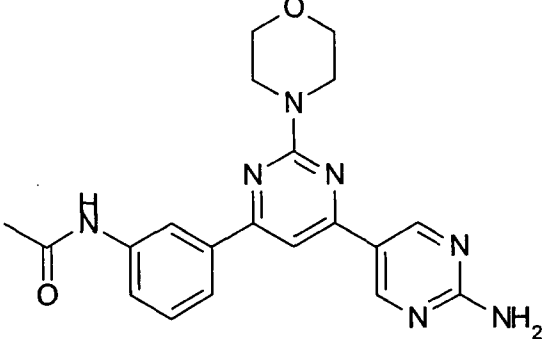
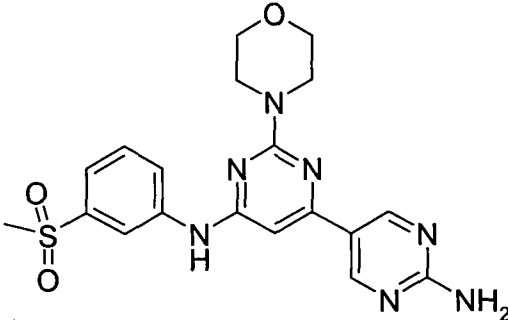
36		3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-N-(2-dimethylamino-ethyl)-benzamide
37		[4-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yloxy)-phenyl]-(4-methylpiperazin-1-yl)-methanone
38		6-[3-(4-Methanesulfonylpiperazin-1-ylmethyl)-phenyl]-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine
39		6-[4-(4-Methanesulfonylpiperazin-1-ylmethyl)-phenyl]-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine
40		6-(3,4-Dimethoxy-phenoxy)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine

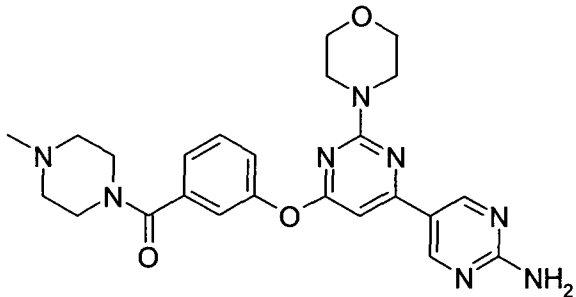
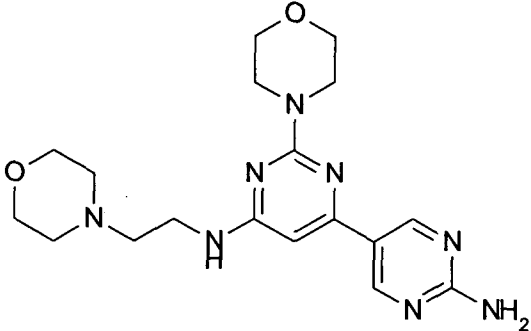
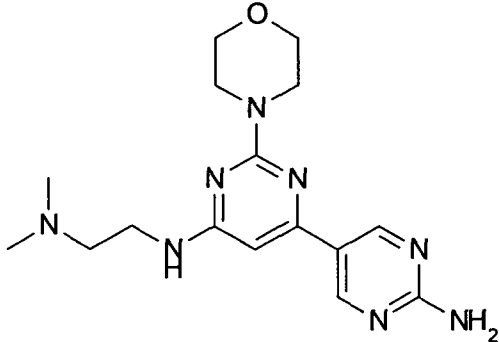
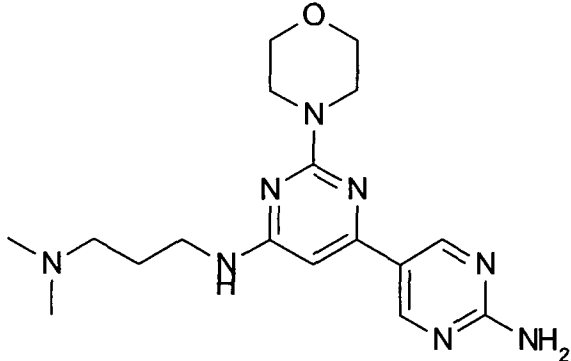
41		6-[3-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine
42		6-(3-([Methyl-(1-methyl-piperidin-4-yl)-amino]-methyl)-phenyl)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine
43		[3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-phenyl]-methanol
44		6-{3-[(Methyl-pyridin-3-ylmethyl-amino)-methyl]-phenyl}-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine
45		1-[3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-benzyl]-4-phenylpiperidin-4-ol

46		2-Morpholin-4-yl-6-[3-(4-pyrimidin-2-yl-piperazin-1-ylmethyl)-phenyl]-[4,5']bipyrimidinyl-2'-ylamine
47		6-(3-Dimethylaminomethyl-phenyl)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine
48		2-Morpholin-4-yl-6-(3-morpholin-4-ylmethyl-phenoxy)-[4,5']bipyrimidinyl-2'-ylamine
49		2-Morpholin-4-yl-N-6-phenyl-[4,5']bipyrimidinyl-6,2'-diamine

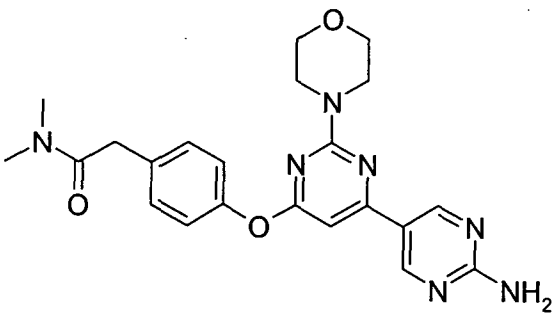
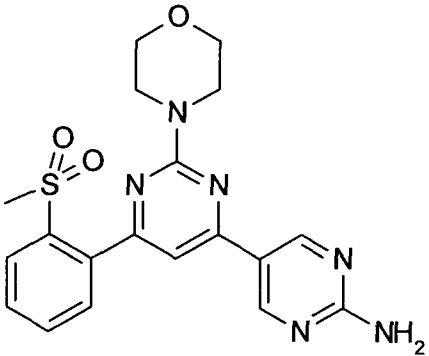
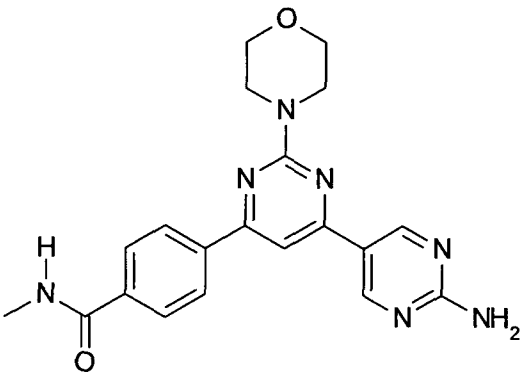
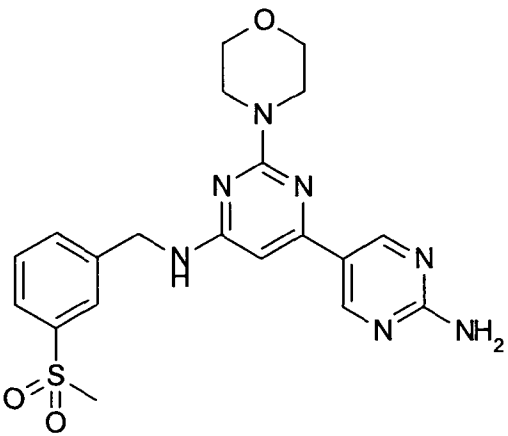
50		6-[3-(4-Methanesulfonyl-piperazin-1-ylmethyl)-phenoxy]-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine
51		3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yloxy)-benzonitrile
52		3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yloxy)-N,N-dimethyl-benzamide
53		3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yloxy)-N-methyl-benzamide
54		[3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yloxy)-phenyl]-(4-methanesulfonyl-piperazin-1-yl)-methanone

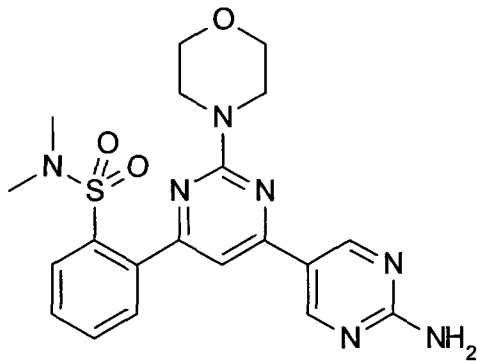
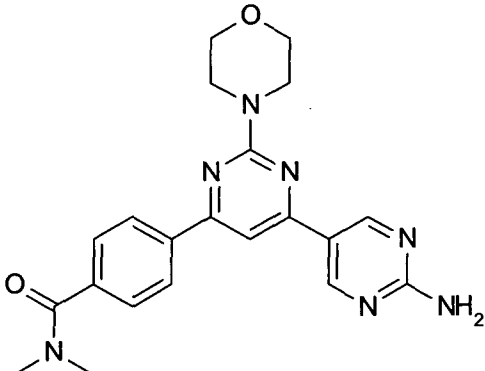
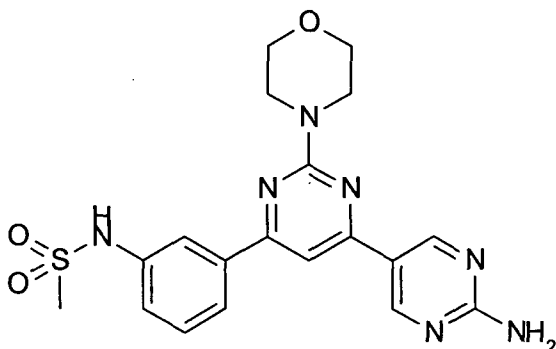
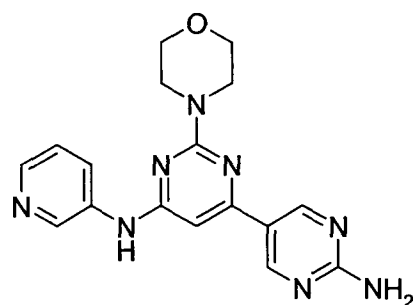
55		6-(4-Dimethylaminomethylphenoxy)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine
56		N-[4-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-phenyl]-N-methylmethanesulfonamide
57		N-[2-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-phenyl]-methanesulfonamide
58		6-(4-Methanesulfonylphenyl)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine

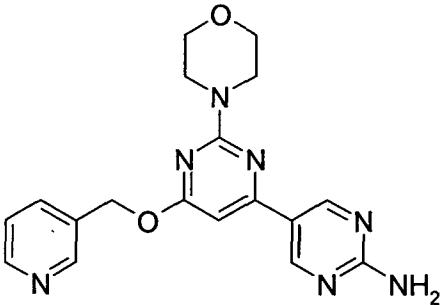
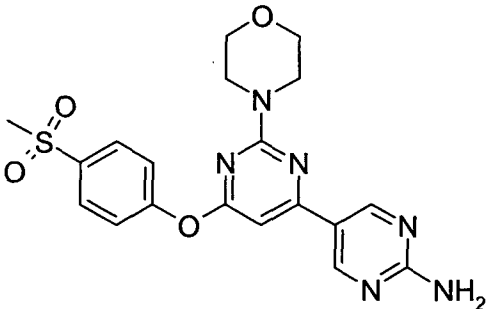
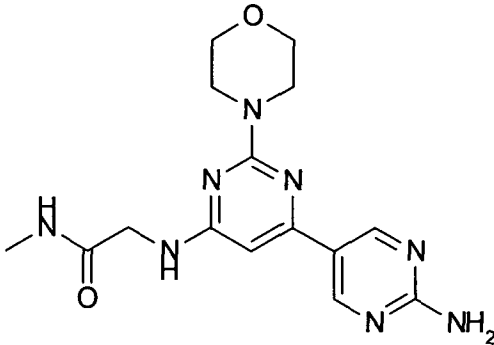
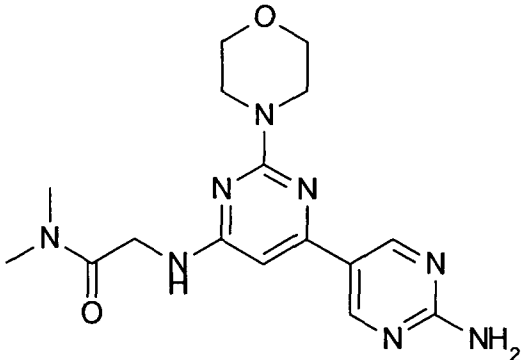
59		6-[4-(4-Methyl-piperazin-1-ylmethyl)-phenoxy]-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine
60		2-Morpholin-4-yl-N-6-phenethyl-[4,5']bipyrimidinyl-6,2'-diamine
61		2-Morpholin-4-yl-6-(4-morpholin-4-ylmethyl-phenoxy)-[4,5']bipyrimidinyl-2'-ylamine
62		N-[3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-phenyl]-acetamide
63		N-6-(3-Methanesulfonyl-phenyl)-2-morpholin-4-yl-[4,5']bipyrimidinyl-6,2'-diamine

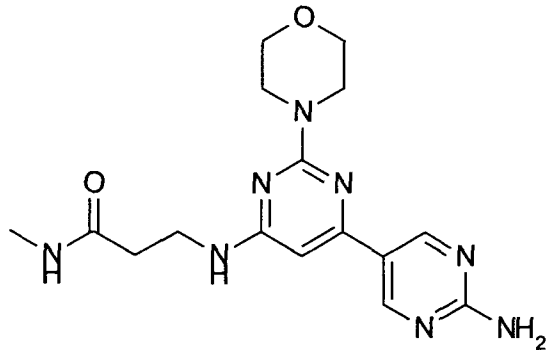
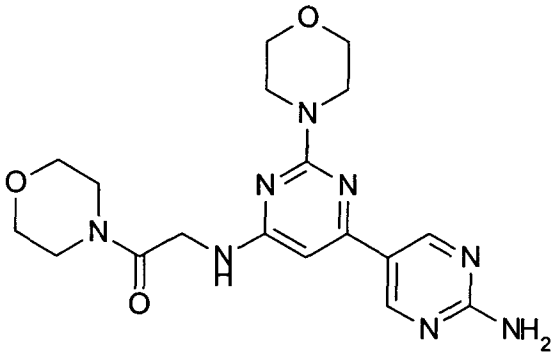
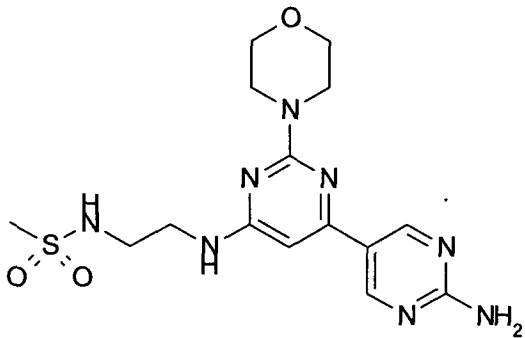
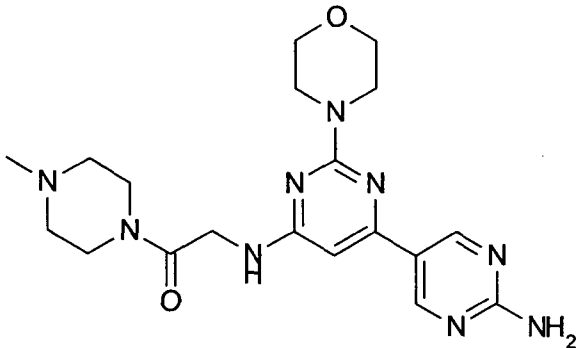
64		[3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yloxy)-phenyl]-(4-methyl-piperazin-1-yl)-methanone
65		2-Morpholin-4-yl-N-6-(2-morpholin-4-yl-ethyl)-[4,5']bipyrimidinyl-6,2'-diamine
66		N-6-(2-Dimethylamino-ethyl)-2-morpholin-4-yl-[4,5']bipyrimidinyl-6,2'-diamine
67		N-6-(3-Dimethylamino-propyl)-2-morpholin-4-yl-[4,5']bipyrimidinyl-6,2'-diamine

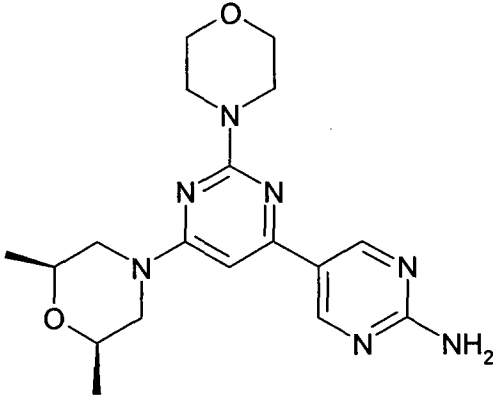
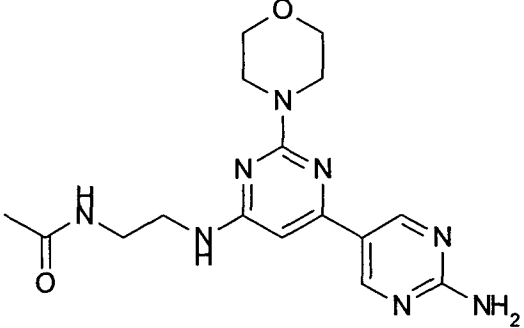
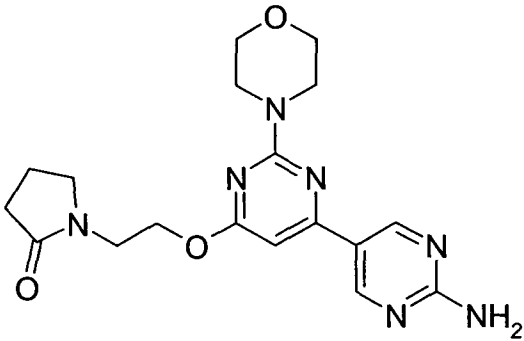
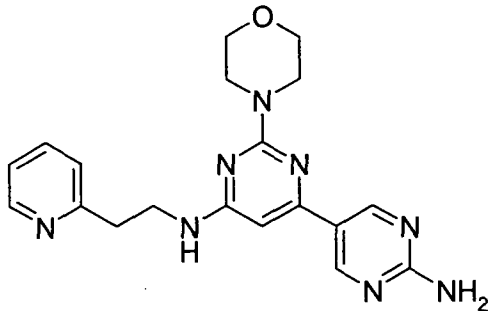
69		N-6,N-6-Bis-(2-methoxy-ethyl)-2-morpholin-4-yl-[4,5']bipyrimidinyl-6,2'-diamine
70		N-6-(3-Fluoro-benzyl)-2-morpholin-4-yl-[4,5']bipyrimidinyl-6,2'-diamine
71		6-[4-(4-Methanesulfonyl-piperazin-1-ylmethyl)-phenoxy]-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine
72		6-Benzyloxy-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine

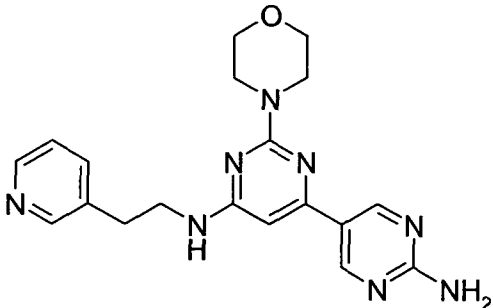
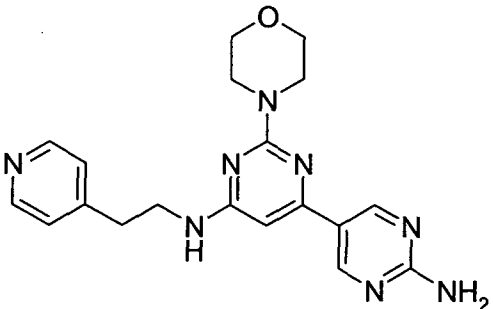
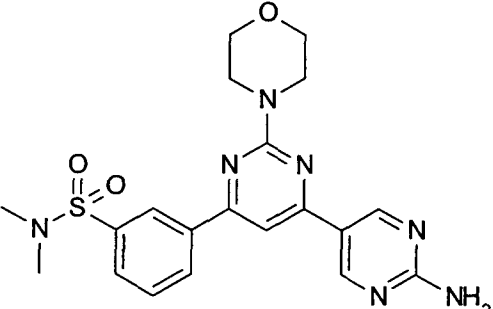
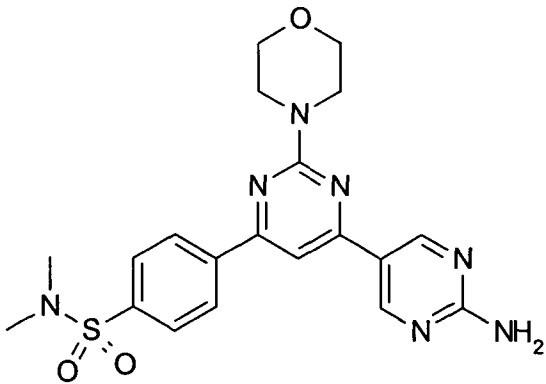
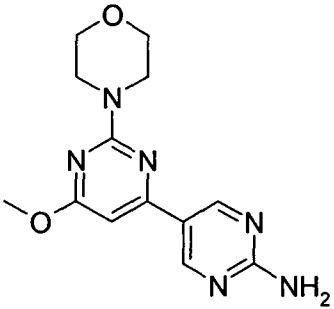
73		2-[4-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yloxy)-phenyl]-N,N-dimethyl-acetamide
74		6-(2-Methanesulfonyl-phenyl)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine
75		4-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-N-methyl-benzamide
76		N-6-(3-Methanesulfonyl-benzyl)-2-morpholin-4-yl-[4,5']bipyrimidinyl-6,2'-diamine

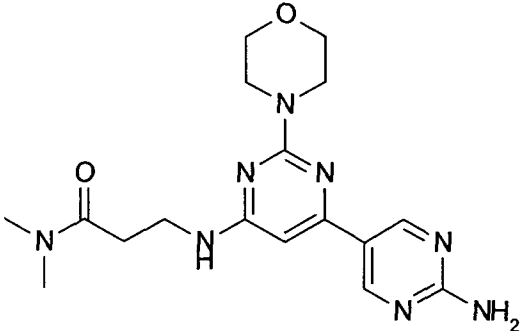
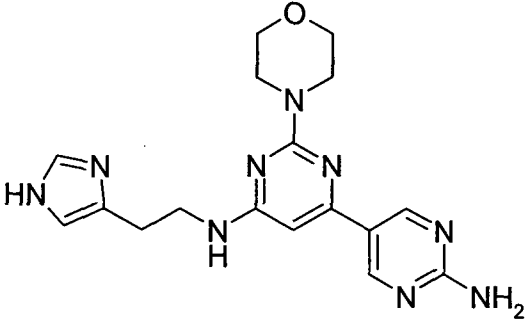
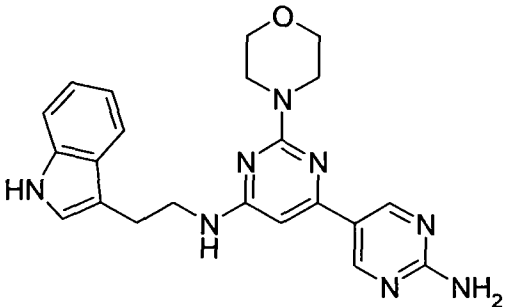
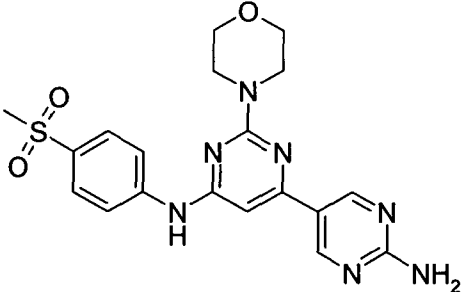
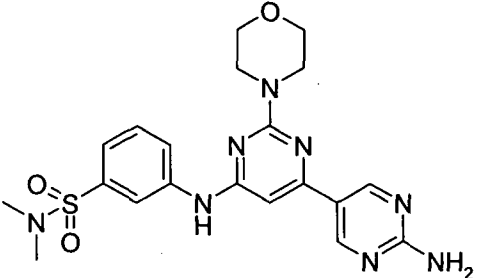
77		2-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-N,N-dimethylbenzenesulfonamide
78		4-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-N,N-dimethylbenzamide
79		N-[3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-phenyl]-methanesulfonamide
80		2-Morpholin-4-yl-N-6-pyridin-3-yl-[4,5']bipyrimidinyl-6,2'-diamine

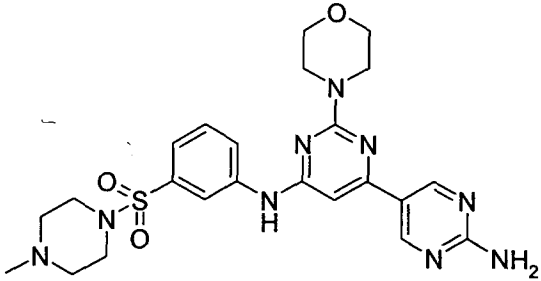
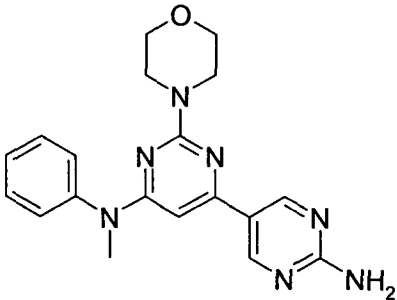
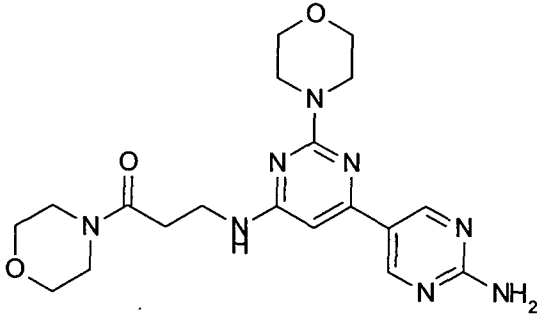
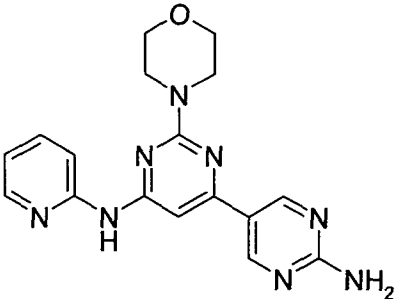
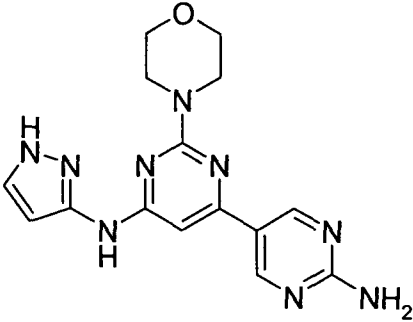
81		2-Morpholin-4-yl-6-(pyridin-3-ylmethoxy)-[4,5']bipyrimidinyl-2'-ylamine
82		6-(4-Methanesulfonylphenoxy)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine
83		2-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-ylamino)-N-methylacetamide
84		2-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-ylamino)-N,N-dimethylacetamide

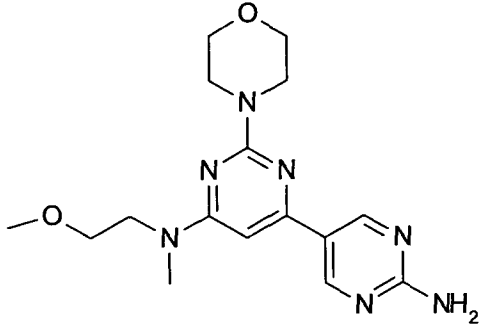
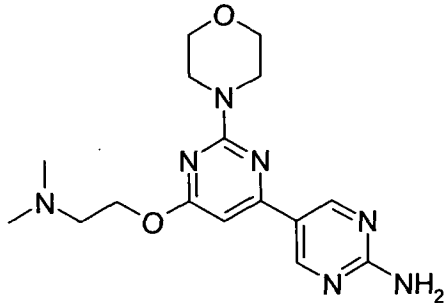
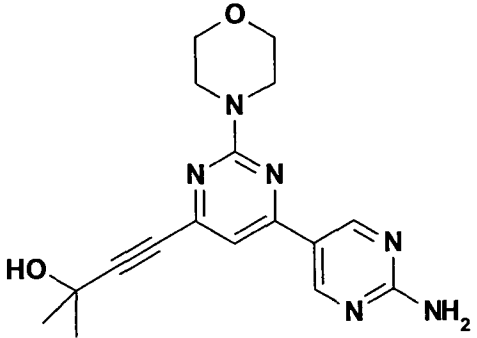
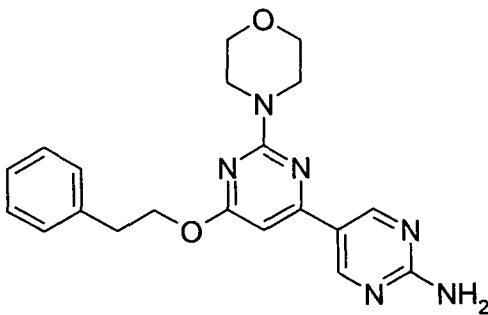
85		3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-ylamino)-N-methylpropionamide
86		2-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-ylamino)-1-morpholin-4-ylethanone
87		N-[2-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-ylamino)-ethyl]-methanesulfonamide
88		2-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-ylamino)-1-(4-methylpiperazin-1-yl)ethanone

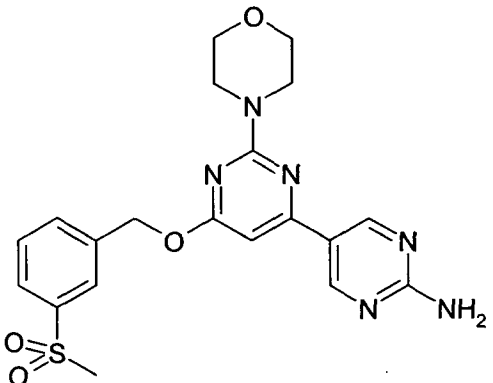
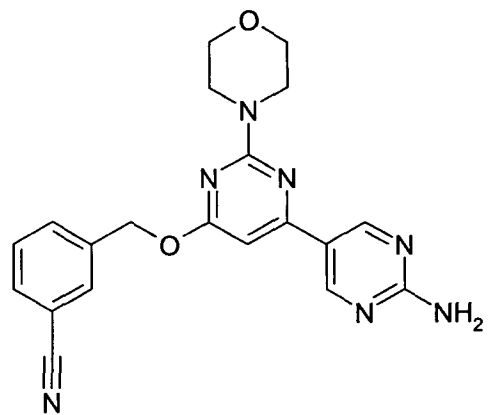
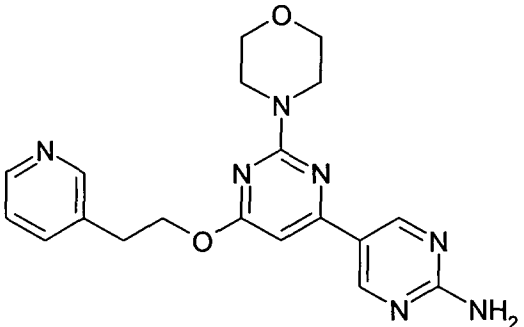
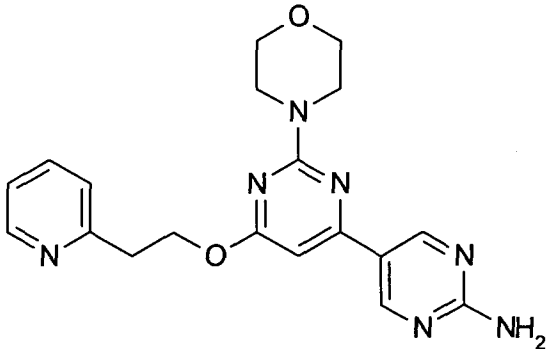
89		6-((2R,6S)-2,6-Dimethyl-morpholin-4-yl)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine
90		N-[2-(2'-Amino-2-morpholin-4-yl)-[4,5']bipyrimidinyl-6-ylamino)-ethyl]-acetamide
91		1-[2-(2'-Amino-2-morpholin-4-yl)-[4,5']bipyrimidinyl-6-yloxy)-ethyl]-pyrrolidin-2-one
92		2-Morpholin-4-yl-N-6-(2-pyridin-2-yl-ethyl)-[4,5']bipyrimidinyl-6,2'-diamine

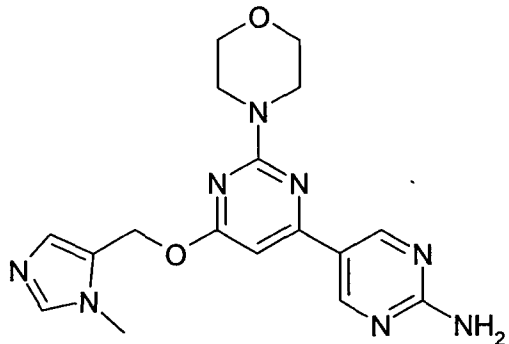
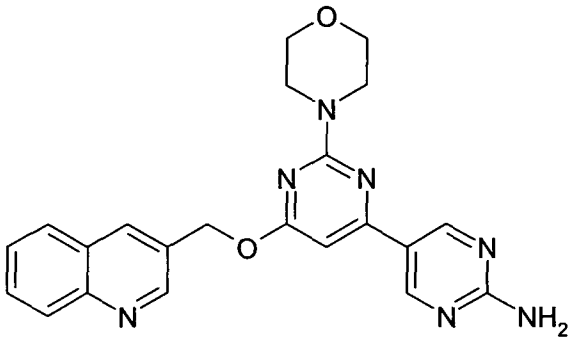
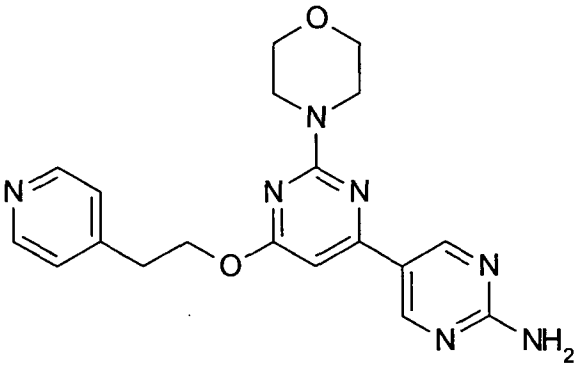
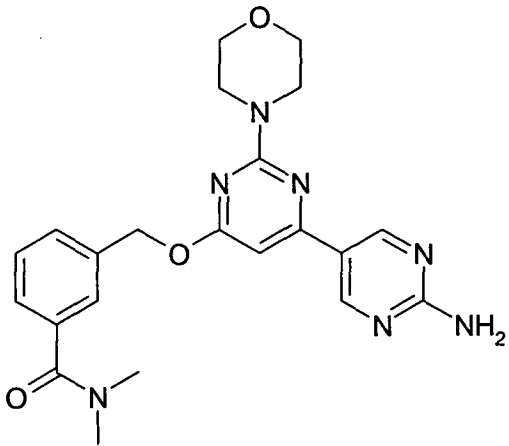
93		2-Morpholin-4-yl-N-6-(2-pyridin-3-yl-ethyl)-[4,5']bipyrimidinyl-6,2'-diamine
94		2-Morpholin-4-yl-N-6-(2-pyridin-4-yl-ethyl)-[4,5']bipyrimidinyl-6,2'-diamine
96		3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-N,N-dimethylbenzenesulfonamide
97		4-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-N,N-dimethylbenzenesulfonamide
98		6-Methoxy-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine

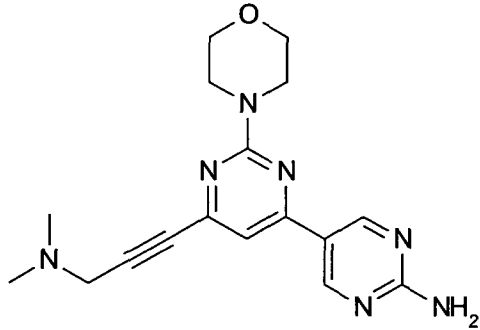
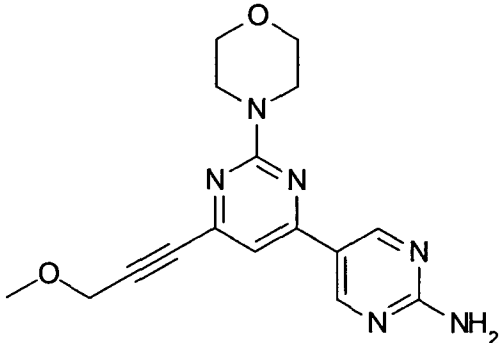
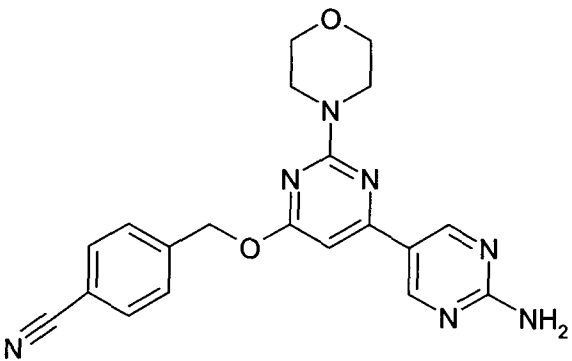
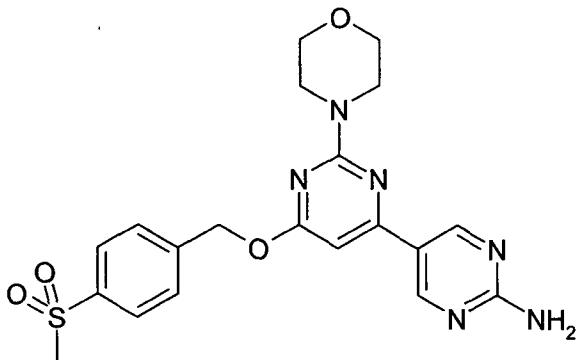
99		3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-ylamino)-N,N-dimethylpropionamide
101		N-6-[2-(1H-Imidazol-4-yl)-ethyl]-2-morpholin-4-yl-[4,5']bipyrimidinyl-6,2'-diamine
102		N-6-[2-(1H-Indol-3-yl)-ethyl]-2-morpholin-4-yl-[4,5']bipyrimidinyl-6,2'-diamine
103		N-6-(4-Methanesulfonyl-phenyl)-2-morpholin-4-yl-[4,5']bipyrimidinyl-6,2'-diamine
104		3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-ylamino)-N,N-dimethylbenzenesulfonamide

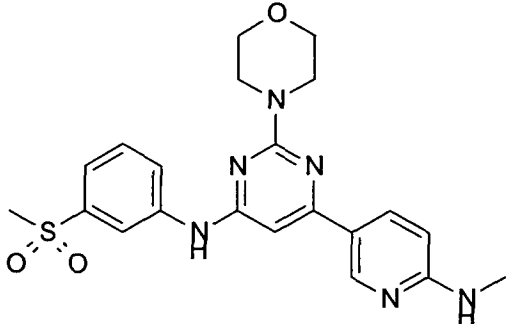
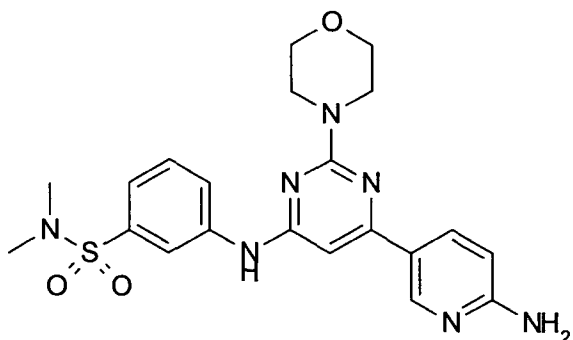
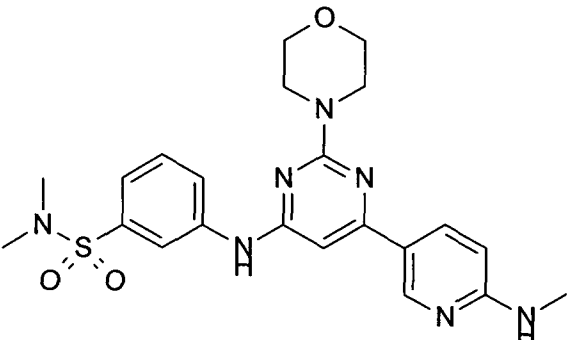
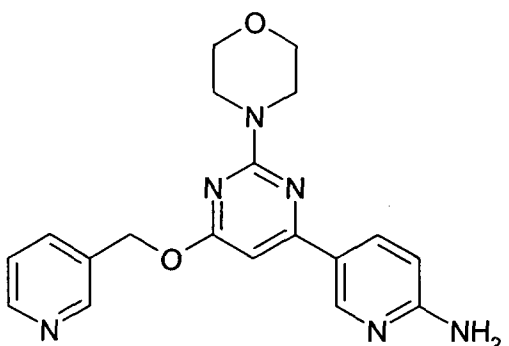
105		N-6-[3-(4-Methyl-piperazine-1-sulfonyl)-phenyl]-2-morpholin-4-yl-[4,5']bipyrimidinyl-6,2'-diamine
106		N-6-Methyl-2-morpholin-4-yl-N-6-phenyl-[4,5']bipyrimidinyl-6,2'-diamine
107		3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-ylamino)-1-morpholin-4-yl-propan-1-one
109		2-Morpholin-4-yl-N-6-pyridin-2-yl-[4,5']bipyrimidinyl-6,2'-diamine
110		2-Morpholin-4-yl-N-6-(1H-pyrazol-3-yl)-[4,5']bipyrimidinyl-6,2'-diamine

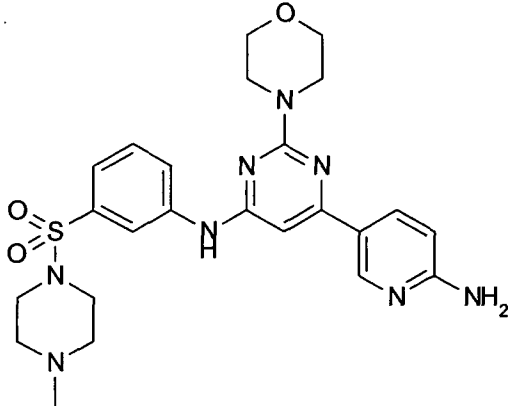
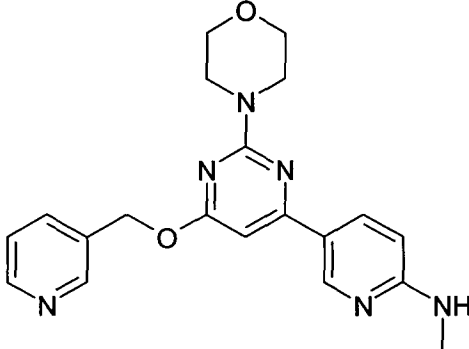
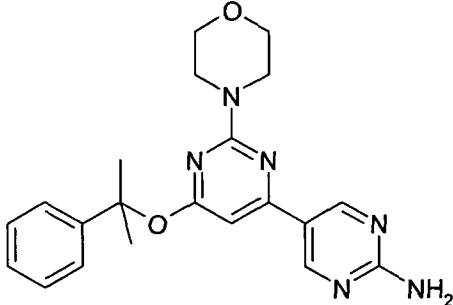
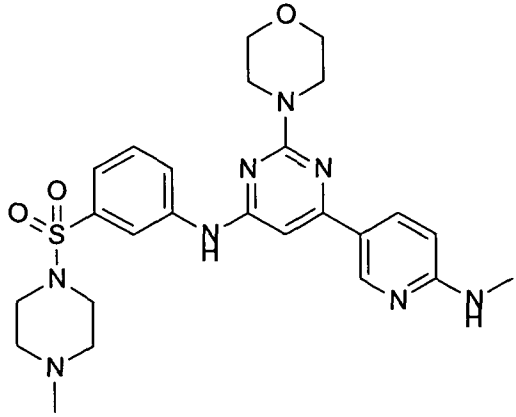
111		N-6-(2-Methoxy-ethyl)-N-6-methyl-2-morpholin-4-yl-[4,5']bipyrimidinyl-6,2'-diamine
112		6-(2-Dimethylamino-ethoxy)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine
114		4-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-2-methyl-but-3-yn-2-ol
115		2-Morpholin-4-yl-6-phenethyloxy-[4,5']bipyrimidinyl-2'-ylamine

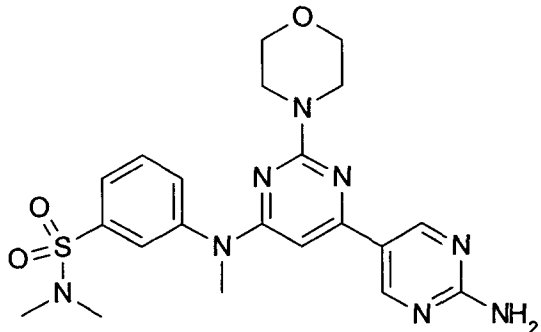
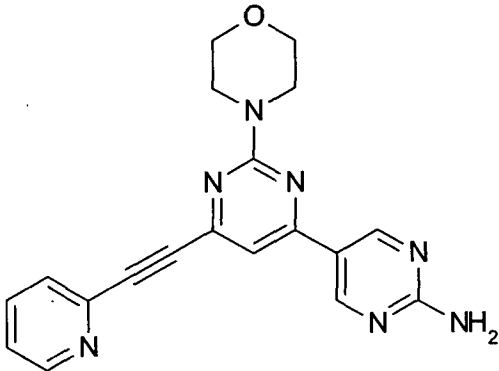
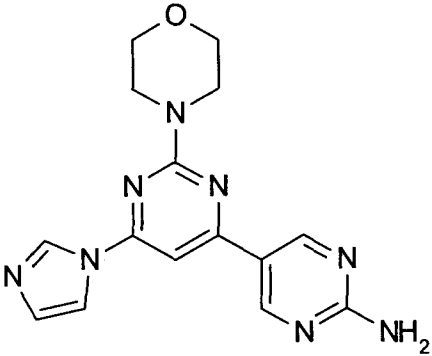
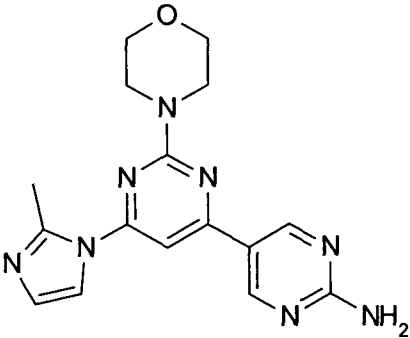
116		6-(3-Methanesulfonylbenzyloxy)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine
117		3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yloxymethyl)-benzonitrile
118		2-Morpholin-4-yl-6-(2-pyridin-3-yl-ethoxy)-[4,5']bipyrimidinyl-2'-ylamine
119		2-Morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-[4,5']bipyrimidinyl-2'-ylamine

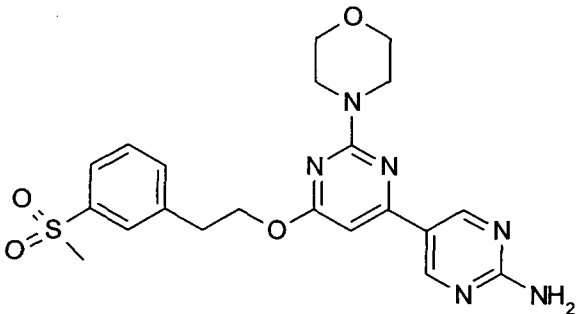
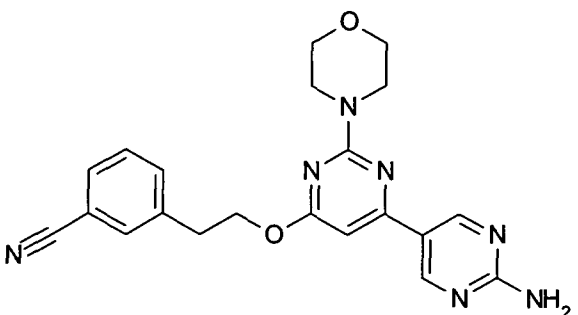
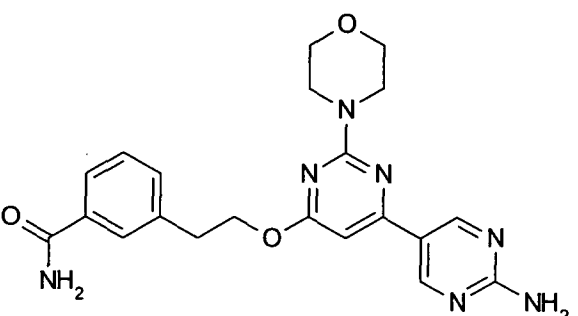
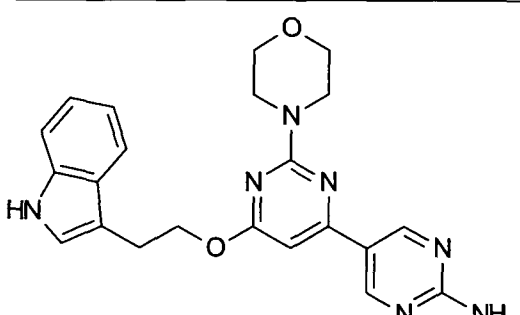
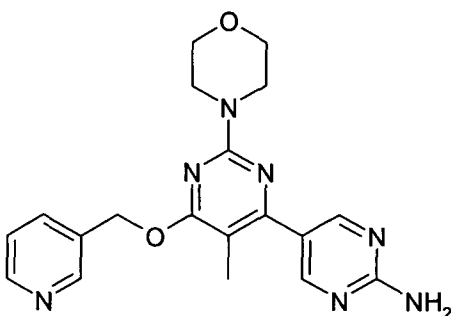
120		6-(3-Methyl-3H-imidazol-4-ylmethoxy)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine
121		2-Morpholin-4-yl-6-(quinolin-3-ylmethoxy)-[4,5']bipyrimidinyl-2'-ylamine
122		2-Morpholin-4-yl-6-(2-pyridin-4-yl-ethoxy)-[4,5']bipyrimidinyl-2'-ylamine
123		3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-ylloxymethyl)-N,N-dimethylbenzamide

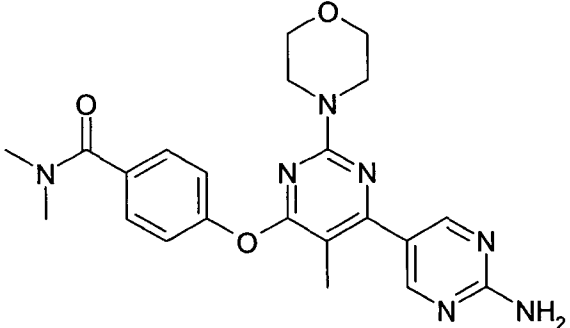
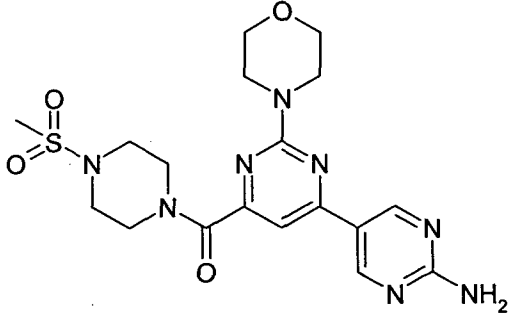
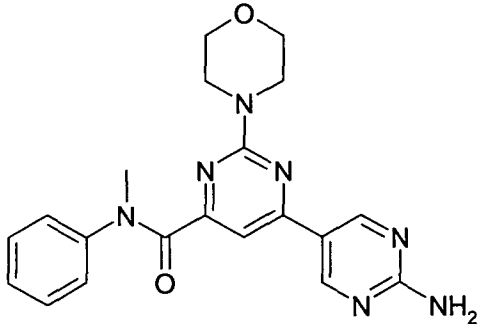
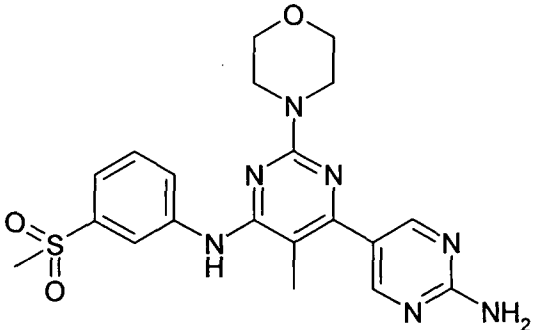
124		6-(3-Dimethylamino-prop-1-ynyl)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine
125		6-(3-Methoxy-prop-1-ynyl)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine
126		4-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yloxymethyl)-benzonitrile
127		6-(4-Methanesulfonyl-benzyloxy)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine

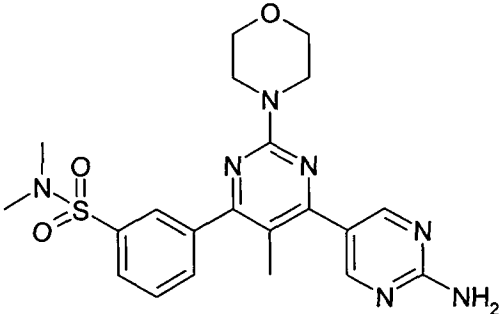
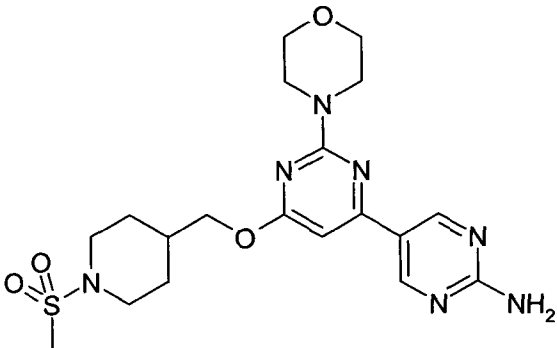
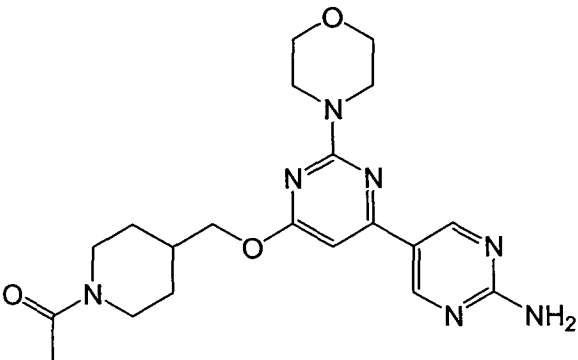
129		(3-Methanesulfonyl-phenyl)-[6-(6-methylamino-pyridin-3-yl)-2-morpholin-4-yl-pyrimidin-4-yl]-amine
130		3-[6-(6-Amino-pyridin-3-yl)-2-morpholin-4-yl-pyrimidin-4-ylamino]-N,N-dimethylbenzenesulfonamide
131		N,N-Dimethyl-3-[6-(6-methylamino-pyridin-3-yl)-2-morpholin-4-yl-pyrimidin-4-ylamino]-benzenesulfonamide
132		5-[2-Morpholin-4-yl-6-(pyridin-3-ylmethoxy)-pyrimidin-4-yl]-pyridin-2-ylamine

133		6-(6-Amino-pyridin-3-yl)-2-morpholin-4-yl-pyrimidin-4-yl]-[3-(4-methyl-piperazine-1-sulfonyl)-phenyl]-amine
134		Methyl-{5-[2-morpholin-4-yl-6-(pyridin-3-ylmethoxy)-pyrimidin-4-yl]-pyridin-2-yl}-amine
135		6-(1-Methyl-1-phenyl-ethoxy)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine
136		[6-(6-Methylamino-pyridin-3-yl)-2-morpholin-4-yl-pyrimidin-4-yl]-[3-(4-methyl-piperazine-1-sulfonyl)-phenyl]-amine

137		3-[(2'-Amino-2-morpholin-4-yl)-[4,5']bipyrimidinyl-6-yl)-methyl-amino]-N,N-dimethyl-benzenesulfonamide
138		2-Morpholin-4-yl-6-pyridin-2-ylethynyl-[4,5']bipyrimidinyl-2'-ylamine
139		6-Imidazol-1-yl-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine
140		6-(2-Methyl-imidazol-1-yl)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine

141		6-[2-(3-Methanesulfonyl-phenyl)-ethoxy]-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine
142		3-[2-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yloxy)-ethyl]-benzonitrile
143		3-[2-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yloxy)-ethyl]-benzamide
144		6-[2-(1H-Indol-3-yl)-ethoxy]-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine
145		5-Methyl-2-morpholin-4-yl-6-(pyridin-3-ylmethoxy)-[4,5']bipyrimidinyl-2'-ylamine

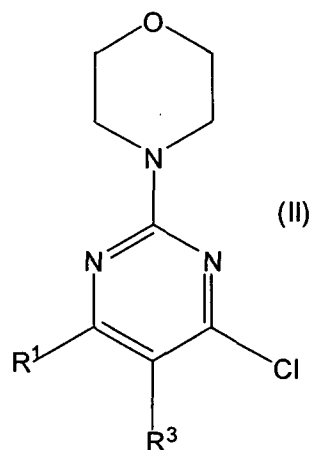
146		4-(2'-Amino-5-methyl-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yloxy)-N,N-dimethyl-benzamide
147		(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-(4-methanesulfonyl-piperazin-1-yl)-methanone
148		2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-carboxylic acid methyl-phenyl-amide
150		N-6-(3-Methanesulfonyl-phenyl)-5-methyl-2-morpholin-4-yl-[4,5']bipyrimidinyl-6,2'-diamine

151		3-(2'-Amino-5-methyl-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-N,N-dimethylbenzenesulfonamide
152		6-(1-Methanesulfonyl-piperidin-4-ylmethoxy)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine
153		1-[4-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yloxymethyl)-piperidin-1-yl]-ethanone

and the pharmaceutically acceptable salts thereof.

Morpholino pyrimidines of the invention may be produced by a process which comprises a palladium-mediated (Suzuki-type) cross-coupling reaction as the last step.

- 5 Thus, a morpholino pyrimidine of formula (I) may be produced by a process which comprises treating a compound of formula (II):

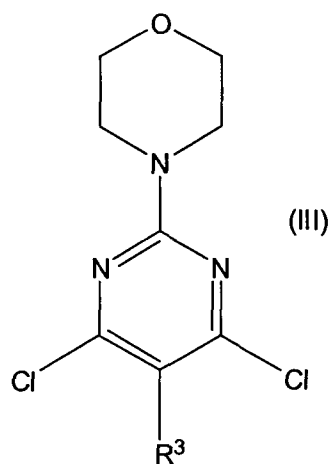


wherein R^1 and R^3 are as defined above, with a boronic acid or ester thereof of formula $R^2B(OR^{15})_2$, in which R^2 is as defined above and each R^{15} is H or C_1-C_6 alkyl or the two groups OR^{15} form, together with the boron atom to which they are attached, a

- 5 pinacolato boronate ester group, in the presence of a suitable base and a Pd catalyst. A suitable solvent is acetonitrile. A suitable temperature range for this reaction is room temperature to 80-180°C. This reaction may be performed thermally or in a microwave reactor.

10 The intermediates of formula (II) are known compounds or may be synthesised by routine synthetic chemical techniques.

For instance, a compound of formula (II) wherein R^1 is a group $-Y-R^6$ in which Y is $-O-(CR_2)_n-$ and R^6 is as defined above may be produced by a process which comprises treating a compound of the following formula (III):



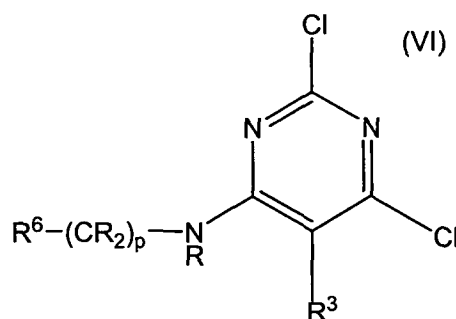
- 15 wherein R^3 is as defined above, with a compound of formula $HO-(CR_2)_n-R^6$ in the presence of a base. A suitable base is sodium hydride or potassium carbonate. A

suitable solvent is N,N-dimethylformamide or acetonitrile. A suitable temperature range for this reaction is room temperature to 100°C.

A compound of formula (II) wherein R^1 is a group $-Y-R^6$ in which Y is $-NR-(CR_2)_n-$ may be prepared by treating a compound of formula (III) as defined above
 5 with an amine of formula $HNR-(CR_2)_n-R^6$ in the presence of a base. A suitable base is sodium hydride or potassium carbonate. A suitable solvent is N,N-dimethylformamide, tetrahydrofuran or acetonitrile. A suitable temperature range for this reaction is room temperature to 100°C.

A compound of formula (II) wherein R^1 is a group $-Y-R^6$ in which Y is a direct
 10 bond and R^6 is an unsaturated 5- to 12-membered carbocyclic or heterocyclic ring which is aromatic, may be prepared by treating a compound of formula (III) as defined above with a boronic acid or ester thereof of formula $R^1B(OR^{15})_2$, in which R^1 is as defined above and each R^{15} is H or C_1-C_6 alkyl or the two groups OR^{15} form, together with the boron atom to which they are attached, a pinacolato boronate ester group, in the
 15 presence of a suitable base and a Pd catalyst. A suitable solvent is acetonitrile. A suitable temperature range for this reaction is room temperature to 80-180°C. This reaction may be performed thermally or in a microwave reactor.

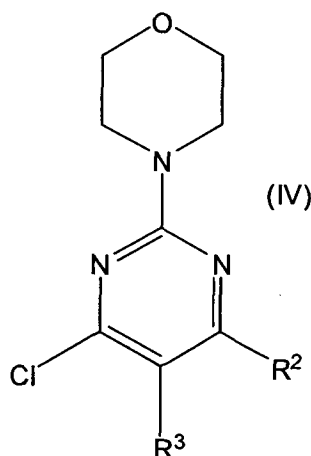
A compound of formula (II) wherein R^1 is a group $-Y-R^6$ in which Y is a linker
 group $-(CR_2)_p-NR-(CR_2)_n-$ in which p is 0 may be produced by a process which
 20 comprises treating a compound of formula (VI):



with morpholine in the presence of a solvent.

A compound of formula (VI) may be produced by a process which comprises
 25 treating 2,4,6-trichloropyrimidine with an amine of formula $R^6-(CR_2)_p-NRH$ in the presence of a base in an appropriate solvent.

A morpholino pyrimidine of formula (I) may also be produced by a process which comprises treating a compound of formula (IV):

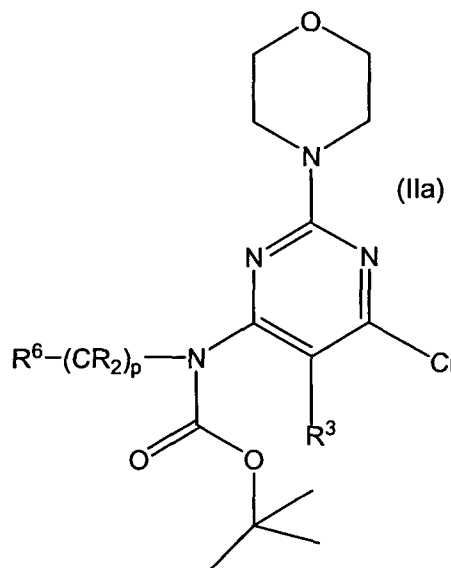


wherein R^2 and R^3 are as defined above, with a boronic acid or ester thereof of formula $R^1B(OR^{15})_2$, in which R^1 is $-Y-R^6$ in which Y is a direct bond and R^6 is a 5- to 12-membered aryl or heteroaryl group and each R^{15} is H or C_1-C_6 alkyl or the two groups OR^{15} form, together with the boron atom to which they are attached, a pinacolato boronate ester group, in the presence of a suitable base and a Pd catalyst. A suitable solvent is acetonitrile. A suitable temperature range for this reaction is room temperature to 80-180°C. This reaction may be performed thermally or in a microwave reactor.

A morpholino pyrimidine of formula (I) in which R^1 is a group $-Y-R^6$ wherein Y is an alkynylene group and R^6 is as defined above may be produced by a process which comprises submitting a compound of formula (IV) as defined above to Sonogashira coupling with a compound of formula $HC\equiv C-(CR_2)_n-R^6$ in the presence of a palladium catalyst, a copper (I) cocatalyst and an amine base.

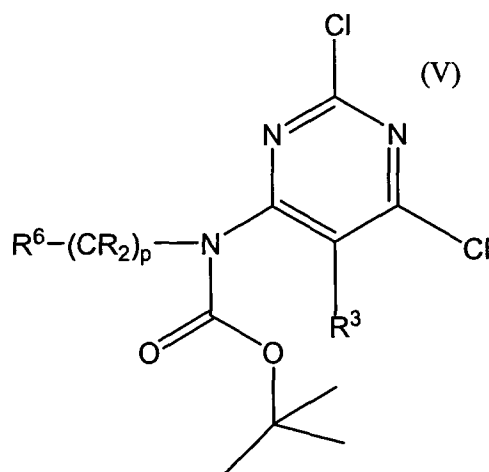
A compound of formula (IV) as defined above may be produced by a process which comprises by treating a compound of formula (III) as defined above with a boronic acid or ester thereof of formula $R^2B(OR^{15})_2$, in which R^2 is as defined above and each R^{15} is H or C_1-C_6 alkyl or the two groups OR^{15} form, together with the boron atom to which they are attached, a pinacolato boronate ester group, in the presence of a suitable base and a Pd catalyst. A suitable solvent is acetonitrile. A suitable temperature range for this reaction is room temperature to 80-180°C. This reaction may be performed thermally or in a microwave reactor.

A compound of formula (I) in which R^1 is a group $-Y-R^6$ in which Y is a linker group $-(CR_2)_p-NH-(CR_2)_n-$ as defined above in which p is 0, may be produced by a process which comprises treating a compound of formula (IIa):



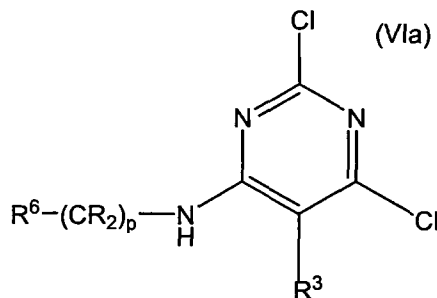
- 5 wherein R^3 , R^6 , R and p are as defined above for formula (I), with a boronic acid or ester thereof of formula $R^2B(OR^{15})_2$, in which R^2 is as defined above and each R^{15} is H or C_1-C_6 alkyl or the two groups OR^{15} form, together with the boron atom to which they are attached, a pinacolato boronate ester group, in the presence of a suitable base and a Pd catalyst. A suitable solvent is acetonitrile. A suitable temperature range for this
- 10 reaction is room temperature to 80-180°C. This reaction may be performed thermally or in a microwave reactor.

A compound of formula (IIa) may be prepared by a process which comprises treating a compound of formula (V):



wherein R^3 , R^6 , R and p are as defined above for formula (I), with morpholine in an appropriate solvent, followed by separation of the two resulting isomeric compounds.

A compound of formula (V) may be prepared by treatment of a compound of formula (VIa):



wherein R^3 , R^6 , R and p are as defined above for formula (I), with di-tert-butyl dicarbonate in an appropriate solvent. A compound of formula (VI) may be prepared by a process which comprises treating 2,4,6-trichloropyrimidine with an amine of formula $R^6-(CR_2)_p-NH_2$ in the presence of a base in an appropriate solvent.

A morpholino pyrimidine of the invention may be converted into a pharmaceutically acceptable salt, and a salt may be converted into the free compound, by conventional methods. Examples of pharmaceutically acceptable salts include salts with inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulphuric acid, nitric acid and phosphoric acid; and organic acids such as methanesulfonic acid, benzenesulphonic acid, formic acid, acetic acid, trifluoroacetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid, tartaric acid, citric acid, ethanesulfonic acid, aspartic acid and glutamic acid. Typically the salt is a mesylate, a hydrochloride, a phosphate, a benzenesulphonate or a sulphate. Most typically the salt is a mesylate or a hydrochloride.

The salts, for instance salts with any of the inorganic or organic acids mentioned above, may be mono-salts, bis-salts or tris-salts. Thus, for example, the mesylate salt may be the mono-mesylate or the bis-mesylate.

The morpholino pyrimidines of the invention and their salts may exist as hydrates or solvates.

Compounds of the present invention have been found in biological tests to be inhibitors of PI3 kinase. In one embodiment the compounds are inhibitors of the p110 α

isoform of PI3 kinase. The compounds may show selectivity for the p110 α isoform over one or more of the other isoforms of PI3 kinase, i.e. selectivity over one or more of the p110 β , p110 δ and p110 γ isoforms.

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. Such abnormal cell growth, function or behaviour is typically 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 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. A human or animal patient suffering from an immune disorder, cancer, cardiovascular disease, viral infection, inflammation, a metabolism/endocrine disorder or a neurological disorders 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.

Diseases and conditions treatable according to the methods of this invention include, but are not limited to, cancer, stroke, diabetes, hepatomegaly, cardiovascular disease, Alzheimer's disease, cystic fibrosis, viral disease, autoimmune diseases, atherosclerosis, restenosis, psoriasis, allergic disorders, inflammation, neurological disorders, a hormone-related disease, conditions associated with organ transplantation, immunodeficiency disorders, destructive bone disorders, proliferative disorders, infectious diseases, conditions associated with cell death, thrombin-induced platelet aggregation, chronic myelogenous leukemia (CML), liver disease, pathologic immune conditions involving T cell activation, and CNS disorders in a patient. In one embodiment, a human patient is treated with a compound of the invention and a pharmaceutically acceptable carrier, adjuvant, or vehicle, wherein said compound is present in an amount to detectably inhibit PI3 kinase activity.

Cancers which can be treated according to the methods of this invention include, but are not limited to, breast, ovary, cervix, prostate, testis, genitourinary tract, esophagus, larynx, glioblastoma, neuroblastoma, stomach, skin, keratoacanthoma, lung, epidermoid carcinoma, large cell carcinoma, non-small cell lung carcinoma (NSCLC),
5 small cell carcinoma, lung adenocarcinoma, bone, colon, adenoma, pancreas, adenocarcinoma, thyroid, follicular carcinoma, undifferentiated carcinoma, papillary carcinoma, seminoma, melanoma, sarcoma, bladder carcinoma, liver carcinoma and biliary passages, kidney carcinoma, myeloid disorders, lymphoid disorders, hairy cells, buccal cavity and pharynx (oral), lip, tongue, mouth, pharynx, small intestine, colon-
10 rectum, large intestine, rectum, brain and central nervous system, Hodgkin's and leukemia.

Cardiovascular diseases which can be treated according to the methods of this invention include, but are not limited to, restenosis, cardiomegaly, atherosclerosis, myocardial infarction, and congestive heart failure.

15 Neurodegenerative disease which can be treated according to the methods of this invention include, but are not limited to, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease, and cerebral ischemia, and neurodegenerative disease caused by traumatic injury, glutamate neurotoxicity and hypoxia.

20 Inflammatory diseases which can be treated according to the methods of this invention include, but are not limited to, rheumatoid arthritis, psoriasis, contact dermatitis, and delayed hypersensitivity reactions.

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
25 tablets, liquid solutions or suspensions or parenterally, for example intramuscularly, intravenously or subcutaneously. The compound may therefore be given by injection or infusion.

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
30 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
5 dosage or according to a divided dose schedule.

Typically a dose to treat human patients may range from about 10 mg to about 1000 mg of a compound of the invention. A typical dose may be about 100 mg to about 300 mg of the compound. A dose may be administered once a day (QID), twice per day (BID), or more frequently, depending on the pharmacokinetic and
10 pharmacodynamic properties, including absorption, distribution, metabolism, and excretion of the particular compound. In addition, toxicity factors may influence the dosage and administration regimen. When administered orally, the pill, capsule, or tablet may be ingested daily or less frequently for a specified period of time. The regimen may be repeated for a number of cycles of therapy.

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

20 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
25 selected from the group consisting of sweetening agents, flavouring agents, colouring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations.

Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of
30 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
5 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
10 or film coating processes.

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,
15 peanut oil, liquid paraffin, or olive oil.

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, hydroxypropylmethyl-cellulose, sodium alginate, polyvinylpyrrolidone gum tragacanth
20 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
25 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.

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
30 sucrose or saccharin.

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.

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. 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.

Such formulations may also contain a demulcent, a preservative and flavouring and coloring agents.

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.

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
5 fatty acids such as oleic acid find use in the preparation of injectables.

C) By inhalation, in the form of aerosols or solutions for nebulizers.

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
10 materials are cocoa butter and poly-ethylene glycols.

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

F) Vaginally, in the form of pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are
15 known in the art to be appropriate.

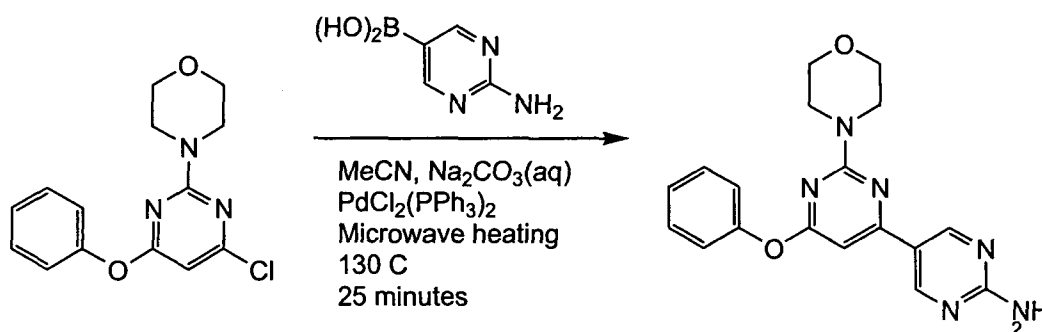
The invention will be further described in the Examples which follow, with reference to the general synthetic procedures shown below.

General Synthetic Procedures

20

A) Suzuki Coupling

A typical Suzuki coupling is shown below in the preparation of Compound 10



A mixture of 4-(4-chloro-6-phenoxy-pyrimidin-2-yl)-morpholine (105mg), 2-aminopyrimidine-5-boronic acid (75mg, 1.5 equivalents), sodium carbonate solution
25

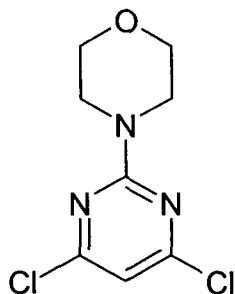
(115mg of sodium carbonate in 1mL of water), $\text{PdCl}_2(\text{PPh}_3)_2$ (13mg, 5%) and acetonitrile (3mL) was heated to 130°C for 25 minutes in the microwave (CEM Discover). The reaction mixture was allowed to cool, poured onto HCl (2N) and washed with ethyl acetate. The acidic phase was then basified (sodium carbonate) resulting in a white precipitate which was collected by filtration and air-dried. Further purification, using flash chromatography yielded 2-morpholin-4-yl-6-phenoxy-[4,5']bipyrimidinyl-2'-ylamine (42mg).

SCX-2 cartridges were also used in the purification of some compounds.

10 B) Amide Coupling:

To a solution of the carboxylic acid in DMF was added carbonyldiimidazole (1.25 eq) and the reaction stirred at room temperature for 1 h. Then, the amine (1.5 eq) and triethylamine if required (1 eq for each HCl salt of the amine) were added and the reaction stirred at room temperature for 16 h. The mixture was then partitioned between water and ethyl acetate and the organics were washed with aqueous brine solution, dried (MgSO₄) and reduced in vacuo.

Reference Example 1: 4-(4,6-dichloro-pyrimidin-2-yl)-morpholine
(Intermediate A1)



20 Method A

To a solution of 2,4,6-trichloropyrimidine (16.42G) in dioxane (90mL) at 0°C, was added diisopropylethylamine (17.15mL) and morpholine (8.7mL). The reaction mixture was allowed to warm to room temperature. After stirring overnight, the reaction mixture was diluted with water (300ml) and a white precipitate was collected by filtration and air-dried. Recrystallisation of this white solid from ethyl acetate/hexane yielded the undesired 4-(2,6-dichloro-pyrimidin-4-yl)-morpholine. The residue was

purified using flash chromatography (ethyl acetate/hexane) to yield the desired title compound (3.24g)

Method B

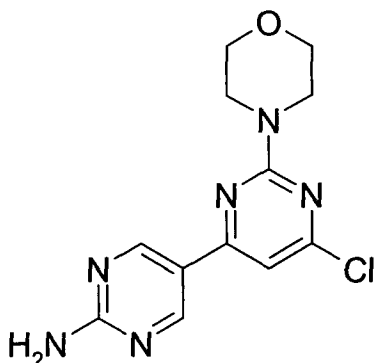
- 5 A mixture of morpholinoformamidine hydrobromide (3.38g), methanol (10mL) and sodium methoxide in methanol (25% wt, 7.35ml) was heated to reflux for 30 minutes. Diethyl malonate (2.69ml) was then added and the reaction mixture was heated for a further 5 hours. The reaction mixture was then cooled and poured onto ice/water (~50ml) and acidified using 2N HCl to give a white precipitate. This was collected by
10 filtration and air-dried to give 2-morpholin-4-yl-pyrimidine-4,6-diol (2.38g).

A mixture of 2-morpholin-4-yl-pyrimidine-4,6-diol (7.23g), phosphorous oxychloride (60mL), N,N-dimethylaniline (0.5mL) was heated to reflux for 6 hours. The reaction mixture was then cooled, poured carefully onto ice/water and the white precipitate collected by filtration to yield the desired title compound (7.11g).

- 15 In an analogous manner, 4-(4,6-dichloro-5-methyl-pyrimidin-2-yl)-morpholine (Intermediate A2) was prepared using diethylmethylmalonate.

Reference Example 2

6-Chloro-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine (Intermediate B)



20

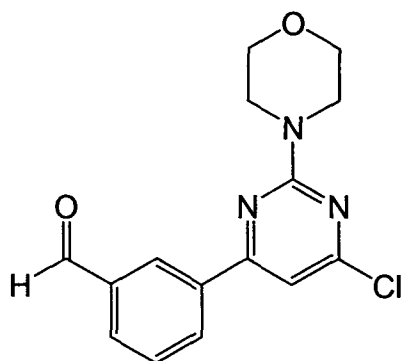
Intermediate A1 (140 mg, 0.60 mmol) and 2-aminopyrimidine-5-boronic acid pinacol ester (1.0 equiv., 83mg) were taken up in acetonitrile (3ml). To this were added sodium carbonate (3 equiv., 191mg) as a solution in water (1ml) and PdCl₂(PPh₃)₂ (0.05 equiv.). The reaction mixture was heated in microwave at 140°C for 30 min.

- 25 Purification using SCX-2 cartridge, flash chromatography and diethyl ether trituration gave 6-chloro-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine (53mg).

The following compound was also isolated from the reaction mixture by flash chromatography purification: 2'-Morpholin-4-yl-[5,4';6',5'']terpyrimidine-2,2''-diamine.

Reference Example 3

3-(6-Chloro-2-morpholin-4-yl-pyrimidin-4-yl)-benzaldehyde (Intermediate C1)

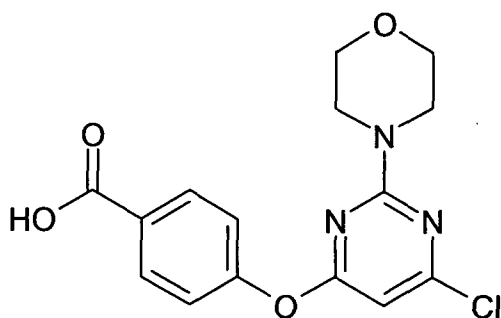


Intermediate A1 (250 mg, 1.07 mmol) and 3-formylboronic acid (1.0 equiv., 160mg) were taken up in acetonitrile (4ml). To this were added sodium carbonate (3 equiv., 340mg) as a solution in water (1ml) and $\text{PdCl}_2(\text{PPh}_3)_2$ (0.05 equiv.). The reaction mixture was heated in microwave at 140°C for 30 min. Purification using DCM/brine extraction and flash chromatography gave 3-(6-chloro-2-morpholin-4-yl-pyrimidin-4-yl)-benzaldehyde (101mg).

4-(6-Chloro-2-morpholin-4-yl-pyrimidin-4-yl)-benzaldehyde (Intermediate C2) was prepared in an analogous manner

Reference Example 4

4-(6-Chloro-2-morpholin-4-yl-pyrimidin-4-yloxy)-benzoic acid (Intermediate D1)



A mixture of Intermediate A1 (251mg), methyl-4-hydroxybenzoate (171mg) and potassium carbonate (222mg) was heated to 80°C in N,N-dimethylformamide for 4 hours. The reaction mixture was then cooled, diluted with ethyl acetate, washed with

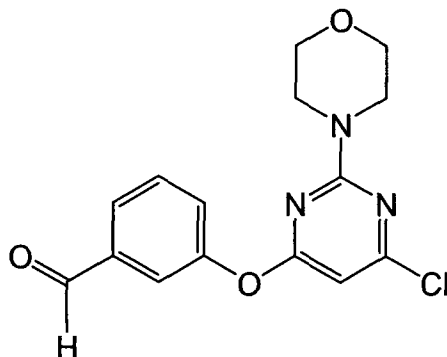
water, dried (MgSO_4) and the solvent removed in vacuo to yield 4-(6-chloro-2-morpholin-4-yl-pyrimidin-4-yloxy)-benzoic acid methyl ester (315mg).

To a solution of 4-(6-chloro-2-morpholin-4-yl-pyrimidin-4-yloxy)-benzoic acid methyl ester in tetrahydrofuran (10mL) and methanol (5mL) was added a solution of sodium hydroxide (43mg) in water (3mL). After stirring for 3 days the reaction mixture was diluted with water and washed with ethyl acetate. The aqueous phase was acidified (HCl, 2N) to yield 4-(6-chloro-2-morpholin-4-yl-pyrimidin-4-yloxy)-benzoic acid as a white precipitate which was collected by filtration (210mg).

3-(6-Chloro-2-morpholin-4-yl-pyrimidin-4-yloxy)-benzoic acid (Intermediate D2) was prepared in an analogous manner using methyl-3-hydroxybenzoate.

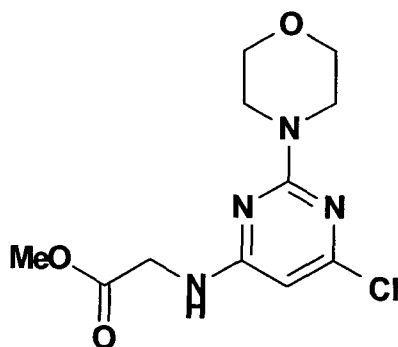
[4-(6-Chloro-2-morpholin-4-yl-pyrimidin-4-yloxy)-phenyl]-acetic acid (Intermediate D3) was prepared in an analogous manner using methyl-4-hydroxyphenylacetate.

15 Reference Example 5 3-(3-Chloro-5-morpholin-4-yl-phenoxy)-benzaldehyde
(Intermediate E1)



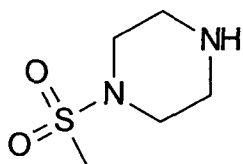
A mixture of Intermediate A, 3-hydroxybenzaldehyde and potassium carbonate in N,N-dimethylformamide was stirred at 80°C for 4 hours. After cooling to room temperature, extraction into ethyl acetate and washing with brine and sat. aq. NaHCO_3 followed by purification on silica yielded 3-(3-chloro-5-morpholin-4-yl-phenoxy)-benzaldehyde

4-(6-Chloro-2-morpholin-4-yl-pyrimidin-4-yloxy)-benzaldehyde (Intermediate E2) was prepared in a similar manner using 4-hydroxybenzaldehyde.

Reference Example 6(6-Chloro-2-morpholin-4-yl-pyrimidin-4-ylamino)-acetic acid methyl ester (Intermediate F1)

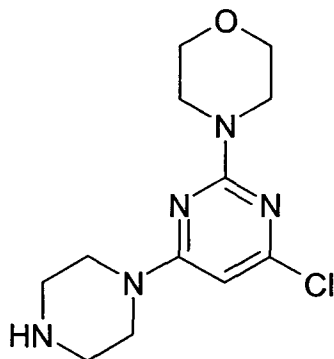
- 5 Intermediate A1 (400mg, 1.71mmol) and glycine methyl ester hydrochloride (1.3 equiv., 279mg) were refluxed in acetonitrile (6ml) with potassium carbonate (2.5 equiv., 591mg) overnight. The reaction mixture was then cooled to room temperature and diluted with water. The precipitate was filtered, washed with water, air-dried to give
 10 solid (417mg).

3-(6-chloro-2-morpholin-4-yl-pyrimidin-4-ylamino)-propionic acid methyl ester (Intermediate F2) was prepared in an analogous manner using beta-alanine methyl ester hydrochloride

15 Reference Example 71-methanesulfonyl-piperazine. HCl salt
(Intermediate G)

- Reaction between N-BOC-piperazine and methane sulfonyl chloride in dichloromethane and triethylamine yielded 4-methanesulfonyl-piperazine-1-carboxylic acid tert-butyl ester. Cleavage of the BOC protecting group using HCl (2M) in
 20 dichloromethane yielded 1-methanesulfonyl-piperazine. HCl salt.

Reference Example 84-(4-Chloro-6-piperazin-1-yl-pyrimidin-2-yl)-morpholine.2HCl. (Intermediate H)



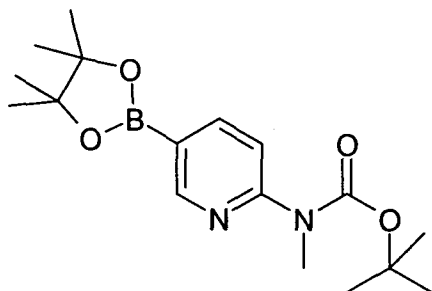
To a solution of 2,4,6-trichloropyrimidine in dioxane at 0°C was added diisopropylethylamine and BOC-piperazine. After stirring overnight at room temperature, the reaction mixture was poured onto water and the white precipitate
 5 collected by filtration. The mixture of 2 isomers was separated by column chromatography, collecting the major isomer, 4-(2,6-dichloro-pyrimidin-4-yl)-piperazine-1-carboxylic acid tert-butyl ester.

To 4-(2,6-dichloro-pyrimidin-4-yl)-piperazine-1-carboxylic acid tert-butyl ester in dioxane was added diisopropylethylamine and morpholine and the reaction mixture
 10 stirred at room temperature overnight. EtOAc/brine extraction yielded 4-(6-chloro-2-morpholin-4-yl-pyrimidin-4-yl)-piperazine-1-carboxylic acid tert-butyl ester.

The protecting group was removed by stirring with HCl in methanol and chloroform overnight. The solvent was removed in vacuo to yield 4-(4-chloro-6-piperazin-1-yl-pyrimidin-2-yl)-morpholine.2HCl.

Reference Example 9

Methyl-[5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridin-2-yl]-carbamic acid tert-butyl ester (Intermediate I)

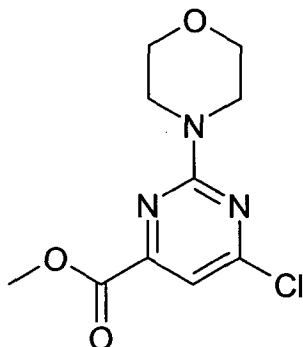


20 Methyl-[5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridin-2-yl]-carbamic acid tert-butyl ester was prepared from tert-butyl 5-bromopyridin-2-

yl(methyl)carbamate according to J. Label Compd. Radiopharm., (2003), 46, 1055-1065, Kumar et al.

Reference Example 10

6-Chloro-2-morpholin-4-yl-pyrimidine-4-carboxylic acid methyl ester (Intermediate J)



To a solution of diethylloxalacetate sodium salt (10 g) in ethanol (15 mL) and water (70 mL) was added an aqueous solution of sodium hydroxide (2.02 g in 10 mL) and the reaction was stirred at 30 °C for 30 minutes. Then, morpholinoformamidine hydrogen bromide (8.09 g) was added and the pH adjusted to 11 with aqueous sodium hydroxide solution. The reaction was heated at 60 °C for 4 h and then cooled to room temperature. Hydrochloric acid was added until the pH reached 1.5. The solid was filtered, washed with water and air dried to give 6-hydroxy-2-morpholin-4-yl-pyrimidine-4-carboxylic acid as an off-white solid.

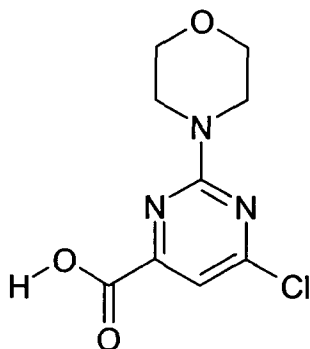
To a suspension of 6-hydroxy-2-morpholin-4-yl-pyrimidine-4-carboxylic acid (10 g) in methanol (20 mL) and toluene (80 mL) at 0°C was added trimethylsilyl diazomethane (26.70 mL of a 2 M solution in ether) dropwise. After stirring at room temperature for 4 h the reaction was quenched with acetic acid (10 mL) and the solid was filtered and air dried to give 6-hydroxy-2-morpholin-4-yl-pyrimidine-4-carboxylic acid methyl ester.

To a suspension of 6-hydroxy-2-morpholin-4-yl-pyrimidine-4-carboxylic acid methyl ester (10.175g) in phosphorus oxychloride (50 mL) was added N,N-dimethylaniline (1 mL) and the reaction was heated at reflux for 5 h. After cooling to room temperature the reaction was poured carefully onto ice-water. The mixture was basified with sodium carbonate and then extracted into ethyl acetate. The organics were

washed with aqueous brine solution, dried (MgSO₄) and reduced in vacuo to give the title compound.

Reference Example 12

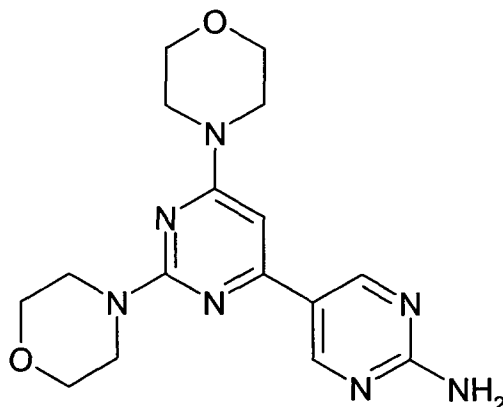
6-Chloro-2-morpholin-4-yl-pyrimidine-4-carboxylic acid (Intermediate K)



The title compound was also isolated from the synthesis of Intermediate J by acidifying the aqueous layer, filtering and air drying the resulting solid.

Reference Example 13

2,6-Di-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine



To a cold solution of 2,4,6-trichloropyrimidine (16g) in methanol (200mL) was added morpholine (15.2ml). The reaction mixture was stirred for 24 hours and the solvent was then removed in vacuo. The residue was dissolved in dichloromethane, washed with water, dried (MgSO₄) and the solvent removed in vacuo. The residue was purified using flash chromatography to yield 4-(6-chloro-2-morpholin-1-yl-pyrimidin-4-yl)-morpholine.

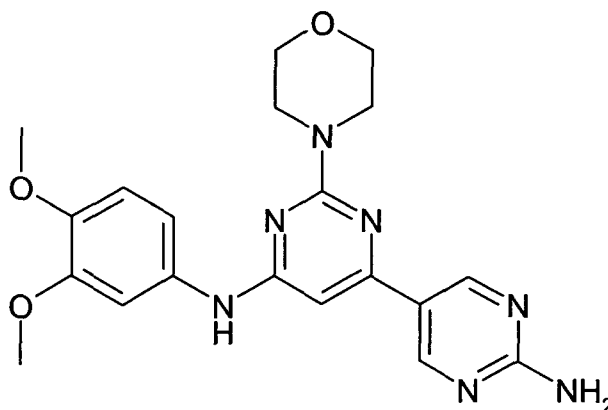
Reaction of 4-(6-chloro-2-morpholin-1-yl-pyrimidin-4-yl)-morpholine with 2-aminopyrimidine-5-boronic acid, pinacol ester using standard Suzuki conditions yielded the desired title compound.

400MHz ¹H NMR CDCl₃

3.64-3.66 (m, 4H, 2 x CH₂), 3.7-3.86 (m, 12H, 6 x CH₂), 5.22 (sbr, 2H, NH₂), 6.17 (s, H, ArH), 8.89 (s, 2H, 2 x ArH).

Reference Example 14

N-6-(3,4-Dimethoxy-phenyl)-2-morpholin-4-yl-[4,5']bipyrimidinyl-6,2'-diamine



To a solution of 2,4,6-trichloropyrimidine (1.45g) in ethanol (20mL) was added sodium carbonate (921mg) and 4-aminoveratrole 91.33g). The reaction mixture was heated to reflux for 3 hours and then cooled, diluted with water, extracted with ethyl acetate, dried (MgSO₄) and the solvent removed in vacuo to yield (2,6-dichloropyrimidin-4-yl)-(3,4-dimethoxy-phenyl)-amine (618mg).

To a solution of (2,6-dichloro-pyrimidin-4-yl)-(3,4-dimethoxy-phenyl)-amine (381mg), in tetrahydrofuran (10ml) was added 4-dimethylaminopyridine (cat.) and di-tert butyl dicarbonate (554mg). After 2 hours the reaction mixture was diluted with ethyl acetate, washed with water, dried (MgSO₄) and the solvent removed in vacuo to yield (2,6-dichloro-pyrimidin-4-yl)-(3,4-dimethoxy-phenyl)-carbamic acid tert-butyl ester (424mg).

To a solution of (2,6-dichloro-pyrimidin-4-yl)-(3,4-dimethoxy-phenyl)-carbamic acid tert-butyl ester (424mg) in N,N-dimethylformamide (5ml) was added diisopropylethylamine (203μL) and morpholine (102 μL). After 1 hour the reaction mixture was diluted with ethyl acetate, washed with water, dried (MgSO₄) and the solvent removed in vacuo. The residue was purified using flash chromatography to yield (6-chloro-2-morpholin-4-yl-pyrimidin-4-yl)-(3,4-dimethoxy-phenyl)-carbamic acid tert-

butyl ester (desired isomer, 136mg) and also (2-chloro-6-morpholin-4-yl-pyrimidin-4-yl)-(3,4-dimethoxy-phenyl)-carbamic acid tert-butyl ester (196mg).

Reaction of (6-chloro-2-morpholin-4-yl-pyrimidin-4-yl)-(3,4-dimethoxy-phenyl)-carbamic acid tert-butyl ester with 2-aminopyrimidine-5-boronic acid, pinacol ester using standard Suzuki conditions yielded the desired title compound.

¹H NMR (400MHz, CDCl₃)

3.78-3.92 (14H, m), 5.20 (2H, s, br.), 6.19 (1H, s), 6.49 (1H, s), 6.88 (2H, s), 7.01 (1H, s), 8.85 (2H, s).

MH⁺ 410

Example 1

3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-ylamino)-benzoic acid (32)

The title compound was prepared by an analogous process to that described in Reference Example 13 using methyl-3-aminobenzoate.

NMR and LCMS analysis showed that the methyl ester group had hydrolysed to the carboxylic acid during the Suzuki reaction, giving the title compound.

NMR: (DMSO, 400MHz): 3.69 (t, 4H, 2xCH₂, J = 4.6Hz); 3.79 (t, 4H, 2xCH₂, J = 4.5Hz); 6.45 (s, 1H, ArH); 7.05 (s, 2H, NH₂); 7.41 (dd, 1H, ArH, J = 7.9Hz); 7.53 (d, 1H, ArH, J = 7.8Hz); 7.72 (m, 1H, ArH); 8.64 (s, 1H, ArH); 8.81 (s, 2H, 2xArH); 9.55 (s, 1H, NH).

MS: (ESI⁺): MH⁺ = 394.12

Example 2

6-(4-Methanesulfonyl-piperazin-1-yl)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine (4)

A mixture of Intermediate A1 (198mg), Intermediate G (230mg) and potassium carbonate (293mg) was stirred in acetonitrile (10ml) at room temperature. After 24 hours the reaction mixture was diluted with ethyl acetate, washed with water, dried (MgSO₄) and the solvent removed in vacuo. The residue was recrystallised from ethyl acetate/hexane to yield 4-[4-chloro-6-(4-methanesulfonyl-piperazin-1-yl)-pyrimidin-2-yl]-morpholine (206mg).

Reaction of 4-[4-chloro-6-(4-methanesulfonyl-piperazin-1-yl)-ymidin-2-yl]-morpholine with 2-aminopyrimidine-5-boronic acid, pinacol ester using standard Suzuki conditions yielded the desired title compound.

¹H NMR (400MHz, CDCl₃)

2.80 (3H,s), 3.28-3.24 (4H,m), 3.82-3.75 (12H,m), 5.20 (2H,s,br.), 6.16 (1H,s), 8.91 (2H,s).

The following compounds were prepared in a similar manner starting with the appropriate amine:

10

6-(4-Methyl-piperazin-1-yl)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine (**5**) was prepared using N-methylpiperazine.

¹H NMR (400MHz, CDCl₃)

2.32 (3H, s), 2.54-2.50 (4H, m), 3.68-3.72 (4H, m), 3.73-3.80 (8H, m), 5.22 (2H,s,br.), 6.13 (1H,s), 8.88 (2H,s)
MH+ 357

6-(4-Dimethylamino-piperidin-1-yl)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine (**7**) was prepared using 4-dimethylaminopiperidine.

20

¹H NMR (400MHz, CDCl₃)

1.48-1.60 (2H,m), 1.95 (2H,d), 2.30 (6H,s), 2.42-2.47 (1H,m), 2.90-3.00 (2H,m), 3.78-3.85 (8H,m), 4.48 (2H,d), 5.19 (2H,s,br.), 6.20 (1H,s), 8.90 (2H,s)
MH+ 385

25 2-Morpholin-4-yl-N-6-pyridin-3-ylmethyl-[4,5']bipyrimidinyl-6,2'-diamine (**8**) was prepared using 3-(aminomethyl)pyridine.

400MHz ¹H NMR CDCl₃

3.66-3.68 (m, 4H, 2 x CH₂), 3.73-3.75 (m, 4H, 2 x CH₂), 4.56 (d, 2H, CH₂, J = 5.9Hz), 4.93 (t, H, NH, J = 5.6Hz), 5.10 (sbr, 2H, NH₂), 5.94 (s, H, ArH), 7.18 -7.21 (m, H, ArH), 7.60 (m, H, ArH), 8.46 (m, H, ArH), 8.55 (m, H, ArH), 8.77 (s, 2H, 2 x ArH).
MH+ = 365.19

2-Morpholin-4-yl-N-6-pyridin-2-ylmethyl-[4,5']bipyrimidinyl-6,2'-diamine (**15**) was prepared using 2-(aminomethyl)pyridine.

400MHz 1H NMR CDCl₃

3.77-3.79 (m, 4H, 2 x CH₂), 3.84-3.85 (m, 4H, 2 x CH₂), 4.73 (d, 2H, CH₂, J = 5.04Hz), 5.19 (sbr, 2H, NH₂), 5.85 (m, H, NH), 6.12 (s, H, ArH), 7.23 (t, H, ArH, J = 6.02Hz), 7.34 (d, H, ArH, J = 7.75Hz), 7.69 (t, H, ArH, J = 7.67Hz), 8.61 (d, H, ArH, J = 7.67Hz), 8.61 (d, H, ArH, J = 4.46Hz), 8.88 (s, 2H, 2 x ArH).

MH⁺ = 365.16

10 N-6-Benzyl-2-morpholin-4-yl-[4,5']bipyrimidinyl-6,2'-diamine (**16**) was prepared using benzylamine.

400MHz 1H NMR CDCl₃

3.76-3.79 (m, 4H, 2 x CH₂), 3.84-3.86 (m, 4H, 2 x CH₂), 4.61 (d, 2H, CH₂, J = 5.67Hz), 5.04 (sbr, H, NH), 5.32 (sbr, 2H, NH₂), 7.30-7.37 (m, 5H, 5 x ArH), 8.86 (s, 2H, 2 x ArH).

MH⁺ = 364.16

N-6-Benzyl-N-6-methyl-2-morpholin-4-yl-[4,5']bipyrimidinyl-6,2'-diamine (**18**) was prepared using N-benzylmethylamine

20 1H NMR (400MHz, CDCl₃)

3.03 (3H,s), 3.70-3.78 (4H,m), 3.80-3.85 (4H,m), 4.70 (2H,s), 5.20 (2H,s,br.), 7.25-7.35 (5H,m), 8.90 (2H,s).

MH⁺ 378

25 2-Morpholin-4-yl-N-6-pyridin-4-ylmethyl-[4,5']bipyrimidinyl-6,2'-diamine (**20**) was prepared using 4-(aminomethyl)pyridine.

400MHZ 1H NMR CDCl₃

3.74-3.76 (m, 4H, 2 x CH₂), 3.79-3.81 (m, 4H, 2 x CH₂), 4.65 (d, 2H, CH₂, J = 6.09Hz), 5.12 m. H, NH), 5.25 (sbr, 2H, NH₂), 6.03 (s, H, ArH), 7.26 (d, 2H, 2 x ArH, J = 3.78Hz), 8.58 (d, 2H, 2 x ArH, J = 4.5Hz), 8.86 (s, 2H, 2 x ArH)

MH⁺ = 365.16

1-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-4-phenyl-piperidin-4-ol (**21**) was prepared using 4-hydroxy-4-phenylpiperidine.

¹H NMR (400MHz, CDCl₃)

1.90 (2H,d), 2.12 (2H,td), 3.49 (2H,t), 3.78-3.85 (8H,m), 4.35 (2H,d), 5.17 (2H,s,br.),
5 6.25 (1h,s), 7.27-7.30 (1H,m), 7.36-7.40 (2H,m), 7.50 (2H,d), 8.90 (2H,s)

N-6-[2-(3,4-Dimethoxy-phenyl)-ethyl]-N-6-methyl-2-morpholin-4-yl-[4,5']bipyrimidinyl-6,2'-diamine (**23**) was prepared using 2-(3,4-dimethoxyphenyl)-N-methylethylamine.

10 ¹H NMR (400MHz, CDCl₃)

2.88 (2H,t), 3.01 (3H,s), 3.72-3.86 (16H), 5.20 (2H,s,br.), 6.01 (1H,s), 6.70 (1H,s), 6.73 (1H,dd), 6.80 (1H,d), 8.90 (1H,s)

MH+ 452

15 2-Morpholin-4-yl-N-6-phenethyl-[4,5']bipyrimidinyl-6,2'-diamine (**60**) was prepared using phenethylamine.

¹H NMR (400MHz, CDCl₃)

3.01 (2H,t), 3.70-3.80 (2H,m), 3.82-3.90 (8H,m), 4.74 91H,br.), 5.20 (2H,s,br.), 6.01 (1H,s), 7.30-7.40 (5H,m), 8.90 92H,s),

20 MH+ 378

2-Morpholin-4-yl-N-6-(2-morpholin-4-yl-ethyl)-[4,5']bipyrimidinyl-6,2'-diamine (**65**) was prepared using 4-(2-aminoethyl)morpholine.

NMR (CDCl₃): 2.50-2.54 (4H, m), 2.61-2.65 (2H, m), 3.47-3.51 (2H, m), 3.75-3.81

25 (8H, m), 3.84-3.87 (4H, m), 5.22 (2H, br), 5.28 (1H, br), 6.04 (1H, s), 8.90 (2H, s)

MS (ESI+): MH+ 387.22 (40%)

N-6-(2-Dimethylamino-ethyl)-2-morpholin-4-yl-[4,5']bipyrimidinyl-6,2'-diamine (**66**) was prepared using N,N-dimethylethylenediamine;

30 NMR (CDCl₃): 2.29 (6H, s), 2.55 (2H, t), 3.44-3.47 (2H, m), 3.77-3.80 (4H, m), 3.84-3.87 (4H, m), 5.20 (2H, br), 5.32 (1H, br), 6.03 (1H, s), 8.89 (2H, s)

MS (ESI+): MH+ 345.21 (30%)

N-6-(3-Dimethylamino-propyl)-2-morpholin-4-yl-[4,5']bipyrimidinyl-6,2'-diamine (**67**) was prepared using 3-dimethylaminopropylamine.

NMR (CDCl₃): 1.76-1.83 (2H, m), 2.28 (6H, s), 2.42-2.45 (2H, m), 3.46-3.49 (2H, m), 3.78-3.80 (4H, m), 3.83-3.86 (4H, m), 5.21 (2H, br), 5.60 (1H, br), 6.01 (1H, s), 8.89 (2H, s)

MS (ESI⁺): MH⁺ 359.20 (15%)

N-6,N-6-Bis-(2-methoxy-ethyl)-2-morpholin-4-yl-[4,5']bipyrimidinyl-6,2'-diamine (**69**) was prepared using bis-(2-methoxy-ethyl)-amine.

NMR (CDCl₃): 3.38 (6H, s), 3.59-3.63 (4H, m), 3.75-3.82 (12H, m), 5.20 (2H, br), 6.20 (1H, s), 8.88 (2H, s)

MS (ESI⁺): MH⁺ 390.22 (100%)

N-6-(3-Fluoro-benzyl)-2-morpholin-4-yl-[4,5']bipyrimidinyl-6,2'-diamine (**70**) was prepared using 3-fluorobenzylamine.

NMR (CDCl₃): 3.76-3.79 (4H, m), 3.82-3.85 (4H, m), 4.62 (2H, d), 5.06 (1H, br), 5.22 (2H, br), 6.02 (1H, s), 6.97-7.02 (1H, m), 7.07 (1H, d), 7.13 (1H, d), 7.28-7.35 (1H, m), 8.86 (2H, s)

MS (ESI⁺): MH⁺ 382.17 (100%)

N-6-(3-Methanesulfonyl-benzyl)-2-morpholin-4-yl-[4,5']bipyrimidinyl-6,2'-diamine (**76**) was prepared using 3-methanesulfonylbenzylamine.

NMR (CDCl₃): 3.07 (3H, s), 3.75-3.78 (4H, m), 3.80-3.84 (4H, m), 4.73 (2H, d), 5.10 (1H, br), 5.19 (2H, br), 6.04 (1H, s), 7.55-7.59 (1H, m), 7.66 (1H, d), 7.87 (1H, d), 7.97 (1H, br, s), 8.86 (2H, s)

MS (ESI⁺): MH⁺ 442.15 (100%)

6-((2R,6S)-2,6-Dimethyl-morpholin-4-yl)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine (**89**) was prepared using cis-2,6-dimethylpiperazine.

¹H NMR (400MHz, CDCl₃)

1.30 (6H,d), 2.59 (2H,t), 3.65-3.70 (2H,m), 3.78-3.85 (8H,m), 4.18 (2H,d), 5.20 (2H,s,br.), 6.16 (1H,s), 8.90 (2H,s)

MH+ 372

N-6-(2-Methoxy-ethyl)-N-6-methyl-2-morpholin-4-yl-[4,5']bipyrimidinyl-6,2'-diamine (**111**) was prepared using (2-methoxyethyl)methylamine.

5 NMR (CDCl₃): 3.15 (3H, s), 3.38 (3H, s), 3.61(2H, t), 3.75-3.79 (6H,m), 3.82-3.85 (4H, m), 5.20 (2H, br), 6.13 (1H, s), 8.90 (2H, s)

MS (ESI+): MH+ 346.17 (100%)

10 2-Morpholin-4-yl-N-6-(2-pyridin-2-yl-ethyl)-[4,5']bipyrimidinyl-6,2'-diamine (**92**) was prepared using 2-(2-aminoethyl)pyridine.

NMR: DMSO: 3.32-3.34 (2H, m), 3.72-3.78 (10H, m), 6.02 (1H, s, Ar), 7.17-7.23 (2H, m,Ar), 7.38-7.39 (1H, m, Ar), 7.64-7.68 (1H, m, Ar), 8.45 (1H, s, Ar) and 8.79 (2H,s,Ar).

MS: (ESI+): MH+ 379.12

15

2-Morpholin-4-yl-N-6-(2-pyridin-3-yl-ethyl)-[4,5']bipyrimidinyl-6,2'-diamine (**93**) was prepared using 3-(2-aminoethyl)pyridine.

20 NMR: CDCl₃: 2.88 (2 H, t, J 7.0, CH₂), 3.58 (2 H, t, J 7.0, CH₂), 3.67-3.74 (8 H, m), 5.94 (1 H, s), 7.22 (1 H, dd, J 5.0 and 7.8, Ar), 7.54 (1 H, d, J 7.8, Ar), 8.31-8.34 (2 H, m, Ar) and 8.74 (2 H, s, Ar).

MS: (ESI+): MH+ 379.13

2-Morpholin-4-yl-N-6-(2-pyridin-4-yl-ethyl)-[4,5']bipyrimidinyl-6,2'-diamine (**94**) was prepared using 4-(2-aminoethyl)pyridine.

25 NMR: MeOD: 2.99 (2 H, t, J 7.0, CH₂), 3.70 (2 H, t, J 7.0, CH₂), 3.72-3.76 (4 H, m), 3.79-3.81 (4 H, m), 6.13 (1 H, s, Ar), 7.33 (2 H, d, J 6.0, Ar), 8.43 (2 H, d, J 6.0, Ar) and 8.82 (2 H, s, Ar).

MS: (ESI+): MH+ 379.15

30 N-6-[2-(1H-Imidazol-4-yl)-ethyl]-2-morpholin-4-yl-[4,5']bipyrimidinyl-6,2'-diamine (**101**) was prepared using histamine.

NMR: CDCl₃: 2.81 (2 H, t, J 7.0, CH₂), 3.25 (1 H, s, NH), 3.54-3.57 (2 H, m, CH₂), 3.68-3.70 (4 H, m, CH₂), 3.72-7.73 (4 H, m, CH₂), 5.99 (1 H, s, Ar), 6.73 (1 H, s, Ar), 7.47 (1 H, s, Ar) and 8.73 (2 H, s, Ar).

MS: (ESI⁺): MH⁺ 368.17

5

N-6-[2-(1H-Indol-3-yl)-ethyl]-2-morpholin-4-yl-[4,5']bipyrimidinyl-6,2'-diamine (**102**) was prepared using tryptamine

NMR: DMSO: 2.93-2.97 (2 H, m, CH₂), 3.57-3.59 (2 H, m, CH₂), 3.64-3.66 (4 H, m, CH₂), 3.69-3.71 (4 H, m, CH₂), 6.19 (1 H, s, Ar), 6.98-7.00 (1 H, m, Ar), 7.05-7.09 (1 H, m, Ar), 7.10 (1 H, s, Ar), 7.34 (1 H, d, J 7.5, Ar), 7.55 (1 H, d, J 7.5, Ar) and 8.77 (2 H, s, Ar).

10

MS: (ESI⁺): MH⁺ 417.14

Example 3

N-[4-(2'-Amino-2-morpholin-4-yl-[4, 5']bipyrimidinyl-6-yl)-phenyl]-methanesulfonamide (12)

15

Intermediate A1 (100mg, 0.43 mmol) and N-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylmethanesulfonamide (134mg, 0.45 mmol) were taken up in acetonitrile (2ml). To this were added sodium carbonate (3 equiv., 136mg) as a solution in water (0.5ml) and PdCl₂(PPh₃)₂ (0.05 equiv.). The reaction mixture was heated in microwave at 180°C for 20 min. Purification using SCX-2 cartridge and flash chromatography gave N-[4-(6-chloro-2-morpholin-4-yl-pyrimidin-4-yl)-phenyl]-ethane-sulfonamide (70mg).

20

N-[4-(6-Chloro-2-morpholin-4-yl-pyrimidin-4-yl)-phenyl]-ethane-sulfonamide (69mg) and 2-aminopyrimidine-5-boronic acid pinacol ester (1.8 equiv., 47mg) were taken up in acetonitrile (2ml). To this were added sodium carbonate (3 equiv., 60mg) as a solution in water (0.5ml) and PdCl₂(PPh₃)₂ (0.05 equiv.). The reaction mixture was heated in microwave at 140°C for 30 min. Purification using SCX-2 cartridge, flash chromatography and diethyl ether trituration gave the title compound as a white solid (11mg).

25

NMR (DMSO-d₆): 3.05 (3H, s), 3.70-3.75 (4H, m), 3.86-3.91 (4H, m), 7.19 (2H, br), 7.30 (2H, d), 7.69 (1H, s), 8.24 (2H, d), 9.11 (2H, s)

30

MS (ESI⁺): MH⁺ 469.15 (100%)

The following compounds were prepared using an analogous procedure with the appropriate commercially available boronic acids or boronic acid pinacol esters:

6-(3-Methanesulfonyl-phenyl)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine (**6**) was prepared using 3-methoxysulphonylphenyl boronic acid.

¹H NMR (400MHz, CDCl₃)

3.13 (3H,s), 3.81-3.86 (4H,m), 3.98-4.02 (4H,m), 5.30 (2H,s,br.), 7.30 (1H,s), 7.70 (1H,t), 8.10 (1H,d), 8.40 (1H,d), 8.66 (1H,s), 9.02 (2H,s).

MH+ 413

N-[4-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-phenyl]-acetamide (**13**) was prepared using 4'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)acetamide.

NMR (DMSO-d₆): 2.08 (3H, s), 3.70-3.75 (4H, m), 3.86-3.91 (4H, m), 7.19 (2H, br), 7.68-7.76 (3H, m), 8.24 (2H, d), 9.11 (2H, s), 10.15 (1H, br)

MS (ESI+): MH+ 392 (25%)

3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-benzamide (**14**) was prepared using 3-carbamoylphenylboronic acid.

NMR (DMSO-d₆): 3.70-3.75 (4H, m), 3.86-3.91 (4H, m), 7.19 (2H, br), 7.50 (1H, br), 7.62 (1H, t), 7.80 (1H, s), 8.02 (1H, d), 8.11 (1H, br), 8.41 (1H, d), 8.66 (1H, s), 9.13 (2H, s)

MS (ESI+): MH+ 378 (10%)

3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-N-methyl-benzamide (**17**) was prepared using 3-(N-methylaminocarbonyl)benzeneboronic acid.

NMR (DMSO-d₆): 2.84 (3H, d), 3.70-3.75 (4H, m), 3.86-3.91 (4H, m), 7.19 (2H, br), 7.61 (1H, t), 7.80 (1H, s), 7.95 (1H, d), 8.39 (1H, d), 8.55 (1H, br), 8.62 (1H, s), 9.13 (2H, s)

MS (ESI+): MH+ 392 (15%)

[3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-phenyl]-(4-methyl-piperazin-1-yl)-methanone (**19**) was prepared using N-[4-methyl-piperazine-3-(4,4,5,5-tetramethyldioxaborolan-2-yl)benzamide.

5 NMR (CDCl₃): 2.36 (3H, s), 2.36-2.62 (2H+2H, br), 3.48-3.55 (2H, br), 3.80-3.90 (2H, br), 3.83-3.87 (4H, m), 3.99-4.02 (4H, m), 5.32 (2H, br), 7.29 (1H, s), 7.52-7.58 (2H, m), 8.14-8.20 (2H, m), 9.04 (2H, s)
MS (ESI⁺): MH⁺ 461 (10%)

10 N-[2-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-phenyl]-methanesulfonamide (**57**) was prepared using N-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanesulfonamide.

NMR (DMSO): 3.11 (3H, s), 3.72-3.75 (4H, m), 3.79-3.82 (4H, m), 7.23-7.28 (1H, m), 7.29 (2H, s), 7.52-7.56 (1H, m), 7.60-7.63 (1H, m), 7.76 (1H, s), 8.21-8.24 (1H, m), 9.14 (2H, s)
15 MS (ESI⁺): MH⁺ 428.16 (25%), (MH+AcN) 469.16 (100%)

N-[3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-phenyl]-acetamide (**62**) was prepared using 3-acetamidobenzeneboronic acid.

20 NMR (DMSO): 2.08 (3H, s), 3.72-3.75 (4H, m), 3.87-3.90 (4H, m), 7.23 (2H, br), 7.40-7.44 (1H, m), 7.68 (1H, s), 7.87 (1H, d), 7.91 (1H, d), 8.32 (1H, s), 9.11 (2H, s), 10.08 (1H, br)
MS (ESI⁺): MH⁺ 392.15 (15%), (MH+AcN) 433.19 (100%)

25 4-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-N-methyl-benzamide (**75**) was prepared using 4-(N-methylaminocarbonyl)phenylboronic acid.

NMR (CDCl₃): 3.08 (3H, d), 3.85-3.88 (4H, m), 4.00-4.03 (4H, m), 5.30 (2H, br), 7.33 (1H, s), 7.90 (2H, d), 8.17 (2H, d), 9.05 (2H, s)
MS (ESI⁺): MH⁺ 392.19 (20%), (MH+AcN) 433.19 (100%)

30 2-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-N,N-dimethyl-benzenesulfonamide (**77**) was prepared using 2-(N,N-dimethylsulphamoyl)phenylboronic acid.

NMR (DMSO): 2.65 (3H, s), 3.66-3.69 (4H, m), 3.77-3.79 (4H, m), 7.19 (2H, br), 7.23 (1H, s), 7.52 (1H, d), 7.69-7.78 (2H, m), 7.90 (1H, d), 9.01 (2H, s)
MS (ESI+): MH⁺ 442.15 (15%), (MH+AcN) 483.15 (100%)

- 5 4-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-N,N-dimethyl-benzamide (**78**) was prepared using 4-(N,N-dimethylaminocarbonyl)phenylboronic acid.

NMR (DMSO): 2.94 (3H, br), 3.02 (3H, br), 3.72-3.75 (4H, m), 3.86-3.89 (4H, m), 7.20 (2H, br), 7.54 (2H, d), 7.81 (1H, s), 8.33 (2H, d), 9.14 (2H, s)
MS (ESI+): MH⁺ 406.23 (50%), (MH+AcN) 447.18(100%)

10

N-[3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-phenyl]-methanesulfonamide (**79**) was prepared using N-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanesulfonamide.

- 15 NMR (DMSO): 3.01 (3H, s), 3.72-3.75 (4H, m), 3.86-3.89 (4H, m), 7.20 (2H, br), 7.37 (1H, d), 7.41-7.46 (1H, m), 7.68 (1H, s), 7.93 (1H, d), 8.09 (1H, s), 9.11 (2H, s)
MS (ESI+): MH⁺ 469.12 (100%)

3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-N,N-dimethyl-benzenesulfonamide (**96**) was prepared using 3-(N,N-dimethylsulphonamido)

- 20 benzeneboronic acid.

NMR (DMSO): 2.68 (6H, s), 3.71-3.76 (4H, m), 2.86-3.91 (4H, m), 7.23 (2H, br), 7.78-7.92 (3H, m), 8.51 (1H, s), 8.59 (1H, d), 9.14 (2H, s)
MS (ESI+): (MH+AcN) 483.12 (100%)

- 25 4-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-N,N-dimethyl-benzenesulfonamide (**97**) was prepared using 4-(N,N-dimethylsulphonamido) benzeneboronic acid

- 30 NMR (DMSO): 2.67 (6H, s), 3.71-3.76 (4H, m), 2.86-3.91 (4H, m), 7.23 (2H, br), 7.87 (1H, s), 7.89 (2H, d), 8.50 (2H, d), 9.15 (2H, s)
MS (ESI+): (MH+AcN) 483.12 (100%)

3-(2'-Amino-5-methyl-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-N,N-dimethylbenzenesulfonamide was prepared in an analogous manner to Compound 96 using Intermediate A2.

NMR: MeOD: 2.20 (3 H, s, Me), 2.67 (6 H, s, Me), 3.68-3.70 (4 H, m), 3.71-3.74 (4 H, m), 7.08 (2 H, s, NH₂), 7.75-7.78 (1 H, m, Ar), 7.82-7.85 (1 H, m, Ar), 7.96-8.00 (2 H, m, Ar) and 8.66 (2 H, s, Ar).

MS: (ESI⁺): MH⁺ 456.17

Example 4

3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-benzenesulfonamide (24)

6-Chloro-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine (Intermediate B) (51mg, 0.174mmol) and benzenesulfonamide-3-boronic acid pinacol ester (1.8 equiv., 89mg) were taken up in acetonitrile (3ml). To this were added sodium carbonate (3 equiv., 55mg) as a solution in water (1ml) and PdCl₂(PPh₃)₂ (0.05 equiv.). The reaction mixture was heated in microwave at 140°C for 30 min. Purification using SCX-2 cartridge, flash chromatography and trituration gave the title compound as a white solid (40mg).

NMR (DMSO-d₆): 3.73-3.76 (4H, m), 3.89-3.91 (4H, m), 7.24 (2H, br), 7.46 (2H, br), 7.73 (1H, t), 7.81 (1H, s), 7.97 (1H, d), 8.49 (1H, d), 8.70 (1H, s), 9.14 (2H, s)

MS (ESI⁺): MH⁺ 455.12 (100%)

The following compounds have been prepared using an analogous procedure with the appropriate commercially available boronic acids or boronic acid pinacol esters.

2-Morpholin-4-yl-6-phenyl-[4,5']bipyrimidinyl-2'-ylamine (**28**) was prepared using phenyl boronic acid.

NMR (CDCl₃): 3.84-3.87 (4H, m), 4.00-4.03 (4H, m), 5.29 (2H, br), 7.30 (1H, s), 7.50-7.54 (3H, m), 8.10-8.13 (2H, m), 9.04 (2H, s)

MS (ESI⁺): MH⁺ 335 (15%)

2-Morpholin-4-yl-6-pyridin-4-yl-[4,5']bipyrimidinyl-2'-ylamine (**30**) was prepared using 4-pyridineboronic acid.

NMR (CDCl₃): 3.84-3.87 (4H, m), 4.00-4.03 (4H, m), 5.29 (2H, br), 7.30 (1H, s), 7.95 (2H, d), 8.79 (2H, d), 9.04 (2H, s)

MS (ESI⁺): MH⁺ 336.12 (35%)

- 5 2'-Morpholin-4-yl-[5,4';6',5'']terpyrimidin-2-ylamine (**31**) was prepared using pyrimidine-5-boronic acid.

NMR (CDCl₃): 3.84-3.87 (4H, m), 4.00-4.03 (4H, m), 5.33 (2H, br), 7.26 (1H, s), 9.04 (2H, s), 9.34 (1H, s), 9.40 (2H, s)

MS (ESI⁺): MH⁺AcN 378 (100%)

10

3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-N-(2-dimethylamino-ethyl)-benzamide (**36**) was prepared using N-(2-dimethylaminoethyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide.

NMR (CDCl₃): 2.29 (6H, s), 2.57 (2H, t), 3.56-3.61 (2H, m), 3.84-3.87 (4H, m), 4.00-

- 15 4.03 (4H, m), 5.33 (2H, br), 6.92 (1H, br), 7.34 (1H, s), 7.58 (1H, m), 7.89 (1H, d), 8.23 (1H, d), 8.56 (1H, s), 9.05 (2H, s)

MS (ESI⁺): MH⁺ 449.22 (70%)

6-(4-Methanesulfonyl-phenyl)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine (**58**)

- 20 was prepared using 4-(methanesulfonyl)benzeneboronic acid.

NMR (DMSO): 3.29 (3H, s), 3.72-3.75 (4H, m), 3.88-3.91 (4H, m), 7.27 (2H, br), 7.88 (1H, s), 8.06 (2H, d), 8.51 (2H, d), 9.15 (2H, s)

MS (ESI⁺): MH⁺ 413.16 (10%), (MH⁺AcN) 454.16 (100%)

- 25 6-(2-Methanesulfonyl-phenyl)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine (**74**) was prepared using (2-methylsulfonyl)phenylboronic acid.

NMR (CDCl₃): 3.33 (3H, s), 3.79-3.82 (4H, m), 3.90-3.93 (4H, m), 5.30 (2H, br), 7.01 (1H, s), 7.49 (1H, d), 7.64-7.69 (1H, m), 7.72-7.77 (1H, m), 8.22 (1H, d), 9.01 (2H, s)

MS (ESI⁺): MH⁺ 454.17 (100%).

30

Example 5 **6-[3-(4-Methanesulfonyl-piperazin-1-ylmethyl)-phenyl]-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine (38)**

Intermediate C1 (100mg, 0.33mmol) and Intermediate G (1.2 equiv., 80mg) were taken up in 1,2-dichloroethane (5ml). To this was added sodium triacetoxyborohydride (2.4equiv., 170mg) and trimethyl orthoformate (0.1ml) and the reaction mixture was stirred at room temperature overnight. Purification by DCM/aqueous NaHCO₃ extraction, SCX-2 cartridge and flash chromatography gave 4-{4-chloro-6-[3-(4-methanesulfonyl-piperazin-1-ylmethyl)-phenyl]-pyrimidin-2-yl}-morpholine as a white solid (95mg).

4-{4-Chloro-6-[3-(4-methanesulfonyl-piperazin-1-ylmethyl)-phenyl]-pyrimidin-2-yl}-morpholine (90mg, 0.20mmol) and 2-aminopyrimidine-5-boronic acid pinacol ester (1.8 equiv., 80mg) were taken up in acetonitrile (3ml). To this were added sodium carbonate (3 equiv., 64mg) as a solution in water (1ml) and PdCl₂(PPh₃)₂ (0.05 equiv.). The reaction mixture was heated in microwave at 140°C for 30 min. Purification using SCX-2 cartridge, flash chromatography and trituration with hot DCM gave the title compound as a white solid (105mg).

NMR (CDCl₃): 2.61-2.64 (4H, m), 2.81 (3H, s), 3.27-3.30 (4H, m), 3.67 (2H, s), 3.84-3.87 (4H, m), 4.00-4.03 (4H, m), 5.32 (2H, br), 7.28 (1H, s), 7.47-7.49 (2H, m), 7.99 (1H, s), 8.01-8.04 (1H, m), 9.04 (2H, s)

MS (ESI⁺): MH⁺ 511.17 (100%)

The following compounds were prepared in an analogous manner, using the appropriate amine and either Intermediate C1 or Intermediate C2.

6-[4-(4-Methanesulfonyl-piperazin-1-ylmethyl)-phenyl]-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine (39) was prepared using Intermediate G.

NMR (CDCl₃): 2.60-2.63 (4H, m), 2.81 (3H, s), 3.27-3.30 (4H, m), 3.64 (2H, s), 3.84-3.87 (4H, m), 4.00-4.03 (4H, m), 5.29 (2H, br), 7.29 (1H, s), 7.46 (2H, d), 8.06 (2H, d), 9.04 (1H, s)

MS (ESI⁺): MH⁺ 511.17 (65%)

6-[3-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine (**41**) was prepared using N-methylpiperazine

NMR (CDCl₃): 2.32 (3H,s), 2.50-2.60 (8H,br), 3.64 (2H, s), 3.84-3.87 (4H, m), 4.00-4.03 (4H, m), 5.28 (2H, br), 7.29 (1H, s), 7.44-7.50 (2H, m), 7.98-8.02 (2H, m), 9.05

5 (2H, s)

MS (ESI⁺): MH⁺ 447.2 (20%)

6-(3-([Methyl-(1-methyl-piperidin-4-yl)-amino]-methyl)-phenyl)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine (**42**) was prepared from 1-methyl-4-

10 (methyldamino)piperidine

NMR (CDCl₃): 1.70-1.76 (2H, br), 1.80-1.88 (2H, br), 1.94-2.00 (2H, br), 2.27 (3H, s), 2.30 (2H, br), 2.48-2.53 (1H, m), 2.93-3.03 (2H, br), 3.71 (2H, s), 3.84-3.87 (4H, m), 4.00-4.03 (4H, m), 5.28 (2H, br), 7.30 (1H, s), 7.43-7.50 (2H, m), 7.98-8.01 (2H, m), 9.04 (2H, s)

15 MS (ESI⁺): MH⁺ 475.33 (10%)

6-{3-[(Methyl-pyridin-3-ylmethyl-amino)-methyl]-phenyl}-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine (**44**) was prepared using N-methyl-N-(3-pyridylmethyl)amine.

20 NMR (CDCl₃): 2.27 (3H, s), 3.59 (2H, s), 3.68 (2H, s), 3.85-3.88 (4H, m), 4.00-4.03 (4H, m), 5.30 (2H, br), 7.30 (1H, s), 7.46-7.55 (2H, m), 7.73 (1H, d, J=7.8Hz), 8.00 (1H, d), 8.06 (1H, s), 8.53 (1H, d), 8.62 (1H, d), 9.05 (2H, s)

MS (ESI⁺): MH⁺ 469.25 (40%)

25 1-[3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-benzyl]-4-phenyl-piperidin-4-ol (**45**) was prepared using 4-hydroxy-4-phenylpiperidine.

NMR (CDCl₃): 1.77-1.81 (2H, br. d), 2.17-2.25 (2H, m), 2.53-2.59 (2H, br. t), 2.84-2.87 (2H, br. d), 3.50 (2H, s), 3.84-3.87 (4H, m), 4.00-4.03 (4H, m), 5.30 (2H, br), 7.23-7.30 (2H, m), 7.36-7.40 (2H, m), 7.46-7.50 (2H, m), 7.53-7.55 (2H, m), 8.01 (1H, d),

30 8.06 (1H, s), 9.05 (2H, s)

MS (ESI⁺): MH⁺ 524.34 (50%)

2-Morpholin-4-yl-6-[3-(4-pyrimidin-2-yl-piperazin-1-ylmethyl)-phenyl]-[4,5']bipyrimidinyl-2'-ylamine (**46**) was prepared using 2-piperazin-1-yl-pyrimidine. NMR (CDCl₃): 2.56-2.59 (4H, m), 3.68 (2H, s), 3.84-3.88 (8H, m), 4.00-4.03 (4H, m), 5.28 (2H, br), 6.49 (1H, t), 7.30 (1H, s), 7.47-7.54 (2H, m), 8.01-8.05 (2H, m), 8.32 (2H, d), 9.05 (2H, s)
MS (ESI⁺): MH⁺ 511.2 (50%)

6-(3-Dimethylaminomethyl-phenyl)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine (**47**) was prepared using dimethylamine. NMR (CDCl₃): 2.23 (6H, br. s), 3.47 (2H, s), 3.75-3.78 (4H, m), 3.90-3.93 (4H, m), 5.20 (2H, br), 7.22 (1H, s), 7.38 (2H, m), 7.92-7.96 (2H, m), 8.96 (2H, s)
MS (ESI⁺): MH⁺ 392.2 (20%)

Example 6 [3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-phenyl]-methanol (43)

[3-(6-Chloro-2-morpholin-4-yl-pyrimidin-4-yl)-phenyl]-methanol was isolated by column chromatography from the reactions between 3-(6-chloro-2-morpholin-4-yl-pyrimidin-4-yl)-benzaldehyde and a secondary amine.

[3-(6-Chloro-2-morpholin-4-yl-pyrimidin-4-yl)-phenyl]-methanol (53mg, 0.173mmol) and 2-aminopyrimidine-5-boronic acid pinacol ester (1.8 equiv., 69mg) were taken up in acetonitrile (3ml). To this were added sodium carbonate (55mg) as a solution in water (1ml) and PdCl₂(PPh₃)₂ (0.05 equiv.). The reaction mixture was heated in microwave at 140°C for 30 min. Purification using SCX-2 cartridge, flash chromatography and trituration with diethyl ether gave the title compound as a white solid (24mg).
NMR (CDCl₃): 1.79 (1H, br), 3.84-3.87 (4H, m), 4.00-4.03 (4H, m), 4.84 (2H, s), 5.30 (2H, br), 7.30 (1H, s), 7.49-7.54 (2H, m), 8.02-8.05 (1H, m), 8.12 (1H, s), 9.04 (2H, s)
MS (ESI⁺): MH⁺ 365.16 (18%)

Example 7**2-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-ylamino)-N-methyl-acetamide (83)**

Intermediate F1 (70mg, 0.24mmol) was suspended in a solution of methylamine in methanol (2M, 2ml) and stirred at room temperature overnight. The reaction mixture
5 was diluted with water and the precipitate was filtered, washed with water and air-dried to give 2-(6-chloro-2-morpholin-4-yl-pyrimidin-4-ylamino)-N-methyl-acetamide (58mg).

2-(6-Chloro-2-morpholin-4-yl-pyrimidin-4-ylamino)-N-methyl-acetamide (56mg, 0.20mmol) and 2-aminopyrimidine-5-boronic acid pinacol ester (1.8 equiv.,
10 78mg) were taken up in acetonitrile (3ml). To this were added sodium carbonate (64mg) as a solution in water (1ml) and PdCl₂(PPh₃)₂ (5%). The reaction mixture was heated in microwave at 140°C for 30 min. Purification using SCX-2 cartridge, flash chromatography and diethyl ether/DCM trituration gave the title compound as a white solid (22mg).

15 NMR (DMSO): 2.59 (2H, d), 3.61-3.64 (4H, m), 3.67-3.71 (4H, m), 3.83 (2H, d), 6.29 (1H, s), 6.98 (2H, br), 7.75 (1H, br), 8.78 (2H, s)
MS (ESI+): MH⁺ 345.12 (85%)

The following compounds were prepared in an analogous manner using

20 Intermediate F1 and the appropriate amine:

2-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-ylamino)-N,N-dimethyl-acetamide (84) was prepared using dimethylamine

NMR (DMSO): 2.87 (3H, s), 3.02 (3H, s), 3.63-3.66 (4H, m), 3.67-3.69 (4H, m), 4.13
25 (2H, d), 6.39 (1H, s), 6.98 (3H, br), 8.81 (2H, s)
MS (ESI+): MH⁺ 359.12 (100%)

2-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-ylamino)-1-morpholin-4-yl-ethanone (86) was prepared using morpholine.

30 NMR (DMSO): 3.44-3.52 (4H, br), 3.55-3.62 (4H, br), 3.63-3.66 (4H, m), 3.68-3.70 (4H, m), 4.16 (2H, d), 6.39 (1H, br), 6.99 (3H, br), 8.80 (2H, br)
MS (ESI+): MH⁺ 401.15 (100%)

2-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-ylamino)-1-(4-methyl-piperazin-1-yl)-ethanone (**88**) was prepared using N-methylpiperazine.

NMR (DMSO): 2.20 (3H, s), 2.23-2.36 (4H, br), 3.45-3.49 (4H, br), 3.63-3.66 (4H, m), 3.67-3.69 (4H, m), 4.16 (2H, d), 6.48 (1H, s), 6.98-7.00 (3H, br), 8.78-8.82 (2H, br)

5 MS (ESI+): MH+ 414.18 (100%)

The following compounds were prepared in an analogous manner Intermediate F2 and the appropriate amine.

10 3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-ylamino)-N-methyl-propionamide (**85**) was prepared using methylamine.

NMR (DMSO): 2.35 (2H, m), 2.57 (3H, d), 3.47-3.52 (2H, m), 3.63-3.66 (4H, m), 3.68-3.70 (4H, m), 6.22 (1H, br), 6.96 (3H, br), 7.77 (1H, br), 8.78 (2H, br)

MS (ESI+): MH+ 359.12 (100%)

15

3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-ylamino)-N,N-dimethyl-propionamide (**99**) was prepared using dimethylamine.

NMR (CDCl₃): 2.62 (2H, t), 3.00 (6H, d), 3.77-3.80 (2H+4H, m), 3.83-3.85 (4H, m), 5.20 (2H, br), 5.52 (1H, br t), 6.00 (1H, s), 8.87 (2H, s)

20 MS (ESI+): MH+ 373.16 (100%)

3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-ylamino)-1-morpholin-4-yl-propan-1-one (**107**) was prepared using morpholine.

NMR (CDCl₃): 2.62 (2H, t), 3.45 (2H, t), 3.66-3.70 (6H, m), 3.77-3.81 (6H, m), 3.83-3.85 (4H, m), 5.18 (2H, br), 5.41 (1H, br), 6.00 (1H, s), 8.87 (2H, s)

25

MS (ESI+): MH+ 415.15 (100%)

Example 8

N-[2-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-ylamino)-ethyl]-methanesulfonamide (**87**)

30

Intermediate A1 (300mg, 1.28mmol) and N-BOC-ethylenediamine (1.3 equiv., 264ul) were refluxed in acetonitrile (3ml) with potassium carbonate (1.5 equiv., 230mg) overnight. The reaction mixture was then cooled to room temperature and diluted with

water. The precipitate was filtered, washed with water and air-dried to give [2-(6-chloro-2-morpholin-4-yl-pyrimidin-4-ylamino)-ethyl]-carbamic acid tert-butyl ester (453mg).

[2-(6-Chloro-2-morpholin-4-yl-pyrimidin-4-ylamino)-ethyl]-carbamic acid tert-butyl ester (453mg, 1.27mmol) was dissolved in DCM (10ml), to this was added a solution of hydrogen chloride in diethyl ether (2M, 5ml) and the reaction mixture was stirred at room temperature overnight. Volatiles were removed *in vacuo*, the residue triturated with diethyl ether to give N-1*-(6-chloro-2-morpholin-4-yl-pyrimidin-4-yl)-ethane-1,2-diamine hydrochloride as a foamy solid (441mg).

N-1*-(6-Chloro-2-morpholin-4-yl-pyrimidin-4-yl)-ethane-1,2-diamine hydrochloride (150mg, 0.51mmol) was dissolved in pyridine (1ml), to this was added methanesulfonyl chloride (1.2 equiv., 47ul) and the reaction mixture was stirred at room temperature overnight. Volatiles were removed *in vacuo*, the residue was partitioned between DCM and brine, organics dried (MgSO₄), filtered, evaporated *in vacuo* and purified by column chromatography to give N-[2-(6-chloro-2-morpholin-4-yl-pyrimidin-4-ylamino)-ethyl]-methanesulfonamide as a foamy solid (53mg).

To N-[2-(6-Chloro-2-morpholin-4-yl-pyrimidin-4-ylamino)-ethyl]-methanesulfonamide (53mg, 0.158mmol) and 2-aminopyrimidine-5-boronic acid pinacol ester (63mg) in acetonitrile (3ml) was added sodium carbonate (3 equiv., 51mg) as a solution in water (1ml) and PdCl₂(PPh₃)₂ (0.05 equiv.). The reaction mixture was heated in microwave at 140°C for 30 min. Purification using SCX-2 cartridge, flash chromatography and diethyl ether trituration gave the title compound as beige solid (19mg).

NMR (DMSO): 2.90 (3H, s), 3.12-3.14 (2H, m), 3.49 (2H, m), 3.64-3.66 (4H, m), 3.69-3.71 (4H, m), 5.75 (1H, s), 6.21 (1H, br), 6.97 (2H, br), 7.10 (1H, br), 8.79 (2H, br)
MS (ESI+): MH⁺ 395.10 (100%)

N-[2-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-ylamino)-ethyl]-acetamide (**90**) was prepared in an analogous manner using acetyl chloride.

NMR (DMSO): 1.81 (3H, s), 3.15-3.22 (2H, m), ~ 3.30 (2H, under H₂O peak), 3.63-3.66 (4H, m), 3.67-3.70 (4H, m), 6.20 (1H, br), 6.98 (3H, br), 7.90 (1H, br), 8.80 (2H, br)

MS (ESI+): MH⁺ 359.15 (100%)

Example 9 **4-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-2-methyl-but-3-yn-2-ol (114)**

- 5 To Intermediate B (30mg, 0.103mmol), 2-methyl-3-butyn-2-ol (1.2 equiv., 12ul) and copper (I) iodide (0.022 equiv., 0.5mg) in acetonitrile (2ml) were added triethylamine (2 equiv., 29ul) and PdCl₂(PPh₃)₂ (0.05 equiv., 3.5mg). The reaction mixture was heated in microwave at 180°C for 10 min. Purification using SCX-2 cartridge and flash chromatography gave the title compound as a beige solid (16mg).
- 10 NMR (CDCl₃): 1.67 (6H, s), 2.13 (1H, br), 3.78-3.82 (4H, m), 3.89-3.92 (4H, m), 5.31 (2H, br), 6.94 (1H, s), 8.95 (2H, s)
- MS (ESI+): MH⁺ 341.10 (100%)

- 15 The following compounds were prepared in an analogous manner using the appropriate starting material.

- 6-(3-Dimethylamino-prop-1-ynyl)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine (124) was prepared from 1-dimethylamino-2-propyne.
- 20 NMR (CDCl₃): 2.38 (6H, s), 3.50 (2H, s), 3.74-3.78 (4H, m), 3.85-3.88 (4H, m), 5.27 (2H, br), 6.91 (1H, s), 8.91 (2H, s)
- MS (ESI+): MH⁺ 340.16 (100%)

- 6-(3-Methoxy-prop-1-ynyl)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine (125) was prepared from methylpropargyl ether.
- 25 NMR (CDCl₃): 3.50 (3H, s), 3.78-3.82 (4H, m), 3.89-3.92 (4H, m), 4.38 (2H, s), 5.31 (2H, br), 6.97 (1H, s), 8.95 (2H, s)
- MS (ESI+): MH⁺ 327.13 (15%)

- 2-Morpholin-4-yl-6-pyridin-2-ylethynyl-[4,5']bipyrimidinyl-2'-ylamine (138) was prepared from 2-ethynylpyridine.
- 30 NMR (CDCl₃): 3.80-3.84 (4H, m), 3.92-3.96 (4H, m), 5.32 (2H, br), 7.15 (1H, s), 7.32-7.36 (1H, m), 7.65 (1H, d), 7.72-7.77 (1H, m), 8.69 (1H, d), 8.97 (2H, s)

MS (ESI+): MH⁺ 360.12 (100%)

Example 10 **2-Morpholin-4-yl-6-phenoxy-[4,5']bipyrimidinyl-2'-ylamine**
(10)

5 A mixture of Intermediate A1 (204mg), phenol (90mg) and potassium carbonate (180mg) in N,N-dimethylformamide (5mL) was stirred at 80°C for 5 hours. The reaction mixture was then cooled, diluted with ethyl acetate, washed with water, dried (MgSO₄) and the solvent removed in vacuo to yield 4-(4-chloro-6-phenoxy-pyrimidin-2-yl)-morpholine.

10 Reaction of 4-(4-chloro-6-phenoxy-pyrimidin-2-yl)-morpholine with 2-aminopyrimidine-5-boronic acid, pinacol ester using standard Suzuki conditions yielded the desired title compound.

¹H NMR (400MHz, CDCl₃). 3.70-3.80 (8H,m), 5.20 (2H,s,br.), 6.32 91H,s), 7.20 (2H,d), 7.24-7.27 (1H,m), 7.38-7.42 (2H,m), 8.90 (2H,s)

15 MH⁺ 351

The following compounds were prepared in a similar manner commencing with the appropriate starting material:

20 6-(3,5-Difluoro-phenoxy)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine (**34**) was prepared from 3,5-difluorophenol.

NMR: (DMSO, 400MHz): 3.61 (br s, 8H, 4xCH₂); 6.83 (s, 1H, ArH); 7.06-7.17 (m, 3H, 3xArH); 7.18 (br s, 2H, NH₂); 8.97 (s, 2H), 2xArH).

MS: (ESI+): MH⁺ = 387.10

25

6-(2,6-Dimethyl-phenoxy)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine (**35**) was prepared from 2,6-dimethylphenol.

NMR: (DMSO, 400MHz): 2.08 (s, 6H, 2xCH₃); 3.52-3.56 (m, 8H, 4xCH₂); 6.75 (s, 1H, ArH); 7.06-7.12 (m, 3H, 3xArH); 7.14 (br s, 2H, NH₂); 8.94 (s, 2H, 2xArH).

30 MS: (ESI+): MH⁺ = 379.14

6-(3,4-Dimethoxy-phenoxy)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine (**40**) was prepared using 3,4-dimethoxyphenol.

NMR: (CDCl₃, 400MHz): 3.65-3.69 (m, 8H, 2xCH₂); 3.78 (s, 3H, CH₃); 3.84 (s, 3H, CH₃); 5.19 (br s, 2H, NH₂); 6.22 (s, 1H, ArH); 6.65 (d, 1H, ArH, J = 8.0Hz); 6.67 (s, 1H, ArH); 6.80 (d, 1H, ArH, J = 8.7Hz); 8.79 (s, 2H, 2xArH).

MS: (ESI+): MH⁺ = 411.16

3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yloxy)-benzonitrile (**51**) was prepared from 3-cyanophenol.

10 NMR: (CDCl₃, 400MHz): 3.62 (br s, 8H, 4xCH₂); 5.25 (br s, 2H, NH₂); 6.38 (s, 1H, ArH); 7.34-7.47 (m, 4H, 4xArH); 8.85 (s, 2H, 2xArH).

MS: (ESI+): MH⁺ = 376.13

15 6-(4-Methanesulfonyl-phenoxy)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine (**82**) was prepared from 4-methylsulphonylphenol.

NMR: (DMSO, 400MHz): 3.25 (s, 3H, CH₃); 3.61 (br s, 8H, 4xCH₂); 6.89 (s, 1H, ArH); 7.20 (br s, 2H, NH₂); 7.50 (d, 2H, 2xArH, J = 8.8Hz); 7.99 (d, 2H, 2xArH, J = 8.8Hz); 8.99 (s, 2H, 2xArH).

MS: (ESI+): MH⁺ = 429.10

20

Example 11 4-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yloxy)-N,N-dimethyl-benzamide (26)

To a solution of Intermediate D1 (70mg) in dry N,N-dimethylformamide (2mL) was added 1,1-carbonyldiimidazole (42mg). After 2 hours dimethylamine hydrochloride (25mg) and triethylamine (41μL) were added. The reaction mixture was stirred overnight before water was added to yield a precipitate. This was collected by filtration and air-dried to yield 4-(6-chloro-2-morpholin-4-yl-pyrimidin-4-yloxy)-N,N-dimethyl-benzamide (76mg).

30 Reaction of 4-(6-chloro-2-morpholin-4-yl-pyrimidin-4-yloxy)-N,N-dimethyl-benzamide with 2-aminopyrimidine-5-boronic acid, pinacol ester using standard Suzuki conditions yielded the desired title compound.

¹H NMR (400MHz, CDCl₃)

2.95-3.15 (6H,br.), 3.70-3.75 (8H,br.), 5.30 (2H,s,br.), 6.40 (1H,s), 7.20 (2H,d), 7.50 (2H,d), 8.90 (2H,s).

MH+422

- 5 4-(2'-Amino-5-methyl-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yloxy)-N,N-dimethyl-benzamide (**146**) was prepared as above using Intermediate A2
- NMR: MeOD: 2.31 (3 H, s, Me), 3.03 (3 H, s, Me), 3.13 (3 H, s, Me), 3.60-3.63 (4 H, m), 3.64-3.68 (4 H, m), 7.32-7.39 (3 H, m, Ar), 7.56-7.60 (1 H, m, Ar) and 8.90 (2 H, s, Ar).
- 10 MS: (ESI+): MH+ 436.22

The following compounds were prepared in an analogous manner using one of Intermediate D1, Intermediate D2 and Intermediate D3 and the appropriate amine.

- 15 4-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yloxy)-N-methyl-benzamide (**27**) was prepared using Intermediate D1 and methylamine.
- 1H NMR (400MHz, DMSO)
- 2.79 (3H,d), 3.60 (8H,br.), 6.80 (1H,s), 7.11 (2H,s,br.), 7.28 (2H,d), 7.91 (2H,d), 8.41 (1H,q), 8.99 (2H,s)
- 20 MH+408

[4-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yloxy)-phenyl]-(4-methyl-piperazin-1-yl)-methanone (**37**) was prepared using Intermediate D1 and N-methylpiperazine.

- 25 1H NMR (400MHz, CDCl₃)
- 2.40 (3H,s), 2.40-2.55 (4H,br.), 3.50-3.70 (12H,br.), 5.30 (2H,s,br.), 6.40 (1H,s), 7.20 (2H,d), 7.50 (2H,d), 8.90 (2H,s).
- MH+477

- 30 3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yloxy)-N,N-dimethyl-benzamide (**52**) was prepared using Intermediate D2 and dimethylamine.HCl.

NMR: (CDCl₃, 400MHz): 3.02 (br s, 3H); 3.13 (br s, 3H); 3.73 (br s, 8H); 5.30 (br s, 2H); 6.41 (s, 1H); 7.23-7.33 (m, 3H); 7.44-7.48 (m, 1H, ArH); 8.91 (s, 2H, 2xArH).

MS: (ESI+): MH⁺ = 422.19

- 5 3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yloxy)-N-methyl-benzamide (**53**) was prepared using Intermediate D2 and methylamine.HCl.

NMR: (CDCl₃, 400MHz): 2.96 (d, 3H); 3.63 (br s, 8H); 5.19 (br s, 2H); 6.02 (br s, 1H); 6.32 (s, 1H); 7.22-7.25 (m, 1H); 7.37 (dd, 1H); 7.53 (s, 1H); 7.54 (d, 1H); 8.82 (s, 2H).

MS: (ESI+): MH⁺ = 408.16

10

[3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yloxy)-phenyl]-(4-methanesulfonyl-piperazin-1-yl)-methanone (**54**) was prepared using Intermediate D2 and Intermediate G.

NMR: (CDCl₃, 400MHz): 2.83 (s, 3H, CH₃); 3.28 (br s, 4H, 2xCH₂); 3.73 (br s, 12H, 6xCH₂); 5.30 (s, 2H, NH₂); 6.42 (s, 1H, ArH); 7.25-7.32 (m, 3H, 3xArH); 7.50 (dd, 1H, ArH, J = 7.9Hz); 8.92 (s, 2H, 2xArH);

15

MS: (ESI+): MH⁺ = 541.25

3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yloxy)-phenyl]-(4-methyl-piperazin-1-yl)-methanone (**64**) was prepared using was prepared using Intermediate D2 and N-methylpiperazine.

20

NMR: (CDCl₃, 400MHz): 2.50 (s, 3H, CH₃); 2.50 (br s, 2H, CH₂); 2.40 (br s, 2H, CH₂); 3.39 (br s, 2H, CH₂); 3.64 (br s, 8H, 4xCH₂); 3.71 (br s, 2H, CH₂); 5.22 (s, 2H, NH₂); 6.32 (s, 1H, ArH); 7.15 (s, 1H, ArH); 7.17-7.22 (m, 2H, 2xArH); 7.38 (dd, 1H, ArH, J = 7.8Hz); 8.82 (s, 2H, 2xArH).

25

MS: (ESI+): MH⁺ = 477.23

2-[4-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yloxy)-phenyl]-N,N-dimethyl-acetamide (**73**) was prepared using Intermediate D3 and dimethylamine. HCl.

30

NMR: (CDCl₃, 400MHz): 2.92 (s, 3H, CH₃); 2.97 (s, 3H, CH₃); 3.65 (s, 2H, CH₂); 3.67 (br s, 8H, 4xCH₂); 5.17 (s, 2H, NH₂); 6.26 (s, 1H, ArH); 7.06 (d, 2H, 2xArH, J = 8.5Hz); 7.22 (d, 2H, 2xArH, J = 8.5Hz); 8.80 (s, 2H, 2xArH).

MS: (ESI+): MH⁺ = 436.44

Example 12 **2-Morpholin-4-yl-N-6-phenyl-[4,5']bipyrimidinyl-6,2'-diamine (49)**

5 To a solution of N-BOC-aniline(171mg) in dry N,N-dimethylformamide (was added sodium hydride (60% dispersion in mineral oil, 59mg). After stirring for 15 minutes, Intermediate A1 (197mg) was added and the reaction mixture was heated to 80°C for 5 hours. The reaction mixture was then cooled, diluted with ethyl acetate, washed with brine, dried (MgSO₄) and the solvent removed in vacuo. The residue was
10 purified using flash chromatography to yield (6-chloro-2-morpholin-4-yl-pyrimidin-4-yl)-phenyl-carbamic acid tert-butyl ester.

 Reaction of (6-chloro-2-morpholin-4-yl-pyrimidin-4-yl)-phenyl-carbamic acid tert-butyl ester with 2-aminopyrimidine-5-boronic acid, pinacol ester using standard Suzuki conditions yielded the desired title compound (the BOC group was cleaved
15 during the Suzuki reaction).

1H NMR (400MHz, CDCl₃)

3.79-3.83 (4H,m), 3.88-3.91 (4H,m), 5.20 (2H,s), 6.30 (1H,s), 6.61 (1H,s,br.), 7.11-7.14 (1H,m), 7.35-7.40 (4H,m), 8.85 (2H,s)

MH⁺350

20

Example 13 **N-[4-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-phenyl]-N-methyl-methanesulfonamide (56)**

 Standard Suzuki reaction between Intermediate A1 and t-butyl-N-methyl-N-[4-(tetramethyldioxaboronyl)phenyl]carbamate yielded [4-(6-chloro-2-morpholin-4-yl-pyrimidin-4-yl)-phenyl]-methyl-carbamic acid tert-butyl ester. Cleavage of the BOC
25 grup using HCl in ether yielded [4-(6-chloro-2-morpholin-4-yl-pyrimidin-4-yl)-phenyl]-methyl-amine.

 Reaction of [4-(6-chloro-2-morpholin-4-yl-pyrimidin-4-yl)-phenyl]-methyl-amine with methane sulphonyl chloride in dichloromethane using triethylamine as base
30 yielded N-[4-(6-chloro-2-morpholin-4-yl-pyrimidin-4-yl)-phenyl]-N-methyl-methanesulfonamide.

Reaction of N-[4-(6-chloro-2-morpholin-4-yl-pyrimidin-4-yl)-phenyl]-N-methyl-methanesulfonamide with 2-aminopyrimidine-5-boronic acid, pinacol ester using standard Suzuki conditions yielded the desired title compound.

NMR (CDCl₃): 2.90 (3H, s), 3.41 (3H, s), 3.84-3.87 (4H, m), 3.99-4.02 (4H, m), 5.29 (2H, br), 7.26 (1H, s), 7.53 (2H, d), 8.12 (2H, d), 9.30 (2H, s)

MS (ESI⁺): MH⁺ 442.13 (10%), (MH+AcN) 483.2 (100%)

Example 14

6-Benzoyloxy-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine (72)

To benzyl alcohol in DMF at 0°C was slowly added sodium hydride. After 20 minutes, Intermediate A was added and heated to 95°C overnight. EtOAc/brine extraction followed by purification on silica yielded 4-(4-benzyloxy-6-chloro-pyrimidin-2-yl)-morpholine.

4-(4-Benzoyloxy-6-chloro-pyrimidin-2-yl)-morpholine was reacted with 2-aminopyrimidine-5-boronic acid pinacol ester in General Suzuki Procedure A.

Purification using an SCX cartridge yielded the title compound.

NMR: (CDCl₃, 400MHz): 3.71 (t, 4H); 3.79 (t, 4H); 5.16 (br s, 2H); 5.32 (s, 2H, CH₂); 6.29 (s, 1H, ArH); 7.24-7.37 (m, 5H, 5xArH); 8.82 (s, 2H, 2xArH).

MS: (ESI⁺): MH⁺ = 365.15

The following compounds were prepared in an analogous manner using the appropriate alcohol.

2-Morpholin-4-yl-6-(pyridin-3-ylmethoxy)-[4,5']bipyrimidinyl-2'-ylamine (**81**) was prepared from 3-pyridylcarbinol.

NMR: (DMSO, 400MHz): 3.67 (t, 4H, J = 4.7Hz); 3.77 (t, 4H, 2xCH₂, J = 4.6Hz); 5.44 (s, 2H, CH₂); 6.66 (s, 1H, ArH); 7.10 (br s, 2H, NH₂); 7.41-7.44 (m, 1H, ArH); 7.86-7.89 (m, 1H, ArH); 8.54-8.55 (m, 1H, ArH); 8.68 (s, 1H, ArH); 8.92 (s, 2H, 2xArH).

MS: (ESI⁺): MH⁺ = 366.14

5-Methyl-2-morpholin-4-yl-6-(pyridin-3-ylmethoxy)-[4,5']bipyrimidinyl-2'-ylamine (**145**) was prepared from 3-pyridylcarbinol and Intermediate A2.

NMR: MeOD: 2.23 (3 H, s, Me), 3.78-3.80 (4 H, m), 3.83-3.86 (4 H, m), 5.81 (2 H, s, CH₂), 8.21 (1 H, dd, J 8.1 and 5.8, Ar), 8.83-8.85 (1 H, m, Ar), 8.86 (2 H, s, Ar), 8.91 (1 H, d, J 5.8, Ar) and 9.10 (1 H, s, Ar).

MS: (ESI⁺): MH⁺ 380.18

5

5-[2-Morpholin-4-yl-6-(pyridin-3-ylmethoxy)-pyrimidin-4-yl]-pyridin-2-ylamine (**132**) was also prepared from 3-pyridylcarbinol, followed by Suzuki coupling with 2-aminopyridine-5-boronic acid pinacol ester

10 NMR: (CDCl₃, 400MHz): 3.80 (t, 4H, 2xCH₂); 3.88 (t, 4H, 2xCH₂); 4.66 (br s, 2H, NH₂); 5.44 (s, 2H, CH₂); 6.41 (s, 1H, ArH); 6.56 (d, 1H, ArH, J = 8.7Hz); 7.27-7.34 (m, 1H, ArH); 7.77-7.80 (dt, 1H, ArH); 8.08-8.10 (dd, 1H, ArH, J = 8.6Hz, 2.3Hz); 8.59-8.61 (dd, 1H, ArH, J = 4.8Hz, 1.6Hz); 8.72 (d, 1H, ArH, J = 1.7Hz); 8.72-8.75 (m, 1H, ArH).

MS: (ESI⁺): MH⁺ = 365.14

15

Methyl-{5-[2-morpholin-4-yl-6-(pyridin-3-ylmethoxy)-pyrimidin-4-yl]-pyridin-2-yl}-amine (**134**) was also prepared from 3-pyridylcarbinol, followed by Suzuki coupling with Intermediate I.

20 NMR: (CDCl₃, 400MHz): 3.01 (d, 3H, CH₃); 3.79 (t, 4H, 2xCH₂); 3.88 (t, 4H, 2xCH₂); 4.81 (q, 1H, NH); 5.44 (s, 2H, CH₂); 6.40 (s, 1H, ArH); 6.44 (d, 1H, ArH); 7.31-7.34 (m, 1H, ArH); 7.77-7.80 (dt, 1H, ArH); 8.09 (dd, 1H, ArH); 8.59 (dd, 1H, ArH); 8.72 (d, 1H, ArH); 8.79 (d, 1H, ArH).

MS: (ESI⁺): MH⁺ = 379.14

25 1-[2-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yloxy)-ethyl]-pyrrolidin-2-one (**91**) was prepared from 1-(2-hydroxyethyl)-2-pyrrolidinone.

NMR: (CDCl₃&MeOD, 400MHz): 1.89-1.94 (m, 2H, CH₂); 2.26 (t, 2H, CH₂, J = 8.1Hz); 3.44 (t, 2H, CH₂, J = 7.1Hz); 3.53 (t, 2H, CH₂, J = 5.4Hz); 3.65-3.72 (m, 8H, 4xCH₂); 4.35 (t, 2H, CH₂, J = 5.3Hz); 6.18 (s, 1H, ArH); 8.72 (s, 2H, 2xArH).

30 MS: (ESI⁺): MH⁺ = 386.14

6-(2-Dimethylamino-ethoxy)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine (**112**) was prepared from N,N-dimethylethanolamine.

NMR: (CDCl₃, 400MHz): 2.35 (s, 6H, 2xCH₃); 2.72 (t, 2H, CH₃, J = 5.8Hz); 3.80 (t, 4H, 2xCH₂, J = 4.5Hz); 3.87 (t, 4H, 2xCH₂, J = 4.3Hz); 4.45 (t, 2H, CH₂, J = 5.8Hz);
5 5.25 (br s, 2H, NH₂); 6.37 (s, 1H, ArH); 8.90 (s, 2H, 2xArH).

MS: (ESI+): MH⁺ = 346.17

2-Morpholin-4-yl-6-phenethyloxy-[4,5']bipyrimidinyl-2'-ylamine (**115**) was prepared using phenethylalcohol.

10 NMR: (CDCl₃, 400MHz): 3.01 (t, 2H, CH₂, J = 7.2Hz); 3.70 (t, 4H, 2xCH₂, J = 4.4Hz); 3.77 (t, 4H, 2xCH₂, J = 4.3Hz); 4.64 (t, 2H, CH₂, J = 7.2Hz); 5.13 (br s, 2H, NH₂); 6.22 (s, 1H, ArH); 7.16-7.27 (m, 5H, 5xArH); 8.81 (s, 2H, 2xArH).

MS: (ESI+): MH⁺ = 379.12

15 6-(3-Methanesulfonyl-benzyloxy)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine (**116**) was prepared from (3-methanesulfonyl-phenyl)-methanol.

NMR: (CDCl₃, 400MHz): 3.09 (s, 3H, CH₃); 3.80 (t, 4H, 2xCH₂, J = 4.5Hz); 3.87 (t, 4H, 2xCH₂, J = 4.5Hz); 5.27 (br s, 2H, NH₂); 5.49 (s, 2H, CH₂); 6.41 (s, 1H, ArH); 7.62 (dd, 1H, ArH, J = 7.7Hz); 7.74 (d, 1H, ArH, J = 7.7Hz); 7.93 (d, 1H, ArH, J = 7.8Hz);
20 8.07 (s, 1H, ArH); 8.92 (s, 2H, 2xArH).

MS: (ESI+): MH⁺ = 443.09

(3-Methanesulfonyl-phenyl)-methanol was prepared as follows: To 3-Methanesulfonyl-benzoic acid in THF at 0°C was added dropwise a borane-THF
25 complex and the reaction mixture stirred at room temperature overnight. Excess hydride was destroyed by slow addition of a water/THF mixture. The aqueous phase was saturated with potassium carbonate then extracted with ether. The organics were dried with MgSO₄ and the solvent reduced in vacuo to yield (3-methanesulfonyl-phenyl)-methanol as a clear oil.

30 3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yloxymethyl)-benzonitrile (**117**) was prepared from 3-hydroxymethyl-benzonitrile

NMR: (CDCl₃, 400MHz): 3.79 (t, 4H); 3.86 (t, 4H, 2xCH₂, J = 4.5Hz); 5.27 (br s, 2H, NH₂); 5.44 (s, 2H, CH₂); 6.39 (s, 1H, ArH); 7.51 (dd, 1H, ArH, J = 7.8Hz); 7.64 (d, 1H, ArH, J = 7.8Hz); 7.68 (d, 1H, ArH, J = 8.0Hz); 7.76 (s, 1H, ArH); 8.92 (s, 2H, 2xArH).
MS: (ESI+): MH⁺ = 390.19

5

3-Hydroxymethyl-benzonitrile was prepared as follows: To 3-cyanobenzaldehyde in dry MeOH at 0°C was added NaBH₄ and the reaction stirred at room temperature for 2 hours. The mixture was quenched with 50:50 H₂O:sat. aq. NaHCO₃ then extracted into MeOH-EtOAc to yield 3-hydroxymethyl-benzonitrile.

10

2-Morpholin-4-yl-6-(2-pyridin-3-yl-ethoxy)-[4,5']bipyrimidinyl-2'-ylamine (**118**) was prepared from 3-(2-hydroxyethyl)pyridine.

NMR: (CDCl₃, 400MHz): 3.11 (t, 2H, CH₂); 3.80 (t, 4H, 2xCH₂); 3.86 (t, 4H, 2xCH₂); 4.57 (t, 2H, CH₂); 5.25 (br s, 2H, NH₂); 6.30 (s, 1H, ArH); 7.26-7.28 (m, 1H, ArH); 7.62 (d, 1H, ArH, J = 7.8Hz); 8.52 (m, 1H, ArH); 8.57 (s, 1H, ArH); 8.91 (s, 2H, 2xArH).

15

MS: (ESI+): MH⁺ = 380.12

6-(3-Methyl-3H-imidazol-4-ylmethoxy)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine (**120**) was prepared from (1-methyl-1H-imidazol-5-yl)methanol.

20

NMR: (CDCl₃&CD₃OD, 400MHz): 3.24 (t, 4H, 2xCH₂, J = 4.6Hz); 3.65 (s, 3H, CH₃); 3.81 (t, 4H, 2xCH₂, J = 4.6Hz); 5.11 (s, 2H, CH₂); 6.38 (s, 1H, ArH); 6.87 (s, 1H, ArH); 7.32 (s, 1H, ArH); 8.75 (s, 2H, 2xArH).

MS: (ESI+): MH⁺ = 369.18

25

2-Morpholin-4-yl-6-(quinolin-3-ylmethoxy)-[4,5']bipyrimidinyl-2'-ylamine (**121**) was prepared from quinolin-3-yl-methanol.

NMR: (CDCl₃, 400MHz): 3.71 (t, 4H); 3.80 (t, 4H, 2xCH₂); 5.14 (br s, 2H, NH₂); 5.53 (s, 2H, CH₂); 6.32 (s, 1H, ArH); 7.50 (dd, 1H, ArH); 7.66 (dd, 1H, ArH, J = 7.7Hz); 7.76 (d, 1H, ArH); 8.05 (d, 1H, ArH); 8.15 (s, 1H, ArH); 8.83 (s, 2H, 2xArH); 8.93 (s, 1H, ArH).

30

MS: (ESI+): MH⁺ = 416.20

Quinolin-3-yl-methanol was prepared as follows: To 3-quinolinecarboxaldehyde in dry MeOH at 0°C was added NaBH₄ and the reaction stirred at room temperature for 2 hours. The mixture was quenched with 50:50 H₂O:sat. aq. NaHCO₃ then extracted into MeOH-EtOAc to yield quinolin-3-yl-methanol.

5

3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yloxymethyl)-N,N-dimethylbenzamide (**123**) was prepared from 3-hydroxymethyl-N,N-dimethylbenzamide NMR: (CDCl₃, 400MHz): 3.00 (br s, 3H, CH₃); 3.13 (br s, 3H, CH₃); 3.79 (t, 4H, 2xCH₂, J = 4.5Hz); 3.87 (t, 4H, 2xCH₂, J = 4.4Hz); 5.27 (br s, 2H, NH₂); 5.43 (s, 2H, CH₂); 6.38 (s, 1H, ArH); 7.37-7.49 (m, 3H, 3xArH); 7.52 (s, 1H, ArH); 8.91 (s, 2H, 2xArH).

10

MS: (ESI+): MH⁺ = 436.24

3-Hydroxymethyl-N,N-dimethylbenzamide was prepared as follows: To 3-carboxybenzaldehyde in DMF was added carbonyldiimidazole. After stirring for 4 hours, triethylamine and dimethylamine.HCl were added and the mixture stirred at room temperature for a weekend. The mixture was quenched with water, extracted into DCM and washed with brine. Drying with MgSO₄ and removal of the solvent in vacuo yielded crude material which was purified on silica to give 3-Formyl-N,N-dimethylbenzamide as a yellow oil.

20

To 3-formyl-N,N-dimethylbenzamide in methanol at 0°C was added NaBH₄ and the reaction stirred at room temperature for 2 hours. Quenching with H₂O/sat.aq. NaHCO₃ followed by extraction into MeOH-EtOAc yielded 3-Hydroxymethyl-N,N-dimethylbenzamide.

25

4-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yloxymethyl)-benzonitrile (**126**) was prepared from 4-hydroxymethylbenzonitrile. NMR: (CDCl₃, 400MHz): 3.68-3.76 (m, 8H, 4xCH₂); 5.16 (br s, 2H, NH₂); 5.38 (s, 2H, CH₂); 6.31 (s, 1H, ArH); 7.45 (d, 2H, 2xArH, J = 8.1Hz); 7.60 (d, 2H, 2xArH, J = 8.3Hz); 8.83 (s, 2H, 2xArH). MS: (ESI+): MH⁺ = 390.16

30

4-Hydroxymethyl-benzonitrile was prepared as follows: To 4-cyanobenzaldehyde in dry MeOH at 0°C was added NaBH₄ and the reaction stirred at room temperature for 2 hours. The mixture was quenched with 50:50 H₂O:sat. aq. NaHCO₃ then extracted into MeOH-EtOAc to yield 4-hydroxymethyl-benzonitrile.

5

6-(4-Methanesulfonyl-benzyloxy)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine (127) was prepared from *p*-(methanesulfonyl)benzylalcohol.

NMR: (DMSO, 400MHz): 3.21 (s, 3H, CH₃); 3.64 (t, 4H, 2xCH₂, J = 4.6Hz); 3.74 (t, 4H, 2xCH₂, J = 4.4Hz); 5.51 (s, 2H, CH₂); 6.69 (s, 1H, ArH); 7.11 (br s, 2H, NH₂), 7.70 (d, 2H, 2xArH, J = 8.3Hz); 7.94 (d, 2H, 2xArH, J = 8.4Hz); 8.93 (s, 2H, 2xArH).
MS: (ESI+): MH⁺ = 443.15

10

6-(1-Methyl-1-phenyl-ethoxy)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine (135) was prepared from 2-phenyl-2-propanol.

15 NMR: (DMSO, 400MHz): 3.49 (m, 3H, CH₃); 3.61 (m, 3H, CH₃); 3.67 (s, 8H, 4xCH₂); 6.19 (s, 1H, ArH); 6.60 (s, 1H, ArH); 7.02 (m, 1H, ArH); 7.05 (s, 2H, NH₂); 7.14 (d, 1H, ArH); 7.98 (s, 1H, ArH); 8.84 (s, 2H, 2xArH).
MS: (ESI+): MH⁺ = 393.14

20 2-Morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-[4,5']bipyrimidinyl-2'-ylamine (119) was prepared from 2-(2-hydroxyethyl)pyridine.

NMR (CDCl₃): 3.28 (2H, t), 3.77-3.80 (4H, m), 3.85-3.88 (4H, m), 4.75 (2H, t), 5.21 (2H, br), 6.29 (1H, s), 7.16-7.19 (1H, m), 7.25-7.28 (1H, m), 7.62-7.66 (1H, m), 8.59 (1H, d), 8.90 (2H, s)

25 MS (ESI+): MH⁺ 380.18 (100%)

2-Morpholin-4-yl-6-(2-pyridin-4-yl-ethoxy)-[4,5']bipyrimidinyl-2'-ylamine (122) was prepared from 4-(2-hydroxyethyl)pyridine.

30 NMR (CDCl₃): 3.10 (2H, t), 3.78-3.81 (4H, m), 3.85-3.88 (4H, m), 4.59 (2H, t), 5.23 (2H, br), 6.29 (1H, s), 7.23 (2H, d), 8.57 (2H, d), 8.90 (2H, s)

MS (ESI+): MH⁺ 380.20 (30%)

6-[2-(3-Methanesulfonyl-phenyl)-ethoxy]-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine (**141**) was prepared from 2-(3-methanesulfonyl-phenyl)-ethanol.

NMR (CDCl₃): 3.07 (3H, s), 3.20 (2H, t), 3.79-3.82 (4H, m), 3.85-3.88 (4H, m), 4.60 (2H, t), 5.23 (2H, br), 6.29 (1H, s), 7.53-7.61 (2H, m), 7.84 (1H, d), 7.90 (1H, s), 8.90

5 (2H, s)

MS (ESI⁺): MH⁺ 457.17 (100%)

2-(3-methanesulfonyl-phenyl)-ethanol was prepared as follows: To a solution of 3-methylsulphonylphenylacetic acid (200mg, 0.93mmol) in dry THF (3ml) at 0°C was added borane-tetrahydrofuran complex (1.0M solution in THF, 1.4 equiv, 1.31ml) dropwise. The reaction was allowed to warm up to room temperature overnight and then quenched with water. DCM/brine extraction gave 2-(3-methanesulfonyl-phenyl)-ethanol as a clear oil (184mg).

15 3-[2-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yloxy)-ethyl]-benzonitrile (**142**) was prepared from 2-(3-cyanol-phenyl)-ethanol.

NMR (CDCl₃): 3.14 (2H, t), 3.79-3.82 (4H, m), 3.85-3.88 (4H, m), 4.57 (2H, t), 5.24 (2H, br), 6.29 (1H, s), 7.42-7.47 (1H, m), 7.52-7.60 (3H, m), 8.91 (2H, s)

MS (ESI⁺): MH⁺ 404.20 (90%)

20

2-(3-cyanol-phenyl)-ethanol was prepared as follows: To a solution of 3-cyanophenylacetic acid (250mg, 1.55mmol) in dry THF (3ml) at 0°C was added borane-tetrahydrofuran complex (1.0M solution in THF, 1.4 equiv, 2.17ml) dropwise. The reaction was allowed to warm up to room temperature overnight and then quenched with water. DCM/brine extraction gave 2-(3-cyanol-phenyl)-ethanol as a yellow oil (170mg).

6-[2-(1H-Indol-3-yl)-ethoxy]-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine (**144**) was prepared from 3-(2-hydroxy-ethyl)-indole-1-carboxylic acid tert-butyl ester.

30 NMR (CDCl₃): 3.27 (2H, t), 3.76-3.80 (4H, m), 3.83-3.87 (4H, m), 4.63 (2H, t), 5.23 (2H, br), 6.33 (1H, s), 7.12 (1H, s), 7.16 (1H, t), 7.24 (1H, t), 7.40 (1H, d), 8.03 (1H, br), 8.91 (2H, s)

MS (ESI+): MH⁺ 418.17 (100%)

3-(2-Hydroxy-ethyl)-indole-1-carboxylic acid tert-butyl ester was prepared as follows: To a solution of tryptophol (200mg, 1.25mmol) in DCM (5ml) were added di-
5 tert-butylidicarbonate (1.5equiv, 410mg) and dimethylaminopyridine (0.05equiv, 8mg) and the reaction mixture was stirred at room temperature overnight. DCM/brine extraction afforded 3-(2-hydroxy-ethyl)-indole-1-carboxylic acid tert-butyl ester as an oil (348mg).

10 Example 15 [4-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-piperazin-1-yl]-phenyl-methanone (3)

To Intermediate H in chloroform was added benzoylchloride and triethylamine. After stirring overnight at room temperature, EtOAc/brine extraction followed by purification on silica yielded [4-(6-Chloro-2-morpholin-4-yl-pyrimidin-4-yl)-piperazin-
15 1-yl]-phenyl-methanone.

[4-(6-Chloro-2-morpholin-4-yl-pyrimidin-4-yl)-piperazin-1-yl]-phenyl-methanone was reacted with 2-aminopyrimidine-5-boronic acid pinacol ester in General Procedure A. Purification on silica gave the title compound.

NMR: (CDCl₃, 400MHz): 3.64 (br s, 8H, 4xCH₂); 3.68-3.70 (m, 4H, 2xCH₂); 3.73-3.75
20 (m, 4H, 2xCH₂); 5.12 (s, NH₂); 6.10 (s, 1H, ArH); 7.37-7.38 (m, 5H, 5xArH); 8.80 (s, 2H, 2xArH).

MS: (ESI+): MH⁺ = 447.22

6-(4-Benzenesulfonyl-piperazin-1-yl)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine
25 (9) was prepared in an analogous manner using Intermediate H and benzene sulphonyl chloride.

NMR: (CDCl₃, 400MHz): 3.13 (t, 4H, J = 5.1Hz, 2xCH₂); 3.76-3.80 (m, 12H, 2xCH₂ + 4xCH₂); 5.19 (br s, 2H, NH₂); 6.11 (s, 1H, ArH); 7.54-7.65 (m, 3H, 3xArH); 7.79-7.81
(m, 2H, 2xArH); 8.85 (s, 2H, 2xArH).

30 MS: (ESI+): MH⁺ = 483.18

[4-(2'-Amino-2-morpholin-4-yl)-[4,5']bipyrimidinyl-6-yl)-piperazin-1-yl]-morpholin-4-yl-methanone (11) was prepared in an analogous manner using Intermediate H and morpholine carbonyl chloride.

NMR: (CDCl₃, 400MHz): 3.18-3.27 (m, 8H, 4xCH₂); 3.54-3.59 (m, 8H, 4xCH₂); 3.63-3.71 (m, 8H, 4xCH₂); 5.06 (s, 2H, NH₂); 6.04 (s, 1H, ArH); 8.75 (s, 2H, 2xArH).

MS: (ESI+): MH⁺ = 456.21

Example 16

6-(4-Benzyl-piperazin-1-yl)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine (33)

To Intermediate H in acetonitrile was added potassium carbonate and benzylbromide. After heating to reflux overnight, EtOAc/brine extraction followed by purification on silica yielded 4-[4-(4-Benzyl-piperazin-1-yl)-6-chloro-pyrimidin-2-yl]-morpholine.

4-[4-(4-Benzyl-piperazin-1-yl)-6-chloro-pyrimidin-2-yl]-morpholine was reacted with 2-aminopyrimidine-5-boronic acid pinacol ester in General Procedure A. Purification on silica yielded the title compound.

NMR: (CDCl₃, 400MHz): 2.55 (t, 4H, 2xCH₂, J = 5.1Hz); 3.58 (s, 2H); 3.68 (t, 4H, 2xCH₂, J = 5.0Hz); 3.75-3.84 (m, 8H, 4xCH₂); 5.18 (br s, 2H, NH₂); 6.17 (s, 1H, ArH); 7.29-7.37 (m, 5H, 5xArH); 8.88 (s, 2H, 2xArH).

MS: (ESI+): MH⁺ = 433.17

Example 17

2-Morpholin-4-yl-6-(3-morpholin-4-ylmethyl-phenoxy)-[4,5']bipyrimidinyl-2'-ylamine (48)

To a solution of Intermediate E1 in DCE was added dropwise morpholine and trimethylorthoformate. After stirring at room temperature for 1 hour, sodium triacetoxyborohydride was added and the mixture stirred at room temperature overnight. Quenching with aqueous sodium carbonate, followed by DCM/brine extraction and purification on silica yielded 4-[4-chloro-6-(3-morpholin-1-ylmethyl-phenoxy)-pyrimidin-2-yl]-morpholine.

4-[4-Chloro-6-(3-morpholin-1-ylmethyl-phenoxy)-pyrimidin-2-yl]-morpholine was reacted with 2-aminopyrimidine-5-boronic acid pinacol ester in General Procedure A to give the title compound.

NMR: (CDCl₃, 400MHz): 2.47 (t, 4H, 2xCH₂, J = 4.5Hz); 3.54 (s, 2H, CH₂); 3.71-3.76 (m, 12H, 6xCH₂); 5.29 (br s, 2H, NH₂); 6.35 (s, 1H, ArH); 7.08-7.23 (m, 3H, 3xArH); 7.37 (dd, 1H, ArH, J = 15.6Hz); 8.89 (s, 2H, 2xArH).

MS: (ESI+): MH⁺ = 450.20

5

6-[3-(4-Methanesulfonyl-piperazin-1-ylmethyl)-phenoxy]-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine (**50**) was prepared in a similar manner using Intermediate E1 and Intermediate G.

10 NMR: (CDCl₃, 400MHz): 2.32 (t, 4H, 2xCH₂); 2.52 (s, 3H, CH₃); 2.99 (t, 4H, 2xCH₂, J = 4.7Hz); 3.32 (s, 2H, CH₂); 3.48 (m, 8H, 4xCH₂); 5.00 (br s, 2H, NH₂); 6.07 (s, 1H, ArH); 6.83-6.94 (m, 3H, 3xArH); 7.11 (dd, 1H, ArH, J = 7.8Hz); 8.61 (s, 2H, 2xArH).
MS: (ESI+): MH⁺ = 527.30

15 6-(4-Dimethylaminomethyl-phenoxy)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine (**55**) was prepared in a similar manner using Intermediate E2 and dimethylamine hydrochloride.

NMR: (CDCl₃, 400MHz): 2.28 (s, 6H, 2xCH₃); 3.46 (s, 2H, CH₂); 3.74-3.76 (m, 8H, 4xCH₂); 5.30 (br s, 2H, NH₂); 6.34 (s, 1H, ArH); 7.14 (d, 2H, 2xArH, J = 8.6Hz); 7.36 (d, 2H, 2xArH, J = 8.4Hz); 8.89 (s, 2xArH, 2H)
20 MS: (ESI+): MH⁺ = 408.20

6-[4-(4-Methyl-piperazin-1-ylmethyl)-phenoxy]-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine (**59**) was prepared in similar manner using Intermediate E1 and N-methylpiperazine.

25 NMR: (DMSO, 400MHz): 2.15 (s, 3H, CH₃); 2.33 (br s, 4H, 2xCH₂); 2.36 (br s, 4H, 2xCH₂); 3.47 (s, 2H, CH₂); 3.58 (br s, 8H, 4xCH₂); 6.75 (s, 1H, ArH); 7.14 (d, 2H, 2xArH, J = 8.5Hz); 7.18 (s, 2H, NH₂); 7.33 (d, 2H, 2xArH); 8.94 (s, 2H, 2xArH).
MS: (ESI+): MH⁺ = 463.26

30 2-Morpholin-4-yl-6-(4-morpholin-4-ylmethyl-phenoxy)-[4,5']bipyrimidinyl-2'-ylamine (**61**) was prepared in a similar manner using Intermediate E2 and morpholine.

NMR: (CDCl₃, 400MHz): 2.49 (t, 4H, 2xCH₂, J = 4.4Hz); 3.55 (s, 2H, CH₂); 3.74-3.76 (m, 12H, 6xCH₂); 5.29 (br s, 2H, NH₂); 6.33 (s, 1H, ArH); 7.14 (d, 2H, 2xArH, J = 8.5Hz); 7.38 (d, 2H, 2xArH, J = 8.4Hz); 8.88 (s, 2H, 2xArH);
MS: (ESI+): MH⁺ = 450.25

5

6-[4-(4-Methanesulfonyl-piperazin-1-ylmethyl)-phenoxy]-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine (**71**) was prepared using Intermediate E2 and Intermediate G.

NMR: (CDCl₃, 400MHz): 2.52 (t, 4H, 2xCH₂); 2.72 (s, 3H, CH₃); 3.20 (t, 4H, 2xCH₂, J = 4.5Hz); 3.53 (s, 2H, CH₂); 3.66 (br s, 8H, 4xCH₂); 5.18 (s, 2H, NH₂); 6.24 (s, 1H, ArH); 7.07 (d, 2H, 2xArH, J = 8.4Hz); 7.28 (d, 2H, 2xArH); 8.80 (s, 2H, 2xArH)
MS: (ESI+): MH⁺ = 527.32

10

Example 18 **6-Methoxy-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine**
(98)

15

To Intermediate A in DMF was added sodium methoxide in methanol and stirred at room temperature overnight. EtOAc/brine extraction yielded 4-(4-Chloro-6-methoxy-pyrimidin-2-yl)-morpholine.

4-(4-Chloro-6-methoxy-pyrimidin-2-yl)-morpholine was reacted with 2-aminopyrimidine-5-boronic acid pinacol ester in General Procedure A to yield the title compound.

20

NMR: (CDCl₃, 400MHz): 3.71 (t, 4H, 2xCH₂, J = 4.7Hz); 3.80 (t, 4H, 2xCH₂, J = 4.6Hz); 3.86 (s, 3H, CH₃); 5.19 (br s, 2H, NH₂); 6.22 (s, 1H, ArH); 8.82 (s, 2H, 2xArH).
MS: (ESI+): MH⁺ = 289.12

25

Example 19 **N-6-(3-Methanesulfonyl-phenyl)-2-morpholin-4-yl-[4,5']bipyrimidinyl-6,2'-diamine (63)**

To a solution of 3-methylsulphonylaniline hydrochloride salt (177 mg) in THF (20 mL) was added sodium hydride (68 mg) and the reaction was stirred at room temperature for 30 minutes. Then a solution of intermediate A (200 mg) in THF (5 mL) was added and the reaction was heated at reflux for 16 h. After cooling to room temperature the reaction was quenched with water (20 mL) and extracted into ethyl

30

acetate (2 x 20 mL). The combined organics were washed with aqueous brine solution (2 x 20 mL), dried (MgSO₄) reduced in vacuo and purified by column chromatography to give (6-chloro-2-morpholin-4-yl-pyrimidin-4-yl)-(3-methanesulfonyl-phenyl)-amine as a yellow solid.

- 5 (6-Chloro-2-morpholin-4-yl-pyrimidin-4-yl)-(3-methanesulfonyl-phenyl)-amine was reacted with 2-aminopyrimidine-5-boronic acid pinacol ester in general procedure A. Purification by column chromatography yielded the title compound.
NMR: DMSO: 3.19 (3 H, s, Me), 3.68-3.71 (4 H, m), 3.79-3.82 (4 H, m), 6.48 (1 H, s, Ar), 7.11 (2 H, s, NH), 7.46-7.47 (1 H, m, Ar), 7.58 (1 H, t, J 7.0, Ar), 7.71-7.73 (1 H, m, Ar), 8.69 (1 H, s, Ar), 8.83 (2 H, s, Ar) and 9.80 (1 H, s, Ar).
10 MS: (ESI+): MH⁺ 428.13

N-6-(3-Methanesulfonyl-phenyl)-5-methyl-2-morpholin-4-yl-[4,5']bipyrimidinyl-6,2'-diamine (**150**) was prepared in an analogous manner using Intermediate A2.

- 15 NMR: MeOD: 2.12 (3 H, s, Me), 3.01 (3 H, s, Me), 3.22 (1 H, s, NH), 3.68 (8 H, s), 7.42-7.44 (1 H, m, Ar), 7.48-7.51 (1 H, m, Ar), 7.68-7.70 (1 H, m, Ar), 8.42 (2 H, s, Ar) and 8.49 (1 H, s, Ar).
MS: (ESI+): MH⁺ 442.17

- 20 The following compounds were prepared in an analogous manner using the appropriate aniline, and the appropriate boronic acid or boronate ester

2-Morpholin-4-yl-N-6-pyridin-3-yl-[4,5']bipyrimidinyl-6,2'-diamine (**80**) was prepared using 3-aminopyridine.

- 25 NMR: CDCl₃: 3.70-3.73 (4 H, m), 3.75-3.77 (4 H, m), 6.26 (1 H, s), 7.21 (1 H, dd, J 8.0 and 4.5, Ar), 8.06-8.09 (2 H, m, Ar), 8.61 (1 H, s, Ar) and 8.89 (2 H, s, Ar).
MS: (ESI+): MH⁺ 351.13

- 2-Morpholin-4-yl-N-6-pyridin-2-yl-[4,5']bipyrimidinyl-6,2'-diamine (**109**) was prepared
30 using 2-aminopyridine.

NMR: DMSO: 3.70-3.72 (4 H, m), 3.75-3.77 (4 H, m), 6.95-6.97 (1 H, m, Ar), 7.09 (2 H, s, NH₂), 7.17 (1 H, s, Ar), 7.71-7.72 (1 H, m, Ar), 7.91-7.93 (1 H, m, Ar), 8.27-8.29 (1 H, m, Ar), 8.81 (2 H, s, Ar) and 9.72 (1 H, s, NH).

MS: (ESI⁺): MH⁺ 351.12

5

N-6-(4-Methanesulfonyl-phenyl)-2-morpholin-4-yl-[4,5']bipyrimidinyl-6,2'-diamine (**103**) was prepared using 4-methylsulphonyl aniline.

NMR: DMSO: 3.12 (3 H, s, Me), 3.69-3.72 (4 H, m, CH₂), 3.81-3.83 (4 H, m, CH₂), 6.53 (1 H, s, Ar), 7.10 (2 H, s, NH₂), 7.84 (2 H, d, J 7.5, Ar), 7.91 (2 H, d, J 7.5, Ar), 8.81 (2 H, s, Ar) and 9.82 (1 H, s, NH).

10

MS: (ESI⁺): MH⁺ 428.08

N-6-Methyl-6-morpholin-4-yl-N-6-phenyl-[4,5']bipyrimidinyl-6,2'-diamine (**106**) was prepared using N-methylaniline.

15 NMR: DMSO: 3.41 (3 H, s), 3.71-3.73 (4 H, m), 3.79-3.83 (4 H, m), 5.12 (2 H, s, NH₂), 5.86 (1 H, s, Ar), 7.18-7.26 (3 H, m, Ar), 7.35-7.39 (2 H, m, Ar) and 8.63 (2 H, s, Ar).

MS: (ESI⁺): MH⁺ 364.13

(3-Methanesulfonyl-phenyl)-[6-(6-methylamino-pyridin-3-yl)-2-morpholin-4-yl-

20 pyrimidin-4-yl]-amine (**129**) was prepared as described for compound (**63**) followed by Suzuki coupling with Intermediate I.

NMR (DMSO): 2.72 (3H, d), 3.19 (3H, s), 3.68-3.72 (4H, m), 3.77-3.81 (4H, m), 6.45 (1H, s), 6.52 (1H, d), 6.93 (1H, br), 7.48 (1H, d), 7.60 (1H, t), 7.71 (1H, d), 8.00 (1H, d), 8.69 (1H, s), 8.72 (1H, s), 9.72 (1H, s)

25 MS (ESI⁺): MH⁺ 441.13 (100%)

Example 20

2-Morpholin-4-yl-N-6-(1H-pyrazol-3-yl)-[4,5']bipyrimidinyl-6,2'-diamine (110)

To a solution of 3-aminopyrazole (300 mg) in dichloromethane (8 mL) was added di-tertbutyldicarbonate (280 mg) and the reaction was stirred at room temperature for 16 h. The reaction was quenched with water (20 mL) and extracted into dichloromethane (2 x 20 mL). The combined organics were dried (MgSO₄) reduced in

30

vacuo and purified by column chromatography to give 3-amino-pyrazole-1-carboxylic acid tert-butyl ester as a white solid.

To a solution of 3-amino-pyrazole-1-carboxylic acid tert-butyl ester (156 mg) in THF (20 mL) was added sodium hydride (34 mg) and the reaction was stirred at room temperature for 30 minutes. Then a solution of Intermediate A (200 mg) in THF (5 mL) was added and the reaction was heated at reflux for 16 h. After cooling to room temperature the reaction was quenched with water (20 mL) and extracted into ethyl acetate (2 x 20 mL). The combined organics were washed with aqueous brine solution (2 x 20 mL), dried (MgSO₄) reduced in vacuo and purified by column chromatography to give 3-(6-chloro-2-morpholin-4-yl-pyrimidin-4-ylamino)-pyrazole-1-carboxylic acid tert-butyl ester as a white solid.

3-(6-Chloro-2-morpholin-4-yl-pyrimidin-4-ylamino)-pyrazole-1-carboxylic acid tert-butyl ester was reacted with 2-aminopyrimidine-5-boronic acid pinacol ester in general procedure A to yield the title compound.

NMR: DMSO: 3.64-3.68 (4 H, m), 3.81-3.83 (4 H, m), 5.41 (2 H, s, NH), 5.72 (1 H, s), 5.88-5.89 (1 H, m), 7.10 (1 H, s), 7.12 (1 H, s), 8.31-8.38 (1 H, m) and 8.91 (2 H, s, Ar). MS: (ESI⁺): MH⁺ 340.15

Example 21

3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-ylamino)-N,N-dimethyl-benzenesulfonamide (104)

To a solution of 3-nitrobenzenesulfonyl chloride (400 mg) in dichloromethane (10 mL) was added triethylamine (0.57 mL), dimethylaminopyridine (10 mg) and dimethylamine hydrochloride (134 mg) and the mixture was stirred at room temperature for 16 h. The reaction was partitioned between dichloromethane (20 mL) and water (20 mL) and the organics were washed with aqueous brine solution (2 x 20 mL), dried (MgSO₄) and reduced in vacuo to give N,N-dimethyl-3-nitro-benzenesulfonamide as a white solid.

To a solution of N,N-dimethyl-3-nitro-benzenesulfonamide (384 mg) in ethanol (10 mL) was added water (5 mL), iron (466 mg), acetic acid (10 mL) and concentrated hydrochloric acid (3 drops) and the mixture was heated at reflux for 4 h. After cooling to room temperature, the mixture was filtered through Celite, washing with ethyl acetate

(20 mL). Water (30 mL) was added and the mixture was basified with potassium carbonate.

The product was extracted into ethyl acetate (2 x 20 mL) and the combined organics were washed with aqueous brine solution (2 x 20 mL), dried (MgSO₄) and
5 reduced in vacuo to give 3-amino-N,N-dimethyl-benzenesulfonamide as a white solid.

To a solution of 3-amino-N,N-dimethyl-benzenesulfonamide (171 mg) in THF (20 mL) was added sodium hydride (34 mg) and the reaction was stirred at room temperature for 30 minutes. Then a solution of intermediate A (200 mg) in THF (5 mL) was added and the reaction was heated at reflux for 16 h. After cooling to room
10 temperature the reaction was quenched with water (20 mL) and extracted into ethyl acetate (2 x 20 mL). The combined organics were washed with aqueous brine solution (2 x 20 mL), dried (MgSO₄) reduced in vacuo and purified by column chromatography to give 3-(6-chloro-2-morpholin-4-yl-pyrimidin-4-ylamino)-N,N-dimethyl-benzenesulfonamide.

15 3-(6-Chloro-2-morpholin-4-yl-pyrimidin-4-ylamino)-N,N-dimethyl-benzenesulfonamide was reacted with 2-aminopyrimidine-5-boronic acid pinacol ester in general procedure A to yield the title compound.

NMR: DMSO: 2.63 (6 H, s, Me), 3.69-3.70 (4 H, m, CH₂), 3.77-3.79 (4 H, m, CH₂),
6.47 (1 H, s, Ar), 7.08 (2 H, s, NH₂), 3.30 (1 H, d, J 7.5, Ar), 7.57 (1 H, t, J 7.5, Ar),
20 7.71 (1 H, d, J 7.5, Ar), 8.59 (1 H, s, Ar), 8.82 (2 H, s, Ar) and 9.74 (1 H, s, NH).

MS: (ESI⁺): MH⁺ 457.12

3-[6-(6-Amino-pyridin-3-yl)-2-morpholin-4-yl-pyrimidin-4-ylamino]-N,N-dimethyl-benzenesulfonamide (**130**) was prepared in a similar manner using 2-aminopyridine-5-
25 boronic acid pinacol ester for the last step.

NMR (CDCl₃): 2.67 (3H, s), 3.72-3.75 (4H, m), 3.81-3.85 (4H, m), 4.55 (2H, br), 6.23 (1H, s), 6.47 (1H, d), 6.52 (1H, br s), 7.35-7.45 (3H, m), 8.00 (1H, d), 8.28 (1H, s), 8.62 (1H, s)

MS (ESI⁺): MH⁺ 456.17 (15%)

30

N,N-Dimethyl-3-[6-(6-methylamino-pyridin-3-yl)-2-morpholin-4-yl-pyrimidin-4-ylamino]-benzenesulfonamide (**131**) was prepared in a similar manner using Intermediate I for the last step.

5 NMR (DMSO): 2.62 (6H, s), 2.72 (3H, d), 3.68-3.72 (4H, m), 3.77-3.81 (4H, m), 6.45 (1H, s), 6.52 (1H, d), 6.93 (1H, br), 7.28 (1H, d), 7.60 (1H, t), 7.71 (1H, d), 8.00 (1H, d), 8.62 (1H, s), 8.72 (1H, s), 9.72 (1H, s)
MS (ESI+): MH⁺ 470.16 (65%)

10 N-6-[3-(4-Methyl-piperazine-1-sulfonyl)-phenyl]-2-morpholin-4-yl-[4,5']bipyrimidinyl-6,2'-diamine (**105**) was prepared in a similar manner by replacing dimethylamine with N-methylpiperazine

15 NMR: DMSO: 2.25 (3 H, s, Me), 2.47-2.50 (4 H, m), 2.99-3.01 (4 H, m, CH₂), 3.77-3.80 (4 H, m, CH₂), 3.84-3.87 (4 H, m, CH₂), 6.32-6.33 (1 H, m, Ar), 7.29-7.31 (1 H, m, Ar), 7.39-7.42 (1 H, m, Ar), 7.55-7.57 (1 H, m, Ar), 8.55 (1 H, s, Ar) and 8.85 (2 H, s, Ar).
MS: (ESI+): MH⁺ 512.16

20 6-(6-Amino-pyridin-3-yl)-2-morpholin-4-yl-pyrimidin-4-yl]-[3-(4-methyl-piperazine-1-sulfonyl)-phenyl]-amine (**133**) was prepared in a similar manner using 2-aminopyridine-5-boronic acid pinacol ester for the last step

NMR (CDCl₃): 2.29 (3H, s), 2.49-2.52 (4H, m), 3.08-3.10 (4H, m), 3.72-3.75 (4H, m), 3.81-3.85 (4H, m), 4.65 (2H, br), 6.23 (1H, s), 6.47 (1H, d), 6.52 (1H, br s), 7.40-7.55 (3H, m), 8.09 (1H, d), 8.34 (1H, s), 8.72 (1H, s)
MS (ESI+): MH⁺ 511.16 (10%)

25

[6-(6-Methylamino-pyridin-3-yl)-2-morpholin-4-yl-pyrimidin-4-yl]-[3-(4-methyl-piperazine-1-sulfonyl)-phenyl]-amine (**136**) was prepared in a similar manner using Intermediate I for the last step.

30 NMR (DMSO): 2.14 (3H, s), 2.36-2.38 (4H, m), 2.84 (3H, d), 2.88-2.91 (4H, m), 3.68-3.72 (4H, m), 3.77-3.81 (4H, m), 6.45 (1H, s), 6.52 (1H, d), 6.93 (1H, br), 7.28 (1H, d), 7.55 (1H, t), 7.70 (1H, d), 7.99 (1H, d), 8.58 (1H, s), 8.67 (1H, s), 9.70 (1H, s)
MS (ESI+): MH⁺ 525.29 (10%)

Example 22**6-Imidazol-1-yl-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine (139)**

To imidazole (1.1 equiv., 32mg) in dry THF (2ml) was added sodium hydride (60% wt suspension in mineral oil, 1.5 equiv., 26mg) and the reaction mixture was stirred at room temperature for 20 min. Next added intermediate A (100mg, 0.43mmol) and the reaction mixture was refluxed for 5 hours. DCM/brine extraction and column purification gave 4-(4-chloro-6-imidazol-1-yl-pyrimidin-2-yl)-morpholine as a white solid (60mg). 4-(4-Chloro-6-imidazol-1-yl-pyrimidin-2-yl)-morpholine was reacted with amino-2-pyrimidine-5-boronic acid pinacol ester in General Procedure A to give 6-imidazol-1-yl-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine as a white solid (55mg). NMR (CDCl₃): 3.82-3.86 (4H, m), 3.94-3.98 (4H, m), 5.34 (2H, br), 6.81 (1H, s), 7.23 (1H, s), 7.68 (1H, s), 8.44 (1H, s), 8.99 (2H, s) MS (ESI⁺): MH⁺ 325.15 (100%)

The following compounds were prepared in a similar manner using the appropriate starting materials.

6-(2-Methyl-imidazol-1-yl)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine (140)

NMR (CDCl₃): 2.75 (3H, s), 3.82-3.85 (4H, m), 3.92-3.96 (4H, m), 5.37 (2H, br), 6.80 (1H, s), 7.05 (1H, s), 7.40 (1H, s), 8.98 (2H, s) MS (ESI⁺): MH⁺ 339.14 (100%)

Example 23**3-[2-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yloxy)-ethyl]-benzamide (143)**

To 3-[2-(2'-amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yloxy)-ethyl]-benzonitrile 96mg, 0.24mmol (described above) in MeOH (5ml) was added sodium hydroxide (1 equiv, 9.5mg) in water (0.5ml) and hydrogen peroxide (30% solution in water, 5 equiv., 0.12ml). The reaction mixture was heated at 40°C overnight, then cooled to room temperature and diluted with water. A precipitate was filtered, washed with water, air-dried, and purified by preparative HPLC to give 3-[2-(2'-amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yloxy)-ethyl]-benzamide as a white solid (11mg).

NMR (DMSO): 3.08 (2H, t), 3.65-3.69 (4H, m), 3.72-3.76 (4H, m), 4.56 (2H, t), 6.56 (1H, s), 7.09 (2H, br), 7.30 (1H, br), 7.39 (1H, t), 7.45 (1H, t), 7.73 (1H, d), 7.83 (1H, s), 7.91 (1H, br), 8.91 (2H, s)

MS (ESI+): MH⁺ 422.14 (100%)

5

Example 24 **(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-(4-methanesulfonyl-piperazin-1-yl)-methanone (147)**

Intermediate K was reacted with Intermediate G using general procedure B. Purification by column chromatography yielded (6-chloro-2-morpholin-4-yl-pyrimidin-4-yl)-(4-methanesulfonyl-piperazin-1-yl)-methanone as an off-white solid.

10

(6-Chloro-2-morpholin-4-yl-pyrimidin-4-yl)-(4-methanesulfonyl-piperazin-1-yl)-methanone was reacted with 2-aminopyrimidine-5-boronic acid pinacol ester in general procedure A. Purification by column chromatography yielded the title compound.

15

NMR: DMSO: 2.96 (3 H, s, Me), 3.14-3.16 (2 H, m), 3.22-3.25 (2 H, m), 3.53-3.56 (2 H, m), 3.69-3.72 (4 H, m), 3.73-3.75 (2 H, m), 3.75-3.79 (4 H, m), 7.24 (3 H, s, Ar) and 9.00 (2 H, s, Ar).

MS: (ESI+): MH⁺ 449.13

The following compound was prepared in a similar manner using the appropriate amine:

20

2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-carboxylic acid methyl-phenyl-amide (**148**) was prepared using N-methylaniline

25

NMR: DMSO: 3.39 (3 H, s, Me), 3.42-3.50 (8 H, m), 7.14-7.22 (4 H, m, Ar), 7.24-7.30 (2 H, m, Ar) and 8.90 (2 H, s, Ar).

MS: (ESI+): MH⁺ 392.12

Example 25 **6-(1-Methanesulfonyl-piperidin-4-ylmethoxy)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine (152)**

30

To N-Boc-4-piperidine methanol in THF at 0°C was added NaH. After stirring for 10 minutes, Intermediate A was added and the reaction heated in the microwave at 130°C for 25 minutes. The mixture was poured onto water and the solid filtered. The

product was purified on silica, then re-dissolved in DCM and MeOH. HCl in ether was added and after stirring overnight, the solid was filtered and washed with ether.

To 4-[4-Chloro-6-(piperidin-4-ylmethoxy)-pyrimidin-2-yl]-morpholine.HCl and triethylamine in DCM at 0°C was added dropwise methanesulfonylchloride. After stirring overnight, the reaction mixture was quenched with water, extracted into DCM and washed with brine. Drying over MgSO₄ and removal of the solvent in vacuo yielded 4-[4-chloro-6-(1-methanesulfonyl-piperidin-4-ylmethoxy)-pyrimidin-2-yl]-morpholine. 4-[4-Chloro-6-(1-methanesulfonyl-piperidin-4-ylmethoxy)-pyrimidin-2-yl]-morpholine was reacted with 2-aminopyrimidine-5-boronic acid pinacol ester in General Procedure A to give the title compound.

NMR: (DMSO, 400MHz): 1.28-1.38 (m, 2H, CH₂); 1.82 -1.90 (m, 3H,); 2.45-2.75 (m, 2H, CH₂); 2.84 (s, 3H, CH₃); 3.59 (d, 2H, CH₂); 3.67 (t, 4H, 2xCH₂); 3.75 (t, 4H, 2xCH₂); 4.20 (d, 2H, CH₂); 6.59 (s, 1H, ArH); 7.08 (s, 2H, NH₂); 8.91 (s, 2H, 2xArH). MS: (ESI+): MH⁺ = 450.19

1-[4-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yloxymethyl)-piperidin-1-yl]-ethanone (**153**) was prepared in an analogous manner by using acetyl chloride.

NMR: (CDCl₃, 400MHz): 1.26-1.35 (m, 2H, CH₂); 1.84 (d, 1H, CH); 1.92 (d, 1H, CH); 2.02-2.06 (m, 1H, CH); 2.12 (s, 3H, CH₃); 2.58-2.65 (td, 1H, CH); 3.07-3.14 (td, 1H, CH); 3.80 (t, 4H, 2xCH₂); 3.87 (t, 4H, 2xCH₂); 3.90 (d, 1H, CH); 4.16-4.26 (m, 2H, CH₂); 4.70 (d, 1H, CH); 5.27 (br s, 2H, NH₂); 6.30 (s, 1H, ArH); 8.91 (s, 2H, 2xArH). MS: (ESI+): MH⁺ = 414.23

Example 26 Biological Testing

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

(i) PI3K Biochemical Screening

Compound inhibition of PI3K was determined in a radiometric assay using purified, recombinant enzyme and ATP at a concentration of 1micromole 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 10 micromole or less.

5 (ii) Cellular Proliferation Inhibition

Cells were seeded at optimal density in a 96 well plate and incubated for 4 days in the presence of test compound. Alamar BlueTM was subsequently added to the assay medium, and cells were incubated for 6 hours before reading at 544nm excitation, 590nm emission. EC₅₀ values were calculated using a sigmoidal dose response curve fit.

10 All the compounds tested had an EC₅₀s of 10 micromole or less in the range of cell lines utilized.

Example 27 Tablet composition

15 Tablets, each weighing 0.15 g and containing 25 mg of a compound of the invention are manufactured as follows:

Composition for 10,000 tablets

Active compound (250 g)

Lactose (800 g)

20 Corn starch (415g)

Talc powder (30 g)

Magnesium stearate (5 g)

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

Example 28 Injectable Formulation**Formulation A**

	Active compound	200 mg
5	Hydrochloric Acid Solution 0.1M or	
	Sodium Hydroxide Solution 0.1M q.s. to pH	4.0 to 7.0
	Sterile water q.s. to	10 ml

The compound of the invention is 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

10 hydroxide as appropriate. The batch is 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 overseals.

Formulation B

15	Active Compound	125 mg
	Sterile, Pyrogen-free, pH 7 Phosphate	
	Buffer, q.s. to	25 ml
	Active compound	200 mg
	Benzyl Alcohol	0.10 g
20	Glycofurol 75	1.45 g
	Water for injection q.s to	3.00 ml

The active compound is dissolved in the glycofurol. The benzyl alcohol is then added and dissolved, and water added to 3 ml. The mixture is then filtered through a sterile micropore filter and sealed in sterile 3 ml glass vials (type 1).

25

Example 29 Syrup Formulation

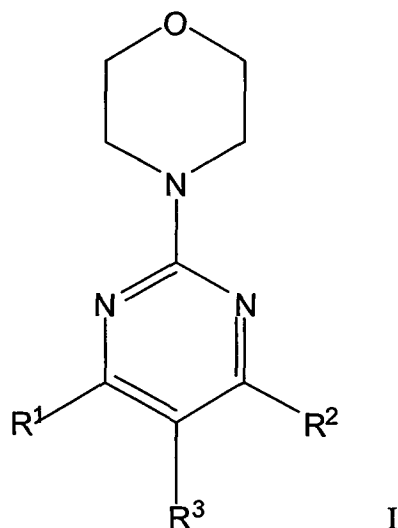
	Active compound	250 mg
	Sorbitol Solution	1.50 g
30	Glycerol	2.00 g
	Sodium benzoate	0.005 g

Flavour	0.0125 ml
Purified Water q.s. to	5.00 ml

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

CLAIMS

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



5

wherein

R^1 is selected from $-Y-R^6$ and $-NR^4R^5$;

R^2 is a N-containing monocyclic heteroaryl group selected from pyridyl, isoxazolyl, imidazolyl, pyrazolyl, pyrrolyl, thiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, oxazolyl, furanyl, thienyl, triazolyl and tetrazolyl and which is unsubstituted or substituted by $-CN$, $-NR^{10}R^{11}$, $-OR^{10}$, $-C(O)R^{10}$, $-NR^{10}C(O)R^{11}$, $-N(C(O)R^{11})_2$, $-NR^{10}C(O)NR^{10}R^{11}$, $-SO_2R^{10}R^{11}$, $-SO_2NR^{10}R^{11}$, $-C(=O)OR^{10}$, $-C(=O)NR^{10}R^{11}$, halo- C_1-C_6 alkyl and unsubstituted C_1-C_{12} alkyl;

10

R^3 is selected from H, C_1-C_6 alkyl and C_1-C_6 alkoxy;

Y is selected from a direct bond, $-(CR_2)_m-$, C_2-C_6 alkenylene, C_2-C_6 alkynylene, $-(CR_2)_p-O-(CR_2)_t-$, $-(CR_2)_p-NR-(CR_2)_t-$, $-(CR_2)_p-NR-(CR_2)_n-C(O)-$, $-(CR_2)_p-NR-C(O)-(CR_2)_n-$, $-(CR_2)_p-C(O)-NR-(CR_2)_t-$, $-(CR_2)_p-C(O)-(CR_2)_n-NR-(CR_2)_t-$ and $-(CR_2)_p-C(O)-(CR_2)_n-$;

15

R^6 is selected from an unsaturated 5- to 12-membered carbocyclic or heterocyclic ring, a saturated 5-, 6- or 7- membered N-containing heterocyclic group which is unsubstituted or substituted, C_1-C_6 alkyl, $-NR_2$, $-OR$, $-NR(CO)R$ and $-C(O)NR_2$;

20

R^4 and R^5 , which are the same or different, are both C_1 - C_6 alkyl which is unsubstituted or substituted, or R^4 and R^5 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;

5 each R , which are the same or different when more than one is present in a given group, is independently H, C_1 - C_6 alkyl which is unsubstituted or substituted or a 5- to 12-membered aryl or heteroaryl group which is unsubstituted or substituted;

R^{10} and R^{11} , which are the same or different, are independently selected from H, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl and C_3 - C_8 cycloalkyl;

10 n is 0 or an integer of 1 to 6;

m is an integer of 1 to 6;

p is 0 or an integer of 1 to 6; and

t is 0 or an integer of 1 to 6, with the proviso that t is an integer of 2 to 6 when R^6 is linked to Y through a constituent O or N atom of R^6 ;

15 or a pharmaceutically acceptable salt thereof;

with the provisos that:

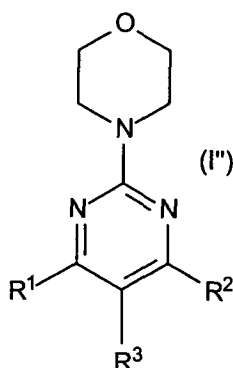
(i) when R^2 is a 4-pyridyl group and R^3 is H then R^1 is other than a phenyl group which is unsubstituted or substituted;

20 (ii) when R^2 is a pyridyl group and R^3 is H then R^1 is other than a dimethylamino group, a morpholine group or a piperazinyl group which is unsubstituted or substituted by C_1 - C_6 alkyl, phenyl or heteroaryl;

(iii) when R^2 is a thiazole group, R^1 is $-Y-R^6$ in which Y is a direct bond and R^3 is H, then R^6 is other than a 5 – 12 membered aryl group; and

25 (iv) when R^1 is $-Y-R^6$ in which Y is a group $-C(O)-NH-$, R^3 is H and R^6 is an a 5 – 12 membered aryl group, then R^2 is other than an unsubstituted pyrazole ring.

2. A compound which is a morpholino pyrimidine of formula (I''):



wherein

R^1 is $-Y-R^6$;

R^2 is a N-containing monocyclic heteroaryl group which is selected from
 5 pyridyl, isoxazolyl, imidazolyl, pyrazolyl, pyrrolyl, thiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, oxazolyl, furanyl, thienyl, triazolyl and tetrazolyl and which is substituted by $-NR^{10}R^{11}$, $-OR^{10}$, $-C(O)R^{10}$, $-NR^{10}C(O)R^{11}$, $-N(C(O)R^{11})_2$, $-NR^{10}C(O)NR^{10}R^{11}$, $-SO_2R^{10}R^{11}$, $-SO_2NR^{10}R^{11}$, $-C(=O)OR^{10}$, $-C(=O)NR^{10}R^{11}$, halo- C_1-C_6 alkyl and unsubstituted C_1-C_{12} alkyl;

10 R^3 is selected from H, C_1-C_6 alkyl and C_1-C_6 alkoxy;

Y is C_2-C_6 alkynylene or $-O-(CR_2)_t$;

R^6 is selected from C_1-C_6 alkyl, $-NR_2$, $-OR$, $-NR(CO)R$, $-C(O)NR_2$, an
 unsaturated 5- to 12-membered carbocyclic or heterocyclic ring which is unsubstituted
 or substituted and a saturated 5-, 6- or 7- membered N-containing heterocyclic group
 15 which is unsubstituted or substituted, said saturated N-containing heterocyclic group
 being C-linked to Y when Y is $-O-(CR_2)_t$;

R^4 and R^5 , which are the same or different, are both C_1-C_6 alkyl which is
 unsubstituted or substituted, or R^4 and R^5 together form, with the nitrogen atom to
 which they are attached, a saturated 5-, 6- or 7- membered N-containing heterocyclic
 20 group which is unsubstituted or substituted;

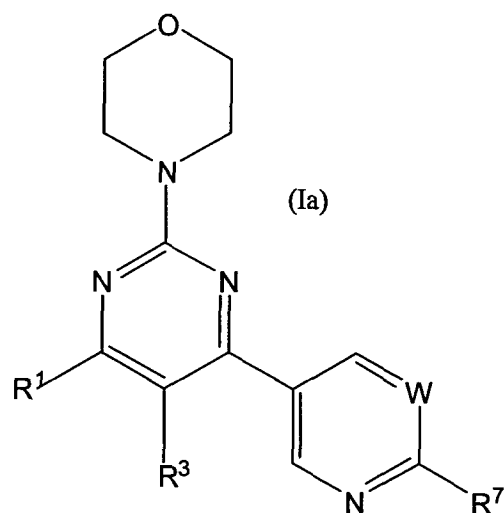
each R , which are the same or different when more than one is present in a given
 group, is independently H or C_1-C_6 alkyl which is unsubstituted or substituted;

R^{10} and R^{11} , which are the same or different, are independently selected from H,
 C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl and C_3-C_8 cycloalkyl; and

25 t is 0 or an integer of 1 to 6;

or a pharmaceutically acceptable salt thereof.

3. A compound according to claim 1 or 2 which is a morpholino pyrimidine of formula (Ia):



5

wherein

R^1 and R^3 are as defined in claim 1 or 2;

W is CR or N;

R is H or C_1-C_6 alkyl which is unsubstituted or substituted; and

10

R^7 is selected from $-NR^{10}R^{11}$, $-OR^{10}$, $-C(O)R^{10}$, $-NR^{10}C(O)R^{11}$, $-N(C(O)R^{11})_2$, $-NR^{10}C(O)NR^{10}R^{11}$, $-SO_2R^{10}R^{11}$, $-SO_2NR^{10}R^{11}$, $-C(=O)OR^{10}$, $-C(=O)NR^{10}R^{11}$, halo- C_1-C_6 alkyl and unsubstituted C_1-C_{12} alkyl, wherein R^{10} and R^{11} are as defined in claim 1;

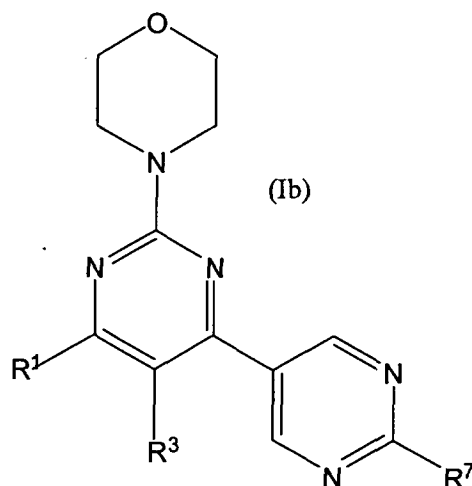
or a pharmaceutically acceptable salt thereof;

15

with the proviso that, when W is CR and R^3 is H, R^1 is other than a piperazinyl group which is substituted by a phenyl or heteroaryl group.

4. A compound according to claim 1 or 2 which is a morpholino pyrimidine of formula (Ib):

20



wherein

R^1 and R^3 are as defined in claim 1 or 2; and

R^7 is selected from $-NR^{10}R^{11}$, $-OR^{10}$, $-C(O)R^{10}$, $-NR^{10}C(O)R^{11}$, $-N(C(O)R^{11})_2$,
 5 $-NR^{10}C(O)NR^{10}R^{11}$, $-SO_2R^{10}R^{11}$, $-SO_2NR^{10}R^{11}$, $-C(=O)OR^{10}$, $-C(=O)NR^{10}R^{11}$, halo-
 C_1-C_6 alkyl and unsubstituted C_1-C_{12} alkyl, wherein R^{10} and R^{11} are as defined in claim
 1;

or a pharmaceutically acceptable salt thereof.

10 5. A compound according to claim 3 or 4 wherein R^7 is $-NR^{10}R^{11}$, $-OR^{10}$ or
 unsubstituted C_1-C_{12} alkyl, wherein R^{10} and R^{11} are as defined in claim 1.

6. A compound which is selected from:

[4-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-piperazin-1-yl]-phenyl-
 15 methanone;
 6-(4-Methanesulfonyl-piperazin-1-yl)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine;
 6-(4-Methyl-piperazin-1-yl)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine;
 6-(3-Methanesulfonyl-phenyl)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine;
 6-(4-Dimethylamino-piperidin-1-yl)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine;
 20 2-Morpholin-4-yl-N-6-pyridin-3-ylmethyl-[4,5']bipyrimidinyl-6,2'-diamine;
 6-(4-Benzenesulfonyl-piperazin-1-yl)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine;
 2-Morpholin-4-yl-6-phenoxy-[4,5']bipyrimidinyl-2'-ylamine;
 [4-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-piperazin-1-yl]-morpholin-4-
 yl-methanone;

- N-[4-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-phenyl]-methanesulfonamide;
- N-[4-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-phenyl]-acetamide;
- 3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-benzamide;
- 5 2-Morpholin-4-yl-N-6-pyridin-2-ylmethyl-[4,5']bipyrimidinyl-6,2'-diamine;
- N-6-Benzyl-2-morpholin-4-yl-[4,5']bipyrimidinyl-6,2'-diamine;
- 3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-N-methyl-benzamide;
- N-6-Benzyl-N-6-methyl-2-morpholin-4-yl-[4,5']bipyrimidinyl-6,2'-diamine;
- [3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-phenyl]-(4-methyl-piperazin-
- 10 1-yl)-methanone;
- 2-Morpholin-4-yl-N-6-pyridin-4-ylmethyl-[4,5']bipyrimidinyl-6,2'-diamine;
- 1-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-4-phenyl-piperidin-4-ol;
- N-6-[2-(3,4-Dimethoxy-phenyl)-ethyl]-N-6-methyl-2-morpholin-4-yl-[4,5']bipyrimidinyl-6,2'-diamine;
- 15 3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-benzenesulfonamide;
- 4-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yloxy)-N,N-dimethyl-benzamide;
- 4-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yloxy)-N-methyl-benzamide;
- 2-Morpholin-4-yl-6-phenyl-[4,5']bipyrimidinyl-2'-ylamine;
- 2-Morpholin-4-yl-6-pyridin-4-yl-[4,5']bipyrimidinyl-2'-ylamine;
- 20 2'-Morpholin-4-yl-[5,4';6',5'']terpyrimidin-2'-ylamine;
- 3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-ylamino)-benzoic acid;
- 6-(4-Benzyl-piperazin-1-yl)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine;
- 6-(3,5-Difluoro-phenoxy)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine;
- 6-(2,6-Dimethyl-phenoxy)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine;
- 25 3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-N-(2-dimethylamino-ethyl)-benzamide;
- [4-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yloxy)-phenyl]-(4-methyl-piperazin-1-yl)-methanone;
- 6-[3-(4-Methanesulfonyl-piperazin-1-ylmethyl)-phenyl]-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine;
- 30 6-[4-(4-Methanesulfonyl-piperazin-1-ylmethyl)-phenyl]-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine;

- 6-(3,4-Dimethoxy-phenoxy)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine;
 6-[3-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine;
 6-(3-([Methyl-(1-methyl-piperidin-4-yl)-amino]-methyl)-phenyl)-2-morpholin-4-yl-
 5 [4,5']bipyrimidinyl-2'-ylamine;
 [3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-phenyl]-methanol;
 6-{3-[(Methyl-pyridin-3-ylmethyl-amino)-methyl]-phenyl}-2-morpholin-4-yl-
 [4,5']bipyrimidinyl-2'-ylamine;
 1-[3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-benzyl]-4-phenyl-piperidin-
 10 4-ol;
 2-Morpholin-4-yl-6-[3-(4-pyrimidin-2-yl-piperazin-1-ylmethyl)-phenyl]-
 [4,5']bipyrimidinyl-2'-ylamine;
 6-(3-Dimethylaminomethyl-phenyl)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine;
 2-Morpholin-4-yl-6-(3-morpholin-4-ylmethyl-phenoxy)-[4,5']bipyrimidinyl-2'-ylamine;
 15 2-Morpholin-4-yl-N-6-phenyl-[4,5']bipyrimidinyl-6,2'-diamine;
 6-[3-(4-Methanesulfonyl-piperazin-1-ylmethyl)-phenoxy]-2-morpholin-4-yl-
 [4,5']bipyrimidinyl-2'-ylamine;
 3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yloxy)-benzonitrile;
 3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yloxy)-N,N-dimethyl
 20 -benzamide;
 3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yloxy)-N-methyl-benzamide;
 [3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yloxy)-phenyl]-(4-
 methanesulfonyl-piperazin-1-yl)-methanone;
 6-(4-Dimethylaminomethyl-phenoxy)-2-morpholin-4-yl-[4,5']bipyrimidinyl
 25 -2'-ylamine;
 N-[4-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-phenyl]-N-methyl-
 methanesulfonamide;
 N-[2-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-phenyl]-
 methanesulfonamide;
 30 6-(4-Methanesulfonyl-phenyl)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine;
 6-[4-(4-Methyl-piperazin-1-ylmethyl)-phenoxy]-2-morpholin-4-yl-[4,5']bipyrimidinyl-
 2'-ylamine;

- 2-Morpholin-4-yl-N-6-phenethyl-[4,5']bipyrimidinyl-6,2'-diamine;
 2-Morpholin-4-yl-6-(4-morpholin-4-ylmethyl-phenoxy)-[4,5']bipyrimidinyl-2'-ylamine;
 N-[3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-phenyl]-acetamide;
 N-6-(3-Methanesulfonyl-phenyl)-2-morpholin-4-yl-[4,5']bipyrimidinyl-6
 5 ,2'-diamine;
 [3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yloxy)-phenyl]-(4-
 methyl-piperazin-1-yl)-methanone;
 2-Morpholin-4-yl-N-6-(2-morpholin-4-yl-ethyl)-[4,5']bipyrimidinyl-6,2'-diamine;
 N-6-(2-Dimethylamino-ethyl)-2-morpholin-4-yl-[4,5']bipyrimidinyl-6,2'-diamine;
 10 N-6-(3-Dimethylamino-propyl)-2-morpholin-4-yl-[4,5']bipyrimidinyl-6,2'-diamine;
 N-6,N-6-Bis-(2-methoxy-ethyl)-2-morpholin-4-yl-[4,5']bipyrimidinyl-6,2'-diamine;
 N-6-(3-Fluoro-benzyl)-2-morpholin-4-yl-[4,5']bipyrimidinyl-6,2'-diamine;
 6-[4-(4-Methanesulfonyl-piperazin-1-ylmethyl)-phenoxy]-2-morpholin-4-yl-
 [4,5']bipyrimidinyl-2'-ylamine;
 15 6-Benzylloxy-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine;
 2-[4-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yloxy)-phenyl]-N
 ,N-dimethyl-acetamide;
 6-(2-Methanesulfonyl-phenyl)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine;
 4-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-N-methyl-benzamide;
 20 N-6-(3-Methanesulfonyl-benzyl)-2-morpholin-4-yl-[4,5']bipyrimidinyl-6,2'-diamine;
 2-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-N,N-dimethyl-
 benzenesulfonamide;
 4-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-N,N-dimethyl-benzamide;
 N-[3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-phenyl]-
 25 methanesulfonamide;
 2-Morpholin-4-yl-N-6-pyridin-3-yl-[4,5']bipyrimidinyl-6,2'-diamine;
 2-Morpholin-4-yl-6-(pyridin-3-ylmethoxy)-[4,5']bipyrimidinyl-2'-ylamine;
 6-(4-Methanesulfonyl-phenoxy)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-
 ylamine;
 30 2-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-ylamino)-N-methyl-acetamide;
 2-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-ylamino)-N,N-dimethyl-
 acetamide;

- 3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-ylamino)-N-methyl-propionamide;
 2-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-ylamino)-1-morpholin-4-yl-
 ethanone;
 N-[2-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-ylamino)-ethyl]-
 5 methanesulfonamide;
 2-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-ylamino)-1-(4-methyl-piperazin-1-
 yl)-ethanone;
 6-((2R,6S)-2,6-Dimethyl-morpholin-4-yl)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-
 ylamine;
 10 N-[2-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-ylamino)-ethyl]-acetamide;
 1-[2-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yloxy)-ethyl]-pyrrolidin-2-one;
 2-Morpholin-4-yl-N-6-(2-pyridin-2-yl-ethyl)-[4,5']bipyrimidinyl-6,2'-diamine;
 2-Morpholin-4-yl-N-6-(2-pyridin-3-yl-ethyl)-[4,5']bipyrimidinyl-6,2'-diamine;
 2-Morpholin-4-yl-N-6-(2-pyridin-4-yl-ethyl)-[4,5']bipyrimidinyl-6,2'-diamine;
 15 3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-N,N-dimethyl-
 benzenesulfonamide;
 4-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-N,N-dimethyl-
 benzenesulfonamide;
 6-Methoxy-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine;
 20 3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-ylamino)-N,N-dimethyl-
 propionamide;
 N-6-[2-(1H-Imidazol-4-yl)-ethyl]-2-morpholin-4-yl-[4,5']bipyrimidinyl
 -6,2'-diamine;
 N-6-[2-(1H-Indol-3-yl)-ethyl]-2-morpholin-4-yl-[4,5']bipyrimidinyl-6,
 25 2'-diamine;
 N-6-(4-Methanesulfonyl-phenyl)-2-morpholin-4-yl-[4,5']bipyrimidinyl-6
 ,2'-diamine;
 3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-ylamino)-N,N-dimeth
 yl-benzenesulfonamide;
 30 N-6-[3-(4-Methyl-piperazine-1-sulfonyl)-phenyl]-2-morpholin-4-yl-[4,5']bipyrimidinyl-
 6,2'-diamine;
 N-6-Methyl-2-morpholin-4-yl-N-6-phenyl-[4,5']bipyrimidinyl-6,2'-diamine;

- 3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-ylamino)-1-morpholin-4-yl-propan-1-one;
- 2-Morpholin-4-yl-N-6-pyridin-2-yl-[4,5']bipyrimidinyl-6,2'-diamine;
- 2-Morpholin-4-yl-N-6-(1H-pyrazol-3-yl)-[4,5']bipyrimidinyl-6,2'-diamine;
- 5 N-6-(2-Methoxy-ethyl)-N-6-methyl-2-morpholin-4-yl-[4,5']bipyrimidinyl-6,2'-diamine;
- 6-(2-Dimethylamino-ethoxy)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine;
- 4-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-2-methyl-but-3-yn-2-ol;
- 2-Morpholin-4-yl-6-phenethyloxy-[4,5']bipyrimidinyl-2'-ylamine;
- 6-(3-Methanesulfonyl-benzyloxy)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine;
- 10 3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yloxymethyl)-benzonitrile;
- 2-Morpholin-4-yl-6-(2-pyridin-3-yl-ethoxy)-[4,5']bipyrimidinyl-2'-ylamine;
- 2-Morpholin-4-yl-6-(2-pyridin-2-yl-ethoxy)-[4,5']bipyrimidinyl-2'-ylamine;
- 6-(3-Methyl-3H-imidazol-4-ylmethoxy)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine;
- 15 2-Morpholin-4-yl-6-(quinolin-3-ylmethoxy)-[4,5']bipyrimidinyl-2'-ylamine;
- 2-Morpholin-4-yl-6-(2-pyridin-4-yl-ethoxy)-[4,5']bipyrimidinyl-2'-ylamine;
- 3-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yloxymethyl)-N,N-dimethylbenzamide;
- 6-(3-Dimethylamino-prop-1-ynyl)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine;
- 20 6-(3-Methoxy-prop-1-ynyl)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine;
- 4-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yloxymethyl)-benzonitrile;
- 6-(4-Methanesulfonyl-benzyloxy)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine;
- (3-Methanesulfonyl-phenyl)-[6-(6-methylamino-pyridin-3-yl)-2-morpholin-4-yl-pyrimidin-4-yl]-amine;
- 25 3-[6-(6-Amino-pyridin-3-yl)-2-morpholin-4-yl-pyrimidin-4-ylamino]-N,N-dimethylbenzenesulfonamide;
- N,N-Dimethyl-3-[6-(6-methylamino-pyridin-3-yl)-2-morpholin-4-yl-pyrimidin-4-ylamino]-benzenesulfonamide;
- 5-[2-Morpholin-4-yl-6-(pyridin-3-ylmethoxy)-pyrimidin-4-yl]-pyridin-2-ylamine;
- 30 6-(6-Amino-pyridin-3-yl)-2-morpholin-4-yl-pyrimidin-4-yl-[3-(4-methyl-piperazine-1-sulfonyl)-phenyl]-amine;

Methyl- {5-[2-morpholin-4-yl-6-(pyridin-3-ylmethoxy)-pyrimidin-4-yl]-pyridin-2-yl}-amine;

6-(1-Methyl-1-phenyl-ethoxy)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine;

[6-(6-Methylamino-pyridin-3-yl)-2-morpholin-4-yl-pyrimidin-4-yl]-[3-(4-methyl-

5 piperazine-1-sulfonyl)-phenyl]-amine;

3-[(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-methyl-amino]-N,N-dimethyl-benzenesulfonamide;

2-Morpholin-4-yl-6-pyridin-2-ylethynyl-[4,5']bipyrimidinyl-2'-ylamine;

6-Imidazol-1-yl-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine;

10 6-(2-Methyl-imidazol-1-yl)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine;

6-[2-(3-Methanesulfonyl-phenyl)-ethoxy]-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine;

3-[2-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yloxy)-ethyl]-benzonitrile;

3-[2-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yloxy)-ethyl]-benzamide;

15 6-[2-(1H-Indol-3-yl)-ethoxy]-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine;

5-Methyl-2-morpholin-4-yl-6-(pyridin-3-ylmethoxy)-[4,5']bipyrimidinyl-2'-ylamine;

4-(2'-Amino-5-methyl-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yloxy)-N,N-dimethyl-benzamide;

(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-(4-methanesulfonyl-piperazin-1-

20 yl)-methanone;

2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-carboxylic acid methyl-phenyl-amide;

N-6-(3-Methanesulfonyl-phenyl)-5-methyl-2-morpholin-4-yl-[4,5']bipyrimidinyl-6,2'-diamine;

25 3-(2'-Amino-5-methyl-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yl)-N,N-dimethyl-benzenesulfonamide;

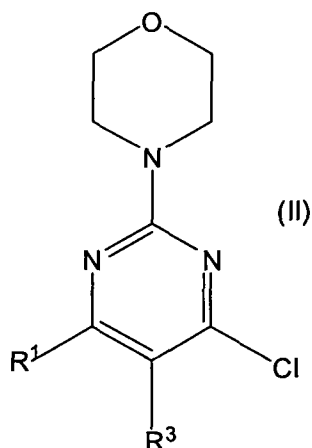
6-(1-Methanesulfonyl-piperidin-4-ylmethoxy)-2-morpholin-4-yl-[4,5']bipyrimidinyl-2'-ylamine; and

1-[4-(2'-Amino-2-morpholin-4-yl-[4,5']bipyrimidinyl-6-yloxymethyl)-piperidin-1-yl]-

30 ethanone;

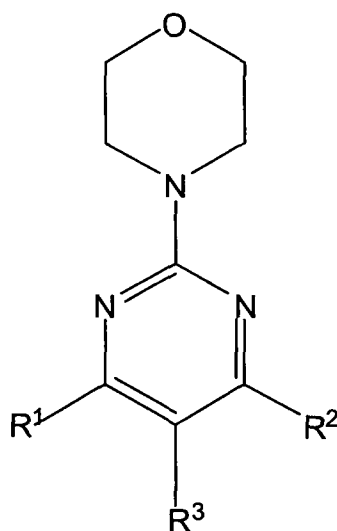
and the pharmaceutically acceptable salts thereof.

7. A process for producing a compound as defined in claim 1, which process comprises treating a compound of formula (II):



wherein R^1 and R^3 are as defined in claim 1, with a boronic acid or ester thereof of formula $R^2B(OR^{15})_2$, in which R^2 is as defined in claim 1 and each R^{15} is H or C_1-C_6 alkyl or the two groups OR^{15} form, together with the boron atom to which they are attached, a pinacolato boronate ester group, in the presence of a suitable base and a Pd catalyst.

10 8. A process for producing a pharmaceutically acceptable salt as defined in claim 1, which process comprises treating a morpholino pyrimidine of formula (I):



wherein R^1 , R^2 and R^3 are as defined in claim 1, with a suitable acid in a suitable solvent.

9. A process according to claim 8 wherein the acid is selected from hydrochloric acid, hydrobromic acid, hydroiodic acid, sulphuric acid, nitric acid, phosphoric acid, methanesulfonic acid, benzenesulphonic acid, formic acid, acetic acid, trifluoroacetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid, tartaric acid, citric acid, ethanesulfonic acid, aspartic acid and glutamic acid.

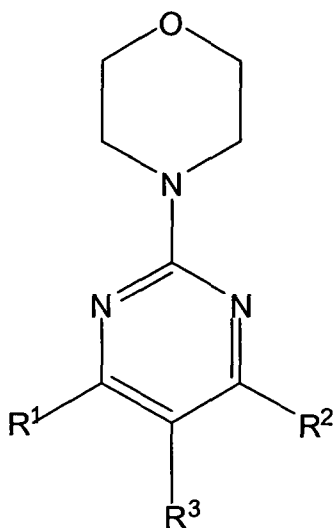
10. A pharmaceutical composition which comprises a pharmaceutically acceptable carrier or diluent and, as an active ingredient, a compound as claimed in any one of claims 1 to 6.

11. A composition according to claim 10, which is formulated for oral administration.

12. A compound as defined in any one of claims 1 to 6 for use in a method of treatment of the human or animal body by therapy.

13. A compound for use in a method of treating a disease or disorder arising from abnormal cell growth, function or behaviour, which compound is a morpholino pyrimidine of formula (I):

(I)



wherein

R^1 is selected from $-Y-R^6$ and $-NR^4R^5$;

R^2 is a N-containing monocyclic heteroaryl group which is selected from pyridyl, isoxazolyl, imidazolyl, pyrazolyl, pyrrolyl, thiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, oxazolyl, furanyl, thienyl, triazolyl and tetrazolyl and which is unsubstituted or substituted by $-CN$, $-NR^{10}R^{11}$, $-OR^{10}$, $-C(O)R^{10}$, $-NR^{10}C(O)R^{11}$, $-N(C(O)R^{11})_2$, $-NR^{10}C(O)NR^{10}R^{11}$, $-SO_2R^{10}R^{11}$, $-SO_2NR^{10}R^{11}$, $-C(=O)OR^{10}$, $-C(=O)NR^{10}R^{11}$, halo- C_1 - C_6 alkyl and unsubstituted C_1 - C_{12} alkyl;

R^3 is selected from C_1 - C_6 alkyl and C_1 - C_6 alkoxy;

Y is selected from a direct bond, $-(CR_2)_m-$, C_2 - C_6 alkenylene, C_2 - C_6 alkynylene, $-(CR_2)_p-O-(CR_2)_t-$, $-(CR_2)_p-NR-(CR_2)_t-$, $-(CR_2)_p-NR-(CR_2)_n-C(O)-$, $-(CR_2)_p-NR-C(O)-(CR_2)_n-$, $-(CR_2)_p-C(O)-NR-(CR_2)_t-$, $-(CR_2)_p-C(O)-(CR_2)_n-NR-(CR_2)_t-$ and $-(CR_2)_p-C(O)-(CR_2)_n-$;

R^3 is selected from an unsaturated 5- to 12-membered carbocyclic or heterocyclic ring, a saturated 5-, 6- or 7- membered N-containing heterocyclic group which is unsubstituted or substituted, C_1 - C_6 alkyl, $-NR_2$, $-OR$, $-NR(CO)R$ and $-C(O)NR_2$;

R^4 and R^5 , which are the same or different, are both C_1 - C_6 alkyl which is unsubstituted or substituted, or R^4 and R^5 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;

each R , which are the same or different when more than one is present in a given group, is independently H, C_1 - C_6 alkyl which is unsubstituted or substituted or a 5- to 12-membered aryl or heteroaryl group which is unsubstituted or substituted;;

R^{10} and R^{11} , which are the same or different, are independently selected from H, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl and C_3 - C_8 cycloalkyl;

n is 0 or an integer of 1 to 6; m is an integer of 1 to 6; p is 0 or an integer of 1 to 6; and

t is 0 or an integer of 1 to 6, with the proviso that t is an integer of 2 to 6 when R^6 is linked to Y through a constituent O or N atom of R^6 ;

or a pharmaceutically acceptable salt thereof;

with the provisos that:

- (i) when R^2 is a 4-pyridyl group, R^1 is other than a morpholine group, a piperazine group or a dimethylamino group;
- (ii) when R^2 is a thiazole group and R^1 is $-Y-R^6$ in which Y is a direct bond, then R^6 is other than an unsaturated 5 – 12 membered carbocyclic ring; and
- (iii) when R^1 is $-Y-R^6$ in which Y is a group $-C(O)-NH-$ and R^6 is an unsaturated 5 – 12 membered carbocyclic ring, then R^2 is other than an unsubstituted pyrazole ring.
- 10 14. Use of a compound as defined in claim 13 in the manufacture of a medicament for treating a disease or disorder arising from abnormal cell growth, function or behaviour.
- 15 15. A compound according to claim 13 or a use according to claim 14, wherein the abnormal cell growth, function or behaviour is associated with PI3 kinase.
- 20 16. A compound according to claim 13 or a use according to claim 14 wherein the disease or disorder is selected from cancer, immune disorders, cardiovascular disease, viral infection, inflammation, metabolism/endocrine disorders and neurological disorders.
17. A compound or use according to claim 16 wherein the cancer is selected from solid tumours of the colon, breast, brain, liver, ovarian, gastric, lung, and head and neck.
- 25 18. A compound or use according to claim 17 wherein the cancer is selected from glioblastoma, melanoma, prostate, endometrial, ovarian, breast, lung, head and neck, hepatocellular, and thyroid cancers.
- 30 19. A compound or use according to claim 18 wherein the cancer is selected from breast, ovary, cervix, prostate, testis, genitourinary tract, esophagus, larynx, glioblastoma, neuroblastoma, stomach, skin, keratoacanthoma, lung, epidermoid carcinoma, large cell carcinoma, non-small cell lung carcinoma (NSCLC), small cell carcinoma, lung adenocarcinoma, bone, colon, adenoma, pancreas, adenocarcinoma,

thyroid, follicular carcinoma, undifferentiated carcinoma, papillary carcinoma, seminoma, melanoma, sarcoma, bladder carcinoma, liver carcinoma and biliary passages, kidney carcinoma, myeloid disorders, lymphoid disorders, hairy cells, buccal cavity and pharynx (oral), lip, tongue, mouth, pharynx, small intestine, colon-rectum,
5 large intestine, rectum, brain and central nervous system. Hodgkin's and leukemia.

20. A method of treating a disease or disorder arising from abnormal cell growth, function or behaviour, which method comprises administering to a patient in need thereof a compound as defined in claim 13.

10

21. A method according to claim 20, wherein the abnormal cell growth, function or behaviour is associated with P13 kinase.

15

22. A method according to claim 20 or 21, wherein the disease or disorder is selected from the group consisting of cancer, immune disorders, cardiovascular disease, viral infection, inflammation, metabolism/endocrine disorders and neurological disorders.

20

23. A method according to claim 22, wherein the disease or disorder is selected from cancer, immune disorders, cardiovascular disease, viral infection, inflammation, metabolism/endocrine disorders and neurological disorders.

25

24. A method according to claim 23, wherein the cancer is selected from glioblastoma, melanoma, prostate, endometrial, ovarian, breast, lung, head and neck, hepatocellular, and thyroid cancers.

30

25. A method according to claim 23, wherein the cancer is selected from breast, ovary, cervix, prostate, testis, genitourinary tract, esophagus, larynx, glioblastoma, neuroblastoma, stomach, skin, keratoacanthoma, lung, epidermoid carcinoma, large cell carcinoma, non-small cell lung carcinoma (NSCLC), small cell carcinoma, lung adenocarcinoma, bone, colon, adenoma, pancreas, adenocarcinoma, thyroid, follicular carcinoma, undifferentiated carcinoma, papillary carcinoma, seminoma, melanoma, sarcoma, bladder carcinoma, liver carcinoma and biliary passages, kidney carcinoma,

myeloid disorders, lymphoid disorders, hairy cells, buccal cavity and pharynx (oral), lip, tongue, mouth, pharynx, small intestine, colon-rectum, large intestine, rectum, brain and central nervous system. Hodgkin's and leukemia.

INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2008/003910

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D239/42 C07D239/47 C07D239/48 C07D401/14 C07D403/14
A61K31/506 A61P35/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/084786 A (NOVARTIS AG [CH]; BURGER MATTHEW [US]; NI ZHI-JIE [US]; PECCHI SABINA) 26 July 2007 (2007-07-26) the whole document	1-25
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☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

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

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

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

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

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

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

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

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

* & * document member of the same patent family

Date of the actual completion of the international search

18 March 2009

Date of mailing of the international search report

30/03/2009

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INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2008/003910

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2008/003910

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
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Information on patent family members

International application No

PCT/GB2008/003910

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