

PYRIMIDINE-2,4-DIAMINE DERIVATIVES FOR TREATMENT OF CANCER

Field of the Invention

The invention relates to novel compounds, compositions and methods for
5 treatment of cancer. In particular, the invention relates to novel compounds,
compositions and methods for the treatment of cancers through inhibition of
MTH1.

Background of the Invention

10 The listing or discussion of an apparently prior-published document in this
specification should not necessarily be taken as an acknowledgement that the
document is part of the state of the art or is common general knowledge.

Background

15 Dysfunctional redox regulation of cellular signalling and an increased ROS
(Reactive oxygen species) tension have been demonstrated to play a crucial role
in cancer etiology, progression and metastasis (Zhang et al., Antioxid Redox
Signal 15(11)2011:2876-2908). ROS mediates tumor-promoting characteristics,
such as e.g. unrestrained proliferation, survival signaling, increased migration,
20 angiogenesis. ROS are generated during cell metabolism and are highly reactive
with macromolecules such as DNA, proteins and lipids. Exposure of nucleic acids
to ROS can create more than 20 oxidatively modified nucleotides, of which 8-oxo-
7,8-dihydroxyguanine (8-oxo-dG) is most abundant. 8-oxo-dG plays a pivotal role
in mutagenesis (Sekiguchi and Tsuzuki., Oncogene 21(58)2002:8895-906) . To
25 protect themselves from carcinogenic effects, mammalian cells are armed with a
set of repair enzymes to remove the oxidized nucleotides to maintain genome
integrity. One of these protective enzymes is MTH1 (MutT homologue 1, 8-oxo-
dGTPase, NUDT1). Interestingly, MTH1 is upregulated in various cancer forms,
suggesting that the cancer cell rely on MTH1 function to survive the increased
30 DNA lesion (Human Proteinatlas, Koketsu et al., Hepatogastroenterology,
51(57)2004:638-41). Suppression of MTH1 level and activity by using RNAi
technology, leads to reduced cancer cell survival, premature senescence and
DNA strand breaks (Rai et al, PNAS, 106(1)2009:169-174), Helleday et al
unpublished data). Interestingly, lung cancers which spontaneously form in OGG-
35 +/- mice are prevented from forming in crosses with the MTH1-/- mice, suggesting

that MTH1 is required for lung cancer cells to survive (Sakumi et al., Cancer Res 63, 2003: 902). We have observed that downregulation of MTH1 protein levels in human colon cancer tumors in xenograft mice model reduced tumor growth and significantly shrunk the tumour (Helleday et al, unpublished data).

5 In tumour cells, reducing the capacity to eliminate oxidised dNTPs by inhibiting MTH1 activity, will reduce cancer cell survival and hence be a promising novel anticancer therapy, either as monotherapy in cancer forms with high oxidative stress levels and/or in combination with radiotherapy and chemotherapy drugs.

10 Shortcomings and complications with current treatment

Today's treatment of cancer is not effective for all patients with diagnosed disease also including a large proportion of patients that experience adverse effects from treatments with existing therapies or where resistance to on-going therapy is developed over time.

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Prior art

Engelhardt, H. et al. *Journal of Medicinal Chemistry* (2013), 56(11), 4264-4276 and US patent application US 2010/0016344 disclose certain 6-aryl-2,4-diaminopyrimidines having an additional pyrimidine appendage as histamine H4 receptor modulators. The compounds are claimed to be useful for a various diseases including cancer pain, but their use in the treatment of cancer as such is neither disclosed or suggested.

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International patent application WO 2013/066839 discloses 6-(3-pyridyl)-(2,4-diaminopyrimidines as HDAC inhibitors. However, the substituent on the 4-amino group contains a prerequisite 5-trifluoromethyl-1,2,4-oxadiazol-3-yl group.

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2,4-Diaminopyrimidines substituted in the 6-position with 3-aminoindazoles have been described in international patent application WO 2010/059658. Although also indazoles without the amino groups are mentioned, it is evident from the examples that the 3-amino substituent on the indazole is required for activity. The same document also describes 2,4-diaminopyrimidines substituted in the 6-position by a 3-cyano-2-fluorophenyl group. However, these compounds are merely precursors to the 3-aminoindazoles mentioned above and there is no disclosure or suggestions in the document that they possess any anti-cancer activity.

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International patent application WO 2006/078886 describes 2,4-diamino-pyrimidines substituted in the 6-position by an aryl group as wnt modulators. The 4-aryl group is lacking any substituents or must be substituted in the 3-position by methoxy. The document does not disclose or suggest compounds with any other
5 substituent-pattern, nor does it mention or suggest the use of such compounds in the treatment of cancer. Moreover, in all examples the 4-amino group of the pyrimidine is substituted by either 1,3-benzodioxol-5-ylmethyl or by 4-hydroxy-phenethyl. Several scientific publications describe the use of one of the compounds (N4-(1,3-benzodioxol-5-ylmethyl)-6-(3-methoxyphenyl)-2,4-
10 pyrimidinediamine) as a tool to investigate the wnt-pathway.

International patent application WO 86/04583 describes aziridinyl substituted anti-neoplastic compounds. There is only one compound that has both a 6-aryl substituent and a 4-N-alkyl group attached to 2-aminopyrimidine core. The compound has besides the aziridinyl group a fluorine in the 5-position of the
15 pyrimidine ring. Both the aziridinyl and the fluorine are implied to be important for the activity and there is nothing that suggests that anti-neoplastic activity can be obtained without at least one of these substituents.

British patent application GB 681712 describes 2,4-diaminopyrimidines substituted in the 6-position by an aryl group for use in the treatment of cancer,
20 but in only one example the aryl is phenyl and the 4-amino group is substituted by an alkyl. In this compound the phenyl is unsubstituted and the alkyl is methyl. There is no disclosure in this documents of compounds in which the 6-phenyl may be substituted by other groups than chloro or nitro in the *para*-position, that the 6-phenyl may contain more than one substituent or that the 4-alkylamino-
25 group is larger than methyl or may carry substituents.

Two publications from the group of H. Junjappa (*Indian Journal Chemistry* (1985), 24B 466; *Synthesis* (1980), 748) describe the synthesis of certain 2-amino-4-(N-alkylamino)-6-arylpyrimidines. The publications do not mention or suggest the
30 use of the synthesized compounds in the treatment of cancer.

There are numerous 2-amino-4-(N-alkylamino)-6-arylpyrimidines that are, or that at some point have been stated to be, commercially available but that do not have any ascribed pharmaceutical use, nor any other use, ascribed to them.

35 MTH1 inhibitors have been described in Streib, M. *et al. Angewandte Chemie*,

Int., Ed. (2013), Vol. 52. The compounds are organometallic and are not 2-amino-4-(N-alkylamino)-6-arylpyrimidines.

Summary of the invention

5 Although the finding of oncogenes and development of new anticancer treatments and diagnosis have improved the life length of cancer patients, there is still a high medical need to find more effective and less toxic treatments for e.g. breast cancer, leukemia, colon or lung cancer. Our preliminary data suggests that MTH1 inhibitors have the potential to be very effective against cancer forms with
 10 dysfunctional redox status, with minimal general toxic effects. MTH1 inhibition may also be a suitable adjuvant therapy to be used in conjunction with radiotherapies or other chemotherapeutic approaches.

The present invention aims at providing new treatments for cancer that can be
 15 achieved by inhibition of MTH1

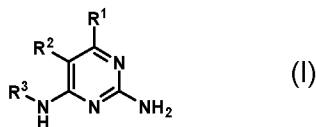
Brief description of the drawings

Figure 1. Effect on cell survival following MTH1 siRNA depletion in various human
 20 cancer and normal cell lines.

Figure 2. MTH1 inhibitor reduce cell survival in various cancer cell lines, with less effect on normal immortalised cells (VH10 and BJ hTERT)

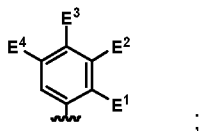
25 Detailed description of the Invention

There is provided a compound of formula I,



for use in the treatment of cancer
 30 wherein:

R¹ represents heteroaryl connected to the pyrimidine of formula I via a carbon atom of the heteroaryl ring, which heteroaryl ring is optionally substituted by one or more substituents selected from Y¹, -C₁₋₆alkyl optionally substituted by one or more Y² and heterocycloalkyl optionally substituted by one or more Y³; or aryl
 5 represented by



E¹ represents hydrogen, Y^{1a}, -C₁₋₆alkyl optionally substituted by one or more Y² or heterocycloalkyl optionally substituted by one or more Y³;

E² represents hydrogen, Y^{1b}, -C₁₋₆alkyl optionally substituted by one or more Y² or
 10 heterocycloalkyl optionally substituted by one or more Y³;

E³ and E⁴ each independently represents hydrogen, Y¹, -C₁₋₆alkyl optionally substituted by one or more Y² or heterocycloalkyl optionally substituted by one or more Y³;

15 R² represents hydrogen, halogen, -CN, -C₁₋₁₂alkyl optionally substituted by one or more Z¹, or heterocycloalkyl optionally substituted by one or more Z²;

R³ represents -C₁₋₁₂alkyl optionally substituted by one or more Z¹ or heterocycloalkyl optionally substituted by one or more Z²; or

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R² and R³ are linked together to form, along with the atoms to which they are attached, a 5- to 8-membered non-aromatic ring, wherein the link formed by R² and R³ is optionally substituted by one or more substituents selected from Z³ and -C₁₋₉alkyl optionally substituted by one or more Z⁴;

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each Y¹ independently represents halogen, -CN, -C(O)R^a, -C(O)N(R^b)R^c, -C(O)OR^d, -N(R^e)R^f, -N(R^g)C(O)R^h, -N(Rⁱ)C(O)OR^j, -N(R^k)C(O)N(R^l)R^m, -NO₂, -N(Rⁿ)S(O)₂R^o, -OR^p, -OC(O)R^q, -OS(O)₂R^r, -S(O)_mR^s, -S(O)₂N(R^t)R^u, heterocycloalkyl optionally substituted by one or more substituents selected from

30 W², aryl optionally substituted by one or more substituents selected from W³ or heteroaryl optionally substituted by one or more substituents selected from W³;

Y^{1a} represents halogen, -CN, -C(O)R^a, -C(O)N(R^b)R^c, -C(O)OR^d, -N(R^e)R^f,

-N(R^g)C(O)R^h, -N(Rⁱ)C(O)OR^j, -N(R^k)C(O)N(R^l)R^m, -NO₂, -N(Rⁿ)S(O)₂R^o,
 -OR^{px}, -OC(O)R^q, -OS(O)₂R^r, -S(O)_mR^s, -S(O)₂N(R^t)R^u, heterocycloalkyl optionally
 substituted by one or more substituents selected from W², aryl optionally
 substituted by one or more substituents selected from W³ or heteroaryl optionally
 5 substituted by one or more substituents selected from W³;

Y^{1b} represents halogen, -CN, -C(O)R^a, -C(O)N(R^b)R^c, -C(O)OR^d, -N(R^e)R^f,
 -N(R^g)C(O)R^h, -N(Rⁱ)C(O)OR^j, -N(R^k)C(O)N(R^l)R^m, -NO₂, -N(Rⁿ)S(O)₂R^o,
 -OR^{py}, -OC(O)R^q, -OS(O)₂R^r, -S(O)_mR^s, -S(O)₂N(R^t)R^u, heterocycloalkyl optionally
 10 substituted by one or more substituents selected from W², aryl optionally
 substituted by one or more substituents selected from W³ or heteroaryl optionally
 substituted by one or more substituents selected from W³;

each R^a, R^b, R^c, R^d, R^e, R^g, R^h, Rⁱ, R^k, R^l, R^m, Rⁿ, R^p, R^q, R^s, R^t and R^u
 15 independently represents hydrogen, -C₁₋₆ alkyl optionally substituted by one or
 more substituents selected from W¹, heterocycloalkyl optionally substituted by
 one or more substituents selected from W², aryl optionally substituted by one or
 more substituents selected from W³, or heteroaryl optionally substituted by one or
 more substituents selected from W³; or

20 any two R^b and R^c, R^e and R^f, R^l and R^m and/or R^t and R^u are linked together to
 form, along with the nitrogen atom to which they are attached, a 3- to 8-
 membered monocyclic or bicyclic ring, which ring optionally contains one or two
 further heteroatoms and which ring optionally is substituted by one or more
 25 substituents selected from W², C₁₋₃alkyl optionally substituted by one or more
 substituents selected from W¹, and =O;

each R^f, Rⁱ, R^o, R^r and R^{px} independently represents C₁₋₆ alkyl optionally
 substituted by one or more substituents selected from W¹, heterocycloalkyl
 30 optionally substituted by one or more substituents selected from W², aryl
 optionally substituted by one or more substituents selected from W³ or heteroaryl
 optionally substituted by one or more substituents selected from W³;

R^{py} represents hydrogen, -C₂₋₆ alkyl optionally substituted by one or more
 35 substituents selected from W¹, heterocycloalkyl optionally substituted by one or

more substituents selected from W^2 , aryl optionally substituted by one or more substituents selected from W^3 , or heteroaryl optionally substituted by one or more substituents selected from W^3 ;

- 5 each Y^2 independently represents halogen, $-CN$, $-C(O)R^{b1}$, $-C(O)N(R^{c1})R^{d1}$, $-C(O)OR^{e1}$, $-N(R^{f1})R^{g1}$, $-N(R^{h1})C(O)R^{i1}$, $-N(R^{j1})C(O)OR^{k1}$, $-N(R^{l1})C(O)N(R^{m1})R^{n1}$, $-N(R^{o1})S(O)_2R^{p1}$, $-OR^{q1}$, $-OC(O)R^{r1}$, $-OS(O)_2R^{s1}$, $-S(O)_mR^{t1}$, $-S(O)_2N(R^{u1})R^{v1}$, heterocycloalkyl optionally substituted by one or more substituents selected from W^1 , aryl optionally substituted by one or more substituents selected from W^2 ,
 10 heteroaryl optionally substituted by one or more substituents selected from W^2 , or $=O$;

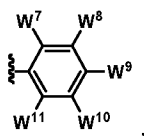
- each Y^3 independently represents halogen, $-R^{a1}$, $-CN$, $-C(O)R^{b1}$, $-C(O)N(R^{c1})R^{d1}$, $-C(O)OR^{e1}$, $-N(R^{f1})R^{g1}$, $-N(R^{h1})C(O)R^{i1}$, $-N(R^{j1})C(O)OR^{k1}$, $-N(R^{l1})C(O)N(R^{m1})R^{n1}$,
 15 $-N(R^{o1})S(O)_2R^{p1}$, $-OR^{q1}$, $-OC(O)R^{r1}$, $-OS(O)_2R^{s1}$, $-S(O)_mR^{t1}$, $-S(O)_2N(R^{u1})R^{v1}$, heterocycloalkyl optionally substituted by one or more substituents selected from W^1 , aryl optionally substituted by one or more substituents selected from W^2 , heteroaryl optionally substituted by one or more substituents selected from W^2 , or $=O$;

- 20 each R^{a1} , R^{b1} , R^{c1} , R^{d1} , R^{e1} , R^{f1} , R^{h1} , R^{i1} , R^{j1} , R^{l1} , R^{m1} , R^{n1} , R^{o1} , R^{q1} , R^{r1} , R^{t1} , R^{u1} and R^{v1} independently represents hydrogen, C_{1-6} alkyl optionally substituted by one or more substituents selected from W^1 , heterocycloalkyl optionally substituted by one or more substituents selected from W^2 , aryl optionally substituted by one or more substituents selected from W^3 , or heteroaryl optionally substituted by one or more substituents selected from W^3 ; or
 25

- any two R^{c1} and R^{d1} , R^{f1} and R^{g1} , R^{m1} and R^{n1} and/or R^{u1} and R^{v1} are linked together to form, along with the nitrogen atom to which they are attached, a 3- to
 30 8-membered monocyclic or bicyclic ring, which ring optionally contains one or two heteroatoms and which ring optionally is substituted by one or more substituents selected from W^2 , C_{1-3} alkyl optionally substituted by one or more substituents selected from W^1 , and $=O$;

each R^{g1} , R^{k1} , R^{p1} and R^{s1} independently represents $-C_{1-6}$ alkyl optionally substituted by one or more substituents selected from W^1 , heterocycloalkyl optionally substituted by one or more substituents selected from W^2 , aryl optionally substituted by one or more substituents selected from W^3 , or heteroaryl optionally substituted by one or more substituents selected from W^3 ;

each Z^1 independently represents halogen, $-CN$, $-C(O)R^{b2}$, $-C(O)N(R^{c2})R^{d2}$, $-C(O)OR^{e2}$, $-N(R^{f2})R^{g2}$, $-N(R^{h2})C(O)R^{i2}$, $-N(R^{j2})C(O)OR^{k2}$, $-N(R^{l2})C(O)N(R^{m2})R^{n2}$, $-N(R^{o2})S(O)_2R^{p2}$, $-OR^{q2}$, $-OC(O)R^{r2}$, $-OS(O)_2R^{s2}$, $-S(O)_mR^{l2}$, $-S(O)_2N(R^{u2})R^{v2}$, heterocycloalkyl optionally substituted by one or more substituents selected from W^5 , aryl represented by



heteroaryl having 1 to 3 nitrogen atoms, one oxygen atom and/or one sulfur atom and optionally substituted by one or more substituents selected from W^6 , or $=O$;

each Z^2 and Z^3 independently represents halogen, $-R^{a2}$, $-CN$, $-C(O)R^{b2}$, $-C(O)N(R^{c2})R^{d2}$, $-C(O)OR^{e2}$, $-N(R^{f2})R^{g2}$, $-N(R^{h2})C(O)R^{i2}$, $-N(R^{j2})C(O)OR^{k2}$, $-N(R^{l2})C(O)N(R^{m2})R^{n2}$, $-N(R^{o2})S(O)_2R^{p2}$, $-OR^{q2}$, $-OC(O)R^{r2}$, $-OS(O)_2R^{s2}$, $-S(O)_mR^{l2}$, $-S(O)_2N(R^{u2})R^{v2}$, heterocycloalkyl optionally substituted by one or more substituents selected from W^5 , aryl optionally substituted by one or more substituents selected from W^6 , or heteroaryl optionally substituted by one or more substituents selected from W^6 ;

each Z^4 independently represents halogen, $-CN$, $-C(O)R^{b2}$, $-C(O)N(R^{c2})R^{d2}$, $-C(O)OR^{e2}$, $-N(R^{f2})R^{g2}$, $-N(R^{h2})C(O)R^{i2}$, $-N(R^{j2})C(O)OR^{k2}$, $-N(R^{l2})C(O)N(R^{m2})R^{n2}$, $-N(R^{o2})S(O)_2R^{p2}$, $-OR^{q2}$, $-OC(O)R^{r2}$, $-OS(O)_2R^{s2}$, $-S(O)_mR^{l2}$, $-S(O)_2N(R^{u2})R^{v2}$, heterocycloalkyl optionally substituted by one or more substituents selected from W^5 , aryl optionally substituted by one or more substituents selected from W^6 , heteroaryl optionally substituted by one or more substituents selected from W^6 , or $=O$;

each R^{a2} , R^{b2} , R^{c2} , R^{d2} , R^{e2} , R^{f2} , R^{h2} , R^{i2} , R^{j2} , R^{l2} , R^{m2} , R^{n2} , R^{o2} , R^{r2} , R^{l2} , R^{u2} and R^{v2} independently represents hydrogen, C_{1-6} alkyl optionally substituted by one or

more substituents selected from W^4 , heterocycloalkyl optionally substituted by one or more substituents selected from W^5 , aryl optionally substituted by one or more substituents selected from W^6 , or heteroaryl optionally substituted by one or more substituents selected from W^6 ; or

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any two R^{c2} and R^{d2} , R^{f2} and R^{g2} , R^{m2} and R^{n2} and/or R^{u2} and R^{v2} are linked together to form, along with the nitrogen atom to which they are attached, a 3- to 8-membered monocyclic or bicyclic ring, which ring optionally contains one or two heteroatoms and which ring optionally is substituted by one or more substituents selected from W^5 , C_{1-3} alkyl optionally substituted by one or more substituents selected from W^4 , and =O;

10

each R^{g2} , R^{k2} , R^{p2} , R^{q2} and R^{s2} independently represents C_{1-6} alkyl optionally substituted by one or more substituents selected from W^4 , heterocycloalkyl optionally substituted by one or more substituents selected from W^5 , aryl optionally substituted by one or more substituents selected from W^6 , or heteroaryl optionally substituted by one or more substituents selected from W^6 ;

15

each W^1 and W^4 independently represents halogen, -CN, $-N(R^{f3})R^{g3}$, $-N(R^{h3})C(O)R^{i3}$, $-N(R^{j3})C(O)OR^{k3}$, $-N(R^{l3})C(O)N(R^{m3})R^{n3}$, $-N(R^{o3})S(O)_2R^{p3}$, $-OR^{q3}$, $-OC(O)R^{r3}$, $-OS(O)_2R^{s3}$, $-S(O)_mR^{t3}$, $-S(O)_2N(R^{u3})R^{v3}$, heterocycloalkyl optionally substituted by one or more substituents selected from G^1 , aryl optionally substituted by one or more substituents selected from G^2 , heteroaryl optionally substituted by one or more substituents selected from G^2 , or =O;

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each W^2 , W^3 , W^5 and W^6 independently represents halogen, $-R^{a3}$, -CN, $-C(O)R^{b3}$, $-C(O)N(R^{c3})R^{d3}$, $-C(O)OR^{e3}$, $-N(R^{f3})R^{g3}$, $-N(R^{h3})C(O)R^{i3}$, $-N(R^{j3})C(O)OR^{k3}$, $-N(R^{l3})C(O)N(R^{m3})R^{n3}$, $-N(R^{o3})S(O)_2R^{p3}$, $-OR^{q3}$, $-OC(O)R^{r3}$, $-OS(O)_2R^{s3}$, $-S(O)_mR^{t3}$, $-S(O)_2N(R^{u3})R^{v3}$, heterocycloalkyl optionally substituted by one or more substituents selected from G^1 , aryl optionally substituted by one or more substituents selected from G^2 , heteroaryl (optionally substituted by one or more substituents selected from G^2 , or =O;

30

each W^7 , W^8 , W^{10} and W^{11} independently represents hydrogen, halogen, $-R^{a3}$, -CN, $-C(O)R^{b3}$, $-C(O)N(R^{c3})R^{d3}$, $-C(O)OR^{e3}$, $-N(R^{f3})R^{g3}$, $-N(R^{h3})C(O)R^{i3}$,

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-N(R^{j3})C(O)OR^{k3}, -N(R^{l3})C(O)N(R^{m3})Rⁿ³, -N(R^{o3})S(O)₂R^{p3}, -OR^{q3}, -OC(O)R^{r3},
 -OS(O)₂R^{s3}, -S(O)_mR^{t3}, -S(O)₂N(R^{u3})R^{v3}, heterocycloalkyl optionally substituted by
 one or more substituents selected from G¹, aryl optionally substituted by one or
 more substituents selected from G², or heteroaryl optionally substituted by one or
 5 more substituents selected from G²;

W⁹ represents hydrogen, halogen, -R^{a3}, -CN, -C(O)R^{b3}, -C(O)N(R^{c3})R^{d3},
 -C(O)OR^{e3}, -N(R^{f3})R^{g3}, -N(R^{h3})C(O)Rⁱ³, -N(R^{j3})C(O)OR^{k3}, -N(R^{l3})C(O)N(R^{m3})Rⁿ³,
 -N(R^{o3})S(O)₂R^{p3}, -OR^{q3x}, -OC(O)R^{r3}, -OS(O)₂R^{s3}, -S(O)_mR^{t3}, -S(O)₂N(R^{u3})R^{v3},
 10 heterocycloalkyl optionally substituted by one or more substituents selected from
 G¹, aryl optionally substituted by one or more substituents selected from G², or
 heteroaryl optionally substituted by one or more substituents selected from G²;

each R^{a3}, R^{b3}, R^{c3}, R^{d3}, R^{e3}, R^{f3}, R^{h3}, Rⁱ³, R^{j3}, R^{l3}, R^{m3}, Rⁿ³, R^{o3}, R^{q3}, R^{r3}, R^{t3}, R^{u3}
 15 and R^{v3} independently represents hydrogen or C₁₋₆ alkyl optionally substituted by
 one or more G³; or

any two R^{c3} and R^{d3}, R^{f3} and R^{g3}, R^{m3} and Rⁿ³ and/or R^{u3} and R^{v3} are linked
 together to form, along with the nitrogen atom to which they are attached, a 4- to
 20 6-membered ring, which ring optionally contains one heteroatom and which ring
 optionally is substituted by one or more G²;

each R^{g3}, R^{k3}, R^{p3}, R^{q3} and R^{s3} independently represents C₁₋₆ alkyl optionally
 substituted by one or more G³;

25

R^{q3x} represents C₂₋₆ alkyl optionally substituted by one or more G³;

each G¹ and G² independently represents halogen, -R^{a4}, -CN, -C(O)R^{b4},
 -C(O)N(R^{c4})R^{d4}, -C(O)OR^{e4}, -N(R^{f4})R^{g4}, -N(R^{h4})C(O)Rⁱ⁴, -N(R^{j4})C(O)OR^{k4},
 30 -N(R^{l4})C(O)N(R^{m4})Rⁿ⁴, -N(R^{o4})S(O)₂R^{p4}, -OR^{q4}, -OC(O)R^{r4}, -OS(O)₂R^{s4}, -S(O)_mR^{t4},
 -S(O)₂N(R^{u4})R^{v4}, or =O;

G³ represents halogen, -CN, -C(O)R^{b4}, -C(O)N(R^{c4})R^{d4}, -C(O)OR^{e4}, -N(R^{f4})R^{g4},
 -N(R^{h4})C(O)Rⁱ⁴, -N(R^{j4})C(O)OR^{k4}, -N(R^{l4})C(O)N(R^{m4})Rⁿ⁴, -N(R^{o4})S(O)₂R^{p4}, -OR^{q4},
 35 -OC(O)R^{r4}, -OS(O)₂R^{s4}, -S(O)_mR^{t4}, -S(O)₂N(R^{u4})R^{v4}, or =O;

each R^{a4} , R^{b4} , R^{c4} , R^{d4} , R^{e4} , R^{f4} , R^{h4} , R^{i4} , R^{j4} , R^{l4} , R^{m4} , R^{n4} , R^{o4} , R^{q4} , R^{r4} , R^{t4} , R^{u4} and R^{v4} independently represents hydrogen or C_{1-6} alkyl optionally substituted by one or more -F; or

5

any two R^{c4} and R^{d4} , R^{f4} and R^{g4} , R^{m4} and R^{n4} and/or R^{u4} and R^{v4} are linked together to form, along with the nitrogen atom to which they are attached, a 3- to 6-membered ring, which ring optionally substituted by one or more -F, $-CH_3$, $-CH_2CH_3$, $-CHF_2$, $-CF_3$, $-CH_2CF_3$, or $=O$;

10

each R^{g4} , R^{k4} , R^{p4} and R^{s4} independently represent C_{1-6} alkyl optionally substituted by one or more -F;

each m independently represents 0, 1 or 2;

15

provided that formula I does not represent

6-(3-pyridinyl)- N^4 -[[4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]methyl]-2,4-pyrimidinediamine,

6-(3-pyridinyl)- N^4 -[[5-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]-2-pyridinyl]methyl]-

20

2,4-pyrimidinediamine,

6-(3-pyridinyl)- N^4 -[[5-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]-2-pyrimidinyl]methyl]-2,4-pyrimidinediamine or

N^4 -[2-(1-aziridinyl)ethyl]-5-fluoro-6-phenyl-2,4-pyrimidinediamine,

25

or a pharmaceutically acceptable salt thereof;

which compounds may be referred to herein as "the compounds of the invention".

30

Pharmaceutically-acceptable salts include acid addition salts and base addition salts. Such salts may be formed by conventional means, for example by reaction of a free acid or a free base form of a compound of formula I with one or more equivalents of an appropriate acid or base, optionally in a solvent, or in a medium in which the salt is insoluble, followed by removal of said solvent, or said medium, using standard techniques (e.g. *in vacuo*, by freeze-drying or by filtration). Salts

35

may also be prepared by exchanging a counter-ion of a compound of the

invention in the form of a salt with another counter-ion, for example using a suitable ion exchange resin. For the avoidance of doubt, solvates are also included within the scope of the invention.

5 Compounds of the invention may contain double bonds and may thus exist as *E* (*entgegen*) and *Z* (*zusammen*) geometric isomers about each individual double bond. All such isomers and mixtures thereof are included within the scope of the invention.

10 Compounds of the invention may also exhibit tautomerism. All tautomeric forms and mixtures thereof are included within the scope of the invention.

Compounds of the invention may also contain one or more asymmetric carbon atoms and may therefore exhibit optical and/or diastereoisomerism.

15 Diastereoisomers may be separated using conventional techniques, e.g. chromatography or fractional crystallisation. The various stereoisomers may be isolated by separation of a racemic or other mixture of the compounds using conventional, e.g. fractional crystallisation or HPLC, techniques. Alternatively the desired optical isomers may be made by reaction of the appropriate optically
20 active starting materials under conditions which will not cause racemisation or epimerisation (i.e. a 'chiral pool' method), by reaction of the appropriate starting material with a 'chiral auxiliary' which can subsequently be removed at a suitable stage, by derivatisation (i.e. a resolution, including a dynamic resolution), for example with a homochiral acid followed by separation of the diastereomeric
25 derivatives by conventional means such as chromatography, or by reaction with an appropriate chiral reagent or chiral catalyst all under conditions known to the skilled person. All stereoisomers and mixtures thereof are included within the scope of the invention.

30 Unless otherwise specified, C_{1-q} alkyl groups (where q is the upper limit of the range) defined herein may be straight-chain or, when there is a sufficient number (i.e. a minimum of two or three, as appropriate) of carbon atoms, be branched-chain, and/or cyclic (so forming a C_{3-q}-cycloalkyl group). When there is a sufficient number (i.e. a minimum of four) of carbon atoms, such groups may also
35 be part cyclic. Such alkyl groups may also be saturated or, when there is a

sufficient number (i.e. a minimum of two) of carbon atoms, be unsaturated (forming, for example, a C_{2-q} alkenyl or a C_{2-q} alkynyl group).

- Unless otherwise specified, C_{1-q} alkylene groups (where q is the upper limit of the range) defined herein may (in a similar manner to the definition of C_{1-q} alkyl) be straight-chain or, when there is a sufficient number (i.e. a minimum of two or three, as appropriate) of carbon atoms, be branched-chain, and/or cyclic (so forming a C_{3-q}-cycloalkylene group). When there is a sufficient number (i.e. a minimum of four) of carbon atoms, such groups may also be part cyclic. Such alkylene groups may also be saturated or, when there is a sufficient number (i.e. a minimum of two) of carbon atoms, be unsaturated (forming, for example, a C_{2-q} alkenylene or a C_{2-q} alkynylene group). Particular alkylene groups that may be mentioned include those that are straight-chained and saturated.
- The term "halo", when used herein, includes fluoro, chloro, bromo and iodo (for example, fluoro and chloro).

- Heterocycloalkyl groups that may be mentioned include non-aromatic monocyclic and bicyclic heterocycloalkyl groups (which groups may further be bridged) in which at least one (e.g. one to four) of the atoms in the ring system is other than carbon (i.e. a heteroatom), and in which the total number of atoms in the ring system is between three and twelve (e.g. between five and ten and, most preferably, between three and eight, e.g. a 5- or 6-membered heterocycloalkyl group). Further, such heterocycloalkyl groups may be saturated or unsaturated containing one or more double and/or triple bonds, forming for example a C_{2-q} (e.g. C_{4-q}) heterocycloalkenyl (where q is the upper limit of the range) or a C_{7-q} heterocycloalkynyl group. C_{2-q} heterocycloalkyl groups that may be mentioned include 7-azabicyclo-[2.2.1]heptanyl, 6-azabicyclo[3.1.1]heptanyl, 6-azabicyclo[3.2.1]-octanyl, 8-azabicyclo[3.2.1]octanyl, aziridiny, azetidiny, dihydropyranyl, dihydropyridyl, dihydropyrrolyl (including 2,5-dihydropyrrolyl), dioxolanyl (including 1,3-dioxolanyl), dioxanyl (including 1,3-dioxanyl and 1,4-dioxanyl), dithianyl (including 1,4-dithianyl), dithiolanyl (including 1,3-dithiolanyl), imidazolidinyl, imidazoliny, morpholiny, 7-oxabicyclo-[2.2.1]heptanyl, 6-oxabicyclo[3.2.1]-octanyl, oxetanyl, oxiranyl, piperaziny, piperidiny, pyranyl, pyrazolidiny, pyrrolidinonyl, pyrrolidinyl, pyrroliny,

quinuclidinyl, sulfolanyl, 3-sulfolenyl, tetrahydropyranyl, tetrahydrofuryl, tetrahydropyridyl (such as 1,2,3,4-tetrahydropyridyl and 1,2,3,6-tetrahydropyridyl), thietanyl, thiranyl, thiolanyl, thiomorpholinyl, trithianyl (including 1,3,5-trithianyl), tropanyl and the like. Substituents on heterocycloalkyl groups may, where
5 appropriate, be located on any atom in the ring system including a heteroatom. Further, in the case where the substituent is another cyclic compound, then the cyclic compound may be attached through a single atom on the heterocycloalkyl group, forming a so-called "spiro"-compound. The point of attachment of heterocycloalkyl groups may be *via* any atom in the ring system including (where
10 appropriate) a heteroatom (such as a nitrogen atom), or an atom on any fused carbocyclic ring that may be present as part of the ring system. Heterocycloalkyl groups may also be in the *N*- or *S*- oxidised form. At each occurrence when mentioned herein, a heterocycloalkyl group is preferably a 3- to 8-membered heterocycloalkyl group (e.g. a 5- or 6-membered heterocycloalkyl group).

15 The term "aryl", when used herein, includes C₆₋₁₄ (e.g. C₆₋₁₀) aromatic groups. Such groups may be monocyclic or bicyclic and, when bicyclic, be either wholly or partly aromatic. C₆₋₁₀ aryl groups that may be mentioned include phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, indanyl, and the like (e.g. phenyl, naphthyl
20 and the like). For the avoidance of doubt, the point of attachment of substituents on aryl groups may be *via* any carbon atom of the ring system.

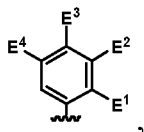
The term "heteroaryl" (or heteroaromatic), when used herein, includes 5- to 10-membered heteroaromatic groups containing one or more heteroatoms selected
25 from oxygen, nitrogen and/or sulfur. Such heteroaryl group may comprise one, or two rings, of which at least one is aromatic. Substituents on heteroaryl/heteroaromatic groups may, where appropriate, be located on any atom in the ring system including a heteroatom. The point of attachment of heteroaryl/heteroaromatic groups may be *via* any atom in the ring system
30 including (where appropriate) a heteroatom. Bicyclic heteroaryl/heteroaromatic groups may comprise a benzene ring fused to one or more further aromatic or non-aromatic heterocyclic rings, in which instances, the point of attachment of the polycyclic heteroaryl/heteroaromatic group may be *via* any ring including the benzene ring or the heteroaryl/heteroaromatic or heterocycloalkyl ring. Examples
35 of heteroaryl/heteroaromatic groups that may be mentioned include pyridinyl,

pyrrolyl, furanyl, thiophenyl, oxadiazolyl, thiadiazolyl, thiazolyl, oxazolyl, pyrazolyl, triazolyl, tetrazolyl, isoxazolyl, isothiazolyl, imidazolyl, imidazopyrimidinyl, pyrimidinyl, indolyl, azaindolyl, pyrazinyl, indazolyl, pyrimidinyl, quinolinyl, isoquinolinyl, benzofuranyl, benzothiophenyl, benzoimidazolyl, benzoxazolyl, benzothiazolyl and benzotriazolyl. The oxides of heteroaryl/ heteroaromatic groups are also embraced within the scope of the invention (e.g. the *N*-oxide). As stated above, heteroaryl includes polycyclic (e.g. bicyclic) groups in which one ring is aromatic (and the other may or may not be aromatic). Hence, other heteroaryl groups that may be mentioned include e.g. benzo[1,3]dioxolyl, benzo[1,4]dioxinyl, indolinyl, 5*H*,6*H*,7*H*-pyrrolo[1,2-*b*]pyrimidinyl, 1,2,3,4-tetrahydroquinolinyl and the like.

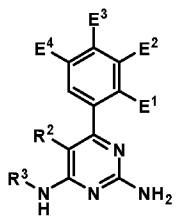
Heteroatoms that may be mentioned include phosphorus, silicon, boron and, preferably, oxygen, nitrogen and sulfur.

For the avoidance of doubt, in cases in which the identity of two or more substituents in a compound of the invention may be the same, the actual identities of the respective substituents are not in any way interdependent.

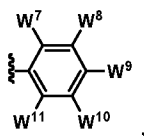
For the avoidance of doubt, when R^1 is defined as



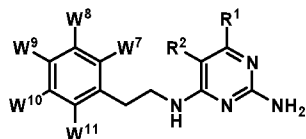
it is connected to the rest of formula I by the bond interrupted by the wiggly line, and formula I can thus be represented by



Likewise, when R^3 is $-C_{1-12}$ alkyl substituted by Z^1 , and Z^1 is represented by



then, if e.g. R^3 is C_2 alkyl, then formula I can be represented by



The present invention also embraces isotopically-labeled compounds of the present invention which are identical to those recited herein, but for the fact that
 5 one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature (or the most abundant one found in nature). All isotopes of any particular atom or element as specified herein are contemplated within the scope of the compounds of the invention. Hence, the compounds of the invention also include deuterated
 10 compounds, i.e. in which one or more hydrogen atoms are replaced by the hydrogen isotope deuterium.

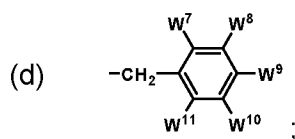
All individual features (e.g. preferred features) mentioned herein may be taken in isolation or in combination with any other feature (including preferred features)
 15 mentioned herein (hence, preferred features may be taken in conjunction with other preferred features, or independently of them).

The skilled person will appreciate that compounds of the invention that are the subject of this invention include those that are stable. That is, compounds of the
 20 invention include those that are sufficiently robust to survive isolation from e.g. a reaction mixture to a useful degree of purity.

Particular compounds of formula I that may be mentioned include those in which:
 R² represents hydrogen or -C₁₋₁₂alkyl optionally substituted by one or more Z¹;
 25 and
 R³ represents -C₁₋₁₂alkyl optionally substituted by one or more Z¹ or heterocycloalkyl optionally substituted by one or more Z².

For example, compounds of formula I that may be mentioned include those in
 30 which R² represents methyl, or preferably, hydrogen and R³ represents:
 (a) -C₁₋₁₂alkyl (for example -C₁₋₆alkyl) optionally substituted by two, or preferably, one Z¹ or

- (b) $-C_{2-6}$ alkyl optionally substituted by two, or preferably, one Z^1 or heterocycloalkyl optionally substituted by two, or preferably, one Z^2 ; or
- (c) $-C_{1-2}$ alkyl optionally substituted with one or more $-F$; or



- 5 (e) $-C_{1-12}$ alkyl (for example $-C_{1-6}$ alkyl) substituted by heteroaryl having 1 to 3 nitrogen atoms, one oxygen atom and/or one sulfur atom and which heteroaryl is optionally substituted by one or more substituents selected from W^3 ; or
- (f) a $-C_{3-6}$ alkyl or a heterocycloalkyl selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclopropylethyl, cyclobutylethyl, cyclopropylpropyl, oxetanyl, tetrahydrofuryl, tetrahydropyranyl, azetidiny, pyrrolidiny, piperidiny, piperaziny or morpholiny wherein the C_{3-6} alkyl is optionally substituted by two, or preferably, one Z^1 and the heterocycloalkyl is optionally substituted by two, or preferably, one Z^2 .

- 15 Particular compounds of formula I that may be mentioned include those in which: R^2 and R^3 are linked together to form, along with the atoms to which they are attached, a 5- to 8-membered non-aromatic ring, wherein the link formed by R^2 and R^3 is optionally substituted by one or more substituents selected from Z^3 or $-C_{1-9}$ alkyl optionally substituted by one or more Z^4 .

20

For example, compounds of formula I that may be mentioned include those in which R^2 and R^3 are linked together to form, along with the atoms to which they are attached, a 5- to 6-membered non-aromatic ring, wherein the non-aromatic ring is:

- 25 (a) unsubstituted; or
- (b) substituted by one or more substituents selected from Z^3 ; or
- (c) substituted by $-C_{1-9}$ alkyl optionally substituted by one or more Z^4 ; or
- (d) substituted by one or more substituents selected from Z^3 and substituted by $-C_{1-9}$ alkyl optionally substituted by one or more Z^4 .

30

Particular compounds of formula I that may be mentioned include those in which: E^1 is Y^{1a} or $-C_{1-6}$ alkyl optionally substituted by one or more Y^2 and at least one of E^2 , E^3 and E^4 represents Y^{1b} or $-C_{1-6}$ alkyl optionally substituted by one or more Y^2 .

Preferred compounds of formula I that may be mentioned include those in which:
 E^1 is Y^{1a} or $-C_{1-3}$ alkyl optionally substituted by one or more Y^2 and at least one of
 E^2 and E^4 represents Y^{1b} , $-C_{1-3}$ alkyl optionally substituted by one or more Y^2 .

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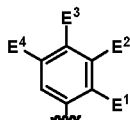
Particular compounds of formula I that may be mentioned include those in which
 R^1 represents heteroaryl.

Preferred compounds of formula I where R^1 represents heteroaryl that may be
 10 mentioned are those where R^1 represents benzofuranyl, benzothiophenyl,
 dihydrobenzofuranyl, indazolyl, indolyl, isoquinolinyl, isoxazolyl, pyridinyl, pyrrolyl
 and quinolinyl.

Particularly preferred compounds of formula I where R^1 represents heteroaryl that
 15 may be mentioned are those where R^1 represents benzofuran-3-yl, benzo-
 thiophen-3-yl, dihydrobenzofuran-7-yl, indol-3-yl, indol-4-yl, indol-5-yl, isoquinolin-
 4-yl, isoxazol-4-yl, pyridin-3-yl, pyridin-4-yl, pyrrol-2-yl and quinolin-5-yl.

For example, compounds of formula I that may be mentioned include those in
 20 which R^1 represents indolyl, e.g. indol-3-yl, indol-4-yl or indol-5-yl, where the
 indolyl is optionally substituted on the nitrogen with $-S(O)_2Ar^x$, where Ar^x is aryl or
 heteroaryl, preferably optionally substituted phenyl, e.g. unsubstituted phenyl or
 phenyl substituted in the 4-position by $-F$, $-Cl$, $-CH_3$ or $-CF_3$.

25 Particular compounds of formula I that may be mentioned include those in which
 R^1 is represented by

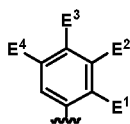


where:

E^2 , E^3 and E^4 represent hydrogen and
 30 E^1 represents hydrogen, or more preferably $-F$, $-Cl$, $-CH_3$, $-CF_3$, CN or $-OCH_3$; or
 E^1 , E^3 and E^4 represent hydrogen and
 E^2 represents $-F$, $-Cl$, $-CH_3$, $-CF_3$, $-CH=CHC(O)OCH_3$, $-CH_2NH_2$, $-CN$,
 $-CH_2N(H)C(O)CH=CH_2$, $-CH_2OH$, $-C(O)N(H)(4\text{-methylphenyl})$, $-N(H)C(O)CH_3$,

- N(H)C(O)CH=CH₂, -N(H)C(O)CH=CHCH₂NMe₂, -N(H)C(O)CH=CHPh,
 -N(H)C(O)C≡CH, -N(H)C(O)(2-hydroxyphenyl), -N(H)C(O)(6-hydroxypyrid-2-yl),
 -N(H)C(O)(5-chloro-2-hydroxyphenyl), -N(H)C(O)CH₂CH₂C(O)(1-pyrrolidinyl),
 -N(H)C(O)CH₂(OH), -N(H)C(O)CH(OH)Ph, -N(H)C(O)C(O)CH₃,
 5 -N(H)C(O)C(O)Ph, -N(H)S(O)₂CH=CH₂, or -OCH₃; or
 E¹, E² and E⁴ represent hydrogen and
 E³ represent -F, -Cl, -CH₃, -CF₃, -C(CH₃)₃, -CH=CH₂, -CH=CHC(O)OH,
 -CH=CHC(O)OCH₃, -CH₂NH₂, , -CN, -CH₂N(H)C(O)CH=CH₂, -CH₂OH, -C(O)H,
 C(O)CH₃, -C(O)CF₃, -C(O)N(H)CH₃, -C(O)N(H)CH₂(2-furanyl),
 10 -C(O)(4-morpholinyl), -C(O)OH, -C(O)OCH₃, -N(H)C(O)CH₃,
 -N(H)C(O)CH=CH₂, -N(H)S(O)₂CH₃, -OCH(CH₃)₂, -OCH₃, -OCF₃, -S(O)₂CH₃, or
 -S(O)₂(4-morpholinyl).

- Other particular compounds of formula I that may be mentioned include those in
 15 which R¹ is represented by



where:

- E³ and E⁴ represent hydrogen; and
 E¹ represents -F and E² represent -F, -Cl, -CH₃ or -CF₃; or
 20 E¹ represents -Cl and E² represents -F, -Cl, -CH₃ or -CF₃; or
 E¹ represents -CH₃ and E² represents -F, -Cl, -CH₃, -CF₃, -CN or
 -N(H)C(O)CH=CH₂; or

- E² and E⁴ represent hydrogen; and
 25 E¹ represents -F and E³ represents -F or phenyl; or
 E¹ represents -Cl and E³ represents -F or -Cl; or
 E¹ represents -CH₃ and E³ represents -Cl or -OCH₂phenyl; or
 E¹ represents -OCH₃ and E³ represents -F; or

- 30 E² and E³ represent hydrogen; and
 E¹ represents -F and E⁴ represents -Cl, -CH₃ or -CN; or
 E¹ represents -Cl and E⁴ represent -F, -Cl, -CH₃, -CF₃ or -OCH₃; or

- E^1 represents $-\text{CH}_3$ and E^4 represent $-\text{F}$, $-\text{Cl}$, $-\text{CH}_3$, $-\text{CF}_3$, $-\text{CN}$,
 $-\text{N}(\text{H})\text{C}(\text{O})\text{CH}=\text{CH}_2$ or $-\text{S}(\text{O})_2(4\text{-morpholinyl})$; or
 E^1 represents $-\text{CF}_3$ and E^4 represents $-\text{F}$ or $-\text{CF}_3$; or
 E^1 represents $-\text{CN}$ and E^4 represents $-\text{Cl}$; or
 5 E^1 represents $-\text{OCH}_3$ and E^4 represents $-\text{F}$, $-\text{Cl}$, Br , $-\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $-\text{C}(\text{CH}_3)_3$,
 $-\text{CN}$ or $-\text{OCH}_3$; or

 E^1 and E^4 represent hydrogen; and
 E^2 represents $-\text{F}$ and E^3 represents $-\text{F}$, $-\text{Cl}$, $-\text{OH}$ or $-\text{OCH}_3$; or
 10 E^2 represents $-\text{Cl}$ and E^3 represents $-\text{F}$ or $-\text{C}(\text{O})(4\text{-morpholinyl})$; or
 E^2 represents $-\text{CH}_3$ and E^3 represents $-\text{F}$ or $-\text{OCH}_3$; or
 E^1 represents $-\text{OCH}_3$ and E^3 represents $-\text{OH}$; or
 E^1 represents $-\text{CH}_2\text{OCH}_3$ and E^3 represents (piperidin-4-yl)methoxy or
 ((1-*tert*butoxycarbonyl)piperidin-4-yl)methoxy; or
 15
 E^1 and E^3 represent hydrogen; and
 E^2 and E^4 represent $-\text{F}$; or
 E^2 and E^4 represent $-\text{CF}_3$; or

 20 E^4 represents hydrogen; and
 E^1 , E^2 and E^3 represent $-\text{F}$; or
 E^1 and E^2 represent $-\text{Cl}$ and E^3 represents $-\text{Cl}$, $-\text{OH}$ or $-\text{OCH}_3$; or
 E^1 and E^2 represent $-\text{CH}_3$ and E^3 represents $-\text{F}$ or $-\text{OCH}_3$; or
 E^2 and E^3 represent $-\text{Cl}$ and E^1 represents $-\text{CH}_3$; or
 25
 E^2 represents hydrogen; and
 E^1 , E^3 and E^4 represent $-\text{F}$; or
 E^3 and E^4 represent $-\text{Cl}$ and E^1 represents $-\text{CH}_3$; or
 E^1 and E^4 represent $-\text{Cl}$ and E^1 represents $-\text{OCH}_3$; or
 30 E^1 and E^4 represent $-\text{CH}_3$ and E^3 represents $-\text{F}$, $-\text{CH}_3$ or $-\text{OCH}_3$; or
 E^1 represents $-\text{F}$, E^3 represents $-\text{CH}_3$ and E^4 represents $-\text{Cl}$; or
 E^1 represents $-\text{Cl}$, E^3 represents $-\text{F}$ and E^4 represents $-\text{CH}_3$; or
 E^1 represents $-\text{Cl}$, E^3 represents $-\text{CH}_3$ and E^4 represents $-\text{F}$; or
 E^1 and E^4 represent $-\text{CH}_3$ and E^3 represents $-\text{F}$; or
 35 E^1 represents $-\text{CH}_3$, E^4 represents $-\text{Cl}$ and E^3 represents $-\text{CF}_3$ or $-\text{OCH}_3$; or

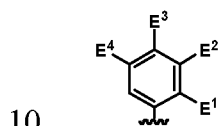
E¹ represents hydrogen; and

E² and E⁴ represent -CH₃ and E³ represents -OH; or

5 E³ represents hydrogen; and

E¹ and E² represent -Cl and E⁴ represents -CH₃.

Preferred particular compounds of formula I that may be mentioned include those in which R¹ is represented by



where:

E¹, E³ and E⁴ represent hydrogen and

E² represents -CH=CHC(O)OCH₃, -CH₂NH₂, -CH₂N(H)C(O)CH=CH₂, -CH₂OH,

-N(H)C(O)CH=CH₂, -N(H)C(O)CH=CHCH₂NMe₂, -N(H)C(O)CH=CHPh,

15 -N(H)C(O)C≡CH, -N(H)C(O)CH₂(OH), -N(H)C(O)CH(OH)Ph, -N(H)C(O)C(O)CH₃,

-N(H)C(O)C(O)Ph or -N(H)S(O)₂CH=CH₂; or

E¹, E² and E⁴ represent hydrogen and

E³ represents -CH=CH₂, -CH=CHC(O)OH, -CH=CHC(O)OCH₃, -CH₂NH₂,

-CH₂N(H)C(O)CH=CH₂, -CH₂OH, -C(O)H, -C(O)CH₃, -C(O)CF₃,

20 -N(H)C(O)CH=CH₂; or

E³ and E⁴ represent hydrogen; and

E¹ represents -F and E² represents -F, -Cl, or -CF₃; or

E¹ represents -Cl and E² represents -Cl, -CH₃ or -CF₃; or

25 E¹ represents -CH₃ and E² represents -Cl, -CH₃, -CN or -N(H)C(O)CH=CH₂; or

E² and E⁴ represent hydrogen; and

E¹ and E³ represent -F; or

E¹ represents -Cl and E³ represents -F or -Cl; or

30 E¹ represents -CH₃ and E³ represents -Cl; or

E² and E³ represent hydrogen; and

E¹ represents -F and E⁴ represents -Cl, -CH₃ or -CN; or

- E^1 represents -Cl and E^4 represents -F, -Cl, -CH₃ or -CF₃; or
 E^1 represents -CH₃ and E^4 represent, -Cl, -CH₃, -CF₃, -CN or
 -N(H)C(O)CH=CH; or
 E^1 represents -CF₃ and E^4 represents -F or -CF₃; or
 5 E^1 represents -CN and E^4 represents -Cl; or

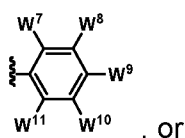
- E^4 represents hydrogen; and
 E^1 , E^2 and E^3 represent -F; or
 E^1 and E^2 represent -CH₃ and E^3 represents -F₃; or
 10 E^2 and E^3 represent -Cl and E^1 represents -CH₃; or

- E^2 represents hydrogen; and
 E^1 , E^3 and E^4 represent -F; or
 E^3 and E^4 represent -Cl and E^1 represents -CH₃; or
 15 E^1 and E^4 represent -CH₃ and E^3 represents -F or -CH₃; or
 E^1 represents -F, E^3 represents -CH₃ and E^4 represents -Cl; or
 E^1 represents -Cl, E^3 represents -F and E^4 represents -CH₃; or
 E^1 represents -Cl, E^3 represents -CH₃ and E^4 represents -F; or
 E^1 and E^4 represent -CH₃ and E^3 represents -F; or
 20 E^1 represents -CH₃, E^3 represents -CF₃ and E^4 represents -Cl; or

- E^1 represents hydrogen; and
 E^2 and E^4 represent -CH₃ and E^3 represents -OH; or
 25 E^3 represents hydrogen; and
 E^1 and E^2 represent -Cl and E^4 represents -CH₃.

Preferred compounds of formula I that may be mentioned include those in which:

- (a) Z^1 is not present or is selected from -F, -CN, -C(O)R^{b2}, -C(O)N(R^{c2})R^{d2},
 30 -C(O)OR^{e2}, -N(R^{f2})R^{g2}, -N(R^{h2})C(O)Rⁱ², -N(R^{j2})C(O)OR^{k2}, -N(R^{l2})C(O)N(R^{m2})Rⁿ²,
 -N(R^{o2})S(O)₂R^{p2}, -OR^{q2}, -S(O)_mRⁱ², -S(O)₂N(R^{u2})R^{v2}, heterocycloalkyl optionally
 substituted by one or more substituents selected from W⁵, aryl represented by



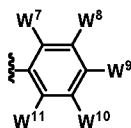
, or

- heteroaryl having 1 to 3 nitrogen atoms, one oxygen atom and/or one sulfur atom and optionally substituted by one or more substituents selected from W^6 ; or
- (b) Z^2 is not present or is selected from -F, $-R^{a2}$, $-C(O)N(R^{c2})R^{d2}$, $-N(R^{f2})R^{g2}$, $-N(R^{h2})C(O)R^{i2}$, $-N(R^{j2})C(O)OR^{k2}$, $-N(R^{l2})C(O)N(R^{m2})R^{n2}$, $-N(R^{o2})S(O)_2R^{p2}$, $-OR^{q2}$, $-S(O)_mR^{l2}$, $-S(O)_2N(R^{u2})R^{v2}$, heterocycloalkyl optionally substituted by one or more substituents selected from W^5 , aryl optionally substituted by one or more substituents selected from W^6 , or heteroaryl optionally substituted by one or more substituents selected from W^6 .
- 10 Other preferred compounds of formula I that may be mentioned include those in which:
- (a) Z^3 is not present or is selected from -F, $-R^{a2}$, $-C(O)N(R^{c2})R^{d2}$, $-N(R^{f2})R^{g2}$, $-N(R^{h2})C(O)R^{i2}$, $-N(R^{j2})C(O)OR^{k2}$, $-N(R^{l2})C(O)N(R^{m2})R^{n2}$, $-N(R^{o2})S(O)_2R^{p2}$, $-OR^{q2}$, $-S(O)_mR^{l2}$, $-S(O)_2N(R^{u2})R^{v2}$, heterocycloalkyl optionally substituted by one or more substituents selected from W^5 , aryl optionally substituted by one or more substituents selected from W^6 , or heteroaryl optionally substituted by one or more substituents selected from W^6 ; and/or
- (b) Z^4 is not present or is selected from -F, $-C(O)N(R^{c2})R^{d2}$, $-N(R^{f2})R^{g2}$, $-N(R^{h2})C(O)R^{i2}$, $-N(R^{j2})C(O)OR^{k2}$, $-N(R^{l2})C(O)N(R^{m2})R^{n2}$, $-N(R^{o2})S(O)_2R^{p2}$, $-OR^{q2}$, $-S(O)_mR^{l2}$, $-S(O)_2N(R^{u2})R^{v2}$, heterocycloalkyl optionally substituted by one or more substituents selected from W^5 , aryl optionally substituted by one or more substituents selected from W^6 , or heteroaryl optionally substituted by one or more substituents selected from W^6 .
- 25 Particularly preferred compounds of formula I that may be mentioned include those in which Z^1 represents -F, -CN, $-C(O)NH_2$, $-C(O)N(R^{c2})R^{d2}$, $-C(O)-(4\text{-morpholinyl})$, $-C(O)OEt$, $-N(H)C(O)Me$, $-N(H)C(O)R^{i2}$, $-N(H)C(O)CH_2NMe_2$, $-N(H)C(O)OCMe_3$, $-N(H)C(O)OCH_2Ph$, $-N(Me)C(O)OCMe_3$, $-N(H)C(O)N(H)Me$, $-N(H)C(O)N(H)CHMe_2$, $-N(H)S(O)_2Me$, $-OMe$, $-OCF_3$ and
- 30 $-OEt$.

Preferred compounds of formula I where Z^1 represents heterocycloalkyl that may be mentioned are those where Z^1 represents dihydropyridinyl, imidazolinyl, morpholinyl, oxanyl, piperazinyl, piperidinyl, pyrrolidinyl and quinuclidinyl, wherein

the heterocycloalkyl is optionally substituted by one or more substituents selected from W^5 .

Preferred compounds of formula I where Z^1 represents



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that may be mentioned are those where each W^7 , W^{10} and W^{11} independently represents hydrogen, halogen, $-R^{a3}$ or $-CN$; and

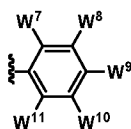
one of W^8 and W^9 represents hydrogen, halogen, $-R^{a3}$ or $-CN$ and the other represents halogen, $-R^{a3}$, $-CN$, $-C(O)R^{b3}$, $-C(O)N(R^{c3})R^{d3}$, $-C(O)OR^{e3}$, $-N(R^{f3})R^{g3}$, $-N(R^{h3})C(O)R^{i3}$, $-N(R^{j3})C(O)OR^{k3}$, $-N(R^{l3})C(O)N(R^{m3})R^{n3}$, $-N(R^{o3})S(O)_2R^{p3}$, $-OR^{q3x}$,

10

$-OC(O)R^{r3}$, $-OS(O)_2R^{s3}$, $-S(O)_mR^{t3}$, $-S(O)_2N(R^{u3})R^{v3}$, heterocycloalkyl optionally substituted by one or more substituents selected from G^1 , aryl optionally substituted by one or more substituents selected from G^2 , or heteroaryl optionally substituted by one or more substituents selected from G^2 .

15

Particularly preferred compounds of formula I where Z^1 represents



that may be mentioned are those where each W^7 , W^{10} and W^{11} independently represents $-F$, $-Cl$, $-CH_3$, $-CF_3$, or more preferably, hydrogen; and

20

one of W^8 and W^9 (preferably W^8) represents $-F$, $-Cl$, $-CH_3$, $-CF_3$, or more preferably, hydrogen, and the other (preferably W^9) represents halogen, $-R^{a3}$, $-CN$, $-C(O)R^{b3}$, $-C(O)N(R^{c3})R^{d3}$, $-C(O)OR^{e3}$, $-N(R^{f3})R^{g3}$, $-N(R^{h3})C(O)R^{i3}$, $-N(R^{j3})C(O)OR^{k3}$, $-N(R^{l3})C(O)N(R^{m3})R^{n3}$, $-N(R^{o3})S(O)_2R^{p3}$, $-OR^{q3x}$, $-OC(O)R^{r3}$, $-OS(O)_2R^{s3}$, $-S(O)_mR^{t3}$, $-S(O)_2N(R^{u3})R^{v3}$, heterocycloalkyl optionally substituted by one or more substituents selected from G^1 , aryl optionally substituted by one or more substituents selected from G^2 , or heteroaryl optionally substituted by one or more substituents selected from G^2 .

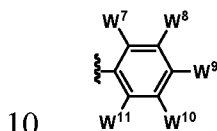
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For example, particular compounds of formula I that may be mentioned include those wherein:

30

- (a) W^8 , W^9 , W^{10} and W^{11} represents hydrogen and W^7 represents -Cl or $-S(O)_2CH_3$; or
- (b) W^7 , W^9 , W^{10} and W^{11} represents hydrogen and W^8 represents -F, -Br, -CN, $-N(H)C(O)CH_3$, $-OCH_3$ or $-S(O)_2CH_3$; or
- 5 (c) W^7 , W^{10} and W^{11} represents hydrogen and:
- (i) W^8 and W^9 represents -F or -Cl; or
- (ii) W^8 represents -F and W^9 represents $-CH_3$.

More particularly preferred compounds of formula I where Z^1 represents



- that may be mentioned are those where W^7 , W^8 , W^{10} and W^{11} are hydrogen and W^9 represents halogen, $-R^{a3}$, -CN, $-C(O)R^{b3}$, $-C(O)N(R^{c3})R^{d3}$, $-C(O)OR^{e3}$, $-N(R^{f3})R^{g3}$, $-N(R^{h3})C(O)R^{i3}$, $-N(R^{j3})C(O)OR^{k3}$, $-N(R^{l3})C(O)N(R^{m3})R^{n3}$, $-N(R^{o3})S(O)_2R^{p3}$, $-OR^{q3x}$, $-S(O)_mR^{t3}$, $-S(O)_2N(R^{u3})R^{v3}$, heterocycloalkyl optionally
- 15 substituted by one or more substituents selected from G^1 , aryl optionally substituted by one or more substituents selected from G^2 , or heteroaryl optionally substituted by one or more substituents selected from G^2 .

- For example, more particularly preferred compounds of formula I that may be
- 20 mentioned are those where where W^7 , W^8 , W^{10} and W^{11} are hydrogen and W^9 represents -F, -Cl, $-CH_3$, cyclopropyl, $-CF_3$, -CN, $-NH_2$, $-N(CH_3)_2$, $-N(H)C(O)CH_3$, $-N(H)C(O)OC(CH_3)_3$, $-SO_2CH_3$, $-SO_2NH_2$, $-S(O)_2N(CH_3)_2$, $-S(O)_2$ -4-morpholinyl, 4-methylpiperazin-1-yl, 4-methylpiperidin-1-ylmethyl and 1,2,3-thiadiazol-4-yl.

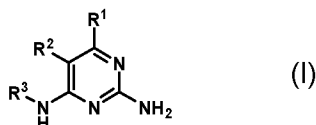
- 25 Preferred compounds of formula I where Z^1 represents heteroaryl that may be mentioned are those where Z^1 represents benzimidazolyl, benzodioxinyl, benzoxazolyl, furanyl, imidazolyl, imidazopyridinyl, indolyl, isoquinolinyl, oxadiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridyl, pyrrolopyridinyl, quinolinyl, thiazolyl, thiophenyl and triazolyl, wherein the heteroaryl is optionally substituted
- 30 by one or more substituents selected from W^6 .

Particularly preferred compounds of formula I where Z^1 represents heteroaryl that may be mentioned are those where Z^1 represents benzimidazol-2-yl, 1,4-benzo-

dioxin-2-yl, benzoxazol-2-yl, furan-2-yl, imidazol-1-yl, imidazol-4-yl, imidazo-
 [1,2-*a*]pyridin-2-yl, indol-3-yl, indol-5-yl, isoquinolin-4-yl, 1,3,4-oxadiazol-2-yl,
 1,2-oxazol-4-yl, pyrazin-3-yl, pyrazol-1-yl, pyrazol-4-yl, pyridin-2-yl, pyridin-3-yl,
 pyridin-4-yl, 5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-5-yl, thiazol-5-yl, thiophen-2-yl,
 1,2,3-triazol-4-yl and 1,2,4-triazol-3-yl, wherein the heteroaryl is optionally
 substituted by one or more substituents selected from W^6 .

More particularly preferred compounds of formula I that may be mentioned are
 those where W^6 represents -F, -Cl, -Br, -CH₃, cyclopropyl, -CF₃, -CN, -NH₂,
 -N(CH₃)₂, -SO₂CH₃, -SO₂NH₂ and -SO₂N(CH₃)₂.

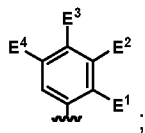
In another embodiment of the invention there is provided a compound of formula
 I,



wherein:

R^1 represents:

indanyl, naphthyl, tetrahydronaphthyl or heteroaryl, the latter connected to the
 pyrimidine of formula I via a carbon atom of the heteroaryl ring, which indanyl,
 naphthyl, tetrahydronaphthyl and heteroaryl rings are optionally substituted by
 one or more substituents selected from Y^1 , -C₁₋₆alkyl optionally substituted by one
 or more Y^2 and heterocycloalkyl optionally substituted by one or more Y^3 ; or
 aryl represented by



25

E^1 , E^2 , E^3 and E^4 represents hydrogen, Y^1 , -C₁₋₆alkyl optionally substituted by one
 or more Y^2 or heterocycloalkyl optionally substituted by one or more Y^3 , but where
 at least one of E^1 , E^2 , E^3 and E^4 is other than hydrogen;

30 R^2 represents hydrogen, halogen or -C₁₋₁₂alkyl optionally substituted by one or
 more Z^1 ;

R³ represents -C₁₋₁₂alkyl substituted by one or more Z¹ or heterocycloalkyl optionally substituted by one or more Z²; or

- 5 R² and R³ are linked together to form, along with the atoms to which they are attached, a 5- to 8-membered non-aromatic ring, wherein the link formed by R² and R³ is optionally substituted by one or more substituents selected from Z³ or -C₁₋₉alkyl optionally substituted by one or more Z⁴;
- 10 each Y¹ independently represents halogen, -CN, -C(O)R^a, -C(O)N(R^b)R^c, -C(O)OR^d, -N(R^e)R^f, -N(R^g)C(O)R^h, -N(Rⁱ)C(O)OR^j, -N(R^k)C(O)N(R^l)R^m, -NO₂, -N(Rⁿ)S(O)₂R^o, -OR^p, -OC(O)R^q, -OS(O)₂R^r, -S(O)_mR^s, -S(O)₂N(R^t)R^u, heterocycloalkyl optionally substituted by one or more substituents selected from W², aryl optionally substituted by one or more substituents selected from W³, or heteroaryl optionally substituted by one or more substituents selected from W³;

- each R^a, R^b, R^c, R^d, R^e, R^g, R^h, Rⁱ, R^k, R^l, R^m, Rⁿ, R^p, R^q, R^s, R^t and R^u independently represents hydrogen, -C₁₋₆ alkyl optionally substituted by one or more substituents selected from W¹, heterocycloalkyl optionally substituted by one or more substituents selected from W², aryl optionally substituted by one or more substituents selected from W³, or heteroaryl optionally substituted by one or more substituents selected from W³; or
- 20 more substituents selected from W¹, heterocycloalkyl optionally substituted by one or more substituents selected from W², aryl optionally substituted by one or more substituents selected from W³, or heteroaryl optionally substituted by one or more substituents selected from W³; or
- 25 any two R^b and R^c, R^e and R^f, Rⁱ and R^m and/or R^t and R^u are linked together to form, along with the nitrogen atom to which they are attached, a 3- to 8-membered monocyclic or bicyclic ring, which ring optionally contains one or two heteroatoms and which ring optionally is substituted by one or more substituents selected from W², C₁₋₃alkyl optionally substituted by one or more substituents selected from W¹, and =O;
- 30 selected from W¹, and =O;

each R^f, R^j, R^o and R^r independently represent -C₁₋₆ alkyl optionally substituted by one or more substituents selected from W¹, heterocycloalkyl optionally substituted by one or more substituents selected from W², aryl optionally substituted by one

or more substituents selected from W^3 or heteroaryl optionally substituted by one or more substituents selected from W^3 ;

each Y^2 independently represents halogen, $-CN$, $-C(O)R^{b1}$, $-C(O)N(R^{c1})R^{d1}$,
 5 $-C(O)OR^{e1}$, $-N(R^{f1})R^{g1}$, $-N(R^{h1})C(O)R^{i1}$, $-N(R^{j1})C(O)OR^{k1}$, $-N(R^{l1})C(O)N(R^{m1})R^{n1}$,
 $-N(R^{o1})S(O)_2R^{p1}$, $-OR^{q1}$, $-OC(O)R^{r1}$, $-OS(O)_2R^{s1}$, $-S(O)_mR^{t1}$, $-S(O)_2N(R^{u1})R^{v1}$,
 heterocycloalkyl optionally substituted by one or more substituents selected from
 W^1 , aryl optionally substituted by one or more substituents selected from W^2 ,
 heteroaryl optionally substituted by one or more substituents selected from W^2 ;

10

each Y^3 independently represents halogen, $-R^{a1}$, $-CN$, $-C(O)R^{b1}$, $-C(O)N(R^{c1})R^{d1}$,
 $-C(O)OR^{e1}$, $-N(R^{f1})R^{g1}$, $-N(R^{h1})C(O)R^{i1}$, $-N(R^{j1})C(O)OR^{k1}$, $-N(R^{l1})C(O)N(R^{m1})R^{n1}$,
 $-N(R^{o1})S(O)_2R^{p1}$, $-OR^{q1}$, $-OC(O)R^{r1}$, $-OS(O)_2R^{s1}$, $-S(O)_mR^{t1}$, $-S(O)_2N(R^{u1})R^{v1}$,
 heterocycloalkyl optionally substituted by one or more substituents selected from
 15 W^1 , aryl optionally substituted by one or more substituents selected from W^2 ,
 heteroaryl optionally substituted by one or more substituents selected from W^2 , or
 $=O$;

each R^{a1} , R^{b1} , R^{c1} , R^{d1} , R^{e1} , R^{f1} , R^{h1} , R^{i1} , R^{j1} , R^{l1} , R^{m1} , R^{n1} , R^{o1} , R^{q1} , R^{r1} , R^{t1} , R^{u1}
 20 and R^{v1} independently represents hydrogen, C_{1-6} alkyl optionally substituted by
 one or more substituents selected from W^1 , heterocycloalkyl optionally substituted
 by one or more substituents selected from W^2 , aryl optionally substituted by one
 or more substituents selected from W^3 , or heteroaryl optionally substituted by one
 or more substituents selected from W^3 ; or

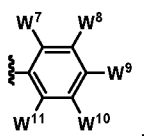
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any two R^{c1} and R^{d1} , R^{f1} and R^{g1} , R^{m1} and R^{n1} and/or R^{u1} and R^{v1} are linked
 together to form, along with the nitrogen atom to which they are attached, a 3- to
 8-membered monocyclic or bicyclic ring, which ring optionally contains one or two
 heteroatoms and which ring optionally is substituted by one or more
 30 substituents selected from W^2 , C_{1-3} alkyl optionally substituted by one or more
 substituents selected from W^1 , and $=O$;

each R^{g1} , R^{k1} , R^{p1} and R^{s1} independently represent $-C_{1-6}$ alkyl optionally
 substituted by one or more substituents selected from W^1 , heterocycloalkyl
 35 optionally substituted by one or more substituents selected from W^2 , aryl

optionally substituted by one or more substituents selected from W^3 , or heteroaryl optionally substituted by one or more substituents selected from W^3 ;

- each Z^1 independently represents halogen, -CN, $-C(O)R^{b2}$, $-C(O)N(R^{c2})R^{d2}$,
 5 $-C(O)OR^{e2}$, $-N(R^{f2})R^{g2}$, $-N(R^{h2})C(O)R^{i2}$, $-N(R^{j2})C(O)OR^{k2}$, $-N(R^{l2})C(O)N(R^{m2})R^{n2}$, $-N(R^{o2})S(O)_2R^{p2}$, $-OR^{q2}$, $-OC(O)R^{r2}$, $-OS(O)_2R^{s2}$, $-S(O)_mR^{t2}$, $-S(O)_2N(R^{u2})R^{v2}$, heterocycloalkyl optionally substituted by one or more substituents selected from W^5 , aryl represented by



- 10 heteroaryl having 1 to 3 nitrogen atoms, one oxygen atom and/or one sulfur atom and optionally substituted by one or more substituents selected from W^6 ;

- each Z^2 and Z^3 independently represents halogen, $-R^{a2}$, -CN, $-C(O)R^{b2}$,
 $-C(O)N(R^{c2})R^{d2}$, $-C(O)OR^{e2}$, $-N(R^{f2})R^{g2}$, $-N(R^{h2})C(O)R^{i2}$, $-N(R^{j2})C(O)OR^{k2}$,
 15 $-N(R^{l2})C(O)N(R^{m2})R^{n2}$, $-N(R^{o2})S(O)_2R^{p2}$, $-OR^{q2}$, $-OC(O)R^{r2}$, $-OS(O)_2R^{s2}$, $-S(O)_mR^{t2}$, $-S(O)_2N(R^{u2})R^{v2}$, heterocycloalkyl optionally substituted by one or more substituents selected from W^5 , aryl optionally substituted by one or more substituents selected from W^6 , or heteroaryl optionally substituted by one or more substituents selected from W^6 ;

- 20 each Z^4 independently represents halogen, -CN, $-C(O)R^{b2}$, $-C(O)N(R^{c2})R^{d2}$, $-C(O)OR^{e2}$, $-N(R^{f2})R^{g2}$, $-N(R^{h2})C(O)R^{i2}$, $-N(R^{j2})C(O)OR^{k2}$, $-N(R^{l2})C(O)N(R^{m2})R^{n2}$, $-N(R^{o2})S(O)_2R^{p2}$, $-OR^{q2}$, $-OC(O)R^{r2}$, $-OS(O)_2R^{s2}$, $-S(O)_mR^{t2}$, $-S(O)_2N(R^{u2})R^{v2}$, heterocycloalkyl optionally substituted by one or more substituents selected from W^5 , aryl optionally substituted by one or more substituents selected from W^6 , heteroaryl optionally substituted by one or more substituents selected from W^6 , or =O;

- each R^{a2} , R^{b2} , R^{c2} , R^{d2} , R^{e2} , R^{f2} , R^{h2} , R^{i2} , R^{j2} , R^{l2} , R^{m2} , R^{n2} , R^{o2} , R^{r2} , R^{t2} , R^{u2} and
 30 R^{v2} independently represents hydrogen or C_{1-6} alkyl optionally substituted by one or more substituents selected from W^4 , heterocycloalkyl optionally substituted by one or more substituents selected from W^5 , aryl optionally substituted by one or

more substituents selected from W^6 , or heteroaryl optionally substituted by one or more substituents selected from W^6 ; or

any two R^{c2} and R^{d2} , R^{f2} and R^{g2} , R^{m2} and R^{n2} and/or R^{u2} and R^{v2} are linked
 5 together to form, along with the nitrogen atom to which they are attached, a 3- to 8-membered monocyclic or bicyclic ring, which ring optionally contains one or two heteroatoms and which ring optionally is substituted by one or more substituents selected from W^5 , C_{1-3} alkyl optionally substituted by one or more substituents selected from W^4 , and =O;

10 each R^{g2} , R^{k2} , R^{p2} , R^{q2} and R^{s2} independently represent $-C_{1-6}$ alkyl optionally substituted by one or more substituents selected from W^4 , heterocycloalkyl optionally substituted by one or more substituents selected from W^5 , aryl optionally substituted by one or more substituents selected from W^6 , or heteroaryl
 15 optionally substituted by one or more substituents selected from W^6 ;

each W^1 and W^4 independently represents halogen, -CN, $-N(R^{f3})R^{g3}$,
 $-N(R^{h3})C(O)R^{i3}$, $-N(R^{j3})C(O)OR^{k3}$, $-N(R^{l3})C(O)N(R^{m3})R^{n3}$, $-N(R^{o3})S(O)_2R^{p3}$, $-OR^{q3}$,
 $-OC(O)R^{r3}$, $-OS(O)_2R^{s3}$, $-S(O)_mR^{t3}$, $-S(O)_2N(R^{u3})R^{v3}$, heterocycloalkyl optionally
 20 substituted by one or more substituents selected from G^1 , aryl optionally substituted by one or more substituents selected from G^2 , heteroaryl optionally substituted by one or more substituents selected from G^2 , or =O;

each W^2 , W^3 , W^5 and W^6 independently represents halogen, $-R^{a3}$, -CN, $-C(O)R^{b3}$,
 25 $-C(O)N(R^{c3})R^{d3}$, $-C(O)OR^{e3}$, $-N(R^{f3})R^{g3}$, $-N(R^{h3})C(O)R^{i3}$, $-N(R^{j3})C(O)OR^{k3}$,
 $-N(R^{l3})C(O)N(R^{m3})R^{n3}$, $-N(R^{o3})S(O)_2R^{p3}$, $-OR^{q3}$, $-OC(O)R^{r3}$, $-OS(O)_2R^{s3}$, $-S(O)_mR^{t3}$,
 $-S(O)_2N(R^{u3})R^{v3}$, heterocycloalkyl optionally substituted by one or more
 30 substituents selected from G^1 , aryl optionally substituted by one or more substituents selected from G^2 , heteroaryl (optionally substituted by one or more substituents selected from G^2 , or =O;

W^7 and W^{11} represents hydrogen;

each W^8 and W^{10} independently represents hydrogen, halogen, $-R^{a3}$, -CN,
 35 $-C(O)R^{b3}$,

- C(O)N(R^{c3})R^{d3}, -C(O)OR^{e3}, -N(R^{f3})R^{g3}, -N(R^{h3})C(O)Rⁱ³, -N(R^{j3})C(O)OR^{k3},
 -N(R^{l3})C(O)N(R^{m3})Rⁿ³, -N(R^{o3})S(O)₂R^{p3}, -OR^{q3}, -OC(O)R^{r3}, -OS(O)₂R^{s3}, -S(O)_mR^{t3},
 -S(O)₂N(R^{u3})R^{v3}, heterocycloalkyl optionally substituted by one or more
 substituents selected from G¹, aryl optionally substituted by one or more
 5 substituents selected from G², or heteroaryl optionally substituted by one or more
 substituents selected from G²;

- W⁹ represents halogen, -R^{a3}, -CN, -C(O)R^{b3}, -C(O)N(R^{c3})R^{d3}, -C(O)OR^{e3},
 -N(R^{f3})R^{g3},
 10 -N(R^{h3})C(O)Rⁱ³, -N(R^{j3})C(O)OR^{k3}, -N(R^{l3})C(O)N(R^{m3})Rⁿ³, -N(R^{o3})S(O)₂R^{p3}, -OR^{q3x},
 -OC(O)R^{r3}, -OS(O)₂R^{s3}, -S(O)_mR^{t3}, -S(O)₂N(R^{u3})R^{v3}, heterocycloalkyl optionally
 substituted by one or more substituents selected from G¹, aryl optionally
 substituted by one or more substituents selected from G², or heteroaryl optionally
 substituted by one or more substituents selected from G²;

- 15 each R^{a3}, R^{b3}, R^{c3}, R^{d3}, R^{e3}, R^{f3}, R^{h3}, Rⁱ³, R^{j3}, R^{l3}, R^{m3}, Rⁿ³, R^{o3}, R^{q3}, R^{r3}, R^{t3}, R^{u3}
 and R^{v3} independently represents hydrogen or -C₁₋₆ alkyl optionally substituted by
 one or more G³; or
- 20 any two R^{c3} and R^{d3}, R^{f3} and R^{g3}, R^{m3} and Rⁿ³ and/or R^{u3} and R^{v3} are linked
 together to form, along with the nitrogen atom to which they are attached, a 4- to
 6-membered ring, which ring optionally contains one heteroatom and which ring
 optionally is substituted by one or more G²;
- 25 each R^{g3}, R^{k3}, R^{p3}, R^{q3} and R^{s3} independently represent C₁₋₆ alkyl optionally
 substituted by one or more G³;

R^{q3x} represents C₂₋₆ alkyl optionally substituted by one or more G³;

- 30 each G¹ and G² independently represents halogen, -R^{a4}, -CN, -C(O)R^{b4},
 -C(O)N(R^{c4})R^{d4}, -C(O)OR^{e4}, -N(R^{f4})R^{g4}, -N(R^{h4})C(O)Rⁱ⁴, -N(R^{j4})C(O)OR^{k4},
 -N(R^{l4})C(O)N(R^{m4})Rⁿ⁴, -N(R^{o4})S(O)₂R^{p4}, -OR^{q4}, -OC(O)R^{r4}, -OS(O)₂R^{s4}, -S(O)_mR^{t4},
 -S(O)₂N(R^{u4})R^{v4}, or =O;

G^3 represents halogen, $-CN$, $-C(O)R^{b4}$, $-C(O)N(R^{c4})R^{d4}$, $-C(O)OR^{e4}$, $-N(R^{f4})R^{g4}$, $-N(R^{h4})C(O)R^{i4}$, $-N(R^{j4})C(O)OR^{k4}$, $-N(R^{l4})C(O)N(R^{m4})R^{n4}$, $-N(R^{o4})S(O)_2R^{p4}$, $-OR^{q4}$, $-OC(O)R^{r4}$, $-OS(O)_2R^{s4}$, $-S(O)_mR^{t4}$, $-S(O)_2N(R^{u4})R^{v4}$, or $=O$;

- 5 each R^{a4} , R^{b4} , R^{c4} , R^{d4} , R^{e4} , R^{f4} , R^{h4} , R^{i4} , R^{j4} , R^{l4} , R^{m4} , R^{n4} , R^{o4} , R^{q4} , R^{r4} , R^{t4} , R^{u4} and R^{v4} independently represents hydrogen or $-C_{1-6}$ alkyl optionally substituted by one or more $-F$; or

- 10 any two R^{c4} and R^{d4} , R^{f4} and R^{g4} , R^{m4} and R^{n4} and/or R^{u4} and R^{v4} are linked together to form, along with the nitrogen atom to which they are attached, a 3- to 6-membered ring, which ring optionally substituted by one or more $-F$, $-CH_3$, $-CH_2CH_3$, $-CHF_2$, $-CF_3$, $-CH_2CF_3$, or $=O$;

- 15 each R^{g4} , R^{k4} , R^{p4} and R^{s4} independently represent C_{1-6} alkyl optionally substituted by one or more $-F$;

each m independently represents 0, 1 or 2;

- 20 provided that formula I does not represent
 6-(3-pyridinyl)- N^4 -[[4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]methyl]-2,4-pyrimidinediamine,
 6-(3-pyridinyl)- N^4 -[[5-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]-2-pyridinyl]methyl]-2,4-pyrimidinediamine,
 6-(3-pyridinyl)- N^4 -[[5-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]-2-pyrimidinyl]-
 25 methyl]-2,4-pyrimidinediamine,
 N^4 -[2-(diethylamino)ethyl]-6-(3,4,5-trimethoxyphenyl)-2,4-pyrimidinediamine,
 N^4 -[3-(4-morpholinyl)propyl]-6-(3,4,5-trimethoxyphenyl)-2,4-pyrimidinediamine, or
 N^4 -[2-(4-morpholinyl)ethyl]-6-(3,4,5-trimethoxyphenyl)-2,4-pyrimidinediamine;
 30 or a pharmaceutically acceptable salt thereof;

which compounds may be referred to herein as "the compounds of the invention".

- 35 Pharmaceutically-acceptable salts include acid addition salts and base addition salts. Such salts may be formed by conventional means, for example by reaction

of a free acid or a free base form of a compound of formula I with one or more equivalents of an appropriate acid or base, optionally in a solvent, or in a medium in which the salt is insoluble, followed by removal of said solvent, or said medium, using standard techniques (e.g. *in vacuo*, by freeze-drying or by filtration). Salts
5 may also be prepared by exchanging a counter-ion of a compound of the invention in the form of a salt with another counter-ion, for example using a suitable ion exchange resin. For the avoidance of doubt, solvates are also included within the scope of the invention.

10 Compounds of the invention may contain double bonds and may thus exist as *E* (*entgegen*) and *Z* (*zusammen*) geometric isomers about each individual double bond. All such isomers and mixtures thereof are included within the scope of the invention.

15 Compounds of the invention may also exhibit tautomerism. All tautomeric forms and mixtures thereof are included within the scope of the invention.

Compounds of the invention may also contain one or more asymmetric carbon atoms and may therefore exhibit optical and/or diastereoisomerism.

20 Diastereoisomers may be separated using conventional techniques, e.g. chromatography or fractional crystallisation. The various stereoisomers may be isolated by separation of a racemic or other mixture of the compounds using conventional, e.g. fractional crystallisation or HPLC, techniques. Alternatively the desired optical isomers may be made by reaction of the appropriate optically
25 active starting materials under conditions which will not cause racemisation or epimerisation (i.e. a 'chiral pool' method), by reaction of the appropriate starting material with a 'chiral auxiliary' which can subsequently be removed at a suitable stage, by derivatisation (i.e. a resolution, including a dynamic resolution), for example with a homochiral acid followed by separation of the diastereomeric
30 derivatives by conventional means such as chromatography, or by reaction with an appropriate chiral reagent or chiral catalyst all under conditions known to the skilled person. All stereoisomers and mixtures thereof are included within the scope of the invention.

Unless otherwise specified, C_{1-q} alkyl groups (where q is the upper limit of the range) defined herein may be straight-chain or, when there is a sufficient number (i.e. a minimum of two or three, as appropriate) of carbon atoms, be branched-chain, and/or cyclic (so forming a C_{3-q}-cycloalkyl group). When there is a
5 sufficient number (i.e. a minimum of four) of carbon atoms, such groups may also be part cyclic. Such alkyl groups may also be saturated or, when there is a sufficient number (i.e. a minimum of two) of carbon atoms, be unsaturated (forming, for example, a C_{2-q} alkenyl or a C_{2-q} alkynyl group).

10 Unless otherwise specified, C_{1-q} alkylene groups (where q is the upper limit of the range) defined herein may (in a similar manner to the definition of C_{1-q} alkyl) be straight-chain or, when there is a sufficient number (i.e. a minimum of two or three, as appropriate) of carbon atoms, be branched-chain, and/or cyclic (so forming a C_{3-q}-cycloalkylene group). When there is a sufficient number (i.e. a
15 minimum of four) of carbon atoms, such groups may also be part cyclic. Such alkylene groups may also be saturated or, when there is a sufficient number (i.e. a minimum of two) of carbon atoms, be unsaturated (forming, for example, a C_{2-q} alkenylene or a C_{2-q} alkynylene group). Particular alkylene groups that may be mentioned include those that are straight-chained and saturated.

20

The term "halo", when used herein, includes fluoro, chloro, bromo and iodo (for example, fluoro and chloro).

Heterocycloalkyl groups that may be mentioned include non-aromatic monocyclic
25 and bicyclic heterocycloalkyl groups (which groups may further be bridged) in which at least one (e.g. one to four) of the atoms in the ring system is other than carbon (i.e. a heteroatom), and in which the total number of atoms in the ring system is between three and twelve (e.g. between five and ten and, most preferably, between three and eight, e.g. a 5- or 6-membered heterocycloalkyl
30 group). Further, such heterocycloalkyl groups may be saturated or unsaturated containing one or more double and/or triple bonds, forming for example a C_{2-q} (e.g. C_{4-q}) heterocycloalkenyl (where q is the upper limit of the range) or a C_{7-q} heterocycloalkynyl group. C_{2-q} heterocycloalkyl groups that may be mentioned include 7-azabicyclo-[2.2.1]heptanyl, 6-azabicyclo[3.1.1]heptanyl,
35 6-azabicyclo[3.2.1]octanyl, 8-azabicyclo[3.2.1]octanyl, aziridinyl, azetidinyl,

dihydropyranyl, dihydropyridyl, dihydropyrrolyl (including 2,5-dihydropyrrolyl), dioxolanyl (including 1,3-dioxolanyl), dioxanyl (including 1,3-dioxanyl and 1,4-dioxanyl), dithianyl (including 1,4-dithianyl), dithiolanyl (including 1,3-dithiolanyl), imidazolidinyl, imidazoliny, 7-oxabicyclo[2.2.1]heptanyl, 6-oxabicyclo[3.2.1]-octanyl, oxetanyl, oxiranyl, piperaziny, piperidinyl, pyranyl, pyrazolidinyl, pyrrolidinonyl, pyrrolidinyl, pyrrolinyl, quinuclidinyl, sulfolanyl, 3-sulfolenyl, tetrahydropyranyl, tetrahydrofuryl, tetrahydropyridyl (such as 1,2,3,4-tetrahydropyridyl and 1,2,3,6-tetrahydropyridyl), thietanyl, thiiranyl, thiolanyl, thiomorpholinyl, trithianyl (including 1,3,5-trithianyl), tropanyl and the like.

Substituents on heterocycloalkyl groups may, where appropriate, be located on any atom in the ring system including a heteroatom. Further, in the case where the substituent is another cyclic compound, then the cyclic compound may be attached through a single atom on the heterocycloalkyl group, forming a so-called “spiro”-compound. The point of attachment of heterocycloalkyl groups may be *via* any atom in the ring system including (where appropriate) a heteroatom (such as a nitrogen atom), or an atom on any fused carbocyclic ring that may be present as part of the ring system. Heterocycloalkyl groups may also be in the *N*- or *S*-oxidised form. At each occurrence when mentioned herein, a heterocycloalkyl group is preferably a 3- to 8-membered heterocycloalkyl group (e.g. a 5- or 6-membered heterocycloalkyl group).

The term “aryl”, when used herein, includes C₆₋₁₄ (e.g. C₆₋₁₀) aromatic groups. Such groups may be monocyclic or bicyclic and, when bicyclic, be either wholly or partly aromatic. C₆₋₁₀ aryl groups that may be mentioned include phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, indanyl, and the like (e.g. phenyl, naphthyl and the like). For the avoidance of doubt, the point of attachment of substituents on aryl groups may be *via* any carbon atom of the ring system.

The term “heteroaryl” (or heteroaromatic), when used herein, includes 5- to 10-membered heteroaromatic groups containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur. Such heteroaryl group may comprise one, or two rings, of which at least one is aromatic. Substituents on heteroaryl/heteroaromatic groups may, where appropriate, be located on any atom in the ring system including a heteroatom. The point of attachment of heteroaryl/heteroaromatic groups may be *via* any atom in the ring system

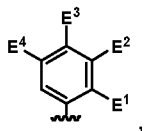
including (where appropriate) a heteroatom. Bicyclic heteroaryl/heteroaromatic groups may comprise a benzene ring fused to one or more further aromatic or non-aromatic heterocyclic rings, in which instances, the point of attachment of the polycyclic heteroaryl/heteroaromatic group may be *via* any ring including the benzene ring or the heteroaryl/heteroaromatic or heterocycloalkyl ring. Examples of heteroaryl/heteroaromatic groups that may be mentioned include pyridinyl, pyrrolyl, furanyl, thiophenyl, oxadiazolyl, thiadiazolyl, thiazolyl, oxazolyl, pyrazolyl, triazolyl, tetrazolyl, isoxazolyl, isothiazolyl, imidazolyl, imidazopyrimidinyl, pyrimidinyl, indolyl, azaindolyl, pyrazinyl, indazolyl, pyrimidinyl, quinolinyl, isoquinolinyl, benzofuranyl, benzothiophenyl, benzoimidazolyl, benzoxazolyl, benzothiazolyl and benzotriazolyl. The oxides of heteroaryl/ heteroaromatic groups are also embraced within the scope of the invention (e.g. the *N*-oxide). As stated above, heteroaryl includes polycyclic (e.g. bicyclic) groups in which one ring is aromatic (and the other may or may not be aromatic). Hence, other heteroaryl groups that may be mentioned include e.g. benzo[1,3]dioxolyl, benzo[1,4]dioxinyl, indolinyl, *5H,6H,7H*-pyrrolo[1,2-*b*]pyrimidinyl, 1,2,3,4-tetrahydroquinolinyl and the like.

Heteroatoms that may be mentioned include phosphorus, silicon, boron and, preferably, oxygen, nitrogen and sulfur.

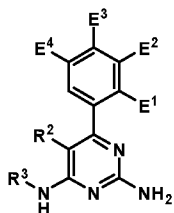
For the avoidance of doubt, in cases in which the identity of two or more substituents in a compound of the invention may be the same, the actual identities of the respective substituents are not in any way interdependent.

25

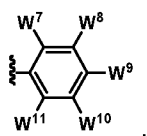
For the avoidance of doubt, when R¹ is defined as



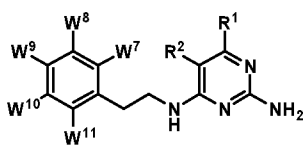
it is connected to the rest of formula I by the bond interrupted by the wiggly line, and formula I can thus be represented by



Likewise, when R³ is -C₁₋₁₂ alkyl substituted by Z¹, and Z¹ is represented by



then, if e.g. R³ is C₂alkyl, then formula I can be represented by



5

The present invention also embraces isotopically-labeled compounds of the present invention which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature (or the most abundant one found in nature). All isotopes of any particular atom or element as specified herein are contemplated within the scope of the compounds of the invention. Hence, the compounds of the invention also include deuterated compounds, i.e. in which one or more hydrogen atoms are replaced by the hydrogen isotope deuterium.

All individual features (e.g. preferred features) mentioned herein may be taken in isolation or in combination with any other feature (including preferred features) mentioned herein (hence, preferred features may be taken in conjunction with other preferred features, or independently of them).

The skilled person will appreciate that compounds of the invention that are the subject of this invention include those that are stable. That is, compounds of the invention include those that are sufficiently robust to survive isolation from e.g. a reaction mixture to a useful degree of purity.

Particular compounds of formula I that may be mentioned include those in which:

R² represents hydrogen or -C₁₋₁₂alkyl optionally substituted by one or more Z¹;

and

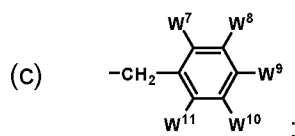
R³ represents -C₁₋₁₂alkyl substituted by one or more Z¹ or heterocycloalkyl optionally substituted by one or more Z².

5

For example, compounds of formula I that may be mentioned include those in which R² represents methyl, or preferably, hydrogen and R³ represents:

(a) -C₁₋₁₂alkyl (for example -C₁₋₆alkyl) substituted by two, or preferably, one Z¹ or;

10 (b) -C₂₋₆alkyl substituted by two, or preferably, one Z¹ or heterocycloalkyl optionally substituted by two, or preferably, one Z²; or



(d) -C₁₋₁₂alkyl (for example -C₁₋₆alkyl) substituted by heteroaryl having 1 to 3 nitrogen atoms, one oxygen atom and/or one sulfur atom and which heteroaryl is optionally substituted by one or more substituents selected from W³; or

15 (e) -C₃₋₆alkyl or a heterocycloalkyl selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclopropylethyl, cyclobutylethyl, cyclopropylpropyl, oxetanyl, tetrahydrofuryl, tetrahydropyranyl, azetidiny, pyrrolidiny, piperidiny, piperaziny or morpholiny

20 wherein the C₃₋₆alkyl is substituted by two, or preferably, one Z¹ and the heterocycloalkyl is optionally substituted by two, or preferably, one Z².

Particular compounds of formula I that may be mentioned include those in which:

25 R² and R³ are linked together to form, along with the atoms to which they are attached, a 5- to 8-membered non-aromatic ring, wherein the link formed by R² and R³ is optionally substituted by one or more substituents selected from Z³ or -C₁₋₉alkyl optionally substituted by one or more Z⁴.

For example, compounds of formula I that may be mentioned include those in which R² and R³ are linked together to form, along with the atoms to which they are attached, a 5- to 6-membered non-aromatic ring, wherein the non-aromatic ring is:

(a) unsubstituted; or

- (b) substituted by one or more substituents selected from Z^3 ; or
- (c) substituted by $-C_{1-9}$ alkyl optionally substituted by one or more Z^4 ; or
- (d) substituted by one or more substituents selected from Z^3 and substituted by $-C_{1-9}$ alkyl optionally substituted by one or more Z^4 .

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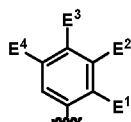
Particular compounds of formula I that may be mentioned include those in which R^1 represents heteroaryl.

- 10 Preferred compounds of formula I where R^1 represents heteroaryl that may be mentioned are those where R^1 represents benzofuranyl, benzothiophenyl, dihydrobenzofuranyl, indazolyl, indolyl, isoquinolinyl, pyridinyl, pyrrolyl and quinolinyl.

- 15 Particularly preferred compounds of formula I where R^1 represents heteroaryl that may be mentioned are those where R^1 represents benzofuran-3-yl, benzothiophen-3-yl, dihydrobenzofuran-7-yl, indol-3-yl, indol-4-yl, indol-5-yl, isoquinolin-4-yl, pyridin-3-yl, pyridin-4-yl, pyrrol-2-yl and quinolin-5-yl.

- 20 For example, compounds of formula I that may be mentioned include those in which R^1 represents indolyl, e.g. indol-3-yl, indol-4-yl or indol-5-yl, where the indolyl is optionally substituted on the nitrogen with $-S(O)_2Ar^x$, where Ar^x is aryl or heteroaryl, preferably optionally substituted phenyl, e.g. unsubstituted phenyl or phenyl substituted in the 4-position by $-F$, $-Cl$, $-CH_3$ or $-CF_3$.

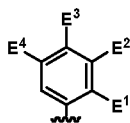
- 25 Preferred compounds of formula I that may be mentioned include those in which R^1 is represented by



where:

- E^2 , E^3 and E^4 represent hydrogen and
- 30 E^1 represents $-F$, $-Cl$, $-CH_3$, $-CF_3$, CN or $-OCH_3$; or
- E^1 , E^3 and E^4 represent hydrogen and E^2 represents $-F$, $-Cl$, $-CH_3$, $-CF_3$, $-CN$; or
- E^1 , E^2 and E^4 represent hydrogen and E^3 represent $-F$, $-Cl$, $-CH_3$, $-CF_3$, $-C(CH_3)_3$, $-CH=CH_2$, $-OCF_3$, $-S(O)_2CH_3$, or $-S(O)_2(4\text{-morpholinyl})$.

Other preferred compounds of formula I that may be mentioned include those in which R¹ is represented by



5 where:

E³ and E⁴ represent hydrogen; and

E¹ represents -F and E² represent -F, -Cl, -CH₃ or -CF₃; or

E¹ represents -Cl and E² represents -F, -Cl, -CH₃ or -CF₃; or

E¹ represents -CH₃ and E² represents -F, -Cl, -CH₃, -CF₃ or -CN; or

10

E² and E⁴ represent hydrogen; and

E¹ represents -Cl and E³ represents -F or -Cl; or

E¹ represents -CH₃ and E³ represents -Cl; or

E¹ represents -OCH₃ and E³ represents -F; or

15

E² and E³ represent hydrogen; and

E¹ represents -F and E⁴ represents -Cl, -CH₃ or -CN; or

E¹ represents -Cl and E⁴ represent -F, -Cl, -CH₃, -CF₃ or -OCH₃; or

E¹ represents -CH₃ and E⁴ represent -F, -Cl, -CH₃, -CF₃ or -CN; or

20 E¹ represents -CF₃ and E⁴ represents -F or -CF₃; or

E¹ represents -CN and E⁴ represents -Cl; or

E¹ represents -OCH₃ and E⁴ represents -F, -Cl, Br, -CH₃, -CH(CH₃)₂, -C(CH₃)₃,
-CN or -OCH₃; or

25 E¹ and E⁴ represent hydrogen; and

E² represents -F and E³ represents -F, -Cl, -OH or -OCH₃; or

E² represents -Cl and E³ represents -F; or

E² represents -CH₃ and E³ represents -F or -OCH₃; or

E¹ represents -OCH₃ and E³ represents -OH; or

30

E¹ and E³ represent hydrogen; and

E² and E⁴ represent -F; or

E² and E⁴ represent -CF₃; or

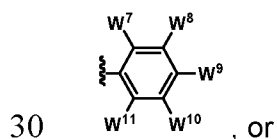
- E^4 represents hydrogen; and
 E^1 , E^2 and E^3 represent -F; or
 E^1 and E^2 represent -Cl and E^3 represents -Cl, -OH or -OCH₃; or
 5 E^1 and E^2 represent -CH₃ and E^3 represents -F or -OCH₃; or
 E^2 and E^3 represent -Cl and E^1 represents -CH₃; or

 E^2 represents hydrogen; and
 E^1 , E^3 and E^4 represent -F; or
 10 E^3 and E^4 represent -Cl and E^1 represents -CH₃; or
 E^1 and E^4 represent -Cl and E^1 represents -OCH₃; or
 E^1 and E^4 represent -CH₃ and E^3 represents -F, -CH₃ or -OCH₃; or
 E^1 represents -F, E^3 represents -CH₃ and E^4 represents -Cl; or
 E^1 represents -Cl, E^3 represents -F and E^4 represents -CH₃; or
 15 E^1 represents -Cl, E^3 represents -CH₃ and E^4 represents -F; or
 E^1 and E^4 represent -CH₃ and E^3 represents -F; or
 E^1 represents -CH₃, E^4 represents -Cl and E^3 represents -CF₃ or -OCH₃; or

 E^1 represents hydrogen; and
 20 E^2 and E^4 represent -CH₃ and E^3 represents -OH; or

 E^3 represents hydrogen; and
 E^1 and E^2 represent -Cl and E^4 represents -CH₃.

- 25 Preferred compounds of formula I that may be mentioned include those in which:
 (a) Z^1 represents halogen, -CN, -C(O)R^{b2}, -C(O)N(R^{c2})R^{d2}, -C(O)OR^{e2},
 -N(R^{f2})R^{g2}, -N(R^{h2})C(O)Rⁱ², -N(R^{l2})C(O)N(R^{m2})Rⁿ², -N(R^{o2})S(O)₂R^{p2}, -OR^{q2},
 -S(O)_mR^{l2}, -S(O)₂N(R^{u2})R^{v2}, heterocycloalkyl optionally substituted by one or more
 substituents selected from W⁵, aryl represented by



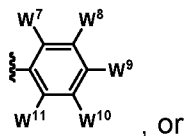
- heteroaryl having 1 to 3 nitrogen atoms, one oxygen atom and/or one sulfur atom
 and optionally substituted by one or more substituents selected from W⁶; or
 (b) Z^2 is not present or is selected from -F, -R^{a2}, -C(O)N(R^{c2})R^{d2}, -N(R^{f2})R^{g2},

- 5
 -N(R^{h2})C(O)Rⁱ², -N(Rⁱ²)C(O)OR^{k2}, -N(R^{l2})C(O)N(R^{m2})Rⁿ², -N(R^{o2})S(O)₂R^{p2}, -OR^{q2},
 -S(O)_mR^{l2}, -S(O)₂N(R^{u2})R^{v2}, heterocycloalkyl optionally substituted by one or more
 substituents selected from W⁵, aryl optionally substituted by one or more
 substituents selected from W⁶, or heteroaryl optionally substituted by one or more
 substituents selected from W⁶.

Other preferred compounds of formula I that may be mentioned include those in which:

- 10 (a) Z³ is not present or is selected from -F, -R^{a2}, -C(O)N(R^{c2})R^{d2}, -N(R^{f2})R^{g2},
 -N(R^{h2})C(O)Rⁱ², -N(Rⁱ²)C(O)OR^{k2}, -N(R^{l2})C(O)N(R^{m2})Rⁿ², -N(R^{o2})S(O)₂R^{p2}, -OR^{q2},
 -S(O)_mR^{l2}, -S(O)₂N(R^{u2})R^{v2}, heterocycloalkyl optionally substituted by one or more
 substituents selected from W⁵, aryl optionally substituted by one or more
 substituents selected from W⁶, or heteroaryl optionally substituted by one or more
 substituents selected from W⁶; and/or
- 15 (b) Z⁴ is not present or is selected from -F, -C(O)N(R^{c2})R^{d2}, -N(R^{f2})R^{g2},
 -N(R^{h2})C(O)Rⁱ², -N(Rⁱ²)C(O)OR^{k2}, -N(R^{l2})C(O)N(R^{m2})Rⁿ², -N(R^{o2})S(O)₂R^{p2}, -OR^{q2},
 -S(O)_mR^{l2}, -S(O)₂N(R^{u2})R^{v2}, heterocycloalkyl optionally substituted by one or more
 substituents selected from W⁵, aryl optionally substituted by one or more
 substituents selected from W⁶, or heteroaryl optionally substituted by one or more
 substituents selected from W⁶.
- 20

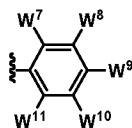
- More particularly preferred compounds of formula I that may be mentioned
 include those in which Z¹ represents -F, -CN, -C(O)N(R^{c2})R^{d2}, -N(R^{f2})R^{g2},
 -N(R^{h2})C(O)Rⁱ², -N(R^{l2})C(O)N(R^{m2})Rⁿ², -N(R^{o2})S(O)₂R^{p2}, -OR^{q2}, -S(O)_mR^{l2},
 25 -S(O)₂N(R^{u2})R^{v2}, heterocycloalkyl optionally substituted by one or more
 substituents selected from W⁵, aryl represented by



- heteroaryl having 1 to 3 nitrogen atoms, one oxygen atom and/or one sulfur atom
 and optionally substituted by one or more substituents selected from W⁶.
- 30

Other more particularly preferred compounds of formula I that may be mentioned
 include those in which Z¹ represents -C(O)N(R^{c2})R^{d2}, -N(R^{f2})R^{g2},

$-N(R^{h2})C(O)R^{i2}$, $-N(R^{l2})C(O)N(R^{m2})R^{n2}$, $-N(R^{o2})S(O)_2R^{p2}$, $-OR^{q2}$, $-S(O)_mR^{l2}$,
 $-S(O)_2N(R^{u2})R^{v2}$ or aryl represented by



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Further compounds of formula I that may be mentioned include those in which
 R^{c2} , R^{f2} , R^{h2} , R^{l2} , R^{m2} , R^{o2} , and R^{u2} represents hydrogen; and
 R^{d2} , R^{g2} , R^{i2} , R^{n2} , R^{p2} , R^{q2} , R^{l2} and R^{v2} represents aryl optionally substituted by
 one or more substituents selected from W^6 , or heteroaryl optionally substituted by
 one or more substituents selected from W^6 .

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Preferred compounds of formula I that may be mentioned are those where where
 Z^1 represents $-OR^{q2}$ and R^{q2} represents aryl optionally substituted by one or more
 substituents selected from W^6 , or heteroaryl optionally substituted by one or more
 substituents selected from W^6 .

15

More preferred compounds of formula I that may be mentioned are those where
 Z^1 represents $-N(R^{f2})R^{g2}$, R^{f2} represents hydrogen and R^{g2} represents aryl
 optionally substituted by one or more substituents selected from W^6 , or heteroaryl
 optionally substituted by one or more substituents selected from W^6 .

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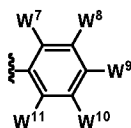
Further preferred compounds of formula I that may be mentioned are those
 where where Z^1 represents $-N(R^{o2})S(O)_2R^{p2}$, R^{o2} represents hydrogen and R^{p2}
 represents aryl optionally substituted by one or more substituents selected from
 W^6 , or heteroaryl optionally substituted by one or more substituents selected from
 W^6 .

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Preferred compounds of formula I where Z^1 represents heterocycloalkyl that may
 be mentioned are those where Z^1 represents dihydropyridinyl, imidazoliny,
 oxanyl, piperazinyl, piperidinyl, pyrrolidinyl and quinuclidinyl, wherein the
 heterocycloalkyl is optionally substituted by one or more substituents selected
 from W^5 .

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Preferred compounds of formula I where Z^1 represents



that may be mentioned are those where:

- 5 (a) each W^8 and W^{10} are independently selected from -F, -Cl, -CH₃, -CN, -CF₃, or more preferably hydrogen and W^9 is selected from -R^{a3}, -CN, -C(O)R^{b3}, -C(O)N(R^{c3})R^{d3}, -C(O)OR^{e3}, -N(R^{f3})R^{g3}, -N(R^{h3})C(O)Rⁱ³, -N(R^{j3})C(O)OR^{k3}, -N(R^{l3})C(O)N(R^{m3})Rⁿ³, -N(R^{o3})S(O)₂R^{p3}, -OR^{q3x}, -OC(O)R^{r3}, -OS(O)₂R^{s3}, -S(O)_mR^{t3}, -S(O)₂N(R^{u3})R^{v3}, heterocycloalkyl optionally substituted by
- 10 one or more substituents selected from G¹, aryl optionally substituted by one or more substituents selected from G², or heteroaryl optionally substituted by one or more substituents selected from G²; and
- (b) each W^9 and W^{10} are independently selected from -F, -Cl, -CH₃, -CN, -CF₃, or more preferably hydrogen and W^8 is selected from -R^{a3}, -CN,
- 15 -C(O)R^{b3}, -C(O)N(R^{c3})R^{d3}, -C(O)OR^{e3}, -N(R^{f3})R^{g3}, -N(R^{h3})C(O)Rⁱ³, -N(R^{j3})C(O)OR^{k3}, -N(R^{l3})C(O)N(R^{m3})Rⁿ³, -N(R^{o3})S(O)₂R^{p3}, -OR^{q3x}, -OC(O)R^{r3}, -OS(O)₂R^{s3}, -S(O)_mR^{t3}, -S(O)₂N(R^{u3})R^{v3}, heterocycloalkyl optionally substituted by one or more substituents selected from G¹, aryl optionally substituted by one or more substituents selected from G², or heteroaryl optionally substituted by one or
- 20 more substituents selected from G².

For example, particular compounds of formula I that may be mentioned include those wherein W^8 and W^{10} represents hydrogen and W^9 represents -F, -Cl, -CH₃, cyclopropyl, -CF₃, -CN, -NH₂, -N(CH₃)₂, -N(H)C(O)CH₃, -N(H)C(O)OC(CH₃)₃,

- 25 -SO₂CH₃, -SO₂NH₂, -S(O)₂N(CH₃)₂, -S(O)₂-4-morpholinyl, 4-methylpiperazin-1-yl, 4-methylpiperidin-1-ylmethyl and 1,2,3-thiadiazol-4-yl; or W^9 and W^{10} represents hydrogen and W^8 represents -F, -Cl, -CN, -CH₃, -NMe₂, -S(O)₂NH₂ or -S(O)₂NMe₂.

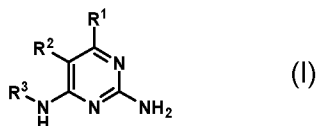
- 30 Preferred compounds of formula I where Z^1 represents heteroaryl that may be mentioned are those where Z^1 represents benzimidazolyl, benzodioxinyl, benzoxazolyl, imidazolyl, imidazopyridinyl, indolyl, isoquinolinyl, oxadiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridyl, pyrrolopyridinyl, quinolinyl, thiazolyl,

thiophenyl and triazolyl, wherein the heteroaryl is optionally substituted by one or more substituents selected from W⁶.

Particularly preferred compounds of formula I where Z¹ represents heteroaryl that may be mentioned are those where Z¹ represents benzimidazol-2-yl, 1,4-benzodioxin-2-yl, benzoxazol-2-yl, imidazol-1-yl, imidazol-4-yl, imidazo[1,2-a]pyridin-2-yl, indol-3-yl, indol-5-yl, isoquinolin-4-yl, 1,3,4-oxadiazol-2-yl, 1,2-oxazol-4-yl, pyrazin-3-yl, pyrazol-1-yl, pyrazol-4-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, 5H,6H,7H-pyrrolo[3,4-b]pyridin-5-yl, thiazol-5-yl, thiophen-2-yl, 1,2,3-triazol-4-yl and 1,2,4-triazol-3-yl, wherein the heteroaryl is optionally substituted by one or more substituents selected from W⁶.

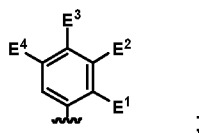
More particularly preferred compounds of formula I that may be mentioned are those where W⁶ represents -F, -Cl, -Br, -CH₃, cyclopropyl, -CF₃, -CN, -NH₂, -N(CH₃)₂, -SO₂CH₃, -SO₂NH₂ and -SO₂N(CH₃)₂.

In yet another embodiment of the invention there is provided a compound of formula I,



wherein:

R¹ represents heteroaryl connected to the pyrimidine of formula I via a carbon atom of the heteroaryl ring, which heteroaryl ring is substituted by one or more substituents selected from Y¹, -C₁₋₆alkyl optionally substituted by one or more Y² and heterocycloalkyl optionally substituted by one or more Y³; or aryl represented by



E¹ represents Y^{1a} or -C₁₋₆alkyl optionally substituted by one or more Y²; and at least one of E², E³ and E⁴ represents Y^{1b} or -C₁₋₆alkyl optionally substituted by one or more Y²;

R² represents hydrogen, halogen, -CN, -C₁₋₁₂alkyl optionally substituted by one or more Z¹, or heterocycloalkyl optionally substituted by one or more Z²;

R³ represents -C₁₋₁₂alkyl optionally substituted by one or more Z¹ or
 5 heterocycloalkyl optionally substituted by one or more Z²; or

R² and R³ are linked together to form, along with the atoms to which they are attached, a 5- to 8-membered non-aromatic ring, wherein the link formed by R² and R³ is optionally substituted by one or more substituents selected from Z³ and
 10 -C₁₋₉alkyl optionally substituted by one or more Z⁴;

each Y¹ independently represents halogen, -CN, -C(O)R^a, -C(O)N(R^b)R^c, -C(O)OR^d, -N(R^e)R^f, -N(R^g)C(O)R^h, -N(Rⁱ)C(O)OR^j, -N(R^k)C(O)N(R^l)R^m, -NO₂, -N(Rⁿ)S(O)₂R^o, -OR^p, -OC(O)R^q, -OS(O)₂R^r, -S(O)_mR^s, -S(O)₂N(R^t)R^u,
 15 heterocycloalkyl optionally substituted by one or more substituents selected from W², aryl optionally substituted by one or more substituents selected from W³ or heteroaryl optionally substituted by one or more substituents selected from W³;

Y^{1a} represents halogen, -CN, -C(O)R^a, -C(O)N(R^b)R^c, -C(O)OR^d, -N(R^e)R^f, -N(R^g)C(O)R^h, -N(Rⁱ)C(O)OR^j, -N(R^k)C(O)N(R^l)R^m, -NO₂, -N(Rⁿ)S(O)₂R^o, -OR^{px}, -OC(O)R^q, -OS(O)₂R^r, -S(O)_mR^s, -S(O)₂N(R^t)R^u, heterocycloalkyl optionally substituted by one or more substituents selected from W², aryl optionally substituted by one or more substituents selected from W³ or heteroaryl optionally substituted by one or more substituents selected from W³;

25 Y^{1b} represents halogen, -CN, -C(O)R^a, -C(O)N(R^b)R^c, -C(O)OR^d, -N(R^e)R^f, -N(R^g)C(O)R^h, -N(Rⁱ)C(O)OR^j, -N(R^k)C(O)N(R^l)R^m, -NO₂, -N(Rⁿ)S(O)₂R^o, -OR^p, -OC(O)R^q, -OS(O)₂R^r, -S(O)_mR^s, -S(O)₂N(R^t)R^u, heterocycloalkyl optionally substituted by one or more substituents selected from W², aryl optionally substituted by one or more substituents selected from W³ or heteroaryl optionally substituted by one or more substituents selected from W³;

each R^a, R^b, R^c, R^d, R^e, R^g, R^h, Rⁱ, R^k, R^l, R^m, Rⁿ, R^p, R^q, R^s, R^t and R^u independently represents hydrogen, -C₁₋₆ alkyl optionally substituted by one or
 35 more substituents selected from W¹, heterocycloalkyl optionally substituted by

one or more substituents selected from W^2 , aryl optionally substituted by one or more substituents selected from W^3 , or heteroaryl optionally substituted by one or more substituents selected from W^3 ; or

- 5 any two R^b and R^c , R^e and R^f , R^l and R^m and/or R^l and R^u are linked together to form, along with the nitrogen atom to which they are attached, a 3- to 8-membered monocyclic or bicyclic ring, which ring optionally contains one or two further heteroatoms and which ring optionally is substituted by one or more substituents selected from W^2 , C_{1-3} alkyl optionally substituted by one or more substituents selected from W^1 , and =O;

- each R^f , R^j , R^o , R^r and R^{px} independently represents C_{1-6} alkyl optionally substituted by one or more substituents selected from W^1 , heterocycloalkyl optionally substituted by one or more substituents selected from W^2 , aryl optionally substituted by one or more substituents selected from W^3 or heteroaryl optionally substituted by one or more substituents selected from W^3 ;

- each Y^2 independently represents halogen, -CN, $-C(O)R^{b1}$, $-C(O)N(R^{c1})R^{d1}$, $-C(O)OR^{e1}$, $-N(R^{f1})R^{g1}$, $-N(R^{h1})C(O)R^{i1}$, $-N(R^{j1})C(O)OR^{k1}$, $-N(R^{l1})C(O)N(R^{m1})R^{n1}$, $-N(R^{o1})S(O)_2R^{p1}$, $-OR^{q1}$, $-OC(O)R^{r1}$, $-OS(O)_2R^{s1}$, $-S(O)_mR^{t1}$, $-S(O)_2N(R^{u1})R^{v1}$, heterocycloalkyl optionally substituted by one or more substituents selected from W^1 , aryl optionally substituted by one or more substituents selected from W^2 , heteroaryl optionally substituted by one or more substituents selected from W^2 , or =O;

- 25 each Y^3 independently represents halogen, $-R^{a1}$, -CN, $-C(O)R^{b1}$, $-C(O)N(R^{c1})R^{d1}$, $-C(O)OR^{e1}$, $-N(R^{f1})R^{g1}$, $-N(R^{h1})C(O)R^{i1}$, $-N(R^{j1})C(O)OR^{k1}$, $-N(R^{l1})C(O)N(R^{m1})R^{n1}$, $-N(R^{o1})S(O)_2R^{p1}$, $-OR^{q1}$, $-OC(O)R^{r1}$, $-OS(O)_2R^{s1}$, $-S(O)_mR^{t1}$, $-S(O)_2N(R^{u1})R^{v1}$, heterocycloalkyl optionally substituted by one or more substituents selected from W^1 , aryl optionally substituted by one or more substituents selected from W^2 , heteroaryl optionally substituted by one or more substituents selected from W^2 , or =O;

- 35 each R^{a1} , R^{b1} , R^{c1} , R^{d1} , R^{e1} , R^{f1} , R^{h1} , R^{i1} , R^{j1} , R^{l1} , R^{m1} , R^{n1} , R^{o1} , R^{q1} , R^{r1} , R^{t1} , R^{u1} and R^{v1} independently represents hydrogen, C_{1-6} alkyl optionally substituted by

one or more substituents selected from W^1 , heterocycloalkyl optionally substituted by one or more substituents selected from W^2 , aryl optionally substituted by one or more substituents selected from W^3 , or heteroaryl optionally substituted by one or more substituents selected from W^3 ; or

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any two R^{c1} and R^{d1} , R^{f1} and R^{g1} , R^{m1} and R^{n1} and/or R^{u1} and R^{v1} are linked together to form, along with the nitrogen atom to which they are attached, a 3- to 8-membered monocyclic or bicyclic ring, which ring optionally contains one or two heteroatoms and which ring optionally is substituted by one or more substituents selected from W^2 , C_{1-3} alkyl optionally substituted by one or more substituents selected from W^1 , and $=O$;

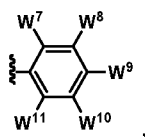
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each R^{g1} , R^{k1} , R^{p1} and R^{s1} independently represents $-C_{1-6}$ alkyl optionally substituted by one or more substituents selected from W^1 , heterocycloalkyl optionally substituted by one or more substituents selected from W^2 , aryl optionally substituted by one or more substituents selected from W^3 , or heteroaryl optionally substituted by one or more substituents selected from W^3 ;

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each Z^1 independently represents halogen, $-CN$, $-C(O)R^{b2}$, $-C(O)N(R^{c2})R^{d2}$, $-C(O)OR^{e2}$, $-N(R^{f2})R^{g2}$, $-N(R^{h2})C(O)R^{i2}$, $-N(R^{j2})C(O)OR^{k2}$, $-N(R^{l2})C(O)N(R^{m2})R^{n2}$, $-N(R^{o2})S(O)_2R^{p2}$, $-OR^{q2}$, $-OC(O)R^{r2}$, $-OS(O)_2R^{s2}$, $-S(O)_mR^{l2}$, $-S(O)_2N(R^{u2})R^{v2}$, heterocycloalkyl optionally substituted by one or more substituents selected from W^5 , aryl represented by

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heteroaryl having 1 to 3 nitrogen atoms, one oxygen atom and/or one sulfur atom and optionally substituted by one or more substituents selected from W^6 , or $=O$;

each Z^2 and Z^3 independently represents halogen, $-R^{a2}$, $-CN$, $-C(O)R^{b2}$, $-C(O)N(R^{c2})R^{d2}$, $-C(O)OR^{e2}$, $-N(R^{f2})R^{g2}$, $-N(R^{h2})C(O)R^{i2}$, $-N(R^{j2})C(O)OR^{k2}$, $-N(R^{l2})C(O)N(R^{m2})R^{n2}$, $-N(R^{o2})S(O)_2R^{p2}$, $-OR^{q2}$, $-OC(O)R^{r2}$, $-OS(O)_2R^{s2}$, $-S(O)_mR^{l2}$, $-S(O)_2N(R^{u2})R^{v2}$, heterocycloalkyl optionally substituted by one or more substituents selected from W^5 , aryl optionally substituted by one or more substituents selected from W^6 , or heteroaryl optionally substituted by one or more

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substituents selected from W^6 ;

each Z^4 independently represents halogen, $-CN$, $-C(O)R^{b2}$, $-C(O)N(R^{c2})R^{d2}$,
 $-C(O)OR^{e2}$, $-N(R^{f2})R^{g2}$, $-N(R^{h2})C(O)R^{i2}$, $-N(R^{j2})C(O)OR^{k2}$, $-N(R^{l2})C(O)N(R^{m2})R^{n2}$,
 5 $-N(R^{o2})S(O)_2R^{p2}$, $-OR^{q2}$, $-OC(O)R^{r2}$, $-OS(O)_2R^{s2}$, $-S(O)_mR^{t2}$, $-S(O)_2N(R^{u2})R^{v2}$,
 heterocycloalkyl optionally substituted by one or more substituents selected from
 W^5 , aryl optionally substituted by one or more substituents selected from W^6 ,
 heteroaryl optionally substituted by one or more substituents selected from W^6 , or
 $=O$;

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each R^{a2} , R^{b2} , R^{c2} , R^{d2} , R^{e2} , R^{f2} , R^{h2} , R^{i2} , R^{j2} , R^{l2} , R^{m2} , R^{n2} , R^{o2} , R^{q2} , R^{r2} , R^{t2} , R^{u2}
 and R^{v2} independently represents hydrogen, C_{1-6} alkyl optionally substituted by
 one or more substituents selected from W^4 , heterocycloalkyl optionally substituted
 by one or more substituents selected from W^5 , aryl optionally substituted by one
 15 or more substituents selected from W^6 , or heteroaryl optionally substituted by one
 or more substituents selected from W^6 ; or

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any two R^{c2} and R^{d2} , R^{f2} and R^{g2} , R^{m2} and R^{n2} and/or R^{u2} and R^{v2} are linked
 together to form, along with the nitrogen atom to which they are attached, a 3- to
 8-membered monocyclic or bicyclic ring, which ring optionally contains one or two
 heteroatoms and which ring optionally is substituted by one or more substituents
 selected from W^5 , C_{1-3} alkyl optionally substituted by one or more substituents
 selected from W^4), and $=O$;

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each R^{g2} , R^{k2} , R^{p2} and R^{s2} independently represents C_{1-6} alkyl optionally
 substituted by one or more substituents selected from W^4 , heterocycloalkyl
 optionally substituted by one or more substituents selected from W^5 , aryl
 optionally substituted by one or more substituents selected from W^6 , or heteroaryl
 optionally substituted by one or more substituents selected from W^6 ;

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each W^1 and W^4 independently represents halogen, $-CN$, $-N(R^{f3})R^{g3}$,
 $-N(R^{h3})C(O)R^{i3}$, $-N(R^{j3})C(O)OR^{k3}$, $-N(R^{l3})C(O)N(R^{m3})R^{n3}$, $-N(R^{o3})S(O)_2R^{p3}$, $-OR^{q3}$,
 $-OC(O)R^{r3}$, $-OS(O)_2R^{s3}$, $-S(O)_mR^{t3}$, $-S(O)_2N(R^{u3})R^{v3}$, heterocycloalkyl optionally
 substituted by one or more substituents selected from G^1 , aryl optionally

substituted by one or more substituents selected from G^2 , heteroaryl optionally substituted by one or more substituents selected from G^2 , or =O;

each W^2 , W^3 , W^5 and W^6 independently represents halogen, $-R^{a3}$, $-CN$, $-C(O)R^{b3}$,
 5 $-C(O)N(R^{c3})R^{d3}$, $-C(O)OR^{e3}$, $-N(R^{f3})R^{g3}$, $-N(R^{h3})C(O)R^{i3}$, $-N(R^{j3})C(O)OR^{k3}$,
 $-N(R^{l3})C(O)N(R^{m3})R^{n3}$, $-N(R^{o3})S(O)_2R^{p3}$, $-OR^{q3}$, $-OC(O)R^{r3}$, $-OS(O)_2R^{s3}$, $-S(O)_mR^{t3}$,
 $-S(O)_2N(R^{u3})R^{v3}$, heterocycloalkyl optionally substituted by one or more
 substituents selected from G^1 , aryl optionally substituted by one or more
 substituents selected from G^2 , heteroaryl (optionally substituted by one or more
 10 substituents selected from G^2 , or =O;

each W^7 , W^8 , W^9 , W^{10} and W^{11} independently represents hydrogen, halogen,
 $-R^{a3}$, $-CN$, $-C(O)R^{b3}$, $-C(O)N(R^{c3})R^{d3}$, $-C(O)OR^{e3}$, $-N(R^{f3})R^{g3}$, $-N(R^{h3})C(O)R^{i3}$,
 $-N(R^{j3})C(O)OR^{k3}$, $-N(R^{l3})C(O)N(R^{m3})R^{n3}$, $-N(R^{o3})S(O)_2R^{p3}$, $-OR^{q3}$, $-OC(O)R^{r3}$,
 15 $-OS(O)_2R^{s3}$, $-S(O)_mR^{t3}$, $-S(O)_2N(R^{u3})R^{v3}$, heterocycloalkyl optionally substituted by
 one or more substituents selected from G^1 , aryl optionally substituted by one or
 more substituents selected from G^2 , or heteroaryl optionally substituted by one or
 more substituents selected from G^2 ;

20 each R^{a3} , R^{b3} , R^{c3} , R^{d3} , R^{e3} , R^{f3} , R^{h3} , R^{i3} , R^{j3} , R^{l3} , R^{m3} , R^{n3} , R^{o3} , R^{q3} , R^{r3} , R^{t3} , R^{u3}
 and R^{v3} independently represents hydrogen or C_{1-6} alkyl optionally substituted by
 one or more G^3 ; or

any two R^{c3} and R^{d3} , R^{f3} and R^{g3} , R^{m3} and R^{n3} and/or R^{u3} and R^{v3} are linked
 25 together to form, along with the nitrogen atom to which they are attached, a 4- to
 6-membered ring, which ring optionally contains one heteroatom and which ring
 optionally is substituted by one or more G^2 ;

each R^{g3} , R^{k3} , R^{p3} , R^{q3} and R^{s3} independently represents C_{1-6} alkyl optionally
 30 substituted by one or more G^3 ;

each G^1 and G^2 independently represents halogen, $-R^{a4}$, $-CN$, $-C(O)R^{b4}$,
 $-C(O)N(R^{c4})R^{d4}$, $-C(O)OR^{e4}$, $-N(R^{f4})R^{g4}$, $-N(R^{h4})C(O)R^{i4}$, $-N(R^{j4})C(O)OR^{k4}$,
 $-N(R^{l4})C(O)N(R^{m4})R^{n4}$, $-N(R^{o4})S(O)_2R^{p4}$, $-OR^{q4}$, $-OC(O)R^{r4}$, $-OS(O)_2R^{s4}$, $-S(O)_mR^{t4}$,
 35 $-S(O)_2N(R^{u4})R^{v4}$, or =O;

G^3 represents halogen, $-CN$, $-C(O)R^{b4}$, $-C(O)N(R^{c4})R^{d4}$, $-C(O)OR^{e4}$, $-N(R^{f4})R^{g4}$, $-N(R^{h4})C(O)R^{i4}$, $-N(R^{j4})C(O)OR^{k4}$, $-N(R^{l4})C(O)N(R^{m4})R^{n4}$, $-N(R^{o4})S(O)_2R^{p4}$, $-OR^{q4}$, $-OC(O)R^{r4}$, $-OS(O)_2R^{s4}$, $-S(O)_mR^{t4}$, $-S(O)_2N(R^{u4})R^{v4}$, or $=O$;

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each R^{a4} , R^{b4} , R^{c4} , R^{d4} , R^{e4} , R^{f4} , R^{h4} , R^{i4} , R^{j4} , R^{l4} , R^{m4} , R^{n4} , R^{o4} , R^{q4} , R^{r4} , R^{t4} , R^{u4} and R^{v4} independently represents hydrogen or C_{1-6} alkyl optionally substituted by one or more $-F$; or

- 10 any two R^{c4} and R^{d4} , R^{f4} and R^{g4} , R^{m4} and R^{n4} and/or R^{u4} and R^{v4} are linked together to form, along with the nitrogen atom to which they are attached, a 3- to 6-membered ring, which ring optionally substituted by one or more $-F$, $-CH_3$, $-CH_2CH_3$, $-CHF_2$, $-CF_3$, $-CH_2CF_3$, or $=O$;

- 15 each R^{g4} , R^{k4} , R^{p4} and R^{s4} independently represent C_{1-6} alkyl optionally substituted by one or more $-F$;

each m independently represents 0, 1 or 2;

- 20 provided that formula I does not represent
 N^4 -cyclopropyl-6-(4-methoxy-2-methylphenyl)-2,4-pyrimidinediamine

or a pharmaceutically acceptable salt thereof;

- 25 which compounds may be referred to herein as "the compounds of the invention".

- Pharmaceutically-acceptable salts include acid addition salts and base addition salts. Such salts may be formed by conventional means, for example by reaction of a free acid or a free base form of a compound of formula I with one or more
 30 equivalents of an appropriate acid or base, optionally in a solvent, or in a medium in which the salt is insoluble, followed by removal of said solvent, or said medium, using standard techniques (e.g. *in vacuo*, by freeze-drying or by filtration). Salts may also be prepared by exchanging a counter-ion of a compound of the invention in the form of a salt with another counter-ion, for example using a

suitable ion exchange resin. For the avoidance of doubt, solvates are also included within the scope of the invention.

5 Compounds of the invention may contain double bonds and may thus exist as *E* (*entgegen*) and *Z* (*zusammen*) geometric isomers about each individual double bond. All such isomers and mixtures thereof are included within the scope of the invention.

10 Compounds of the invention may also exhibit tautomerism. All tautomeric forms and mixtures thereof are included within the scope of the invention.

Compounds of the invention may also contain one or more asymmetric carbon atoms and may therefore exhibit optical and/or diastereoisomerism. Diastereoisomers may be separated using conventional techniques, e.g. chromatography or fractional crystallisation. The various stereoisomers may be isolated by separation of a racemic or other mixture of the compounds using conventional, e.g. fractional crystallisation or HPLC, techniques. Alternatively the desired optical isomers may be made by reaction of the appropriate optically active starting materials under conditions which will not cause racemisation or epimerisation (i.e. a 'chiral pool' method), by reaction of the appropriate starting material with a 'chiral auxiliary' which can subsequently be removed at a suitable stage, by derivatisation (i.e. a resolution, including a dynamic resolution), for example with a homochiral acid followed by separation of the diastereomeric derivatives by conventional means such as chromatography, or by reaction with an appropriate chiral reagent or chiral catalyst all under conditions known to the skilled person. All stereoisomers and mixtures thereof are included within the scope of the invention.

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Unless otherwise specified, C_{1-q} alkyl groups (where q is the upper limit of the range) defined herein may be straight-chain or, when there is a sufficient number (i.e. a minimum of two or three, as appropriate) of carbon atoms, be branched-chain, and/or cyclic (so forming a C_{3-q}-cycloalkyl group). When there is a sufficient number (i.e. a minimum of four) of carbon atoms, such groups may also be part cyclic. Such alkyl groups may also be saturated or, when there is a

30

sufficient number (i.e. a minimum of two) of carbon atoms, be unsaturated (forming, for example, a C_{2-q} alkenyl or a C_{2-q} alkynyl group).

- Unless otherwise specified, C_{1-q} alkylene groups (where q is the upper limit of the range) defined herein may (in a similar manner to the definition of C_{1-q} alkyl) be straight-chain or, when there is a sufficient number (i.e. a minimum of two or three, as appropriate) of carbon atoms, be branched-chain, and/or cyclic (so forming a C_{3-q}-cycloalkylene group). When there is a sufficient number (i.e. a minimum of four) of carbon atoms, such groups may also be part cyclic. Such alkylene groups may also be saturated or, when there is a sufficient number (i.e. a minimum of two) of carbon atoms, be unsaturated (forming, for example, a C_{2-q} alkenylene or a C_{2-q} alkynylene group). Particular alkylene groups that may be mentioned include those that are straight-chained and saturated.
- The term “halo”, when used herein, includes fluoro, chloro, bromo and iodo (for example, fluoro and chloro).

- Heterocycloalkyl groups that may be mentioned include non-aromatic monocyclic and bicyclic heterocycloalkyl groups (which groups may further be bridged) in which at least one (e.g. one to four) of the atoms in the ring system is other than carbon (i.e. a heteroatom), and in which the total number of atoms in the ring system is between three and twelve (e.g. between five and ten and, most preferably, between three and eight, e.g. a 5- or 6-membered heterocycloalkyl group). Further, such heterocycloalkyl groups may be saturated or unsaturated containing one or more double and/or triple bonds, forming for example a C_{2-q} (e.g. C_{4-q}) heterocycloalkenyl (where q is the upper limit of the range) or a C_{7-q} heterocycloalkynyl group. C_{2-q} heterocycloalkyl groups that may be mentioned include 7-azabicyclo-[2.2.1]heptanyl, 6-azabicyclo[3.1.1]heptanyl, 6-azabicyclo[3.2.1]-octanyl, 8-azabicyclo[3.2.1]octanyl, aziridiny, azetidiny, dihydropyranyl, dihydropyridyl, dihydropyrrolyl (including 2,5-dihydropyrrolyl), dioxolanyl (including 1,3-dioxolanyl), dioxanyl (including 1,3-dioxanyl and 1,4-dioxanyl), dithianyl (including 1,4-dithianyl), dithiolanyl (including 1,3-dithiolanyl), imidazolidiny, imidazolinyl, morpholinyl, 7-oxabicyclo-[2.2.1]heptanyl, 6-oxabicyclo[3.2.1]-octanyl, oxetanyl, oxiranyl, piperaziny, piperidiny, pyranyl, pyrazolidiny, pyrrolidinonyl, pyrrolidinyl, pyrrolinyl,

quinuclidinyl, sulfolanyl, 3-sulfolenyl, tetrahydropyranyl, tetrahydrofuryl, tetrahydropyridyl (such as 1,2,3,4-tetrahydropyridyl and 1,2,3,6-tetrahydropyridyl), thietanyl, thiranyl, thiolanyl, thiomorpholinyl, trithianyl (including 1,3,5-trithianyl), tropanyl and the like. Substituents on heterocycloalkyl groups may, where
5 appropriate, be located on any atom in the ring system including a heteroatom. Further, in the case where the substituent is another cyclic compound, then the cyclic compound may be attached through a single atom on the heterocycloalkyl group, forming a so-called "spiro"-compound. The point of attachment of heterocycloalkyl groups may be *via* any atom in the ring system including (where
10 appropriate) a heteroatom (such as a nitrogen atom), or an atom on any fused carbocyclic ring that may be present as part of the ring system. Heterocycloalkyl groups may also be in the *N*- or *S*- oxidised form. At each occurrence when mentioned herein, a heterocycloalkyl group is preferably a 3- to 8-membered heterocycloalkyl group (e.g. a 5- or 6-membered heterocycloalkyl group).

15 The term "aryl", when used herein, includes C₆₋₁₄ (e.g. C₆₋₁₀) aromatic groups. Such groups may be monocyclic or bicyclic and, when bicyclic, be either wholly or partly aromatic. C₆₋₁₀ aryl groups that may be mentioned include phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, indanyl, and the like (e.g. phenyl, naphthyl
20 and the like). For the avoidance of doubt, the point of attachment of substituents on aryl groups may be *via* any carbon atom of the ring system.

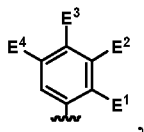
The term "heteroaryl" (or heteroaromatic), when used herein, includes 5- to 10-membered heteroaromatic groups containing one or more heteroatoms selected
25 from oxygen, nitrogen and/or sulfur. Such heteroaryl group may comprise one, or two rings, of which at least one is aromatic. Substituents on heteroaryl/heteroaromatic groups may, where appropriate, be located on any atom in the ring system including a heteroatom. The point of attachment of heteroaryl/heteroaromatic groups may be *via* any atom in the ring system
30 including (where appropriate) a heteroatom. Bicyclic heteroaryl/heteroaromatic groups may comprise a benzene ring fused to one or more further aromatic or non-aromatic heterocyclic rings, in which instances, the point of attachment of the polycyclic heteroaryl/heteroaromatic group may be *via* any ring including the benzene ring or the heteroaryl/heteroaromatic or heterocycloalkyl ring. Examples
35 of heteroaryl/heteroaromatic groups that may be mentioned include pyridinyl,

pyrrolyl, furanyl, thiophenyl, oxadiazolyl, thiadiazolyl, thiazolyl, oxazolyl, pyrazolyl, triazolyl, tetrazolyl, isoxazolyl, isothiazolyl, imidazolyl, imidazopyrimidinyl, pyrimidinyl, indolyl, azaindolyl, pyrazinyl, indazolyl, pyrimidinyl, quinoliny, isoquinoliny, benzofuranyl, benzothiophenyl, benzoimidazolyl, benzoxazolyl, benzothiazolyl and benzotriazolyl. The oxides of heteroaryl/ heteroaromatic groups are also embraced within the scope of the invention (e.g. the *N*-oxide). As stated above, heteroaryl includes polycyclic (e.g. bicyclic) groups in which one ring is aromatic (and the other may or may not be aromatic). Hence, other heteroaryl groups that may be mentioned include e.g. benzo[1,3]dioxolyl, benzo[1,4]dioxinyl, indolinyl, 5*H*,6*H*,7*H*-pyrrolo[1,2-*b*]pyrimidinyl, 1,2,3,4-tetrahydroquinoliny and the like.

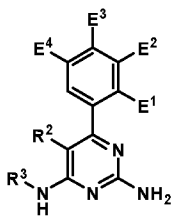
Heteroatoms that may be mentioned include phosphorus, silicon, boron and, preferably, oxygen, nitrogen and sulfur.

For the avoidance of doubt, in cases in which the identity of two or more substituents in a compound of the invention may be the same, the actual identities of the respective substituents are not in any way interdependent.

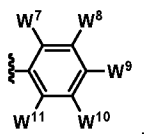
For the avoidance of doubt, when R¹ is defined as



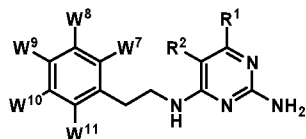
it is connected to the rest of formula I by the bond interrupted by the wiggly line, and formula I can thus be represented by



Likewise, when R³ is -C₁₋₁₂ alkyl substituted by Z¹, and Z¹ is represented by



then, if e.g. R³ is C₂alkyl, then formula I can be represented by



The present invention also embraces isotopically-labeled compounds of the present invention which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass
 5 number different from the atomic mass or mass number usually found in nature (or the most abundant one found in nature). All isotopes of any particular atom or element as specified herein are contemplated within the scope of the compounds of the invention. Hence, the compounds of the invention also include deuterated compounds, i.e. in which one or more hydrogen atoms are replaced by the
 10 hydrogen isotope deuterium.

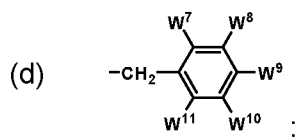
All individual features (e.g. preferred features) mentioned herein may be taken in isolation or in combination with any other feature (including preferred features) mentioned herein (hence, preferred features may be taken in conjunction with
 15 other preferred features, or independently of them).

The skilled person will appreciate that compounds of the invention that are the subject of this invention include those that are stable. That is, compounds of the invention include those that are sufficiently robust to survive isolation from e.g. a
 20 reaction mixture to a useful degree of purity.

Particular compounds of formula I that may be mentioned include those in which:
 R² represents hydrogen or -C₁₋₁₂alkyl optionally substituted by one or more Z¹;
 and
 25 R³ represents -C₁₋₁₂alkyl optionally substituted by one or more Z¹ or heterocycloalkyl optionally substituted by one or more Z².

For example, compounds of formula I that may be mentioned include those in which R² represents methyl, or preferably, hydrogen and R³ represents:
 30 (a) -C₁₋₁₂alkyl (for example -C₁₋₆alkyl) optionally substituted by two, or preferably, one Z¹ or
 (b) -C₂₋₆alkyl optionally substituted by two, or preferably, one Z¹ or heterocycloalkyl optionally substituted by two, or preferably, one Z²; or

(c) $-C_{1-2}$ alkyl optionally substituted with one or more $-F$; or



(e) $-C_{1-12}$ alkyl (for example $-C_{1-6}$ alkyl) substituted by heteroaryl having 1 to 3 nitrogen atoms, one oxygen atom and/or one sulfur atom and which heteroaryl is optionally substituted by one or more substituents selected from W^3 ; or

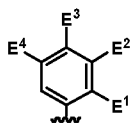
(f) a $-C_{3-6}$ alkyl or a heterocycloalkyl selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclopropylethyl, cyclobutylethyl, cyclopropylpropyl, oxetanyl, tetrahydrofuryl, tetrahydropyranyl, azetidiny, pyrrolidiny, piperidiny, piperaziny or morpholiny
 10 wherein the C_{3-6} alkyl is optionally substituted by two, or preferably, one Z^1 and the heterocycloalkyl is optionally substituted by two, or preferably, one Z^2 .

Particular compounds of formula I that may be mentioned include those in which:
 R^2 and R^3 are linked together to form, along with the atoms to which they are
 15 attached, a 5- to 8-membered (e.g. a 5- to 6 membered) non-aromatic ring,
 wherein the link formed by R^2 and R^3 is optionally substituted by one or more
 substituents selected from Z^3 or $-C_{1-9}$ alkyl optionally substituted by one or more
 Z^4 .

20 For example, compounds of formula I that may be mentioned include those in
 which R^2 and R^3 are linked together to form, along with the atoms to which they
 are attached, a 5- to 6-membered non-aromatic ring, wherein the non-
 aromatic ring is:

- (a) unsubstituted; or
- 25 (b) substituted by one or more substituents selected from Z^3 ; or
- (c) substituted by $-C_{1-9}$ alkyl optionally substituted by one or more Z^4 ; or
- (d) substituted by one or more substituents selected from Z^3 and substituted
 by $-C_{1-9}$ alkyl optionally substituted by one or more Z^4 .

30 Particular compounds of formula I that may be mentioned include those in which:
 R^1 represents

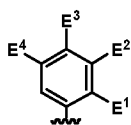


Preferred compounds of formula I that may be mentioned include those in which E¹ represents Y^{1a} or -C₁₋₆alkyl optionally substituted by one or more Y²; and at least one of E², E³ and E⁴ (preferably at least one of E² and E⁴) represents Y^{1b} or -C₁₋₆alkyl optionally substituted by one or more Y².

Particular compounds of formula I that may be mentioned include those in which R¹ represents heteroaryl.

- 10 Preferred compounds of formula I where R¹ represents heteroaryl that may be mentioned are those where R¹ represents benzofuranyl, benzothiophenyl, dihydrobenzofuranyl, indazolyl, indolyl, isoquinolinyl, isoxazolyl, pyridinyl, pyrrolyl and quinolinyl.
- 15 Particularly preferred compounds of formula I where R¹ represents heteroaryl that may be mentioned are those where R¹ represents benzofuran-3-yl, benzo-thiophen-3-yl, dihydrobenzofuran-7-yl, indol-3-yl, indol-4-yl, indol-5-yl, isoquinolin-4-yl, isoxazol-4-yl, pyridin-3-yl, pyridin-4-yl, pyrrol-2-yl and quinolin-5-yl.
- 20 For example, compounds of formula I that may be mentioned include those in which R¹ represents indolyl, e.g. indol-3-yl, indol-4-yl or indol-5-yl, where the indolyl is optionally substituted on the nitrogen with -S(O)₂Ar^x, where Ar^x is aryl or heteroaryl, preferably optionally substituted phenyl, e.g. unsubstituted phenyl or phenyl substituted in the 4-position by -F, -Cl, -CH₃ or -CF₃.

Particular compounds of formula I that may be mentioned include those in which R¹ is represented by



where:

- 30 E³ and E⁴ represent hydrogen; and
E¹ represents -F and E² represent -F, -Cl, -CH₃ or -CF₃; or

- E^1 represents -Cl and E^2 represents -F, -Cl, -CH₃ or -CF₃; or
 E^1 represents -CH₃ and E^2 represents -F, -Cl, -CH₃, -CF₃, -CN or
 -N(H)C(O)CH=CH₂; or
- 5 E^2 and E^4 represent hydrogen; and
 E^1 represents -F and E^3 represents -F or phenyl; or
 E^1 represents -Cl and E^3 represents -F or -Cl; or
 E^1 represents -CH₃ and E^3 represents -Cl or -OCH₂phenyl; or
 E^1 represents -OCH₃ and E^3 represents -F; or
- 10 E^2 and E^3 represent hydrogen; and
 E^1 represents -F and E^4 represents -Cl, -CH₃ or -CN; or
 E^1 represents -Cl and E^4 represent -F, -Cl, -CH₃, -CF₃ or -OCH₃; or
 E^1 represents -CH₃ and E^4 represent -F, -Cl, -CH₃, -CF₃, -CN,
- 15 -N(H)C(O)CH=CH₂ or -S(O)₂(4-morpholinyl); or
 E^1 represents -CF₃ and E^4 represents -F or -CF₃; or
 E^1 represents -CN and E^4 represents -Cl; or
 E^1 represents -OCH₃ and E^4 represents -F, -Cl, Br, -CH₃, -CH(CH₃)₂, -C(CH₃)₃,
 -CN or -OCH₃; or
- 20 E^1 and E^4 represent hydrogen; and
 E^2 represents -F and E^3 represents -F, -Cl, -OH or -OCH₃; or
 E^2 represents -Cl and E^3 represents -F or -C(O)(4-morpholinyl); or
 E^2 represents -CH₃ and E^3 represents -F or -OCH₃; or
- 25 E^1 represents -OCH₃ and E^3 represents -OH; or
 E^1 represents -CH₂OCH₃ and E^3 represents (piperidin-4-yl)methoxy or
 ((1-*tert*butoxycarbonyl)piperidin-4-yl)methoxy; or
- 30 E^1 and E^3 represent hydrogen; and
 E^2 and E^4 represent -F; or
 E^2 and E^4 represent -CF₃; or
- 35 E^4 represents hydrogen; and
 E^1 , E^2 and E^3 represent -F; or
 E^1 and E^2 represent -Cl and E^3 represents -Cl, -OH or -OCH₃; or

E^1 and E^2 represent $-CH_3$ and E^3 represents $-F$ or $-OCH_3$; or

E^2 and E^3 represent $-Cl$ and E^1 represents $-CH_3$; or

E^2 represents hydrogen; and

5 E^1 , E^3 and E^4 represent $-F$; or

E^3 and E^4 represent $-Cl$ and E^1 represents $-CH_3$; or

E^1 and E^4 represent $-Cl$ and E^1 represents $-OCH_3$; or

E^1 and E^4 represent $-CH_3$ and E^3 represents $-F$, $-CH_3$ or $-OCH_3$; or

E^1 represents $-F$, E^3 represents $-CH_3$ and E^4 represents $-Cl$; or

10 E^1 represents $-Cl$, E^3 represents $-F$ and E^4 represents $-CH_3$; or

E^1 represents $-Cl$, E^3 represents $-CH_3$ and E^4 represents $-F$; or

E^1 and E^4 represent $-CH_3$ and E^3 represents $-F$; or

E^1 represents $-CH_3$, E^4 represents $-Cl$ and E^3 represents $-CF_3$ or $-OCH_3$; or

15 E^1 represents hydrogen; and

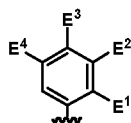
E^2 and E^4 represent $-CH_3$ and E^3 represents $-OH$; or

E^3 represents hydrogen; and

E^1 and E^2 represent $-Cl$ and E^4 represents $-CH_3$.

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Preferred particular compounds of formula I that may be mentioned include those in which R^1 is represented by



where:

25 E^3 and E^4 represent hydrogen; and

E^1 represents $-F$ and E^2 represents $-F$, $-Cl$, or $-CF_3$; or

E^1 represents $-Cl$ and E^2 represents $-Cl$, $-CH_3$ or $-CF_3$; or

E^1 represents $-CH_3$ and E^2 represents $-Cl$, $-CH_3$, $-CN$ or $-N(H)C(O)CH=CH_2$; or

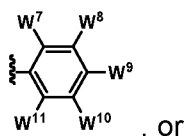
30 E^2 and E^4 represent hydrogen; and

E^1 and E^3 represent $-F$; or

E^1 represents $-Cl$ and E^3 represents $-F$ or $-Cl$; or

E^1 represents $-CH_3$ and E^3 represents $-Cl$; or

- E^2 and E^3 represent hydrogen; and
 E^1 represents -F and E^4 represents -Cl, -CH₃ or -CN; or
 E^1 represents -Cl and E^4 represents -F, -Cl, -CH₃ or -CF₃; or
 5 E^1 represents -CH₃ and E^4 represent, -Cl, -CH₃, -CF₃, -CN or
 -N(H)C(O)CH=CH; or
 E^1 represents -CF₃ and E^4 represents -F or -CF₃; or
 E^1 represents -CN and E^4 represents -Cl; or
- 10 E^4 represents hydrogen; and
 E^1 , E^2 and E^3 represent -F; or
 E^1 and E^2 represent -CH₃ and E^3 represents -F₃; or
 E^2 and E^3 represent -Cl and E^1 represents -CH₃; or
- 15 E^2 represents hydrogen; and
 E^1 , E^3 and E^4 represent -F; or
 E^3 and E^4 represent -Cl and E^1 represents -CH₃; or
 E^1 and E^4 represent -CH₃ and E^3 represents -F or -CH₃; or
 E^1 represents -F, E^3 represents -CH₃ and E^4 represents -Cl; or
 20 E^1 represents -Cl, E^3 represents -F and E^4 represents -CH₃; or
 E^1 represents -Cl, E^3 represents -CH₃ and E^4 represents -F; or
 E^1 and E^4 represent -CH₃ and E^3 represents -F; or
 E^1 represents -CH₃, E^3 represents -CF₃ and E^4 represents -Cl; or
- 25 E^1 represents hydrogen; and
 E^2 and E^4 represent -CH₃ and E^3 represents -OH; or
- E^3 represents hydrogen; and
 E^1 and E^2 represent -Cl and E^4 represents -CH₃.
- 30 Preferred compounds of formula I that may be mentioned include those in which:
 (a) Z^1 is not present or is selected from -F, -CN, -C(O)R^{b2}, -C(O)N(R^{c2})R^{d2},
 -C(O)OR^{e2}, -N(R^{f2})R^{g2}, -N(R^{h2})C(O)Rⁱ², -N(R^{j2})C(O)OR^{k2}, -N(R^{l2})C(O)N(R^{m2})Rⁿ²,
 -N(R^{o2})S(O)₂R^{p2}, -OR^{q2}, -S(O)_mR^{l2}, -S(O)₂N(R^{u2})R^{v2}, heterocycloalkyl optionally
 35 substituted by one or more substituents selected from W⁵, aryl represented by



heteroaryl having 1 to 3 nitrogen atoms, one oxygen atom and/or one sulfur atom and optionally substituted by one or more substituents selected from W^6 ; or

- (b) Z^2 is not present or is selected from -F, $-R^{a2}$, $-C(O)N(R^{c2})R^{d2}$, $-N(R^{f2})R^{g2}$, $-N(R^{h2})C(O)R^{i2}$, $-N(R^{j2})C(O)OR^{k2}$, $-N(R^{l2})C(O)N(R^{m2})R^{n2}$, $-N(R^{o2})S(O)_2R^{p2}$, $-OR^{q2}$, $-S(O)_mR^{l2}$, $-S(O)_2N(R^{u2})R^{v2}$, heterocycloalkyl optionally substituted by one or more substituents selected from W^5 , aryl optionally substituted by one or more substituents selected from W^6 , or heteroaryl optionally substituted by one or more substituents selected from W^6 .

10

Other preferred compounds of formula I that may be mentioned include those in which:

- (a) Z^3 is not present or is selected from -F, $-R^{a2}$, $-C(O)N(R^{c2})R^{d2}$, $-N(R^{f2})R^{g2}$, $-N(R^{h2})C(O)R^{i2}$, $-N(R^{j2})C(O)OR^{k2}$, $-N(R^{l2})C(O)N(R^{m2})R^{n2}$, $-N(R^{o2})S(O)_2R^{p2}$, $-OR^{q2}$, $-S(O)_mR^{l2}$, $-S(O)_2N(R^{u2})R^{v2}$, heterocycloalkyl optionally substituted by one or more substituents selected from W^5 , aryl optionally substituted by one or more substituents selected from W^6 , or heteroaryl optionally substituted by one or more substituents selected from W^6 ; and/or
- (b) Z^4 is not present or is selected from -F, $-C(O)N(R^{c2})R^{d2}$, $-N(R^{f2})R^{g2}$, $-N(R^{h2})C(O)R^{i2}$, $-N(R^{j2})C(O)OR^{k2}$, $-N(R^{l2})C(O)N(R^{m2})R^{n2}$, $-N(R^{o2})S(O)_2R^{p2}$, $-OR^{q2}$, $-S(O)_mR^{l2}$, $-S(O)_2N(R^{u2})R^{v2}$, heterocycloalkyl optionally substituted by one or more substituents selected from W^5 , aryl optionally substituted by one or more substituents selected from W^6 , or heteroaryl optionally substituted by one or more substituents selected from W^6 .

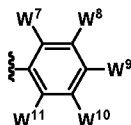
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- Particularly preferred compounds of formula I that may be mentioned include those in which Z^1 represents -F, -CN, $-C(O)NH_2$, $-C(O)N(R^{c2})R^{d2}$, $-C(O)-(4\text{-morpholinyl})$, $-C(O)OEt$, $-N(H)C(O)Me$, $-N(H)C(O)R^{i2}$, $-N(H)C(O)CH_2NMe_2$, $-N(H)C(O)OCMe_3$, $-N(H)C(O)OCH_2Ph$, $-N(Me)C(O)OCMe_3$, $-N(H)C(O)N(H)Me$, $-N(H)C(O)N(H)CHMe_2$, $-N(H)S(O)_2Me$, $-OMe$, $-OCF_3$ and $-OEt$.

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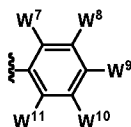
Preferred compounds of formula I where Z^1 represents heterocycloalkyl that may be mentioned are those where Z^1 represents dihydropyridinyl, imidazoliny, morpholinyl, oxanyl, piperazinyl, piperidinyl, pyrrolidinyl and quinuclidinyl, wherein the heterocycloalkyl is optionally substituted by one or more substituents selected from W^5 .

Preferred compounds of formula I where Z^1 represents



that may be mentioned are those where each W^7 , W^{10} and W^{11} independently represents hydrogen, halogen, $-R^{a3}$ or $-CN$; and one of W^8 and W^9 represents hydrogen, halogen, $-R^{a3}$ or $-CN$ and the other represents halogen, $-R^{a3}$, $-CN$, $-C(O)R^{b3}$, $-C(O)N(R^{c3})R^{d3}$, $-C(O)OR^{e3}$, $-N(R^{f3})R^{g3}$, $-N(R^{h3})C(O)R^{i3}$, $-N(R^{j3})C(O)OR^{k3}$, $-N(R^{l3})C(O)N(R^{m3})R^{n3}$, $-N(R^{o3})S(O)_2R^{p3}$, $-OR^{q3x}$, $-OC(O)R^{r3}$, $-OS(O)_2R^{s3}$, $-S(O)_mR^{t3}$, $-S(O)_2N(R^{u3})R^{v3}$, heterocycloalkyl optionally substituted by one or more substituents selected from G^1 , aryl optionally substituted by one or more substituents selected from G^2 , or heteroaryl optionally substituted by one or more substituents selected from G^2 .

Particularly preferred compounds of formula I where Z^1 represents



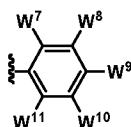
that may be mentioned are those where each W^7 , W^{10} and W^{11} independently represents $-F$, $-Cl$, $-CH_3$, $-CF_3$, or more preferably, hydrogen; and one of W^8 and W^9 (preferably W^8) represents $-F$, $-Cl$, $-CH_3$, $-CF_3$, or more preferably, hydrogen, and the other (preferably W^9) represents halogen, $-R^{a3}$, $-CN$, $-C(O)R^{b3}$, $-C(O)N(R^{c3})R^{d3}$, $-C(O)OR^{e3}$, $-N(R^{f3})R^{g3}$, $-N(R^{h3})C(O)R^{i3}$, $-N(R^{j3})C(O)OR^{k3}$, $-N(R^{l3})C(O)N(R^{m3})R^{n3}$, $-N(R^{o3})S(O)_2R^{p3}$, $-OR^{q3x}$, $-OC(O)R^{r3}$, $-OS(O)_2R^{s3}$, $-S(O)_mR^{t3}$, $-S(O)_2N(R^{u3})R^{v3}$, heterocycloalkyl optionally substituted by one or more substituents selected from G^1 , aryl optionally substituted by one or more substituents selected from G^2 , or heteroaryl optionally substituted by one or more substituents selected from G^2 .

For example, particular compounds of formula I that may be mentioned include those wherein:

- (a) W^8 , W^9 , W^{10} and W^{11} represents hydrogen and W^7 represents -Cl or -S(O)₂CH₃; or
- 5 (b) W^7 , W^9 , W^{10} and W^{11} represents hydrogen and W^8 represents -F, -Br, -CN, -N(H)C(O)CH₃, -OCH₃ or -S(O)₂CH₃; or
- (a) W^7 , W^{10} and W^{11} represents hydrogen and:
- (i) W^8 and W^9 represents -F or -Cl; or
- (ii) W^8 represents -F and W^9 represents -CH₃.

10

More particularly preferred compounds of formula I where Z^1 represents



- that may be mentioned are those where W^7 , W^8 , W^{10} and W^{11} are hydrogen and W^9 represents halogen, -R^{a3}, -CN, -C(O)R^{b3}, -C(O)N(R^{c3})R^{d3}, -C(O)OR^{e3},
 15 -N(R^{f3})R^{g3}, -N(R^{h3})C(O)Rⁱ³, -N(R^{j3})C(O)OR^{k3}, -N(R^{l3})C(O)N(R^{m3})Rⁿ³,
 -N(R^{o3})S(O)₂R^{p3}, -OR^{q3x}, -S(O)_mR^{t3}, -S(O)₂N(R^{u3})R^{v3}, heterocycloalkyl optionally substituted by one or more substituents selected from G¹, aryl optionally substituted by one or more substituents selected from G², or heteroaryl optionally substituted by one or more substituents selected from G².

20

- For example, more particularly preferred compounds of formula I that may be mentioned are those where where W^7 , W^8 , W^{10} and W^{11} are hydrogen and W^9 represents -F, -Cl, -CH₃, cyclopropyl, -CF₃, -CN, -NH₂, -N(CH₃)₂, -N(H)C(O)CH₃,
 -N(H)C(O)OC(CH₃)₃, -SO₂CH₃, -SO₂NH₂, -S(O)₂N(CH₃)₂, -S(O)₂-4-morpholinyl,
 25 4-methylpiperazin-1-yl, 4-methylpiperidin-1-ylmethyl and 1,2,3-thiadiazol-4-yl.

- Preferred compounds of formula I where Z^1 represents heteroaryl that may be mentioned are those where Z^1 represents benzimidazolyl, benzodioxinyl, benzoxazolyl, furanyl, imidazolyl, imidazopyridinyl, indolyl, isoquinolinyl,
 30 oxadiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridyl, pyrrolopyridinyl, quinolinyl, thiazolyl, thiophenyl and triazolyl, wherein the heteroaryl is optionally substituted by one or more substituents selected from W⁶.

Particularly preferred compounds of formula I where Z¹ represents heteroaryl that may be mentioned are those where Z¹ represents benzimidazol-2-yl, 1,4-benzodioxin-2-yl, benzoxazol-2-yl, furan-2-yl, imidazol-1-yl, imidazol-4-yl, imidazo-
[1,2-a]pyridin-2-yl, indol-3-yl, indol-5-yl, isoquinolin-4-yl, 1,3,4-oxadiazol-2-yl,
5 1,2-oxazol-4-yl, pyrazin-3-yl, pyrazol-1-yl, pyrazol-4-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, 5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridin-5-yl, thiazol-5-yl, thiophen-2-yl, 1,2,3-triazol-4-yl and 1,2,4-triazol-3-yl, wherein the heteroaryl is optionally substituted by one or more substituents selected from W⁶.

10 More particularly preferred compounds of formula I that may be mentioned are those where W⁶ represents -F, -Cl, -Br, -CH₃, cyclopropyl, -CF₃, -CN, -NH₂, -N(CH₃)₂, -SO₂CH₃, -SO₂NH₂ and -SO₂N(CH₃)₂.

15 In one embodiment, the compound according to the invention is selected from the compounds of Examples 1-454

As discussed hereinbefore, compounds of the invention are indicated as pharmaceuticals. According to a further aspect of the invention there is provided a compound of the invention, as hereinbefore defined, for use as a
20 pharmaceutical.

In another aspect of the invention the use of a compound of the invention, as hereinbefore defined, is provided for the manufacture of a medicament for the treatment of cancer.

25 Although compounds of the invention may possess pharmacological activity as such, certain pharmaceutically-acceptable (e.g. "protected") derivatives of compounds of the invention may exist or be prepared which may not possess such activity, but may be administered parenterally or orally and thereafter be
30 metabolised in the body to form compounds of the invention. Such compounds (which may possess some pharmacological activity, provided that such activity is appreciably lower than that of the "active" compounds to which they are metabolised) may therefore be described as "prodrugs" of compounds of the
35 invention.

By “prodrug of a compound of the invention”, we include compounds that form a compound of the invention, in an experimentally-detectable amount, within a predetermined time, following enteral or parenteral administration (e.g. oral or parenteral administration). All prodrugs of the compounds of the invention are
5 included within the scope of the invention.

Furthermore, certain compounds of the invention may possess no or minimal pharmacological activity as such, but may be administered parenterally or orally, and thereafter be metabolised in the body to form compounds of the invention
10 that possess pharmacological activity as such. Such compounds (which also includes compounds that may possess some pharmacological activity, but that activity is appreciably lower than that of the “active” compounds of the invention to which they are metabolised), may also be described as “prodrugs”.

15 Thus, the compounds of the invention are useful because they possess pharmacological activity, and/or are metabolised in the body following oral or parenteral administration to form compounds, which possess pharmacological activity.

20 It is stated herein that the compounds of the invention may be useful in the treatment of cancer. For the purposes of this specification, and for the avoidance of doubt, the term “treatment” includes treatment *per se*, prevention and prophylaxis.

25 In an alternative embodiment, compounds of the invention may be useful in the the treatment of cancer.

Preferably the cancer is selected from the group comprising: Soft Tissue Cancers: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma,
30 liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma,
35 adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma,

leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma); Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor [nephroblastoma], lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochondroma (osteochondromatous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma [pinealoma], glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma [serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma], granulosa-thecal cell tumors, Sertoli- Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma); Hematologic: blood and bone marrow (myeloid leukemia [acute and chronic], acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma [malignant lymphoma]; Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids; neurofibromatosis and Adrenal glands:

neuroblastoma. The term "cancerous cell" as provided herein, includes a cell afflicted by any one of the above identified conditions.

In certain embodiments of the present invention, the cancer is a solid tumor cancer.

- 5 In certain embodiments of the present invention, the cancer is selected from pancreatic cancer, ovarian cancer and colorectal cancer.

In certain embodiments of the present invention, the cancer is selected from colorectal cancer (including Ras mutations), small cell lung cancer, non-small cell lung cancer, and glioma.

- 10 In certain embodiments of the present invention, the cancer is selected from non-small cell lung cancer, ovarian cancer, metastatic breast cancer, pancreatic cancer, hepatobiliary cancer (including hepatocellular cancer, bile duct cancer and cholangiocarcinoma), and gastric cancer.

- 15 In certain embodiments of the present invention, the cancer is selected from colorectal cancer (including Ras mutations), small cell lung cancer, non-small cell lung cancer, ovarian cancer, hepatobiliary cancer (including hepatocellular cancer, bile duct cancer and cholangiocarcinoma), gastric cancer, testicular cancer, and head and neck squamous cell carcinoma.

- 20 In certain embodiments of the present invention, the cancer is selected from leukemia (including acute myeloid leukemia, acute lymphoblastic leukemia, chronic myeloid leukemia, and chronic lymphoid leukemia), lymphoma (including mantle cell lymphoma, Hodgkin's lymphoma and non-Hodgkin's lymphoma), and prostate cancer

- 25 Compounds of the invention will normally be administered orally, intravenously, subcutaneously, buccally, rectally, dermally, nasally, tracheally, bronchially, sublingually, intranasally, topically, by any other parenteral route or *via* inhalation, in a pharmaceutically acceptable dosage form.

- 30 Compounds of the invention may be administered alone, but are preferably administered by way of known pharmaceutical compositions/formulations,

including tablets, capsules or elixirs for oral administration, suppositories for rectal administration, sterile solutions or suspensions for parenteral or intramuscular administration, and the like.

- 5 Compounds of the invention (i.e. compounds that inhibit MTH1) may be administered in the form of tablets or capsules, e.g., time-release capsules that are taken orally. Alternatively, the compounds of the invention may be in a liquid form and may be taken orally or by injection. The compounds of the invention may also be in the form of suppositories, or, creams, gels, and foams e.g. that
10 can be applied to the skin. In addition, they may be in the form of an inhalant that is applied nasally.

Such compositions/formulations may be prepared in accordance with standard and/or accepted pharmaceutical practice.

- 15 According to a further aspect of the invention there is thus provided a pharmaceutical composition/formulation including a compound of the invention, as hereinbefore defined, optionally in admixture with a pharmaceutically acceptable adjuvant, diluent and/or carrier. Such compositions/formulations may
20 be of use in the treatment, prevention and/or prophylaxis of cancer and diseases which benefit by inhibition of MTH1.

- Depending on e.g. potency and physical characteristics of the compound of the invention (i.e. active ingredient), pharmaceutical formulations that may be
25 mentioned include those in which the active ingredient is present in at least 1% (or at least 10%, at least 30% or at least 50%) by weight. That is, the ratio of active ingredient to the other components (i.e. the addition of adjuvant, diluent and carrier) of the pharmaceutical composition is at least 1:99 (or at least 10:90, at least 30:70 or at least 50:50) by weight.

- 30 The invention further provides a process for the preparation of a pharmaceutical formulation, as hereinbefore defined, which process comprises bringing into association a compound of the invention, as hereinbefore defined, or a pharmaceutically acceptable salt thereof with a pharmaceutically-acceptable
35 adjuvant, diluent or carrier.

In yet another aspect the present invention provides methods for the treatment of cancer comprising administering a therapeutically effective amount of a compound of the invention to a subject (e.g. patient) in need of such treatment.

5

"Patients" include mammalian (including human) patients.

The term "effective amount" refers to an amount of a compound, which confers a therapeutic effect on the treated patient. The effect may be objective (i.e. measurable by some test or marker) or subjective (i.e. the subject gives an indication of or feels an effect).

10

Compounds of the invention may also be combined with other therapeutic agents that are useful in the treatment of cancer.

15

According to a further aspect of the invention, there is provided a combination product comprising:

- (A) a compound of the invention, as hereinbefore defined; and
 - (B) another therapeutic agent that is useful in the treatment of cancer,
- wherein each of components (A) and (B) is formulated in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier.

20

Such combination products provide for the administration of a compound of the invention in conjunction with the other therapeutic agent, and may thus be presented either as separate formulations, wherein at least one of those formulations comprises a compound of the invention, and at least one comprises the other therapeutic agent, or may be presented (i.e. formulated) as a combined preparation (i.e. presented as a single formulation including a compound of the invention and the other therapeutic agent).

30

Thus, there is further provided:

- (1) a pharmaceutical formulation including a compound of the invention, as hereinbefore defined, another therapeutic agent that is useful in the treatment of cancer, and a pharmaceutically-acceptable adjuvant, diluent or carrier; and

35

(2) a kit of parts comprising components:

(a) a pharmaceutical formulation including a compound of the invention, as hereinbefore defined, in admixture with a pharmaceutically-acceptable

5 adjuvant, diluent or carrier; and

(b) a pharmaceutical formulation including another therapeutic agent that is useful in the treatment of cancer in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier,

10 which components (a) and (b) are each provided in a form that is suitable for administration in conjunction with the other.

The invention further provides a process for the preparation of a combination product as hereinbefore defined, which process comprises bringing into association a compound of the invention, as hereinbefore defined, or a
15 pharmaceutically acceptable salt thereof with the other therapeutic agent that is useful in the treatment of cancer, and at least one pharmaceutically-acceptable adjuvant, diluent or carrier.

By "bringing into association", we mean that the two components are rendered
20 suitable for administration in conjunction with each other.

Thus, in relation to the process for the preparation of a kit of parts as hereinbefore defined, by bringing the two components "into association with" each other, we include that the two components of the kit of parts may be:
25 (i) provided as separate formulations (i.e. independently of one another), which are subsequently brought together for use in conjunction with each other in combination therapy; or
 (ii) packaged and presented together as separate components of a "combination pack" for use in conjunction with each other in combination therapy.

30

Compounds of the invention may be administered at varying doses. Oral, pulmonary and topical dosages (and subcutaneous dosages, although these dosages may be relatively lower) may range from between about 0.01 mg/kg of body weight per day (mg/kg/day) to about 100 mg/kg/day, preferably about 0.01
35 to about 10 mg/kg/day, and more preferably about 0.1 to about 5.0 mg/kg/day.

For e.g. oral administration, the compositions typically contain between about 0.01 mg to about 2000 mg, for example between about 0.1 mg to about 500 mg, or between 1 mg to about 100 mg, of the active ingredient. Intravenously, the most preferred doses will range from about 0.001 to about 10 mg/kg/hour during constant rate infusion. Advantageously, compounds may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily.

In any event, the physician, or the skilled person, will be able to determine the actual dosage which will be most suitable for an individual patient, which is likely to vary with the route of administration, the type and severity of the condition that is to be treated, as well as the species, age, weight, sex, renal function, hepatic function and response of the particular patient to be treated. The above-mentioned dosages are exemplary of the average case; there can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

Compounds of the invention may also have the advantage that they may be more efficacious than, be less toxic than, be longer acting than, be more potent than, produce fewer side effects than, be more easily absorbed than, and/or have a better pharmacokinetic profile (e.g. higher oral bioavailability and/or lower clearance) than, and/or have other useful pharmacological, physical, or chemical properties over, compounds known in the prior art, whether for use in the above-stated indications or otherwise. In particular, compounds of the invention may have the advantage that they are more efficacious and/or exhibit advantageous properties *in vivo*.

It is contemplated that any method or composition described herein can be implemented with respect to any other method or composition described herein.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention pertains.

Examples

The invention is illustrated by way of the following examples, in which the following abbreviations may be employed.

5	aq	aqueous
	DMF	dimethylformamide
	DMSO	dimethyl sulfoxide
	EtOAc	ethyl acetate
10	EtOH	ethanol
	MeOH	methanol
	MeCN	acetonitrile
	Pd-C	palladium on carbon
	sat.	saturated
15	TFA	trifluoroacetic acid
	THF	tetrahydrofuran
	min.	minutes
	h.	hours
	Hunigs base	<i>N,N</i> -diisopropylethylamine
20	DCM	dichloromethane
	n-BuOH	butan-1-ol
	iPrOH	propan-2-ol
	NEt ₃	triethylamine
	Boc	<i>tert</i> -butoxycarbonyl
25	HATU	(1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo- [4,5-b]pyridinium 3-oxid hexafluorophosphate
	NMP	<i>N</i> -methylpyrrolidine
	LCMS	liquid-chromatography electrospray mass spectroscopy
	NMR	nuclear magnetic resonance
30	NCS	<i>N</i> -chlorosuccinimide
	Pd(PPh ₃) ₄	tetrakis(triphenylphosphine)palladium (0)
	B(OMe) ₃	trimethylborate
	n-BuLi	<i>n</i> -butyl lithium
	MeI	iodomethane
35	NaOMe	sodium methoxide

	CHCl_3	chloroform
	MgSO_4	anhydrous magnesium sulphate
	K_2CO_3	anhydrous potassium carbonate
	NH_4OH	ammonium hydroxide
5	Ac_2O	acetic anhydride
	POCl_3	phosphorus oxychloride

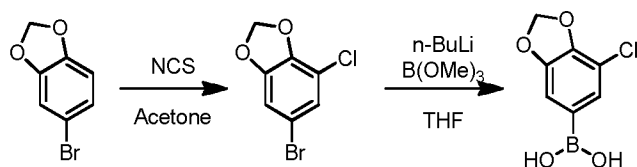
Starting materials and chemical reagents specified in the syntheses described below are commercially available, e.g. from Sigma-Aldrich, Fine Chemicals
 10 Combi-Blocks and other vendors.

In the event that there is a discrepancy between nomenclature and any compounds depicted graphically, then it is the latter that presides (unless contradicted by any experimental details that may be given or unless it is clear
 15 from the context). Final compounds were named using Marvin software version 6.1.

Purification of compounds may be carried out using silica gel column chromatography or preparative reverse phase HPLC (ACE column, acidic
 20 gradients with MeCN- H_2O containing 0.1 % TFA or XBridge column, basic gradients using MeCN- H_2O containing ammonium bicarbonate) to give the products as their free bases or trifluoroacetic acid salts.

Intermediate 1

25 (7-chloro-2H-1,3-benzodioxol-5-yl)boronic acid.



Step 1: 6-bromo-4-chloro-2H-1,3-benzodioxole:

To a solution of 5-bromo-2H-1,3-benzodioxole (60 μL , 0.50 mmol, 1 eq.) in acetonitrile (1 mL) was added 1-chloropyrrolidine-2,5-dione (73 mg, 0.55 mmol,
 30 1.1 eq.). The reaction was stirred overnight at room temperature. After completion of the reaction, the reaction mixture was concentrated and purified by column chromatography (Heptane/EtOAc 100 % $\rightarrow$ 5:1) to afford the desired product as a

colourless solid (104 mg, 89 %). LCMS $[M+H]^+$ 234; ^1H NMR (400 MHz, CD_3OD) δ_H 7.05 (1H, s), 6.93 (1H, s), 2.78 (2H, s).

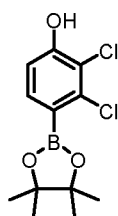
Step 2: (7-chloro-2H-1,3-benzodioxol-5-yl)boronic acid:

- 5 To a solution of 6-bromo-4-chloro-2H-1,3-benzodioxole (104 mg, 0.44 mmol, 1 eq.) in THF (5.8 mL) was added, at $-78^\circ C$, n-BuLi (2.5 M in hexanes, 265 μL , 0.66 mmol, 1.5 eq.). The reaction mixture was stirred at this temperature for 30 min, before addition of $B(OMe)_3$ (248 μL , 2.21 mmol, 5 eq.). The reaction was slowly allowed to warm up to rt, 2N HCl was added, and stirring was continued for
- 10 1 h. The reaction mixture was extracted with EtOAc, and the organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by column chromatography (Pentane/EtOAc 100 % $\rightarrow$ 3:1) to afford the desired product as a white solid (22 mg, 25 %). LCMS $[M+H]^+$ 201; ^1H NMR (400 MHz, $DMSO-d_6$) δ_H 7.34 (1H, s), 6.81 (1H, s), 5.99 (2H, s).

15

Intermediate 2

2,3-dichloro-4-(tetramethyl-1,3,2-dioxaborolan-2-yl)phenol.

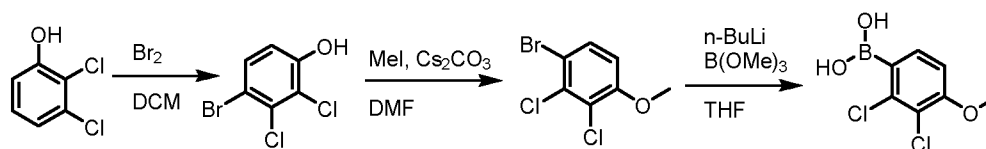


- To a solution of 4-bromo-2,3-dichlorophenol (250 mg, 1.03 mmol, 1 eq.) in THF
- 20 (10 mL) was added, at $-78^\circ C$, n-BuLi (2.5 M in hexanes, 1.25 mL, 3.10 mmol, 3 eq.). The reaction mixture was stirred at this temperature for 30 min, before addition of 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (316 μL , 1.55 mmol, 1.5 eq.). The reaction was slowly allowed to warm up to rt, 2N HCl was added, and stirring was continued for 1 h. The reaction mixture was extracted
- 25 with EtOAc, and the organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by column chromatography (Pentane/EtOAc 100 % $\rightarrow$ 4:1) to afford the desired product as a white solid (102 mg, 34 %). LCMS $[M+H]^+$ 289; ^1H NMR (400 MHz, CD_3OD) δ_H 7.47 (1H, d, $J = 8.1$ Hz), 6.85 (1H, d, $J = 8.1$ Hz), 1.36 (12H, s).

30

Intermediate 3

(2,3-dichloro-4-methoxyphenyl)boronic acid.



Step 1: 4-Bromo-2,3-dichlorophenol.

To a solution of 2,3-dichlorophenol (1.0 g, 6.13 mmol, 1 eq.) in DCM (4 mL) was added, at 0 °C, bromine (348 μ L, 6.75 mmol, 1.1 eq.) over 15 min. The reaction was allowed to warm up to rt over 12 hours. NMR showed unreacted starting material, bromine (0.33 eq.) was added at 0 °C and the reaction was allowed to warm up to rt over 12 hours. The reaction was stopped by addition of Na₂S₂O₃, the organic layer was washed with brine, dried with MgSO₄ and concentrated under reduced pressure. The crude product was purified by column chromatography (Pentane/EtOAc 100 % $\rightarrow$ 25:1) to afford the desired product as a white solid (685 mg, 46 %). LCMS [M+H]⁺ 239; ¹H NMR (400 MHz, DMSO-d₆) δ _H 10.98 (1H, s), 7.54 (1H, d, J = 8.8 Hz), 6.91 (1H, d, J = 8.8 Hz).

Step 2: 1-Bromo-2,3-dichloro-4-methoxybenzene.

To a solution of 4-bromo-2,3-dichlorophenol (200 mg, 0.83 mmol, 1 eq.) in DMF (3 mL) was added Cs₂CO₃ (538 mg, 1.65 mmol, 2 eq.) followed by iodomethane (208 μ L, 3.3 mmol, 4 eq.). The reaction mixture was stirred at 70 °C for 3 h. The reaction was stopped by addition of H₂O, extracted with DCM, dried with MgSO₄ and concentrated under reduced pressure. The crude product was purified by column chromatography (Pentane/EtOAc 100 % $\rightarrow$ 20:1) to afford the desired product as a white solid (190 mg, 89 %). LCMS [M+H]⁺ 256; ¹H NMR (400 MHz, CDCl₃) δ _H 7.47 (1H, d, J = 9.0 Hz), 6.73 (1H, d, J = 8.8 Hz), 3.88 (3H, s).

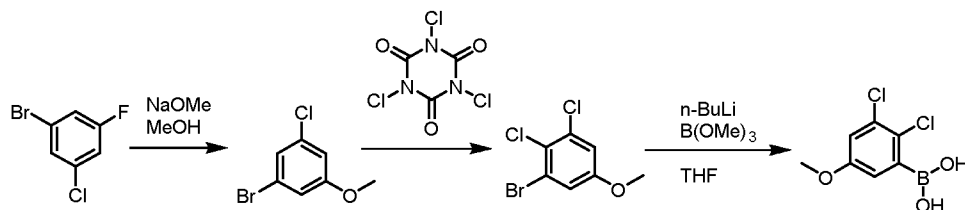
Step 3: (2,3-dichloro-4-methoxyphenyl)boronic acid.

To a solution of 1-bromo-2,3-dichloro-4-methoxybenzene (100 mg, 0.39 mmol, 1 eq.) in THF (5 mL) was added, at -78 °C, n-BuLi (2.5 M in hexanes, 234 μ L, 0.59 mmol, 1.5 eq.). The reaction mixture was stirred at this temperature for 30 min, before addition of B(OMe)₃ (218 μ L, 1.95 mmol, 5 eq.). The reaction was slowly allowed to warm up to rt, 2N HCl was added, and stirring was continued for 1 h. The reaction mixture was extracted with EtOAc, and the organic layer was dried over MgSO₄ and evaporated under reduced pressure. The crude product was purified by column chromatography (Pentane/EtOAc 100 % $\rightarrow$ 3:1) to afford the desired product as a white solid (52 mg, 59 %). LCMS [M+H]⁺ 221; ¹H NMR (400

MHz, DMSO- d_6) δ_H 8.25 (1H, s), 7.35 (1H, d, $J = 8.1$ Hz), 7.10 (1H, d, $J = 8.1$ Hz), 3.87 (3H, s).

Intermediate 4

5 (2,3-dichloro-5-methoxyphenyl)boronic acid.



Step 1: 1-Bromo-3-chloro-5-methoxybenzene.

1-Bromo-3-chloro-5-fluorobenzene (1 g, 4.77 mmol, 1 eq.) was treated at 0 °C with sodium methoxide (25 % in MeOH, 1.2 mL, 5.71 mmol, 1.2 eq.). The reaction mixture was stirred at 100 °C for 3 h. The solution was concentrated under reduced pressure, the crude product was extracted with DCM, washed with H₂O, brine, dried over MgSO₄ and concentrated. The product was obtained as a white solid (747 mg, 71 %). LCMS $[M+H]^+$ 220; ¹H NMR (400 MHz, CD₃Cl) δ_H 7.09 (1H, t, $J = 1.7$ Hz), 6.94 – 6.92 (1H, m), 6.83 – 6.80 (1H, m), 3.77 (3H, s).

15

Step 2: 1-Bromo-2,3-dichloro-5-methoxybenzene.

To a solution of 1-bromo-3-chloro-5-methoxybenzene (300 mg, 1.35 mmol, 1 eq.) in DMF (5 mL) was added trichloro-1,3,5-triazinane-2,4,6-trione (115 mg, 0.49 mmol, 0.36 eq.) and the reaction was stirred at 50 °C for 3 h. The reaction mixture was concentrated and the crude product was purified by column chromatography (Heptane/EtOAc 100 % → 20:1) to afford the desired product as a white solid (253 mg, 73 %). LCMS $[M+H]^+$ 254; ¹H NMR (400 MHz, CD₃Cl) δ_H 7.09 (1H, d, $J = 3.0$ Hz), 6.97 (1H, d, $J = 3.0$ Hz), 3.77 (3H, s).

20

25 Step 3: (2,3-dichloro-5-methoxyphenyl)boronic acid.

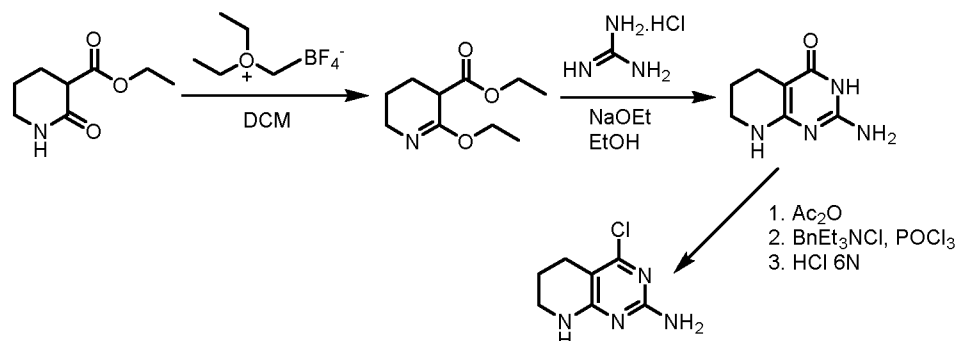
To a solution of 1-bromo-2,3-dichloro-5-methoxybenzene (87 mg, 0.34 mmol, 1 eq.) in THF (4.5 mL) was added, at -78 °C, n-BuLi (2.5 M in hexanes, 205 μ L, 0.51 mmol, 1.5 eq.). The reaction mixture was stirred at this temperature for 30 min, before addition of B(OMe)₃ (191 μ L, 1.70 mmol, 5 eq.). The reaction was slowly allowed to warm up to rt, 2N HCl was added, and stirring was continued for 1 h. The reaction mixture was extracted with EtOAc, and the organic layer was

30

dried over MgSO_4 and evaporated under reduced pressure to afford the desired product as a white solid (75 mg, 100%). LCMS $[\text{M}+\text{H}]^+$ 221.

Intermediate 5

5 4-chloro-5H,6H,7H,8H-pyrido[2,3-d]pyrimidin-2-amine.



Step 1: ethyl 2-ethoxy-3,4,5,6-tetrahydropyridine-3-carboxylate.

To a solution of ethyl 2-oxopiperidine-3-carboxylate (1.5 g, 8.76 mmol, 1 eq.) in DCM (6.5 mL) under N_2 was added a solution of triethyloxonium tetrafluoroborate (2.0 g, 10.51 mmol, 1.2 eq.) in DCM (6.5 mL). The reaction mixture was stirred at room temperature overnight. The solution was poured in water (5 mL) and allowed to stand for 30 min. The organic layer was washed with NaHCO_3 , H_2O , dried over Na_2SO_4 and concentrated under reduced pressure to afford the desired product as a colourless oil (1.2 g, 66 %). ^1H NMR (400 MHz, CDCl_3) δ_{H} 4.15 (2H, q, $J = 7.2$ Hz), 4.00 – 3.98 (2H, m), 3.46 – 3.44 (2H, m), 3.18 – 3.16 (1H, m), 1.97 – 1.95 (2H, m), 1.68 – 1.66 (1H, m), 1.49 – 1.47 (1H, m), 1.25 (3H, t, $J = 7.1$ Hz), 1.20 (3H, t, $J = 7.0$ Hz).

Step 2: 2-amino-3H,4H,5H,6H,7H,8H-pyrido[2,3-d]pyrimidin-4-one.

A solution of sodium ethoxide (21 % in EtOH, 197 μL , 2.51 mmol, 2.5 eq.) was added to the mixture of ethyl 2-ethoxy-3,4,5,6-tetrahydropyridine-3-carboxylate (200 mg, 1 mmol, 1 eq.) and guanidine hydrochloride (96 mg, 1 mmol, 1 eq.) in EtOH (2 mL). The reaction mixture was stirred a reflux overnight. The solvent were removed under vacuum and the obtained solid was dried to afford the desired product as a light yellow solid (116 mg, 70% yield). ^1H NMR (400 MHz, CDCl_3) δ_{H} 9.89 (1H, br s), 6.18 (1H, br s), 6.10 (2H, br s), 3.10 – 3.08 (2H, m), 2.20 – 2.18 (2H, m), 1.61 – 1.59 (2H, m).

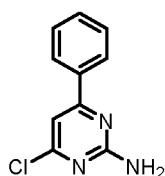
Step 3: 4-chloro-5H,6H,7H,8H-pyrido[2,3-d]pyrimidin-2-amine.

A mixture of 2-amino-5,6,7,8-tetrahydropyrido[2,3-d]pyrimidin-4(3H)-one and acetic anhydride was heated at reflux for 1 h until completion of the reaction as monitored by LCMS. The solvent was removed under reduced pressure and the obtained residue was treated with benzyltriethylammonium chloride (547 mg, 2.4 mmol, 2 eq.) and POCl₃ (671 µL, 7.2 mmol, 6 eq.) and heated at reflux for 1 h. After evaporation of the solvents, ice water was added to the residue and HCl (6N, 5.5 mL) was added. The reaction mixture was heated at 50 °C overnight. After evaporation of the solvents, the residue is diluted in EtOAc and washed with NaHCO₃, brine and dried over Na₂SO₄. The combined organic layers were then evaporated, and the crude product was purified by column chromatography (DCM/MeOH 98/2 200 mL, 95/5 100 mL). The pure product was obtained as a yellow powder (45 mg, 20 %). LCMS [M+H]⁺ 185. ¹H NMR (400 MHz, CDCl₃) δ_H 8.09 – 8.03 (1H, br s), 3.28 – 3.26 (2H, m), 2.53 – 2.51 (2H, m), 1.81 – 1.79 (2H, m).

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Intermediate 6

4-chloro-6-phenylpyrimidin-2-amine.

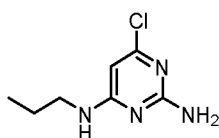


A mixture of 2-amino-4,6-dichloropyrimidine (3 g, 18.29 mmol, 1 eq.), phenylboronic acid (2.45 g, 20.12 mmol, 1.1 eq.), K₂CO₃ (5.06 g, 36.6 mmol, 2 eq.) and Pd(PPh₃)₄ (700 mg, 0.6 mmol, 0.03 eq.) in 1,4-dioxane (15 mL) and water (1 mL) was heated in a sealed tube at 95°C for 12 h. The mixture was run through a plug of silica using EtOAc as eluent, concentrated and purified by column chromatography (1:4 EtOAc/pentane) to give the desired product as a white solid (2.2 g, 60 %). LCMS [M+H]⁺ 206; ¹H NMR (400 MHz, CDCl₃) δ_H 8.27 – 8.20 (2H, m), 8.16 – 8.05 (3H, m), 7.19 (2H, s), 6.76 (1H, s).

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Intermediate 7

6-chloro-4-N-propylpyrimidine-2,4-diamine.

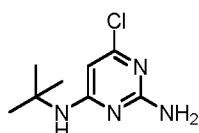


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- A solution of 4,6-dichloropyrimidin-2-amine (820 mg, 5.0 mmol, 1 eq.) in EtOH (40 mL) was treated with propan-1-amine (5.0 ml). The reaction mixture was stirred at 85 °C for 48h. The mixture was cooled, concentrated by evaporation then flash-chromatographed over silica to afford the product as a colorless solid (705 mg; 76%). LCMS $[M+H]^+$ 187.

Intermediate 8

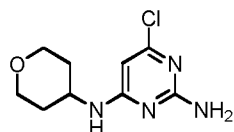
4-N-tert-butyl-6-chloropyrimidine-2,4-diamine.



- To a solution of 4,6-dichloropyrimidin-2-amine (820 mg, 5.0 mmol, 1 eq.) in n-BuOH (20 mL) was added tert-butylamine (365 mg, 5.0 mmol, 1 eq.) and Hünig's base (645 mg, 5.0 mmol, 1 eq.). The reaction mixture was stirred overnight at 95 °C. The mixture was cooled and some unreacted starting material removed by filtration. The filtrate was concentrated and the residue flash-chromatographed over silica to afford the product (0.27 g; 27%). LCMS $[M+H]^+$ 201.

Intermediate 9

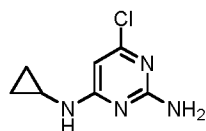
6-chloro-4-N-(oxan-4-yl)pyrimidine-2,4-diamine.



- To a solution of 4,6-dichloropyrimidin-2-amine (492 mg, 3.0 mmol, 1 eq.) in n-BuOH (20 mL) was added tetrahydro-2H-pyran-4-amine (303 mg, 3.0 mmol, 1 eq.) and Hünig's base (387 mg, 3.0 mmol, 1 eq.). The reaction mixture was stirred overnight at 95 °C. The mixture was cooled thr precipitated solid was collected and washed with water to give the product (0.42 g; 37%). LCMS $[M+H]^+$ 229.

Intermediate 10

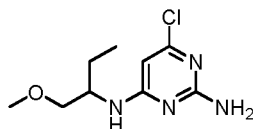
6-chloro-4-N-cyclopropylpyrimidine-2,4-diamine.



To a solution of 4,6-dichloropyrimidin-2-amine (164 mg, 1.0 mmol, 1 eq.) in n-BuOH (5 mL) were added cyclopropanamine (80 μ L, 1.1 mmol, 1.1 eq.) and Hünig's base (260 μ L, 1.5 mmol, 1.5 eq.). The reaction mixture was stirred overnight at 95 °C. The solvent was removed in vacuo. The crude product was diluted in EtOAc and washed with H₂O, brine, dried over MgSO₄ and concentrated to afford the desired product as an off-white solid (152 mg, 82 %). LCMS [M+H]⁺ 185; ¹H NMR (400 MHz, DMSO-d₆) δ _H 7.29 (1H, s), 6.38 (2H, s), 5.85 (1H, s), 3.52 (1H, s), 0.73 – 0.64 (2H, m), 0.53 – 0.35 (2H, m).

10 Intermediate 11

6-chloro-4-N-(1-methoxybutan-2-yl)pyrimidine-2,4-diamine.

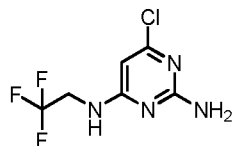


To a solution of 4,6-dichloropyrimidin-2-amine (500 mg, 3.1 mmol, 1 eq.) in n-BuOH (10 mL) were added 1-methoxybutan-2-amine (315 mg, 3.1 mmol, 1 eq.) and Hünig's base (531 μ L, 3.1 mmol, 1 eq.). The reaction mixture was stirred overnight at 95 °C. The solvent was removed in vacuo. The crude product was diluted in EtOAc and washed with H₂O, brine, dried over MgSO₄ and concentrated to afford the desired product as an off-white solid (592 mg, 84 %). LCMS [M+H]⁺ 231.

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Intermediate 12

6-chloro-4-N-(2,2,2-trifluoroethyl)pyrimidine-2,4-diamine.

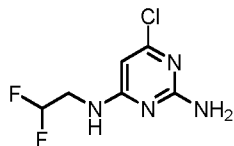


To a solution of 4,6-dichloropyrimidin-2-amine (164 mg, 1.00 mmol, 1 eq.) in n-BuOH (5 mL) were added 2,2,2-trifluoroethanamine hydrochloride (149 mg, 1.1 mmol, 1.1 eq.) and NEt₃ (202 mg, 2.0 mmol, 2 eq.). The reaction mixture was stirred overnight at 90 °C. The solvent was removed in vacuo. The crude product was diluted in EtOAc and washed with H₂O, brine, dried over MgSO₄ and concentrated to afford the desired product as a yellow solid (59 mg, 26 %). LCMS [M+H]⁺ 227.

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Intermediate 13

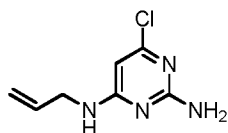
6-chloro-4-N-(2,2-difluoroethyl)pyrimidine-2,4-diamine.



To a solution of 4,6-dichloropyrimidin-2-amine (164 mg, 1.00 mmol, 1 eq.) in n-BuOH (5 mL) were added 2,2-difluoroethanamine hydrochloride (129 mg, 1.1 mmol, 1.1 eq.) and triethylamine (202 mg, 2.0 mmol, 2 eq.). The reaction mixture was stirred overnight at 90 °C. The solvent was removed in vacuo. The crude product was diluted in EtOAc and washed with H₂O, brine, dried over MgSO₄ and concentrated to afford the desired product as a yellow solid (80 mg, 38 %). LCMS [M+H]⁺ 209.

Intermediate 14

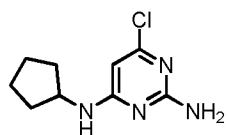
6-chloro-4-N-(prop-2-en-1-yl)pyrimidine-2,4-diamine.



To a solution of 4,6-dichloropyrimidin-2-amine (500 mg, 3.04 mmol, 1 eq.) in n-BuOH (10 mL) were added 2,2-difluoroethanamine hydrochloride (229 µL, 3.04 mmol, 1 eq.) and Hünig's base (584 µL, 3.35 mmol, 1.1 eq.). The reaction mixture was stirred overnight at 95 °C. The solvent was removed in vacuo. The crude product was diluted in EtOAc and washed with H₂O, brine, dried over MgSO₄ and concentrated to afford the desired product as a yellow solid (471 mg, 84 %). LCMS [M+H]⁺ 185.

Intermediate 15

6-chloro-4-N-cyclopentylpyrimidine-2,4-diamine.

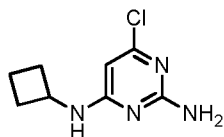


To a solution of 4,6-dichloropyrimidin-2-amine (500 mg, 3.04 mmol, 1 eq.) in n-BuOH (10 mL) were added cyclopentylamine (301 µL, 3.04 mmol, 1 eq.) and Hünig's base (584 µL, 3.35 mmol, 1.1 eq.). The reaction mixture was stirred overnight at 95 °C. The solvent was removed in vacuo. The crude product was

diluted in EtOAc and washed with H₂O, brine, dried over MgSO₄ and concentrated to afford the desired product as a brown foam (620 mg, quantitative). LCMS [M+H]⁺ 213.

5 Intermediate 16

6-chloro-4-N-cyclobutylpyrimidine-2,4-diamine.

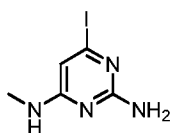


To a solution of 4,6-dichloropyrimidin-2-amine (250 mg, 1.52 mmol, 1 eq.) in n-BuOH (5 mL) were added cyclobutanamine (130 μ L, 1.52 mmol, 1 eq.) and Hünig's base (292 μ L, 1.72 mmol, 1.1 eq.). The reaction mixture was stirred overnight at 95 °C. The solvent was removed in vacuo. The crude product was diluted in EtOAc and washed with H₂O, brine, dried over MgSO₄ and concentrated to afford the desired product as a white solid (248 mg, 80 %). LCMS [M+H]⁺ 199.

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Intermediate 17

6-iodo-4-N-methylpyrimidine-2,4-diamine.

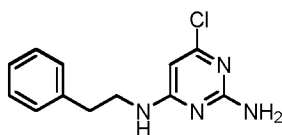


To a suspension of 6-Chloro-4-N-methylpyrimidine-2,4-diamine (1.5 g, 9.43 mmol, 1 eq.) in acetone (6.2 mL) was added sodium iodide (7.9 g, 52.8 mmol, 5.6 eq.) and hydrogen iodide (15 mL). The reaction mixture was stirred at 60 °C for 12 h. The solid was filtered off, dissolved in EtOAc, washed with NaHCO₃, brine, dried over MgSO₄ and concentrated under reduced pressure to afford the desired compound as an orange solid (1.7 g, 73 %). LCMS [M+H]⁺ 251; ¹H NMR (400 MHz, CDCl₃) δ _H 6.27 (1H, s), 2.80 (3H, s).

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Intermediate 18

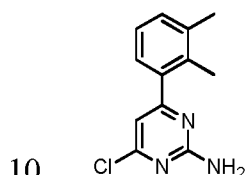
6-chloro-4-N-(2-phenylethyl)pyrimidine-2,4-diamine.



To a solution of 4,6-dichloropyrimidin-2-amine (66 mg, 0.40 mmol, 1 eq.) in n-BuOH (2.5 mL) were added 2-phenylethanamine (75 μ L, 0.60 mmol, 1.1 eq.) and Hünig's base (100 μ g, 0.60 mmol, 1.1 eq.). The reaction mixture was stirred at 95 °C for 3 h. The solvent was removed in vacuo. The crude product was diluted in
 5 EtOAc and washed with H₂O, brine, dried over MgSO₄ and concentrated to afford the desired product as a yellow solid (88 mg, 88 %). LCMS [M+H]⁺ 249.

Intermediate 19

4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine.

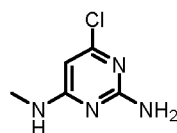


A mixture of 2-amino-4,6-dichloropyrimidine (0.82 g, 5.0 mmol, 1 eq.), 2,3-dimethylphenylboronic acid (0.75 g, 5.0 mmol, 1 eq.), K₂CO₃ (1.38 g, 10.0 mmol, 2 eq.) and palladium tetrakis(triphenylphosphine)palladium (0) (0.12 g, 0.10 mmol, 0.1 eq.) in 1,4-dioxane (20 mL) and water (5 mL) was heated in a sealed
 15 tube at 90 °C for 2.5 hours. The mixture was run through a plug of silica using EtOAc as eluent, concentrated and purified by column chromatography (1:4 EtOAc/pentane) to give the desired product as a white solid (0.76 g, 65 %).
 LCMS [M+H]⁺ 234; ¹H NMR (400 MHz, CD₃OD) δ _H 7.21 - 7.29 (1H, m), 7.20 - 7.09 (2H, m), 6.70 (1H, s), 2.34 (3H, s), 2.23 (3H, s).

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Intermediate 20

4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine.

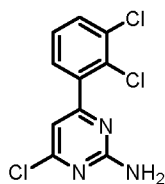


A mixture of 4,6-dichloropyrimidin-2-amine (3.28 g, 20.0 mmol), methanamine (12.0 mL, 24.0 mmol; as a 2 M solution in methanol) and Hünig's base in n-butanol (20 mL) was heated at 95 °C overnight. The mixture was concentrated and the crude was taken up in EtOAc (300 mL) and washed with water (3 x 150 mL). The organic layer was dried over MgSO₄, filtered and concentrated to give
 25 the desired product as a buff solid (2.90 g, 91%). LCMS [M+H]⁺ 159.

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Intermediate 21

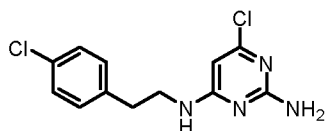
6-chloro-4-N-methylpyrimidine-2,4-diamine.



- A mixture of 4,6-dichloropyrimidin-2-amine (0.50 g, 3.05 mmol), (2,3-dichlorophenyl)boronic acid (0.64 g, 3.35 mmol), sodium carbonate (0.65 g, 6.10 mmol) and palladium tetrakis(triphenylphosphine)palladium (0) (0.088 g, 0.076 mmol) in 1,4-dioxane/water (30 mL; 4:1) was heated in a sealed tube at 95°C for 2 h. The reaction mixture was run through a plug of silica (EtOAc) and then concentrated. Purification by column chromatography (1:4→1:3 EtOAc/hexane) afforded the desired product as a white solid (0.26 g, 31%). LCMS $[M+H]^+$ 274; ^1H NMR (400 MHz, DMSO- d_6) δ_H 6.89 (1H, s) 7.33 (2H, br s) 7.44 - 7.52 (2H, m) 7.71 - 7.81 (1H, m).

Intermediate 22

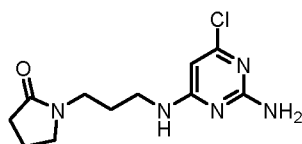
- 6-Chloro-4-N-[2-(4-chlorophenyl)ethyl]pyrimidine-2,4-diamine.



- A mixture of 4,6-dichloropyrimidin-2-amine (0.50 g, 3.05 mmol), 2-(4-chlorophenyl)ethan-1-amine (0.56 mL, 3.96 mmol) and Hünig's base (0.80 mL, 4.57 mmol) in n-butanol (5 mL) was heated in a sealed tube at 95°C overnight. The mixture was concentrated and the crude was taken up in EtOAc (50 mL) and washed with water (3 x 40 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated to give the desired product as a buff solid (0.61 g, 71%). LCMS $[M+H]^+$ 283.

Intermediate 23

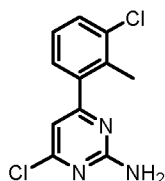
1-{3-[(2-amino-6-chloropyrimidin-4-yl)amino]propyl}pyrrolidin-2-one.



A mixture of 4,6-dichloropyrimidin-2-amine (1.64 g, 10.0 mmol), 1-(3-aminopropyl)pyrrolidin-2-one (1.96 mL, 14.0 mmol) and Hünig's base (2.61 mL, 15.0 mmol) in n-butanol (20 mL) was heated in a sealed tube at 110°C overnight. The mixture was concentrated and the crude was taken up in EtOAc (300 mL) and washed with water (3 x 150 mL). The aqueous layers were combined and extracted with EtOAc (2 x 200 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated to give the desired product as a buff solid (1.63 g, 60%). LCMS [M+H]⁺ 270.

10 Intermediate 24

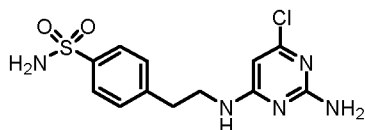
4-chloro-6-(3-chloro-2-methylphenyl)pyrimidin-2-amine.



A stirred mixture of 2-amino-4,6-dichloropyrimidine (0.50 g, 3.1 mmol), 3-chloro-2-methylphenylboronic acid (0.57 g, 3.4 mmol), Na₂CO₃ (1.0 g, 9.8 mmol), palladium tetrakis(triphenylphosphine)palladium (0) (88 mg, 0.076 mmol), dioxane (22 mL) and water (8 mL) were heated in a sealed tube at 90°C for 2 hours. The solvents were removed in vacuo and the remaining solid was added EtOAc (20 mL) and washed with water. The organic phase was dried over MgSO₄ and removed in vacuo. The crude material was purified by flash chromatography (1:4 EtOAc/petroleum ether) to give the desired product as a white solid (365 mg, 47%). LCMS [M+H]⁺ 254; ¹H NMR (400 MHz, DMSO-d₆) δ_H ppm 7.52 - 7.56 (1 H, dd, J₁ = 6.5 Hz, J₂ = 2.5 Hz) 7.30 - 7.33 (2 H, m) 7.26 (2 H, s) 6.79 (1 H, s) 2.32 (3 H, s).

25 Intermediate 25

4-{2-[(2-amino-6-chloropyrimidin-4-yl)amino]ethyl}benzene-1-sulfonamide.

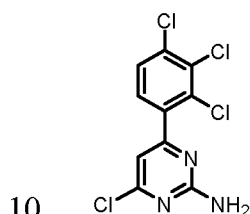


To a suspension of 4,6-dichloropyrimidin-2-amine (800 mg, 4.9 mmol) and 4-(2-aminoethyl)benzenesulfonamide (980 mg, 4.9 mmol) in 2-propanol (10 mL), was added Hünig's base (1.0 mL, 5.7 mmol) and the resulting mixture was heated at

reflux for 15 h. The mixture was then poured into NaHCO₃ (aq) and extracted three times with DCM. The combined organic layers were dried and concentrated and the crude mixture was purified by column chromatography to afford the title compound. LCMS [M+H]⁺ 328; ¹H NMR (400 MHz, CD₃OD) δ_H ppm 7.80 - 7.85 (m, 2 H), 7.41 (d, J=8.6 Hz, 2 H), 5.76 - 5.81 (m, 1 H), 3.54 - 3.64 (m, 2 H), 2.95 (t, J=7.1 Hz, 2 H).

Intermediate 26

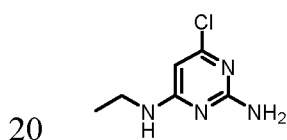
4-chloro-6-(2,3,4-trichlorophenyl)pyrimidin-2-amine.



A mixture of 4,6-dichloropyrimidin-2-amine (82 mg, 0.50 mmol), (2,3,4-trichlorophenyl)-boronic acid (113 mg, 0.50 mmol), potassium carbonate (138 mg, 1.0 mmol) and palladium tetrakis(triphenylphosphine)palladium (0) (14 mg, 0.013 mmol) in 1,4-dioxane/water (8 mL; 4:1) was heated in a sealed tube at 90°C for 2 h. The reaction mixture was run through a plug of silica (EtOAc) and then concentrated and purified by preparative HPLC. LCMS [M+H]⁺ 308.

Intermediate 27

6-chloro-4-N-ethylpyrimidine-2,4-diamine

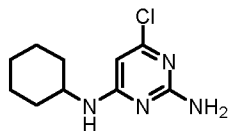


To a solution of 4,6-dichloropyrimidin-2-amine (1 g, 6.09 mmol, 1 eq.) in n-BuOH (18 mL) were added ethaneamine (2M, 3.0 mL, 6.09 mmol, 1 eq.) and Hünig's base (1.17 mL, 6.70 mmol, 1.1 eq.). The reaction mixture was stirred overnight at 95 °C. Ethaneamine (1 eq) was added and the reaction was stirred overnight at 95 °C until complete consumption of starting material (2 additions). The solvent was removed in vacuo. The crude product was taken up in EtOAc and H₂O. The aqueous layer was extracted twice with EtOAc and once with CHCl₃/iPrOH (3:1). The combined organic layers were washed with brine, dried over MgSO₄ and concentrated to afford the desired product as a white solid. LCMS [M+H]⁺ 173; ¹H

NMR (400 MHz, CDCl₃) δ_H 5.76 (1H, s), 4.79 (3H, br s), 3.26 (2H, br s), 1.20 (3H, t, J = 7.2 Hz).

Intermediate 28

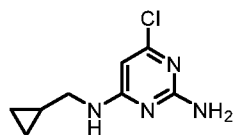
5 6-chloro-4-N-cyclohexylpyrimidine-2,4-diamine.



To a solution of 4,6-dichloropyrimidin-2-amine (1 g, 6.09 mmol, 1 eq.) in n-BuOH (18 mL) were added cyclohexanamine (698 μL, 6.09 mmol, 1 eq.) and Hünig's base (1.17 mL, 6.70 mmol, 1.1 eq.). The reaction mixture was stirred overnight at
 10 95 °C. Cyclohexanamine (1 eq) was added and the reaction was stirred overnight at 95 °C until complete consumption of starting material (2 additions). The solvent was removed in vacuo. The crude product was taken up in EtOAc and H₂O. The aqueous layer was extracted twice with EtOAc and once with CHCl₃/iPrOH (3:1). The combined organic layers were washed with brine, dried over MgSO₄ and
 15 concentrated to afford the desired product as a white solid. LCMS [M+H]⁺ 227; ¹H NMR (400 MHz, CDCl₃) δ_H 5.73 (1H, s), 4.97 (2H, s), 4.79 (1H, br s), 3.45 (1H, br s), 1.97 – 1.92 (2H, m), 1.74 – 1.69 (2H, m), 1.63 – 1.58 (1H, m), 1.39 – 1.32 (2H, m), 1.22 – 1.10 (2H, m).

20 Intermediate 29

6-chloro-4-N-(cyclopropylmethyl)pyrimidine-2,4-diamine.

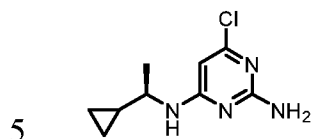


To a solution of 4,6-dichloropyrimidin-2-amine (250 mg, 1.52 mmol, 1 eq.) in n-BuOH (4.5 mL) were added cyclopropylmethanamine (131 μL, 6.09 mmol, 1 eq.) and Hünig's base (292 μL, 6.70 mmol, 1.1 eq.). The reaction mixture was stirred
 25 overnight at 95 °C. The solvent was removed in vacuo. The crude product was taken up in EtOAc and H₂O. The aqueous layer was extracted twice with EtOAc and once with CHCl₃/iPrOH (3:1). The combined organic layers were washed with brine, dried over MgSO₄ and concentrated to afford the desired product as a
 30 white solid. LCMS [M+H]⁺ 199; ¹H NMR (400 MHz, CDCl₃) δ_H 5.75 (1H, s), 4.92 (3H, br s), 3.07 (2H, s), 1.04 – 0.96 (1H, m), 0.55 – 0.49 (2H, m), 0.23 – 0.19 (2H,

m).

Intermediate 30

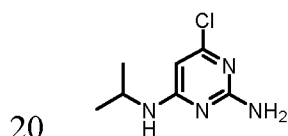
6-chloro-4-N-[(1R)-1-cyclopropylethyl]pyrimidine-2,4-diamine.



To a solution of 4,6-dichloropyrimidin-2-amine (250 mg, 1.52 mmol, 1 eq.) in n-BuOH (4.5 mL) were added (1R)-1-cyclopropylethan-1-amine (141 μ L, 6.09 mmol, 1 eq.) and Hünig's base (292 μ L, 6.70 mmol, 1.1 eq.). The reaction mixture was stirred overnight at 95 °C. The solvent was removed in vacuo. The crude product was taken up in EtOAc and H₂O. The aqueous layer was extracted twice with EtOAc and once with CHCl₃/iPrOH (3:1). The combined organic layers were washed with brine, dried over MgSO₄ and concentrated to afford the desired product as a colourless oil (321 mg, 99%). LCMS [M+H]⁺ 213; ¹H NMR (400 MHz, CDCl₃) δ _H 5.71 (1H, s), 4.97 (2H, s), 4.86 (1H, br s), 3.23 (1H, s), 1.19 (3H, d, J = 6.4 Hz), 0.89 – 0.81 (1H, m), 0.52 – 0.41 (2H, m), 0.31 – 0.25 (1H, m), 0.23 – 0.18 (1H, m).

Intermediate 31

6-chloro-4-N-(propan-2-yl)pyrimidine-2,4-diamine.

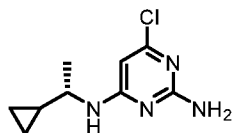


To a solution of 4,6-dichloropyrimidin-2-amine (500 mg, 3.05 mmol, 1 eq.) in n-BuOH (9 mL) were added propan-2-amine (262 μ L, 6.09 mmol, 1 eq.) and Hünig's base (584 μ L, 6.70 mmol, 1.1 eq.). The reaction mixture was stirred overnight at 95 °C. The solvent was removed in vacuo. The crude product was taken up in EtOAc and H₂O. The aqueous layer was extracted twice with EtOAc and once with CHCl₃/iPrOH (3:1). The combined organic layers were washed with brine, dried over MgSO₄ and concentrated to afford the desired product as a white solid (569 mg, 99%). LCMS [M+H]⁺ 187; ¹H NMR (400 MHz, CDCl₃) δ _H 5.74 (1H, s), 4.76 (2H, s), 4.60 (1H, br s), 3.85 (1H, br s), 1.19 (3H, s), 1.18 (3H, s).

30

Intermediate 32

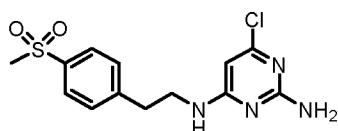
6-chloro-4-N-[(1S)-1-cyclopropylethyl]pyrimidine-2,4-diamine.



To a solution of 4,6-dichloropyrimidin-2-amine (250 mg, 1.52 mmol, 1 eq.) in n-BuOH (4.5 mL) were added (1S)-1-cyclopropylethan-1-amine (141 μ L, 6.09 mmol, 1 eq.) and Hünig's base (292 μ L, 6.70 mmol, 1.1 eq.). The reaction mixture was stirred overnight at 95 °C. The solvent was removed in vacuo. The crude product was taken up in EtOAc and H₂O. The aqueous layer was extracted twice with EtOAc and once with CHCl₃/iPrOH (3:1). The combined organic layers were washed with brine, dried over MgSO₄ and concentrated to afford the desired product as a colourless oil (296 mg, 91%). LCMS [M+H]⁺ 213; ¹H NMR (400 MHz, CDCl₃) δ _H 5.71 (1H, s), 4.99 (2H, s), 4.89 (1H, br s), 3.23 (1H, s), 1.19 (3H, d, J = 6.4 Hz), 0.88 – 0.81 (1H, m), 0.50 – 0.40 (2H, m), 0.31 – 0.25 (1H, m), 0.23 – 0.17 (1H, m).

15 Intermediate 33

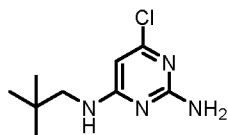
6-chloro-4-N-[2-(4-methanesulfonylphenyl)ethyl]pyrimidine-2,4-diamine.



A mixture of 4,6-dichloropyrimidin-2-amine (500 mg, 3.0 mmol), 2-(4-methylsulfonylphenyl)ethanamine (600 mg, 3.0 mmol) and Hünig's base (0.63 mL, 3.6 mmol) in 2-propanol (10 mL) was heated at reflux for 15 h. The reaction mixture was poured into NaHCO₃ (aq) and extracted three times with DCM. The combined organic layers were dried and concentrated. The crude mixture was purified by column chromatography which afforded the title compound. LCMS [M+H]⁺ 327; ¹H NMR (400 MHz, CDCl₃) δ ppm 7.90 (d, J=8.3 Hz, 2 H), 7.41 (d, J=8.3 Hz, 2 H), 5.77 (s, 1 H), 4.80 - 4.89 (m, 2 H), 4.69 - 4.79 (m, 1 H), 3.56 - 3.67 (m, 2 H), 3.07 (s, 3 H), 3.00 (t, J=6.8 Hz, 2 H).

Intermediate 34

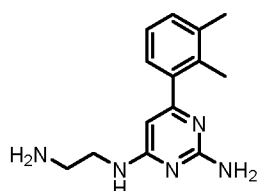
6-chloro-4-N-(2,2-dimethylpropyl)pyrimidine-2,4-diamine.



To a solution of 4,6-dichloropyrimidin-2-amine (250 mg, 1.52 mmol, 1 eq.) in n-BuOH (9 mL) were added 2,2-dimethylpropan-1-amine (6.09 mmol, 1 eq.) and Hünig's base (292 μ L, 6.70 mmol, 1.1 eq.). The reaction mixture was stirred overnight at 95 °C. The solvent was removed in vacuo. The crude product was taken up in EtOAc and H₂O. The aqueous layer was extracted twice with EtOAc and once with CHCl₃/iPrOH (3:1). The combined organic layers were washed with brine, dried over MgSO₄ and concentrated to afford the desired product as a white solid. LCMS [M+H]⁺ 215; ¹H NMR (400 MHz, CDCl₃) δ _H 5.94 (1H, s), 3.24 (2H, br s), 0.98 (9H, s).

Intermediate 35

4-N-(2-aminoethyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.



Step 1: To a suspension of 4,6-dichloropyrimidin-2-amine (500 mg, 3.05 mmol) and Hünig's base (0.80 mL) in 2-propanol (3.0 mL) was added tert-butyl N-(2-aminoethyl)carbamate (586 mg, 3.66 mmol) and the mixture was stirred at 150 °C for 15 min. The crude mixture was poured into NaHCO₃ (aq) and extracted three times with DCM. The combined organic layers were dried and concentrated. Purification by column chromatography (0→10% MeOH in DCM) afforded tert-butyl N-[2-[(2-amino-6-chloro-pyrimidin-4-yl)amino]ethyl]carbamate (850 mg, 2.95 mmol).

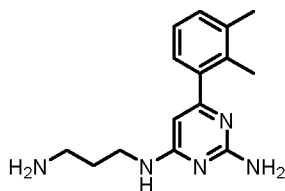
Step 2: tert-Butyl N-[2-[(2-amino-6-chloro-pyrimidin-4-yl)amino]ethyl]carbamate (850 mg, 2.95 mmol), (2,3-dimethylphenyl)boronic acid (532 mg, 3.55 mmol), palladium tetrakis(triphenylphosphine)palladium (0) (34 mg, 0.030 mmol), and K₂CO₃ (1020 mg, 7.39 mmol) were suspended in 1,4-dioxane (10 mL) and H₂O (2.0 mL). The vial was flushed with nitrogen and the resulting mixture was stirred at 90 °C for 16 h. The crude mixture was poured into NaHCO₃ (aq) and extracted three times with DCM. The combined organic layers were dried and

concentrated. Purification by column chromatography (0→10% MeOH in DCM) afforded tert-butyl N-[2-[[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino]ethyl]carbamate (770 mg, 2.15 mmol).

Step 3: tert-Butyl N-[2-[[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino]ethyl]carbamate (770 mg, 2.15 mmol) was dissolved in TFA (6 mL) and the resulting mixture was stirred for 1 h at rt, after which the TFA was distilled off. Purification by column chromatography (5→30% MeOH [containing 1 v/v% NH₄OH] in DCM) afforded 4-N-(2-aminoethyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine (500 mg, 1.94 mmol). LCMS [M+H]⁺ 258.

10 Intermediate 36

4-N-(3-aminopropyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.



Step 1: A vial was charged with 4,6-dichloropyrimidin-2-amine (500 mg, 3.0 mmol) and tert-butyl N-(2-aminopropyl)carbamate (640 mg, 3.7 mmol). Then 2-propanol (3.0 ml) and Hünig's base (0.80 ml) were added and the resulting mixture was heated at 150 °C using microwave irradiation for 15 min. The mixture was then concentrated and purified by column chromatography (2→10% MeOH in DCM) to afford tert-butyl N-[3-[(2-amino-6-chloro-pyrimidin-4-yl)amino]propyl]carbamate (788 mg, 2.61 mmol).

20

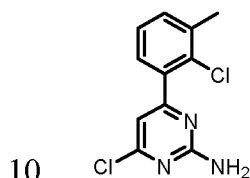
Step 2: tert-Butyl N-[3-[(2-amino-6-chloro-pyrimidin-4-yl)amino]propyl]carbamate (790 mg, 2.6 mmol), (2,3-dimethylphenyl)boronic acid (470 mg, 3.1 mmol), palladium tetrakis(triphenylphosphine)palladium (0) (60 mg, 0.050 mmol), and K₂CO₃ (720 mg 5.2 mmol) were suspended in 1,4-dioxane (6.0 ml) and H₂O (1.5 ml). The resulting mixture was heated at 90 °C for 16 h and then poured into H₂O and extracted three times with DCM. The combined organic layers were dried and concentrated. Purification by column chromatography (1→10% MeOH in DCM) afforded tert-butyl N-[3-[[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino]propyl]carbamate (800 mg, 2.1 mmol).

30

Step 3: tert-Butyl N-[3-[[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino]propyl]carbamate (800 mg, 2.1 mmol) was dissolved in TFA and heated at reflux for 1 h. The TFA was evaporated and the crude residue was purified by column chromatography (2→30% MeOH [containing 1 v/v% NH₄OH] in DCM) to afford 4-N-(3-aminopropyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine (540 mg, 2.0 mmol). LCMS [M+H]⁺ 272.

Intermediate 37

4-chloro-6-(2-chloro-3-methylphenyl)pyrimidin-2-amine.

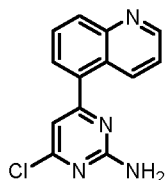


To a suspension of 4,6-dichloropyrimidin-2-amine (250 mg, 1.52 mmol, 1 eq) in dioxane/H₂O (5 mL, 4:1) was added (2-chloro-3-methylphenyl)boronic acid (260 mg, 1.52 mmol, 1 eq) followed by potassium carbonate (421 mg, 3.05 mmol, 2 eq) and Pd(PPh₃)₄ (44 mg, 0.04 mmol, 0.025 eq). The resulting mixture was stirred at 90 °C for 12 hrs. The solvent was removed in vacuo. The residue was taken up in DMF and purified by preparative to afford the desired product as an off-white solid (166 mg, 43%). LCMS [M+H]⁺ 254; ¹H NMR (400 MHz, CDCl₃) δ_H 7.32 – 7.28 (2H, m), 7.25 – 7.21 (1H, m), 6.92 (1H, s), 5.31 (2H, br s), 2.42 (3H, s).

20

Intermediate 38

4-chloro-6-(quinolin-5-yl)pyrimidin-2-amine.



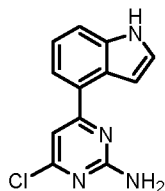
To a suspension of 4,6-dichloropyrimidin-2-amine (150 mg, 0.91 mmol, 1 eq) in dioxane/H₂O (5 mL, 4:1) was added (quinolin-5-yl)boronic acid (158 mg, 0.91 mmol, 1 eq) followed by potassium carbonate (253 mg, 1.83 mmol, 2 eq) and Pd(PPh₃)₄ (26 mg, 0.020 mmol, 0.025 eq). The resulting mixture was stirred at 90 °C for 12 hrs. The solvent was removed in vacuo and the residue was purified by preparative HPLC to afford the desired product as a yellow solid (63 mg, 27%).

30 LCMS [M+H]⁺ 257; ¹H NMR (400 MHz, CDCl₃) δ_H 9.21 – 9.19 (2H, m), 8.62 (1H,

d, J = 8.8 Hz), 8.30 – 7.99 (1H, m), 7.92 (1H, dd, J = 7.2 and 0.8 Hz), 7.81 – 7.77 (1H, m), 6.98 (1H, s), 5.40 (2H, br s).

Intermediate 39

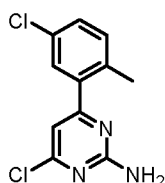
5 4-chloro-6-(1H-indol-4-yl)pyrimidin-2-amine.



To a suspension of 4,6-dichloropyrimidin-2-amine (150 mg, 0.91 mmol, 1 eq) in dioxane/H₂O (5 mL, 4:1) was added (1H-indol-4-yl)boronic acid (147 mg, 0.91 mmol, 1 eq) followed by potassium carbonate (253 mg, 1.83 mmol, 2 eq) and
 10 Pd(PPh₃)₄ (26 mg, 0.02 mmol, 0.025 eq). The resulting mixture was stirred at 90 °C for 12 hrs. The solvent was removed in vacuo and the residue was purified by preparative HPLC to afford the desired product as a yellow solid (111 mg, 50%).
 LCMS [M+H]⁺ 245; ¹H NMR (400 MHz, CDCl₃) δ_H 8.45 (1H, br s), 7.57 (1H, d, J = 7.2 Hz), 7.51 (1H, d, J = 8.0 Hz), 7.35 (1H, t, J = 4.0 Hz), 7.27 (1H, d, J = 7.6 Hz),
 15 7.18 (1H, s), 7.00 – 6.99 (1H, m), 5.90 (2H, br s).

Intermediate 40

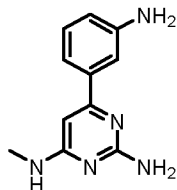
4-chloro-6-(5-chloro-2-methylphenyl)pyrimidin-2-amine.



To a suspension of 4,6-dichloropyrimidin-2-amine (150 mg, 0.91 mmol, 1 eq) in dioxane/H₂O (5 mL, 4:1) was added (5-chloro-2-methylphenyl)boronic acid (155 mg, 0.91 mmol, 1 eq) followed by potassium carbonate (253 mg, 1.83 mmol, 2 eq) and Pd(PPh₃)₄ (26 mg, 0.02 mmol, 0.025 eq). The resulting mixture was stirred at 90 °C for 12 hrs. The solvent was removed in vacuo and the residue
 20 was purified by preparative HPLC to afford the desired product as an off-white solid (98 mg, 42%). LCMS [M+H]⁺ 254; ¹H NMR (400 MHz, CDCl₃) δ_H 7.35 (1H, d, J = 2.0 Hz), 7.28 (1H, dd, J = 8.4 and 2.4 Hz), 7.18 (1H, d, J = 8.4 Hz), 6.72 (1H, s), 5.30 (2H, br s), 2.34 (3H, s).

Intermediate 41

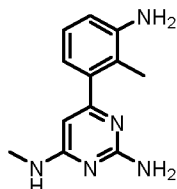
6-(3-aminophenyl)-4-N-methylpyrimidine-2,4-diamine.



5 Tetrakis(triphenylphosphine)palladium (0) (5 mol%) was added to a stirred mixture of 6-chloro-4-N-methylpyrimidine-2,4-diamine (1.00 mmol), (3-aminophenyl)boronic acid (1.3 eq.), sodium carbonate (3.2 eq.), 1,4-dioxane (4 mL) and water (1 mL) in a tube. The tube was sealed and the reaction was heated at 90°C for 5 h and then concentrated. The crude material was taken up in ethyl acetate and washed with water. The organic phase was dried over
10 magnesium sulfate, concentrated and purified by flash chromatography (0→15 % MeOH in DCM) to give the title compound. LCMS [M+H]⁺ 216.

Intermediate 42

6-(3-amino-2-methylphenyl)-4-N-methylpyrimidine-2,4-diamine.

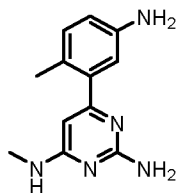


15 Tetrakis(triphenylphosphine)palladium (0) (5 mol%) was added to a stirred mixture of 6-chloro-4-N-methylpyrimidine-2,4-diamine (3.00 mmol), (3-amino-2-methylphenyl)boronic acid (1.3 eq.), sodium carbonate (3.2 eq.), 1,4-dioxane (4 mL) and water (1 mL). The tube was sealed and the reaction was heated at 90°C
20 for 5 h. The mixture was concentrated and purified by column chromatography (13% MeOH in DCM) to give the title compound. LCMS [M+H]⁺ 230; ¹H NMR (400 MHz, DMSO-d₆) δ ppm 6.88 (1 H, t, J=7.71 Hz), 6.71 - 6.81 (1 H, m), 6.61 (1 H, dd, J=7.96, 1.14 Hz), 6.44 (1 H, dd, J=7.58, 1.01 Hz), 5.90 (2 H, br. s.), 5.64 (1 H, s), 4.83 (2 H, s), 2.75 (3 H, d, J=4.55 Hz), 1.98 (3 H, s).

25

Intermediate 43

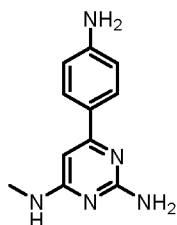
6-(5-amino-2-methylphenyl)-4-N-methylpyrimidine-2,4-diamine.



Tetrakis(triphenylphosphine)palladium (0) (5 mol%) was added to a stirred mixture of 6-chloro-4-N-methylpyrimidine-2,4-diamine (3.0 mmol), (5-amino-2-methylphenyl)boronic acid (1.3 eq.), sodium carbonate (3.2 eq.), 1,4-dioxane (4 mL) and water (1 mL) in a tube. The tube was sealed and the reaction was heated at 90°C for 5 h. The mixture was concentrated and purified by column chromatography (13 % MeOH in DCM) to give the title compound. LCMS $[M+H]^+$ 230.

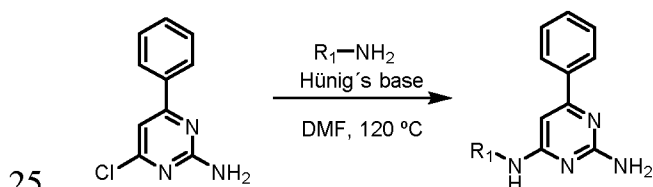
10 Intermediate 44

6-(4-aminophenyl)-4-N-methylpyrimidine-2,4-diamine.



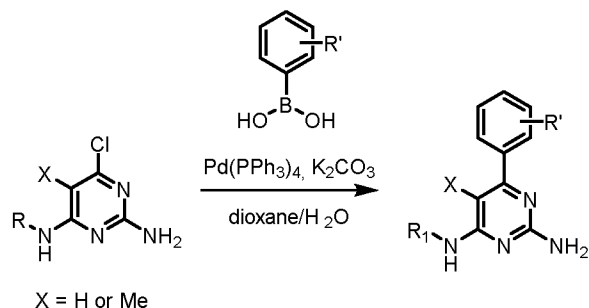
Tetrakis(triphenylphosphine)palladium (0) (5 mol%) was added to a stirred mixture of 6-chloro-4-N-methylpyrimidine-2,4-diamine (1.0 mmol), 4-(tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.3 eq.), sodium carbonate (3.2 eq.), 1,4-dioxane (4 mL) and water (1 mL) in a tube. The tube was sealed and the reaction was heated at 90°C for 5 h and then concentrated. The crude material was taken up in ethyl acetate and washed with water. The organic phase was dried over magnesium sulfate, concentrated and purified by flash chromatography (0→15 % MeOH/DCM) to give the title compound. LCMS $[M+H]^+$ 216; ^1H NMR (400 MHz, CDCl_3) δ_{H} ppm 7.64 (2 H, d, $J=8.53$ Hz), 6.50 - 6.62 (3 H, m), 6.03 (1 H, s), 5.74 (2 H, s), 5.37 (2 H, s), 2.76 (3 H, d, $J=4.77$ Hz).

General procedures



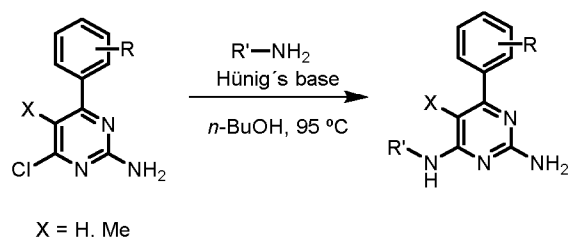
General Procedure 1: To a mixture of 4-chloro-6-phenylpyrimidin-2-amine (1 equiv.) is added Hünig's base (3.4 equiv.) and an appropriate amine (1.6 equiv.) in DMF (500 μ L). The mixture is heated at 120 °C overnight. The crude mixture is purified by preparative HPLC to afford the desired product.

5

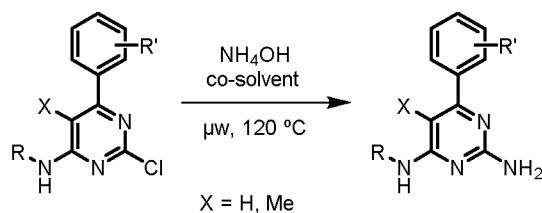


General Procedure 2: To a mixture of a suitable chloropyrimidine derivative (1 equiv.) in 1,4-dioxane/water (4:1) is added the appropriate boronic acid (or boronic ester) derivative (1.3 equiv.), K_2CO_3 (2 equiv.) and $\text{Pd}(\text{PPh}_3)_4$ (0.1 equiv.).

10 The mixture is heated at 95 °C overnight or in a microwave reactor until the reaction is complete as shown by LCMS. The crude mixture is purified by preparative HPLC to afford the desired product.



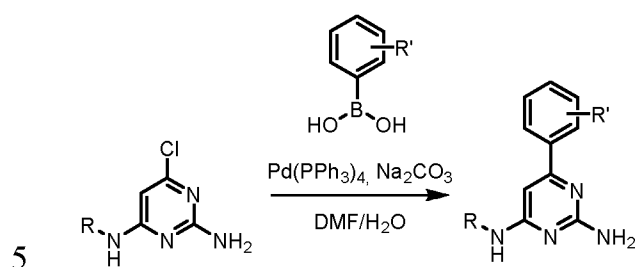
15 *General Procedure 3:* To a mixture of a suitable chloropyrimidine derivative (1 equiv.) is added Hünig's base (3.4 equiv.) and an appropriate amine (1.6 equiv.) in *n*-BuOH (500 μ L). The mixture is heated at 95 °C overnight. The crude mixture was purified by preparative HPLC to afford the desired product.



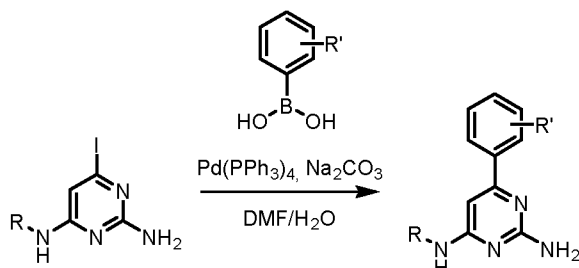
20

General Procedure 4: A solution of an appropriate chloropyrimidine derivative (1 equiv.) in ammonium hydroxide (25% aq.) is heated in the microwave at 120 °C

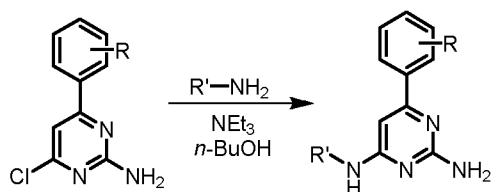
until completion of the reaction as monitored by LCMS. The solvent is then evaporated and the product is dried under vacuum. Further purification by preparative HPLC is performed when required.



General Procedure 5: To a mixture of a suitable chloropyrimidine derivative (1 equiv.) in DMF/water (9:1) is added the appropriate boronic acid (or boronic ester) derivative (1.1 equiv.), Na₂CO₃ (2 equiv.) and Pd(PPh₃)₄ (0.1 equiv.). The mixture is heated at 120 °C overnight or in the microwave until the reaction is complete as shown by LCMS. The crude mixture is then purified by preparative HPLC to afford the desired product.

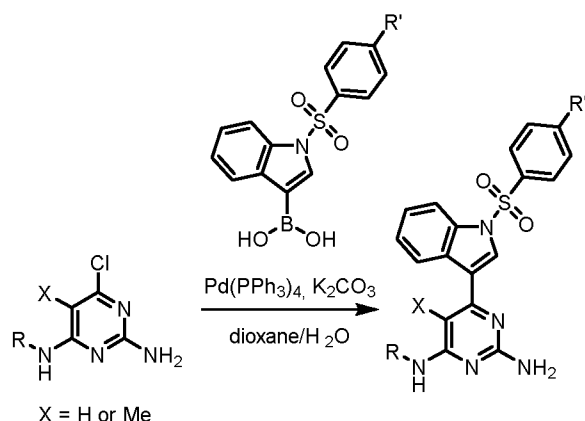


General Procedure 6: To a mixture of a suitable iodopyrimidine derivative (1 equiv.) in DMF/water (20:1) is added the appropriate boronic acid (or boronic ester) derivative (1.3 equiv.), Na₂CO₃ (2 equiv.) and Pd(PPh₃)₄ (0.1 equiv.). The mixture is heated at 120 °C overnight or in a microwave reactor until the reaction is complete as shown by LCMS. The crude mixture is then purified by HPLC to afford the desired product.

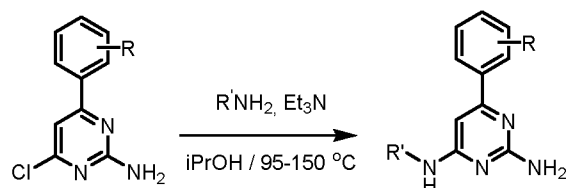


General procedure 7: A mixture of a suitable 6-aryl-4-chloropyrimidin-2-amine (1 equiv.), a suitable amine (1.5 equiv.) and triethylamine (2 equiv.) in *n*-butanol (1.5

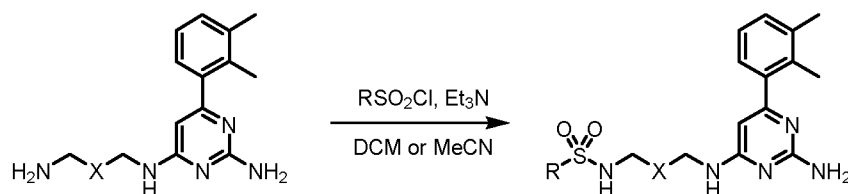
mL) is heated in a sealed tube at 95 °C overnight. Concentrated and purified by preparative HPLC to give the desired product.



- 5 *General Procedure 8:* To a mixture of a suitable 4-chloropyrimidin-2-amine (1 equiv.) in 1,4-dioxane/water (4:1) is added the desired boronic acid (or boronic ester) (1.3 equiv.), K_2CO_3 (2 equiv.) and $Pd(PPh_3)_4$ (0.1 equiv.). The mixture is heated at 95 °C overnight or in a microwave until the reaction is complete as shown by LCMS. The crude mixture is purified by HPLC to afford the desired
- 10 product.

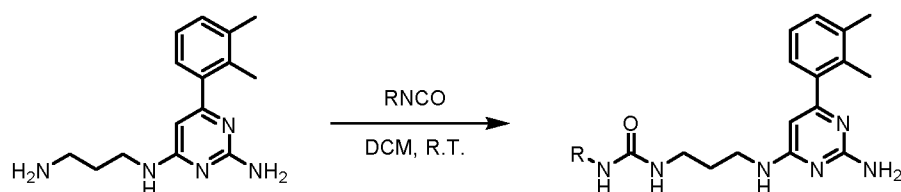


- General procedure 9: A mixture of a suitable amine (1 equiv.), and a suitable chloropyrimidine derivative (1.2 equiv.) and triethylamine (1.5 equiv.) in 2-propanol (1.0 mL) is heated in a sealed tube at 95 °C overnight or at 150 °C for
- 15 15 min in a microwave reactor. The reaction mixture is then concentrated and purified by preparative HPLC or by silica gel chromatography.

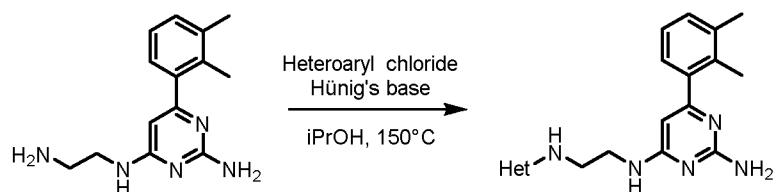


X = CH₂, CH₂CH₂, CH(CH₃)₂ or a bond

General procedure 10: A mixture of an 4-N-(aminoalkyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine (1.0 equiv.), a suitable sulfonyl chloride (1.2 equiv.), and triethylamine (1.5 equiv.) in DCM or MeCN (1.0 mL) is stirred in a sealed tube at rt or 50 °C. After completion the crude mixture is concentrated and purified by preparative HPLC or by silica gel chromatography.



General procedure 11: A mixture of 4-N-(3-aminopropyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine (1.0 eq.) and the corresponding isocyanate (1.05 eq.) is dissolved in DCM. The resulting reaction mixture is stirred at rt until completion according to LCMS. The mixture is then concentrated and purified by preparative HPLC or by silica gel chromatography.



General procedure 12: A mixture of 4-N-(2-aminoethyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine (1.0 equiv.) and the corresponding heteroaryl chloride (1.5 equiv.), and Hunig's base (1.5 equiv.) in 2-propanol (0.5 mL) is stirred in a sealed tube at 150 °C in a microwave reactor for 30 min. The crude mixture is then concentrated and purified by preparative HPLC or by silica gel chromatography.

EXAMPLES

The utility of the compounds of the present invention can be illustrated, for example, by their activity in vitro in the cancer cell clonogenic and/or viability assay described below. The link between activity in tumor cell clonogenic assay and anti-tumor activity in the clinical setting has been well established in the art (e.g. see ref Silverstini et al Stem Cells 1993, 11(6), 258-35).

Example 1

4-N-cyclohexyl-6-phenylpyrimidine-2,4-diamine.

Prepared according to general procedure 1 from cyclohexanamine and 4-chloro-6-phenylpyrimidin-2-amine. LCMS $[M+H]^+$ 269; ^1H NMR (400 MHz, DMSO- d_6) δ_H

5 8.79 – 8.61 (1H, m), 7.78 – 7.67 (2H, m), 7.66 – 7.55 (3H, m), 6.33 (1H, s), 4.05 – 3.85 (1H, m), 2.00 – 1.83 (2H, m), 1.80 – 1.70 (2H, m), 1.41 – 1.10 (6H, m).

Example 2

4-N-ethyl-6-phenylpyrimidine-2,4-diamine.

10 Prepared according to general procedure 1 from ethanamine and 4-chloro-6-phenylpyrimidin-2-amine. LCMS $[M+H]^+$ 215; ^1H NMR (400 MHz, DMSO- d_6) δ_H 8.82 (1H, s), 7.74 – 7.71 (2H, m), 7.67 – 7.57 (3H, m), 6.33 (1H, s), 3.53 – 3.41 (2H, m), 1.18 (3H, t, J = 7.1 Hz).

15 Example 3

4-N-(3-ethoxypropyl)-6-phenylpyrimidine-2,4-diamine.

Prepared according to general procedure 1 from 3-ethoxypropan-1-amine and 4-chloro-6-phenylpyrimidin-2-amine. LCMS $[M+H]^+$ 273; ^1H NMR (400 MHz, DMSO- d_6) δ_H 8.82 (1H, s), 7.74 – 7.71 (2H, m), 7.63 – 7.59 (3H, m), 6.37 (1H, s), 3.45 –

20 3.41 (6H, m), 1.80 (2H, q, J = 6.5 Hz), 1.11 (3H, t, J = 6.5 Hz).

Example 4

6-phenyl-4-N-propylpyrimidine-2,4-diamine.

Prepared according to general procedure 2 from phenylboronic acid and 6-chloro-

25 4-N-propylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 229.

Example 5

6-(4-methanesulfonylphenyl)-4-N-propylpyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (4-methane-

30 sulfonylphenyl)boronic acid and 6-chloro-4-N-propylpyrimidine-2,4-diamine.

LCMS $[M+H]^+$ 307; ^1H NMR (400 MHz, DMSO- d_6) δ_H 8.21 – 8.11 (2H, m), 8.05 – 7.92 (2H, m), 6.42 (1H, s), 3.50 – 3.40 (2H, m), 3.31 (3H, s), 1.68 – 1.51 (2H, m), 0.94 (3H, t, J = 7.1 Hz).

35 Example 6

4-N-(cyclopropylmethyl)-6-phenylpyrimidine-2,4-diamine.

Prepared according to general procedure 1 from cyclopropylmethanamine and 4-chloro-6-phenylpyrimidin-2-amine. LCMS $[M+H]^+$ 241; ^1H NMR (400 MHz, DMSO- d_6) δ_H 8.92 (1H, s), 7.83 – 7.50 (5H, m), 6.39 (1H, s), 3.33 – 3.20 (2H, m),
5 1.15 – 0.95 (1H, m), 0.51 (1H, d, J = 5.8 Hz), 0.27 (1H, d, J = 5.8 Hz).

Example 7

4-N-(oxan-4-yl)-6-phenylpyrimidine-2,4-diamine.

Prepared according to general procedure 1 from oxan-4-amine and 4-chloro-6-phenylpyrimidin-2-amine. LCMS $[M+H]^+$ 271.
10

Example 8

4-N-(furan-2-ylmethyl)-6-phenylpyrimidine-2,4-diamine.

Prepared according to general procedure 1 from furan-2-ylmethanamine and 4-chloro-6-phenylpyrimidin-2-amine. LCMS $[M+H]^+$ 267.
15

Example 9

4-N-(pentan-3-yl)-6-phenylpyrimidine-2,4-diamine.

Prepared according to general procedure 1 from pentan-3-amine and 4-chloro-6-phenylpyrimidin-2-amine. LCMS $[M+H]^+$ 257.
20

Example 10

6-phenyl-4-N-(propan-2-yl)pyrimidine-2,4-diamine.

Prepared according to general procedure 1 from propan-2-amine and 4-chloro-6-phenylpyrimidin-2-amine. LCMS $[M+H]^+$ 229.
25

Example 11

4-N-benzyl-6-phenylpyrimidine-2,4-diamine.

Prepared according to general procedure 1 from phenylmethanamine and 4-chloro-6-phenylpyrimidin-2-amine. LCMS $[M+H]^+$ 277; ^1H NMR (400 MHz, DMSO- d_6) δ_H 7.92 – 7.84 (2H, m), 7.48 – 7.40 (4H, m), 7.37 – 7.27 (4H, m), 7.27 – 7.20 (1H, m), 6.29 (1H, s), 6.06 (2H, s), 4.54 (2H, d, J = 5.9 Hz).
30

Example 12

35 4-N-[2-(morpholin-4-yl)ethyl]-6-phenylpyrimidine-2,4-diamine.

Prepared according to general procedure 1 from 2-(morpholin-4-yl)ethan-1-amine and 4-chloro-6-phenylpyrimidin-2-amine. LCMS $[M+H]^+$ 300.

Example 13

5 6-(4-chlorophenyl)-4-N-cyclopropylpyrimidine-2,4-diamine.

Prepared according to general procedure 1 from cyclopropanamine and 4-chloro-6-phenylpyrimidin-2-amine. LCMS $[M+H]^+$ 261.

Example 14

10 4-N-tert-butyl-6-(4-chlorophenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (4-chlorophenyl)boronic acid and 4-N-tert-butyl-6-chloropyrimidine-2,4-diamine. LCMS $[M+H]^+$ 277; ^1H NMR (400 MHz, DMSO- d_6) δ_H 8.38 (1H, s), 7.75 – 7.66 (4H, m), 6.38 (1H, s), 1.46 (9H, s).

15

Example 15

6-(4-chlorophenyl)-4-N-(oxan-4-yl)pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (4-chlorophenyl)boronic acid and 6-chloro-4-N-(oxan-4-yl)pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 305.

20

Example 16

4-N-cyclopropyl-6-[3-(trifluoromethyl)phenyl]pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from [3-(trifluoromethyl)phenyl]-boronic acid and 6-chloro-4-N-cyclopropylpyrimidine-2,4-diamine. LCMS $[M+H]^+$

25 295.

Example 17

4-N-tert-butyl-6-(4-methoxyphenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (4-methoxyphenyl)boronic acid and 4-N-tert-butyl-6-chloropyrimidine-2,4-diamine. LCMS $[M+H]^+$ 273; ^1H NMR (400 MHz, DMSO- d_6) δ_H 7.65 (2H, d, J = 9.4 Hz), 7.15 (2H, d, J = 9.4 Hz), 6.35 (1H, s), 3.85 (3H, s), 1.45 (9H, s).

Example 18

35 4-N-cyclopropyl-6-(4-methoxyphenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (4-methoxyphenyl)boronic acid and 6-chloro-4-N-cyclopropylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 257; ^1H NMR (400 MHz, DMSO- d_6) δ_H 7.79 – 7.72 (2H, m), 7.17 – 7.15 (2H, m), 6.24 (1H, s), 3.85 (4H, s), 0.83 – 0.81 (2H, m), 0.62 – 0.60 (2H, m).

5

Example 19

6-(3-chlorophenyl)-4-N-cyclopropylpyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (3-chlorophenyl)boronic acid and 6-chloro-4-N-cyclopropylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 261; ^1H NMR (400 MHz, CD_3OD) δ_H 7.78 – 7.76 (1H, m), 7.64 – 7.57 (3H, m), 6.27 (1H, s), 0.89 – 0.87 (2H, m), 0.70 – 0.63 (3H, m).

10

Example 20

4-N-tert-butyl-6-[3-(trifluoromethyl)phenyl]pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from [3-(trifluoromethyl)phenyl]boronic acid and 4-N-tert-butyl-6-chloropyrimidine-2,4-diamine. LCMS $[M+H]^+$ 311.

15

Example 21

6-(3-chlorophenyl)-4-N-(oxan-4-yl)pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (3-chlorophenyl)boronic acid and 6-chloro-4-N-(oxan-4-yl)pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 305; ^1H NMR (400 MHz, CD_3OD) δ_H 7.78 – 7.76 (1H, m), 7.65 – 7.63 (2H, m), 7.59 – 7.57 (1H, m), 6.30 (1H, s), 4.30 – 4.28 (1H, m), 4.02 – 3.98 (2H, m), 3.53 – 3.51 (2H, m), 2.01 – 2.00 (2H, m), 1.65 – 1.63 (2H, m).

25

Example 22

4-N-tert-butyl-6-(3-chlorophenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (3-chlorophenyl)boronic acid and 4-N-tert-butyl-6-chloropyrimidine-2,4-diamine. LCMS $[M+H]^+$ 277; ^1H NMR (400 MHz, CD_3OD) δ_H 7.75 – 7.73 (1H, m), 7.65 – 7.62 (2H, m), 7.59 – 7.55 (2H, m), 1.52 (9H, s).

30

Example 23

4-N-methyl-6-[1-(4-methylbenzenesulfonyl)-1H-indol-3-yl]pyrimidine-2,4-diamine.

35

Prepared according to general procedure 8 from [1-(4-methylbenzenesulfonyl)-1H-indol-3-yl]boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS [M+H]⁺ 394; ¹H NMR (400 MHz, CD₃OD) δ_H 8.36 (1H, s), 8.07 (1H, d, J = 8.3 Hz), 7.93 (2H, d, J = 8.3 Hz), 7.83 (1H, d, J = 7.9 Hz), 7.51 – 7.44 (1H, m), 7.43 – 7.31 (3H, m), 6.46 (1H, s), 3.04 (3H, s), 2.37 (3H, s).

Example 24

6-(2,3-dichlorophenyl)-4-N-(2,2,2-trifluoroethyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (2,3-dichlorophenyl)boronic acid and 6-chloro-4-N-(2,2,2-trifluoroethyl)pyrimidine-2,4-diamine. LCMS [M+H]⁺ 337.

Example 25

6-(3-chlorophenyl)-4-N-(2,2,2-trifluoroethyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (3-chlorophenyl)boronic acid and 6-chloro-4-N-(2,2,2-trifluoroethyl)pyrimidine-2,4-diamine. LCMS [M+H]⁺ 303.

Example 26

6-[1-(benzenesulfonyl)-1H-indol-3-yl]-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 8 from [1-(benzenesulfonyl)-1H-indol-3-yl]boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS [M+H]⁺ 380; ¹H NMR (400 MHz, DMSO-d₆) δ_H 8.43 – 8.25 (2H, m), 8.10 – 8.03 (2H, m), 8.01 – 7.95 (1H, m), 7.77 – 7.68 (1H, m), 7.66 – 7.56 (2H, m), 7.46 – 7.26 (2H, m), 6.74 (1H, br s), 6.32 (1H, s), 6.02 (2H, s), 2.81 (3H, d, J = 5.0 Hz).

Example 27

4-N-cyclopropyl-6-[1-(4-methylbenzenesulfonyl)-1H-indol-3-yl]pyrimidine-2,4-diamine.

Prepared according to general procedure 8 from [1-(4-methylbenzenesulfonyl)-1H-indol-3-yl]boronic acid and 6-chloro-4-N-cyclopropylpyrimidine-2,4-diamine.

LCMS [M+H]⁺ 420; ¹H NMR (400 MHz, CD₃OD) δ_H 8.14 (1H, s), 8.07 (1H, d, J = 7.9 Hz), 8.01 (1H, d, J = 8.2 Hz), 7.86 (2H, d, J = 8.2 Hz), 7.43 – 7.23 (4H, m), 6.43 (1H, s), 2.65 (1H, s), 2.34 (3H, s), 0.88 – 0.74 (2H, m), 0.65 – 0.48 (2H, m).

Example 28

6-[1-(benzenesulfonyl)-1H-indol-3-yl]-4-N-cyclopropylpyrimidine-2,4-diamine.

Prepared according to general procedure 8 from [1-(benzenesulfonyl)-1H-indol-3-yl]boronic acid and 6-chloro-4-N-cyclopropylpyrimidine-2,4-diamine. LCMS

[M+H]⁺ 406; ¹H NMR (400 MHz, CD₃OD) δ_H 8.16 (1H, s), 8.10 – 7.98 (4H, m), 7.66 – 7.58 (1H, m), 7.56 – 7.46 (2H, m), 7.43 – 7.25 (2H, m), 6.43 (1H, s), 2.66
5 (1H, s), 0.84 – 0.81 (2H, m), 0.58 – 0.55 (2H, m).

Example 29

6-[1-(benzenesulfonyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-4-N-methylpyrimidine-2,4-diamine.

- 10 Prepared according to general procedure 8 from [1-(benzenesulfonyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS [M+H]⁺ 381; ¹H NMR (400 MHz, CD₃OD) δ_H 8.55 (1H, d, J = 8.2 Hz), 8.41 – 8.30 (2H, m), 8.22 – 8.11 (2H, m), 7.71 – 7.61 (1H, m), 7.57 – 7.50 (2H, m), 7.37 – 7.28 (1H, m), 6.27 (1H, s), 2.92 (3H, s).

15

Example 30

6-[1-(benzenesulfonyl)-1H-indol-4-yl]-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 8 from [1-(benzenesulfonyl)-1H-indol-4-yl]boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS [M+H]⁺ 380; ¹H NMR (400 MHz, CD₃OD) δ_H 8.08 (1H, d, J = 8.2 Hz), 7.97 – 7.89 (2H, m), 7.73 (1H, d, J = 3.8 Hz), 7.65 – 7.56 (1H, m), 7.53 – 7.45 (3H, m), 7.39 (1H, t, J = 8.2 Hz), 7.10 (1H, d, J = 3.8 Hz), 6.10 (1H, s), 2.89 (3H, s).

25 Example 31

6-[1-(benzenesulfonyl)-1H-indol-5-yl]-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 8 from [1-(benzenesulfonyl)-1H-indol-5-yl]boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS [M+H]⁺

380; ¹H NMR (400 MHz, CD₃OD) δ_H 8.07 – 7.99 (2H, m), 7.98 – 7.89 (2H, m),
30 7.83 – 7.74 (1H, m), 7.71 (1H, d, J = 4.0 Hz), 7.64 – 7.55 (1H, m), 7.54 – 7.45 (2H, m), 6.80 (1H, d, J = 4.0 Hz), 6.21 (1H, s), 2.90 (3H, s).

Example 32

6-(2-methoxyphenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (2-methoxyphenyl)boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 231; ^1H NMR (400 MHz, CD_3OD) δ_H 7.50 (1H, dd, $J = 7.5$ and 1.7 Hz), 7.41 – 7.36 (1H, m), 7.08 (1H, d, $J = 8.3$ Hz), 7.01 (1H, td, $J = 7.5$ and 1.0 Hz), 6.17 (1H, s), 3.84 (3H, s),
5 2.89 (3H, s).

Example 33

6-(4-methoxyphenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (4-methoxyphenyl)boronic acid
10 and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 231.

Example 34

6-[3,5-bis(trifluoromethyl)phenyl]-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 2 from [3,5-
15 bis(trifluoromethyl)phenyl]boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 337; ^1H NMR (400 MHz, CD_3OD) δ_H 8.31 (2H, s), 8.17 (1H, s), 7.55 – 7.20 (3H, br s), 6.45 (1H, s), 3.02 (3H, s).

Example 35

20 6-(isoquinolin-4-yl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (isoquinolin-4-yl)boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 252; ^1H NMR (400 MHz, CD_3OD) δ_H 9.17 (1H, s), 8.78 (1H, s), 8.17 (1H, d, $J = 8.4$ Hz), 8.12 (1H, d, $J = 8.1$ Hz), 7.98 – 7.94 (1H, m), 7.80 – 7.77 (1H, m), 6.54 (1H, s), 3.10 (3H, s).

25

Example 36

4-N-methyl-6-[4-(trifluoromethyl)phenyl]pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from [4-(trifluoromethyl)phenyl]boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-
30 diamine. LCMS $[M+H]^+$ 269; ^1H NMR (400 MHz, CD_3OD) δ_H 7.93 – 7.87 (4H, m), 6.38 (1H, s), 3.04 (3H, s).

Example 37

4-N-methyl-6-[3-(trifluoromethyl)phenyl]pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from [3-(trifluoromethyl)phenyl]boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 269; ^1H NMR (400 MHz, CD_3OD) δ_H 8.05 (1H, s), 7.99 (1H, d, $J = 8.0$ Hz), 7.92 (1H, d, $J = 8.0$ Hz), 7.79 (1H, t, $J = 8.0$ Hz), 6.38 (1H, s),
5 3.05 (3H, s).

Example 38

6-(2,3-dichlorophenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 3 from methanamine and 4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 269; ^1H NMR (400 MHz, CD_3OD) δ_H 7.79 – 7.77 (1H, m), 7.50 – 7.49 (2H, m), 6.12 (1H, s), 3.04 (3H, s).

Example 39

6-(2H-1,3-benzodioxol-5-yl)-4-N-methylpyrimidine-2,4-diamine.

15 Prepared according to general procedure 2 from (2H-1,3-benzodioxol-5-yl)boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 245; ^1H NMR (400 MHz, CD_3OD) δ_H 7.42 – 7.39 (1H, m), 7.36 – 7.35 (1H, m), 6.89 (1H, d, $J = 8.0$ Hz), 6.15 (1H, s), 6.02 (1H, s), 2.92 (3H, s).

20 Example 40

3-[2-amino-6-(methylamino)pyrimidin-4-yl]benzonitrile.

Prepared according to general procedure 2 from (3-cyanophenyl)boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 226; ^1H NMR (400 MHz, CD_3OD) δ_H 8.15 (1H, s), 8.05 – 8.03 (1H, m), 7.95 – 7.92 (1H, m), 7.74 (1H, t, $J = 8.5$ Hz), 6.35 (1H, s), 3.02 (3H, s).

Example 41

N-{3-[2-amino-6-(methylamino)pyrimidin-4-yl]phenyl}acetamide.

Prepared according to general procedure 2 from (3-acetamidophenyl)boronic acid
30 and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 258; ^1H NMR (400 MHz, CD_3OD) δ_H 8.20 (1H, s), 7.56 – 7.52 (2H, m), 7.45 – 7.43 (1H, m), 6.31 (1H, s), 3.06 (3H, s), 2.19 (3H, s).

Example 42

35 4-N-methyl-6-[4-(morpholine-4-sulfonyl)phenyl]pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from [4-(morpholine-4-sulfonyl)phenyl]boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 350; ^1H NMR (400 MHz, CD_3OD) δ_H 7.99 (4H, s), 6.42 (1H, s), 3.76 – 3.72 (4H, m), 3.07 (3H, s), 3.06 – 3.03 (4H, m).

5

Example 43

6-(4-methanesulfonylphenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (4-methanesulfonylphenyl)boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS

10 $[M+H]^+$ 279; ^1H NMR (400 MHz, CD_3OD) δ_H 8.20 – 8.17 (2H, m), 8.00 – 7.97 (2H, m), 6.41 (1H, s), 3.22 (3H, s), 3.08 (3H, s).

Example 44

4-N-methyl-6-[3-(morpholine-4-carbonyl)phenyl]pyrimidine-2,4-diamine.

15 Prepared according to general procedure 2 from [3-(morpholine-4-carbonyl)phenyl]boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 314; ^1H NMR (400 MHz, CD_3OD) δ_H 8.00 – 7.96 (1H, m), 7.92 (1H, s), 7.57 (1H, t, $J = 7.8$ Hz), 7.52 (1H, dt, $J = 7.8$ and 1.4 Hz), 6.27 (1H, s), 3.79 – 3.50 (8H, m), 2.94 (3H, s).

20

Example 45

4-[2-amino-6-(methylamino)pyrimidin-4-yl]-N-(furan-2-ylmethyl)benzamide.

Prepared according to general procedure 2 from {4-[(furan-2-ylmethyl)carbamoyl]phenyl}boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-

25 diamine. LCMS $[M+H]^+$ 324; ^1H NMR (400 MHz, CD_3OD) δ_H 7.93 – 7.90 (4H, m), 7.46 – 7.44 (1H, m), 6.39 – 6.37 (1H, m), 6.34 – 6.32 (1H, m), 6.28 (1H, s), 4.60 (2H, s), 2.94 (3H, s).

Example 46

30 N-{4-[2-amino-6-(methylamino)pyrimidin-4-yl]phenyl}methanesulfonamide.

Prepared according to general procedure 2 from (4-methanesulfonamidophenyl)boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 294; ^1H NMR (400 MHz, CD_3OD) δ_H 7.72 – 7.70 (2H, m), 7.43 – 7.40 (2H, m), 6.29 (1H, s), 3.06 (3H, s), 3.03 (3H, s).

35

Example 47

N-{4-[2-amino-6-(methylamino)pyrimidin-4-yl]phenyl}acetamide.

Prepared according to general procedure 2 from (4-acetamidophenyl)boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 258; ^1H NMR (400 MHz, CD_3OD) δ_H 7.82 – 7.80 (2H, m), 7.75 – 7.73 (2H, m), 6.31 (1H, s), 3.03 (3H, s), 2.18 (3H, d, $J = 2.5$ Hz).

Example 48

4-N-methyl-6-(pyridin-4-yl)pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (pyridin-4-yl)boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 202; ^1H NMR (400 MHz, CD_3OD) δ_H 8.79 (2H, dd, $J = 4.7$ and 1.6 Hz), 7.76 (2H, d, $J = 4.7$ Hz), 6.47 (1H, s), 3.07 (3H, s).

Example 49

6-(6-methoxypyridin-3-yl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (6-methoxypyridin-3-yl)boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 232; ^1H NMR (400 MHz, CD_3OD) δ_H 8.57 (1H, s), 8.03 (1H, d, $J = 7.3$ Hz), 6.98 (1H, d, $J = 7.3$ Hz), 6.30 (1H, s), 4.02 (3H, s), 3.07 (3H, s).

Example 50

6-(2-fluoro-4-phenylphenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (2-fluoro-4-phenylphenyl)boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 295; ^1H NMR (400 MHz, CD_3OD) δ_H 7.75 – 7.61 (5H, m), 7.54 – 7.44 (3H, m), 6.41 (1H, s), 6.30 (1H, s), 3.06 (3H, s).

Example 51

4-[2-amino-6-(methylamino)pyrimidin-4-yl]benzonitrile.

Prepared according to general procedure 2 from (4-cyanophenyl)boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 226; ^1H NMR (400 MHz, CD_3OD) δ_H 8.03 (2H, d, $J = 8.2$ Hz), 7.84 – 7.80 (2H, m), 6.29 (1H, s), 2.93 (3H, s).

Example 52

4-N-methyl-6-(quinolin-5-yl)pyrimidine-2,4-diamine.

- Prepared according to general procedure 2 from (quinolin-5-yl)boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 252; ^1H NMR (400 MHz, CD_3OD) δ_H 8.98 (1H, dd, $J = 4.2$ and 1.9 Hz), 8.49 (1H, d, $J = 8.6$ Hz), 8.26 (1H, d, $J = 8.6$ Hz), 7.95 – 7.91 (1H, m), 7.82 (1H, d, $J = 7.2$ Hz), 7.67 (1H, dd, $J = 8.6$ and 4.2 Hz), 6.23 (1H, s), 3.08 (3H, s).

Example 53

- 10 6-(4-chlorophenyl)-4-N-(prop-2-en-1-yl)pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (4-chlorophenyl)boronic acid and 6-chloro-4-N-(prop-2-en-1-yl)pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 261; ^1H NMR (400 MHz, CD_3OD) δ_H 7.75 – 7.73 (2H, m), 7.64 – 7.62 (2H, m), 6.36 (1H, s), 6.02 – 5.92 (1H, m), 5.33 – 5.31 (1H, m), 5.23 – 5.20 (1H, m), 4.18 – 4.16 (2H, m).

Example 54

6-(4-methoxyphenyl)-4-N-(prop-2-en-1-yl)pyrimidine-2,4-diamine.

- Prepared according to general procedure 2 from (4-methoxyphenyl)boronic acid and 6-chloro-4-N-(prop-2-en-1-yl)pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 257.

Example 55

6-(4-chlorophenyl)-4-N-cyclopentylpyrimidine-2,4-diamine.

- Prepared according to general procedure 2 from (4-chlorophenyl)boronic acid and 6-chloro-4-N-cyclopentylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 289; ^1H NMR (400 MHz, CD_3OD) δ_H 7.60 (2H, d, $J = 8.8$ Hz), 7.51 – 7.49 (2H, m), 6.17 (1H, s), 4.36 (1H, s), 2.00 – 1.93 (2H, m), 1.73 – 1.65 (2H, m), 1.61 – 1.53 (2H, m), 1.50 – 1.43 (2H, m).

- 30 Example 56

4-N-cyclopentyl-6-(4-methoxyphenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from 6-chloro-4-N-cyclopentylpyrimidine-2,4-diamine and (4-methoxyphenyl)boronic acid. LCMS $[M+H]^+$ 285; ^1H NMR (400 MHz, CD_3OD) δ_H 7.68 (2H, d, $J = 9.2$ Hz), 7.12 (2H, d,

J = 9.2 Hz), 6.27 (1H, s), 4.47 (1H, q, J = 6.7 Hz), 3.89 (3H, s), 2.10 – 2.03 (2H, m), 1.82 – 1.79 (2H, m), 1.72 – 1.63 (2H, m), 1.62 – 1.53 (2H, m).

Example 57

5 4-N-cyclopentyl-6-[3-(trifluoromethyl)phenyl]pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from [3-(trifluoromethyl)-phenyl]boronic acid and 6-chloro-4-N-cyclopentylpyrimidine-2,4-diamine. LCMS [M+H]⁺ 323; ¹H NMR (400 MHz, CD₃OD) δ_H 8.17 (1H, s), 8.08 (1H, d, J = 7.9 Hz), 7.74 (1H, d, J = 7.9 Hz), 7.65 (1H, t, J = 7.9 Hz), 6.28 (1H, s), 4.29 (1H, s), 2.09 – 1.99 (2H, m), 1.75 – 1.74 (2H, m), 1.71 – 1.62 (2H, m), 1.60 – 1.49 (2H, m).

Example 58

6-(4-chlorophenyl)-4-N-cyclobutylpyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (4-chlorophenyl)boronic acid
15 and 6-chloro-4-N-cyclobutylpyrimidine-2,4-diamine. LCMS [M+H]⁺ 275; ¹H NMR (400 MHz, CD₃OD) δ_H 7.83 (2H, d, J = 8.4 Hz), 7.45 (2H, d, J = 8.4 Hz), 6.17 (1H, s), 4.42 (1H, s), 2.44 – 2.38 (2H, m), 2.02 – 1.94 (2H, m), 1.83 – 1.76 (2H, m).

Example 59

20 4-N-cyclobutyl-6-(4-methoxyphenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (4-methoxyphenyl)boronic acid and 6-chloro-4-N-cyclobutylpyrimidine-2,4-diamine. LCMS [M+H]⁺ 271; ¹H NMR (400 MHz, CD₃OD) δ_H 7.68 (2H, d, J = 8.5 Hz), 7.14 (2H, d, J = 8.5 Hz), 6.22 (1H, s), 4.64 (1H, q, J = 7.9 Hz), 3.90 (3H, s), 2.46 – 2.38 (2H, m), 2.12 – 2.01 (2H, m),
25 1.87 – 1.78 (2H, m).

Example 60

4-N-cyclobutyl-6-[3-(trifluoromethyl)phenyl]pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from [3-(trifluoromethyl)phenyl]boronic acid and 6-chloro-4-N-cyclobutylpyrimidine-2,4-diamine. LCMS [M+H]⁺ 309; ¹H NMR (400 MHz, CD₃OD) δ_H 7.68 (2H, d, J = 8.5 Hz), 7.14 (2H, d, J = 8.5 Hz), 6.22 (1H, s), 4.64 (1H, q, J = 7.9 Hz), 3.90 (3H, s), 2.46 – 2.38 (2H, m), 2.12 – 2.01 (2H, m), 1.87 – 1.78 (2H, m).

35 Example 61

6-(2,3-dichlorophenyl)-4-N-pentylpyrimidine-2,4-diamine.

Prepared according to general procedure 3 from pentan-1-amine and 4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 325; ^1H NMR (400 MHz, CD_3OD) δ_H 7.80 – 7.78 (1H, m), 7.52 – 7.50 (2H, m), 6.12 (1H, s), 3.54 – 3.50 (2H, m), 1.69 – 1.65 (2H, m), 1.42 – 1.39 (4H, m), 0.98 – 0.95 (3H, m).

Example 62

4-N-cyclopropyl-6-(2,3-dichlorophenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 3 from cyclopropanamine and 4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 295; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.51 (1H, dd, $J = 7.9$ and 1.6 Hz), 7.41 (1H, dd, $J = 7.9$ and 1.6 Hz), 7.28 (1H, t, $J = 7.9$ Hz), 6.35 (1H, s), 5.21 (1H, s), 4.78 (2H, s), 2.63 – 2.47 (1H, m), 0.86 – 0.78 (2H, m), 0.64 – 0.57 (2H, m).

Example 63

4-N-tert-butyl-6-(2,3-dichlorophenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 3 from 2-methylpropan-2-amine and 4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 311.

Example 64

4-N-cyclobutyl-6-(2,3-dichlorophenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 3 from cyclobutanamine and 4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 309; ^1H NMR (400 MHz, CD_3OD) δ_H 7.60 – 7.58 (1H, m), 7.37 – 7.34 (2H, m), 5.89 (1H, s), 4.46 (1H, s), 3.37 (2H, s), 2.43 – 2.35 (2H, m), 2.01 – 1.94 (2H, m), 1.80 – 1.72 (2H, m).

Example 65

4-N-cyclopentyl-6-(2,3-dichlorophenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 3 from cyclopentanamine and 4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 323; ^1H NMR (400 MHz, CD_3OD) δ_H 7.62 – 7.56 (1H, m), 7.40 – 7.34 (2H, m), 5.93 (1H, s), 3.37 (1H, s), 2.09 – 1.98 (2H, m), 1.82 – 1.72 (2H, m), 1.71 – 1.61 (2H, m), 1.58 – 1.48 (2H, m).

Example 66

6-(2,3-dichlorophenyl)-4-N-ethylpyrimidine-2,4-diamine.

Prepared according to general procedure 3 from ethanamine and 4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 283; ^1H NMR (400 MHz, CD_3OD) δ_H 7.62 – 7.57 (1H, m), 7.40 – 7.35 (2H, m), 5.92 (1H, s), 3.44 – 3.36

5 (2H, m), 1.24 (3H, t, $J = 7.1$ Hz).

Example 67

6-(2,3-dichlorophenyl)-4-N-(oxolan-3-yl)pyrimidine-2,4-diamine.

Prepared according to general procedure 3 from oxolan-3-amine and 4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 325; ^1H NMR (400 MHz, CD_3OD) δ_H 7.63 – 7.58 (1H, m), 7.39 – 7.35 (2H, m), 5.98 (1H, s), 4.59 (1H, s), 4.02 – 3.94 (2H, m), 3.90 – 3.82 (1H, m), 3.73 – 3.67 (1H, m), 2.36 – 2.26 (1H, m), 1.99 – 1.89 (1H, m).

15 Example 68

6-(3,4-dichlorophenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (3,4-dichlorophenyl)boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 269; ^1H NMR (400 MHz, CD_3OD) δ_H 7.96 (1H, d, $J = 2.0$ Hz), 7.77 (1H, d, $J = 8.5$ Hz), 7.70 – 7.55

20 (2H, m), 6.35 (1H, s), 3.06 (3H, s).

Example 69

6-(4-tert-butylphenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 5 from (4-tert-butylphenyl)boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 257; ^1H NMR (400 MHz, CD_3OD) δ_H 7.77 (2H, d, $J = 8.7$ Hz), 7.53 – 7.48 (2H, m), 6.22 (1H, s), 2.93 (3H, s), 1.38 (9H, s).

Example 70

30 4-N-methyl-6-(4-methylphenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 5 from (4-methylphenyl)boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 215; ^1H NMR (400 MHz, CD_3OD) δ_H 7.73 (2H, d, $J = 8.9$ Hz), 7.28 (2H, d, $J = 8.9$ Hz), 6.20 (1H, s), 2.93 (3H, s), 2.41 (3H, s).

35

Example 71

6-(2,4-dichlorophenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 5 from (2,4-dichlorophenyl)boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 269; ^1H NMR (400 MHz, CD_3OD) δ_H 7.57 (1H, d, $J = 1.9$ Hz), 7.48 – 7.41 (2H, m), 5.98 (1H, s), 2.92 (3H, s).

Example 72

4-N-methyl-6-(2,4,5-trifluorophenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 5 from (2,4,5-trifluorophenyl)boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 255; ^1H NMR (400 MHz, CD_3OD) δ_H 7.86 – 7.75 (1H, m), 7.31 – 7.24 (1H, m), 6.25 (1H, s), 2.91 (3H, s).

Example 73

6-(4-fluoro-2-methoxyphenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 5 from (4-fluoro-2-methoxyphenyl)boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 249; ^1H NMR (400 MHz, CD_3OD) δ_H 7.57 (1H, dd, $J = 8.5$ and 6.3 Hz), 6.89 (1H, dd, $J = 11.4$ and 2.5 Hz), 6.76 (1H, td, $J = 8.5$ and 2.5 Hz), 6.19 (1H, s), 3.87 (3H, s), 2.90 (3H, s).

Example 74

6-(5-chloro-2-methylphenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 5 from (5-chloro-2-methylphenyl)boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 249; ^1H NMR (400 MHz, CD_3OD) δ_H 7.33 – 7.23 (3H, m), 5.85 (1H, s), 2.92 (3H, s), 2.32 (3H, s).

Example 75

6-(2,4-difluorophenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 5 from (2,4-difluorophenyl)boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 237; ^1H NMR (400 MHz, CD_3OD) δ_H 7.88 – 7.79 (1H, m), 7.10 – 7.00 (2H, m), 6.19 (1H, d, $J = 2.0$ Hz), 2.92 (3H, s).

Example 76

6-(5-fluoro-2-methoxyphenyl)-4-N-methylpyrimidine-2,4-diamine.

- Prepared according to general procedure 5 from (5-fluoro-2-methoxyphenyl)-boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 249; ^1H NMR (400 MHz, CD_3OD) δ_H 7.36 (1H, dd, $J = 9.4$ and 3.1 Hz), 7.15 – 7.04 (2H, m), 6.28 (1H, s), 3.85 (3H, s), 2.91 (3H, s).

Example 77

- 10 6-(2-chlorophenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 5 from (2-chlorophenyl)boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 235; ^1H NMR (400 MHz, CD_3OD) δ_H 7.51 – 7.44 (1H, m), 7.42 – 7.36 (2H, m), 5.98 (1H, s), 2.92 (3H, s).

15

Example 78

4-N-methyl-6-(pyridin-2-yl)pyrimidine-2,4-diamine.

- To a solution of 6-iodo-4-N-methylpyrimidine-2,4-diamine (1 eq.) and 2-(tributylstannyl)pyridine (1.3 eq.) in toluene (1 mL) were added CuI (0.25 eq.) and Pd(PPh_3)₄ (0.05 eq.). The reaction mixture was heated at 120 °C for 1 hour. The crude mixture was purified by HPLC. LCMS $[M+H]^+$ 202.

Example 79

6-(4-methoxy-3-methylphenyl)-4-N-methylpyrimidine-2,4-diamine.

- 25 Prepared according to general procedure 6 from (4-methoxy-3-methylphenyl)-boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 245; ^1H NMR (400 MHz, CD_3OD) δ_H 7.72 – 7.62 (2H, m), 6.99 (1H, d, $J = 8.3$ Hz), 6.18 (1H, s), 3.91 (3H, s), 2.94 (3H, s), 2.28 (3H, s).

- 30 Example 80

6-(3-chloro-4-fluorophenyl)-4-N-methylpyrimidine-2,4-diamine.

- Prepared according to general procedure 6 from (3-chloro-4-fluorophenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 253; ^1H NMR (400 MHz, CD_3OD) δ_H 8.05 – 7.99 (1H, m), 7.87 – 7.79 (1H, m), 7.33 (1H, t, $J = 8.2$ Hz), 6.23 (1H, s), 2.94 (3H, s).

35

Example 81

4-N-methyl-6-[4-(trifluoromethoxy)phenyl]pyrimidine-2,4-diamine.

Prepared according to general procedure 6 from [4-

- 5 (trifluoromethoxy)phenyl]boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 285; ^1H NMR (400 MHz, CD_3OD) δ_H 7.98 – 7.92 (2H, m), 7.38 – 7.32 (2H, m), 6.23 (1H, s), 2.93 (3H, s).

Example 82

- 10 6-(3-fluoro-4-methoxyphenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (3-fluoro-4-methoxyphenyl)-boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 249; ^1H NMR (400 MHz, CD_3OD) δ_H 7.97 – 7.60 (2H, m), 7.21 – 7.12 (1H, m), 6.20 (1H, s), 3.95 (3H, s), 2.94 (3H, s).

15

Example 83

6-(3,4-difluorophenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (3,4-difluorophenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 237; ^1H NMR (400

- 20 MHz, CD_3OD) δ_H 7.86 – 7.77 (1H, m), 7.74 – 7.66 (1H, m), 7.40 – 7.30 (1H, m), 6.23 (1H, s), 2.94 (3H, s).

Example 84

4-N-methyl-6-[4-(propan-2-yloxy)phenyl]pyrimidine-2,4-diamine.

- 25 Prepared according to general procedure 6 from [4-(propan-2-yloxy)phenyl]boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 259.

Example 85

- 30 6-[2-fluoro-3-(trifluoromethyl)phenyl]-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from [2-fluoro-3-(trifluoromethyl)phenyl]boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 287; ^1H NMR (400 MHz, CD_3OD) δ_H 7.98 (1H, t, J = 7.0 Hz), 7.87 (1H, t, J = 7.0 Hz), 7.52 (1H, t, J = 8.0 Hz), 6.27 (1H, d, J = 1.5 Hz),

- 35 3.00 (3H, s).

Example 86

6-(2,3-dimethylphenyl)-4-N-methylpyrimidine-2,4-diamine.

- Prepared according to general procedure 6 from (2,3-dimethylphenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 229; ^1H NMR (400 MHz, CD_3OD) δ_H 7.24 – 7.18 (1H, m), 7.17 – 7.05 (2H, m), 5.82 (1H, s), 2.92 (3H, s), 2.35 (3H, s), 2.22 (3H, s).

Example 87

- 10 6-(3-chloro-2-fluorophenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (3-chloro-2-fluorophenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 253; ^1H NMR (400 MHz, CD_3OD) δ_H 7.71 – 7.65 (1H, m), 7.58 – 7.53 (1H, m), 7.30 – 7.22 (1H, m), 6.18 (1H, d, $J = 2.1$ Hz), 2.93 (3H, s).

15

Example 88

6-(4-chloro-3-fluorophenyl)-4-N-methylpyrimidine-2,4-diamine.

- Prepared according to general procedure 6 from (4-chloro-3-fluorophenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 253; ^1H NMR (400 MHz, CD_3OD) δ_H 7.73 – 7.65 (2H, m), 7.62 – 7.55 (1H, m), 6.34 (1H, s), 3.03 (3H, s).

20

Example 89

4-N-methyl-6-[2-(trifluoromethyl)phenyl]pyrimidine-2,4-diamine.

- 25 Prepared according to general procedure 6 from [2-(trifluoromethyl)phenyl]boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 269; ^1H NMR (400 MHz, CD_3OD) δ_H 7.80 (1H, d, $J = 8.1$ Hz), 7.70 (1H, t, $J = 7.7$ Hz), 7.61 (1H, t, $J = 7.7$ Hz), 7.48 (1H, d, $J = 8.1$ Hz), 5.88 (1H, s), 2.92 (3H, s).

- 30 Example 90

4-N-methyl-6-(1-methyl-1H-indazol-4-yl)pyrimidine-2,4-diamine.

- Prepared according to general procedure 6 from (1-methyl-1H-indazol-4-yl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 255; ^1H NMR (400 MHz, CD_3OD) δ_H 8.42 (1H, s), 7.69 – 7.63 (1H, m), 7.60 – 7.50 (2H, m), 6.33 (1H, s), 4.14 (3H, s), 2.97 (3H, s).

35

Example 91

6-[2-chloro-3-(trifluoromethyl)phenyl]-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from [2-chloro-3-

- 5 (trifluoromethyl)phenyl]boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 303; ^1H NMR (400 MHz, CD_3OD) δ_H 7.90 – 7.85 (1H, m), 7.71 – 7.66 (1H, m), 7.62 – 7.55 (1H, m), 5.95 (1H, s), 2.94 (3H, s).

Example 92

- 10 6-(2-chloro-3-fluorophenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (2-chloro-3-fluorophenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 253; ^1H NMR (400 MHz, CD_3OD) δ_H 7.46 – 7.38 (1H, m), 7.35 – 7.28 (2H, m), 5.98 (1H, s), 2.93 (3H, s).

15

Example 93

6-(2,3-difluorophenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (2,3-difluorophenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 237; ^1H NMR (400

- 20 MHz, CD_3OD) δ_H 7.58 – 7.51 (1H, m), 7.34 – 7.31 (1H, m), 7.29 – 7.22 (1H, m), 6.20 (1H, s), 2.93 (3H, s).

Example 94

6-(3-chloro-2-methylphenyl)-4-N-methylpyrimidine-2,4-diamine.

- 25 Prepared according to general procedure 6 from (3-chloro-2-methylphenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 249; ^1H NMR (400 MHz, CD_3OD) δ_H 7.47 – 7.41 (1H, m), 7.27 – 7.21 (2H, m), 5.85 (1H, s), 2.93 (3H, s), 2.36 (3H, s).

- 30 Example 95

6-(2,3-dichlorophenyl)-4-N,5-dimethylpyrimidine-2,4-diamine.

Step 1: 4-chloro-6-(2,3-dichlorophenyl)-5-methylpyrimidin-2-amine was prepared according to general procedure 2 from 4,6-dichloro-5-methylpyrimidin-2-amine and (2,3-dichlorophenyl)boronic acid (and using DMF instead of dioxane).

35

Step 2: 6-(2,3-dichlorophenyl)-4-N,5-dimethylpyrimidine-2,4-diamine was prepared according to general procedure 3 from methanamine and 4-chloro-6-(2,3-dichlorophenyl)-5-methylpyrimidin-2-amine (prepared in step 1 above).

LCMS $[M+H]^+$ 283; ^1H NMR (400 MHz, CD_3OD) δ_H 7.62 (1H, dd, $J = 7.9$ and 1.9 Hz), 7.41 (1H, t, $J = 7.9$ Hz), 7.27 (1H, dd, $J = 7.9$ and 1.9 Hz), 3.01 (3H, s), 1.71 (3H, s).

Example 96

4-N-cyclopropyl-6-(2,3-dichlorophenyl)-5-methylpyrimidine-2,4-diamine.

Was prepared according to general procedure 3 from cyclopropanamine and 4-chloro-6-(2,3-dichlorophenyl)-5-methylpyrimidin-2-amine (prepared in example 95, step 1 above). LCMS $[M+H]^+$ 309; ^1H NMR (400 MHz, CD_3OD) δ_H 7.83 (1H, dd, $J = 7.7$ and 1.2 Hz), 7.56 (1H, t, $J = 7.8$ Hz), 7.48 (1H, dd, $J = 7.8$ and 1.2 Hz), 3.17 -3.09 (1H, m), 1.79 (3H, s), 0.96 – 0.90 (2H, m), 0.82 – 0.75 (2H, m).

Example 97

6-(7-chloro-2H-1,3-benzodioxol-5-yl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (7-chloro-2H-1,3-benzodioxol-5-yl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 279; ^1H NMR (400 MHz, CD_3OD) δ_H 7.11 (1H, s), 7.04 (1H, s), 6.13 (2H, s), 6.10 (1H, s), 3.04 (3H, s).

Example 98

6-(2,3-dichloro-4-methoxyphenyl)-4-N-methylpyrimidine-2,4-diamine.

Step 1: 4-chloro-6-(2,3-dichloro-5-methoxyphenyl)pyrimidin-2-amine was prepared according to general procedure 2 from 4,6-dichloropyrimidin-2-amine and 2,3-dichloro-4-methoxyphenyl)boronic acid.

Step 2: Prepared according to general procedure 3 from methanamine and 4-chloro-6-(2,3-dichloro-5-methoxyphenyl)pyrimidin-2-amine (prepared in step 1 above). LCMS $[M+H]^+$ 299; ^1H NMR (400 MHz, CD_3OD) δ_H 7.49 (1H, d, $J = 8.6$ Hz), 7.24 (1H, d, $J = 8.6$ Hz), 6.11 (1H, s), 4.01 (3H, s), 3.09 (3H, s).

Example 99

6-(2,3-dichloro-5-methoxyphenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (2,3-dichloro-5-methoxyphenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 299; ^1H NMR (400 MHz, CD_3OD) δ_H 7.38 (1H, d, $J = 2.9$ Hz), 7.12 (1H, d, $J = 2.9$ Hz), 6.13 (1H, s), 3.88 (3H, s), 3.05 (3H, s).

5

Example 100

4-[2-amino-6-(methylamino)pyrimidin-4-yl]phenol.

Prepared according to general procedure 6 from (4-hydroxyphenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 217; ^1H NMR (400 MHz, CD_3OD) δ_H 7.69 (2H, d, $J = 8.5$ Hz), 6.85 (2H, d, $J = 8.5$ Hz), 6.15 (1H, s), 4.59 (1H, s), 2.93 (3H, s).

10

Example 101

{3-[2-amino-6-(methylamino)pyrimidin-4-yl]phenyl}methanol.

Prepared according to general procedure 6 from [3-(hydroxymethyl)phenyl]boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 231; ^1H NMR (400 MHz, CD_3OD) δ_H 7.83 (1H, s), 7.76 – 7.70 (1H, m), 7.45 – 7.41 (2H, m), 6.22 (1H, s), 4.68 (2H, s), 2.92 (3H, s).

15

Example 102

4-[2-amino-6-(methylamino)pyrimidin-4-yl]benzoic acid.

Prepared according to general procedure 6 from 4-(dihydroxyboranyl)benzoic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 245.

20

Example 103

methyl 4-[2-amino-6-(methylamino)pyrimidin-4-yl]benzoate.

Prepared according to general procedure 6 from [4-(methoxycarbonyl)phenyl]boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 259; ^1H NMR (400 MHz, CD_3OD) δ_H 8.12 – 8.06 (2H, m), 7.95 (2H, d, $J = 8.2$ Hz), 6.28 (1H, s), 3.94 (3H, s), 2.93 (3H, s).

25

30

Example 104

6-[3-chloro-4-(morpholine-4-carbonyl)phenyl]-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from [3-chloro-4-(morpholine-4-carbonyl)phenyl]boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine.

35

LCMS $[M+H]^+$ 348; ^1H NMR (400 MHz, CD_3OD) δ_H 7.90 (1H, d, $J = 1.8$ Hz), 7.75 (1H, dd, $J = 7.9$ and 1.8 Hz), 7.59 (1H, d, $J = 7.9$ Hz), 6.35 (1H, s), 3.85 – 3.74 (6H, m), 3.69 – 3.60 (2H, m), 3.04 (3H, s).

5 Example 105

4-[2-amino-6-(methylamino)pyrimidin-4-yl]-2,3-dichlorophenol.

Prepared according to general procedure 6 from 2,3-dichloro-4-(tetramethyl-1,3,2-dioxaborolan-2-yl)phenol and 6-iodo-4-N-methylpyrimidine-2,4-diamine.

10 LCMS $[M+H]^+$ 285; ^1H NMR (400 MHz, CD_3OD) δ_H 7.32 (1H, d, $J = 8.7$ Hz), 7.04 (1H, d, $J = 8.7$ Hz), 6.09 (1H, s), 3.04 (3H, s).

Example 106

methyl (2E)-3-{4-[2-amino-6-(methylamino)pyrimidin-4-yl]phenyl}prop-2-enoate.

15 Prepared according to general procedure 6 from {4-[(1E)-3-methoxy-3-oxoprop-1-en-1-yl]phenyl}boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 285; ^1H NMR (400 MHz, CD_3OD) δ_H 7.82 (4H, s), 7.76 (1H, d, $J = 16.0$ Hz), 6.69 (1H, d, $J = 16.0$ Hz), 6.36 (1H, s), 3.83 (3H, s), 3.04 (3H, s).

Example 107

20 methyl (2E)-3-{3-[2-amino-6-(methylamino)pyrimidin-4-yl]phenyl}prop-2-enoate.

Prepared according to general procedure 6 from {3-[(1E)-3-methoxy-3-oxoprop-1-en-1-yl]phenyl}boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 285; ^1H NMR (400 MHz, CD_3OD) δ_H 7.99 – 7.95 (1H, m), 7.92 – 7.86 (1H, m), 7.83 – 7.73 (2H, m), 7.69 – 7.63 (1H, m), 6.72 (1H, d, $J = 16.0$ Hz), 6.37 (1H, s), 3.83 (3H, s), 3.07 (3H, s).

Example 108

4-[2-amino-6-(methylamino)pyrimidin-4-yl]benzaldehyde.

30 Prepared according to general procedure 6 from (4-formylphenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 229.

Example 109

1-(4-(2-Amino-6-(methylamino)pyrimidin-4-yl)phenyl)ethanone.

35 Prepared according to general procedure 6 from (4-acetylphenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 243; ^1H NMR (400 MHz,

CD₃OD) δ_{H} 8.22 – 8.15 (2H, m), 7.88 – 7.82 (2H, m), 6.38 (1H, s), 3.05 (3H, s), 2.67 (3H, s).

Example 110

5 4-[2-amino-6-(methylamino)pyrimidin-4-yl]-N-methylbenzamide.

Prepared according to general procedure 6 from [4-(methylcarbamoyl)phenyl]boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 258; ^1H NMR (400 MHz, CD₃OD) δ_{H} 8.02 (2H, d, J = 8.5 Hz), 7.83 (2H, d, J = 8.5 Hz), 6.38 (1H, s), 3.06 (3H, s), 2.97 (3H, s).

10

Example 111

6-(4-ethenylphenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (4-ethenylphenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine.

15 LCMS $[M+H]^+$ 227; ^1H NMR (400 MHz, CD₃OD) δ_{H} 7.75 – 7.63 (4H, m), 6.84 (1H, dd, J = 17.5 and 10.7 Hz), 6.34 (1H, s), 5.98 (1H, d, J = 17.5 Hz), 5.43 (1H, d, J = 10.7 Hz), 3.06 (3H, s).

Example 112

20 6-(2,3-dimethylphenyl)-4-N-[2-(piperidin-1-yl)ethyl]pyrimidine-2,4-diamine.

Prepared according to general procedure 7 from 2-(piperidin-1-yl)ethan-1-amine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 326.

Example 113

25 6-(2,3-dimethylphenyl)-4-N-[2-(morpholin-4-yl)ethyl]pyrimidine-2,4-diamine.

Prepared according to general procedure 7 from 2-(morpholin-4-yl)ethan-1-amine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 328.

Example 114

30 4-N-cyclopropyl-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (2,3-dimethylphenyl)boronic acid and 6-chloro-4-N-cyclopropylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 255; ^1H NMR (400 MHz, CD₃OD) δ_{H} 7.42 – 7.31 (1H, m), 7.29 – 7.12 (2H, m), 6.44 (0.3 H, s), 5.95 (0.7 H, s), 3.13. (0.7H, s), 2.68 (0.3H, s), 2.36 (3H, s), 2.25 (3H, s), 0.95 – 0.79 (2H, m), 0.72 – 0.55 (2H, m).

35

Example 115

3-[2-amino-6-(methylamino)pyrimidin-4-yl]-N-(4-methylphenyl)benzamide.

Step 1: A mixture of 6-chloro-4-N-methylpyrimidine-2,4-diamine (48 mg, 0.30 mmol), 3-(dihydroxyboranyl)benzoic acid (60 mg, 0.36 mmol), K₂CO₃ (104 mg, 0.75 mmol) and palladium tetrakis(triphenylphosphine)palladium (0) (17 mg, 0.015 mmol) in 1,4-dioxane (3 mL) and water (1 mL) was heated in a sealed tube at 90°C for 15 h. Concentrated and purified by preparative HPLC. LCMS [M+H]⁺ 245.

10

Step 2: To a mixture of 3-(2-amino-6-(methylamino)pyrimidin-4-yl)benzoic acid (50 mg, 0.47 mmol) and p-toluidine (150 mg, 1.4 mmol) in DMF (2.5 mL) were added HATU (266 mg, 0.70 mmol) and NEt₃ (200 µL, 1.4 mmol). The mixture was stirred at rt overnight. The crude reaction mixture was purified by HPLC. LCMS [M+H]⁺ 334.

15

Example 116

6-(1H-indol-3-yl)-4-N-methylpyrimidine-2,4-diamine.

To a solution of 4-N-methyl-6-[1-(4-methylbenzenesulfonyl)-1H-indol-3-yl]pyrimidine-2,4-diamine (1 eq.; prepared in example 23) in MeOH (2 mL) was added 10% NaOH (1 mL). The reaction mixture was heated at 50 °C overnight and the crude product was purified by HPLC. LCMS [M+H]⁺ 240; ¹H NMR (400 MHz, CD₃OD) δ_H 8.04 (1H, d, J = 7.7 Hz), 7.82 (1H, s), 7.46 – 7.36 (1H, m), 7.21 – 7.09 (2H, m), 6.29 (1H, s), 2.92 (3H, s).

25

Example 117

6-phenyl-4-N-(2-phenylethyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from phenylboronic acid and 6-chloro-4-N-(2-phenylethyl)pyrimidine-2,4-diamine. LCMS [M+H]⁺ 291; ¹H NMR (400 MHz, CD₃OD) δ_H 7.83 – 7.73 (2H, m), 7.47 – 7.37 (3H, m), 7.31 – 7.22 (4H, m), 7.21 – 7.15 (1H, m), 6.17 (1H, s), 3.60 (2H, t, J = 7.3 Hz), 2.91 (2H, t, J = 7.3 Hz).

30

Example 118

6-(2,3-dimethylphenyl)-4-N-(2-phenylethyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (2,3-dimethylphenyl)boronic acid and 6-chloro-4-N-(2-phenylethyl)pyrimidine-2,4-diamine. LCMS [M+H]⁺ 319; ¹H NMR (400 MHz, CD₃OD) δ_H 7.31 – 7.23 (4H, m), 7.21 – 7.15 (2H, m), 7.10 (1H, t, J = 7.0 Hz), 7.05 (1H, d, J = 7.0 Hz), 5.77 (1H, s), 3.64 – 3.50 (2H, m), 2.90 (2H, t, J = 7.6 Hz), 2.31 (3H, s), 2.19 (3H, s).

Example 119

6-(3-chlorophenyl)-4-N-(2,2-difluoroethyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (3-chlorophenyl)boronic acid and 6-chloro-4-N-(2,2-difluoroethyl)pyrimidine-2,4-diamine. LCMS [M+H]⁺ 285.

Example 120

6-(3-chloro-2-methoxypyridin-4-yl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (3-chloro-2-methoxypyridin-4-yl)boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS [M+H]⁺ 266.

Example 121

4-(2,3-dimethylphenyl)-5H,6H,7H,8H-pyrido[2,3-d]pyrimidin-2-amine.

To a solution of 4-chloro-5,6,7,8-tetrahydropyrido[2,3-d]pyrimidin-2-amine (10 mg, 0.054 mmol, 1 eq.) in DMF/water (9:1) is added 2,3-dimethylphenylboronic acid (8.9 mg, 0.060 mmol, 1.1 eq.), Na₂CO₃ (11.5 mg, 0.11 mmol, 2 eq.) and Pd(PPh₃)₄ (3.1 mg, 0.002 mmol, 0.05 eq.). The mixture is heated at 120 °C in a microwave reactor until the reaction is complete as shown by LCMS. The crude mixture is then purified by HPLC to afford the desired product. LCMS [M+H]⁺ 255; ¹H NMR (400 MHz, DMSO-d₆) δ_H 12.05 (1H, br s), 8.88 (1H, br s), 7.37 (1H, d, J = 6.9 Hz), 7.29 (1H, t, J = 7.6 Hz), 7.17 (1H, d, J = 6.3 Hz), 3.34 – 3.32 (2H, m), 2.32 (3H, s), 2.28 – 2.26 (2H, m), 2.09 (3H, s), 1.76 – 1.74 (2H, m).

Example 122

4-(2,3-dichlorophenyl)-5H,6H,7H,8H-pyrido[2,3-d]pyrimidin-2-amine.

To a solution of 4-chloro-5,6,7,8-tetrahydropyrido[2,3-d]pyrimidin-2-amine (10 mg, 0.054 mmol, 1 eq.) in DMF/water (9:1) is added 2,3-dichlorophenylboronic acid (11.3 mg, 0.060 mmol, 1.1 eq.), Na₂CO₃ (11.5 mg, 0.11 mmol, 2 eq.) and Pd(PPh₃)₄ (3.1 mg, 0.002 mmol, 0.05 eq.). The mixture is heated at 120 °C in a

microwave reactor until the reaction is complete as shown by LCMS. The crude mixture is then purified by HPLC to afford the desired product. LCMS $[M+H]^+$ 295.

Example 123

- 5 4-[1-(benzenesulfonyl)-1H-indol-3-yl]-5H,6H,7H,8H-pyrido[2,3-d]pyrimidin-2-amine.

To a solution of 4-chloro-5,6,7,8-tetrahydropyrido[2,3-d]pyrimidin-2-amine (10 mg, 0.054 mmol, 1 eq.) in DMF/water (9:1) is added (1-(phenylsulfonyl)-1H-indol-3-yl)boronic acid (18.0 mg, 0.060 mmol, 1.1 eq.), Na_2CO_3 (11.5 mg, 0.11 mmol, 2
10 eq.) and $Pd(PPh_3)_4$ (3.1 mg, 0.002 mmol, 0.05 eq.). The mixture is heated at 120 °C in a microwave reactor until the reaction is complete as shown by LCMS. The crude mixture is then purified by HPLC to afford the desired product. LCMS $[M+H]^+$ 406; ^1H NMR (400 MHz, $DMSO-d_6$) δ_H 12.03 (1H, br s), 8.03 (1H, br s), 8.36 (1H, s), 8.09 (2H, dd, J = 8.6 Hz and 1.2 Hz), 8.04 (1H, d, J = 8.3 Hz), 7.78 –
15 7.76 (1H, m), 7.68 – 7.66 (2H, m), 7.61 (1H, d, J = 7.8 Hz), 7.48 (1H, ddd, J = 8.4 Hz, 7.3 Hz and 1.1 Hz), 7.38 (1H, ddd, J = 8.0 Hz, 7.2 Hz and 1.0 Hz), 3.38 – 3.36 (2H, m), 2.48 – 2.46 (2H, m), 1.76 – 1.74 (2H, m).

Example 124

- 20 6-(3,5-difluorophenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (3,5-difluorophenyl)boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 237.

Example 125

- 25 6-(2,3-dimethylphenyl)-4-N-[2-(4-methoxyphenyl)ethyl]pyrimidine-2,4-diamine.

Prepared according to general procedure 7 from 2-(4-methoxyphenyl)ethan-1-amine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 349.

Example 126

- 30 6-(2,3-dimethylphenyl)-4-N-[2-(2-methoxyphenyl)ethyl]pyrimidine-2,4-diamine.

Prepared according to general procedure 7 from 2-(2-methoxyphenyl)ethan-1-amine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 349.

Example 127

- 35 6-(2,3-dimethylphenyl)-4-N-[2-(4-methylphenyl)ethyl]pyrimidine-2,4-diamine.

Prepared according to general procedure 7 from 2-(4-methylphenyl)ethan-1-amine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 333.

Example 128

- 5 4-N-[2-(4-chlorophenyl)ethyl]-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.
Prepared according to general procedure 7 from 2-(4-chlorophenyl)ethan-1-amine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 353.

Example 129

- 10 6-(2,3-dimethylphenyl)-4-N-[2-(pyridin-2-yl)ethyl]pyrimidine-2,4-diamine.
Prepared according to general procedure 7 from 2-(pyridin-2-yl)ethan-1-amine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 320.

Example 130

- 15 6-(2,3-dimethylphenyl)-4-N-(2-phenylpropyl)pyrimidine-2,4-diamine.
Prepared according to general procedure 7 from 2-phenylpropan-1-amine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 333.

Example 131

- 20 6-(2,3-dimethylphenyl)-4-N-(3-phenylpropyl)pyrimidine-2,4-diamine.
Prepared according to general procedure 7 from 3-phenylpropan-1-amine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 333.

Example 132

- 25 6-(2,3-dimethylphenyl)-4-N-(2-phenoxyethyl)pyrimidine-2,4-diamine.
Prepared according to general procedure 7 from (2-aminoethoxy)benzene and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 335.

Example 133

- 30 6-(2,3-dimethylphenyl)-4-N-[2-(phenylamino)ethyl]pyrimidine-2,4-diamine.
Prepared according to general procedure 7 from N-(2-aminoethyl)aniline and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 334.

Example 134

- 35 6-(2,3-dimethylphenyl)-4-N-[2-(1H-indol-3-yl)ethyl]pyrimidine-2,4-diamine.

Prepared according to general procedure 7 from 2-(1H-indol-3-yl)ethan-1-amine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 358.

Example 135

- 5 6-(2,3-dimethylphenyl)-4-N-pentylpyrimidine-2,4-diamine.

Prepared according to general procedure 7 from pentan-1-amine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 285.

Example 136

- 10 1-(2-[[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino]ethyl)imidazolidin-2-one.

Prepared according to general procedure 7 from 1-(2-aminoethyl)imidazolidin-2-one and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 327.

- 15 Example 137

1-(3-[[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino]propyl)pyrrolidin-2-one.

Prepared according to general procedure 7 from 1-(3-aminopropyl)pyrrolidin-2-one and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 340.

- 20 Example 138

4-[2-amino-6-(methylamino)pyrimidin-4-yl]-2,6-dimethylphenol.

Prepared according to general procedure 6 from (4-hydroxy-3,5-dimethylphenyl)boronic acid. LCMS $[M+H]^+$ 245; ^1H NMR (400 MHz, CD_3OD) δ_{H} 7.44 (2H, s), 6.12 (1H, s), 2.91 (3H, s), 2.27 (6H, s).

25

Example 139

4-[2-amino-6-(methylamino)pyrimidin-4-yl]-2-methoxyphenol.

Prepared according to general procedure 6 from (4-hydroxy-3-methoxyphenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS

- 30 $[M+H]^+$ 247; ^1H NMR (400 MHz, CD_3OD) δ_{H} 7.46 (1H, s), 7.33 (1H, d, $J = 8.4$ Hz), 6.86 (1H, d, $J = 8.0$ Hz), 6.17 (1H, s), 3.34 (3H, s), 2.92 (3H, s).

Example 140

4-[2-amino-6-(methylamino)pyrimidin-4-yl]-2-fluorophenol.

Prepared according to general procedure 6 from (3-fluoro-4-hydroxyphenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 235.

5 Example 141

5-[2-amino-6-(methylamino)pyrimidin-4-yl]pyridin-2-ol.

Prepared according to general procedure 6 from (6-hydroxypyridin-3-yl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 218; ^1H NMR (400 MHz, CD_3OD) δ_H 7.99 (1H, s), 7.86 (1H, d, $J = 9.6$ Hz), 6.68 (1H, dd, $J = 9.6$ and 0.4 Hz), 6.21 (1H, s), 3.04 (3H, s).

10

Example 142

{4-[2-amino-6-(methylamino)pyrimidin-4-yl]phenyl}methanol.

Prepared according to general procedure 6 from [4-

15 (hydroxymethyl)phenyl]boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 231; ^1H NMR (400 MHz, CD_3OD) δ_H 7.79 (2H, d, $J = 8.0$ Hz), 7.43 (2H, d, $J = 8.4$ Hz), 6.21 (1H, s), 4.65 (2H, s), 2.91 (3H, s).

Example 143

20 4-N-methyl-6-(2-methylphenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (2-methylphenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 215; ^1H NMR (400 MHz, CD_3OD) δ_H 7.29 – 7.23 (4H, m), 5.83 (1H, s), 2.90 (3H, s), 2.33 (3H, s).

25 Example 144

6-[1-(4-chlorobenzenesulfonyl)-1H-indol-3-yl]-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 8 from [1-(4-chlorobenzenesulfonyl)-1H-indol-3-yl]boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 414; ^1H NMR (400 MHz, CD_3OD) δ_H 8.15 (1H, s), 8.08 (1H, d, $J = 8.0$ Hz), 8.04 (1H, d, $J = 8.0$ Hz), 8.00 – 7.98 (2H, m), 7.57 – 7.55 (2H, m), 7.41 (1H, td, $J = 8.4$ and 1.2 Hz), 7.35 (1H, td, $J = 8.0$ and 0.8 Hz), 6.28 (1H, s), 2.29 (3H, s).

30

Example 145

4-N-methyl-6-(4-methyl-1H-indazol-5-yl)pyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (4-methyl-1H-indazol-5-yl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 255.

Example 146

5 4-N-methyl-6-(6-methyl-1H-indazol-5-yl)pyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (6-methyl-1H-indazol-5-yl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 255; ^1H NMR (400 MHz, CD_3OD) δ_{H} 8.12 (1H, d, $J = 0.8$ Hz), 7.88 (1H, s), 7.56 (1H, d, $J = 0.8$ Hz), 6.09 (1H, s), 3.07 (3H, s), 2.50 (3H, d, $J = 0.8$ Hz).

10

Example 147

4-N-methyl-6-(3-methylphenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (3-methylphenyl)boronic acid. LCMS $[M+H]^+$ 215; ^1H NMR (400 MHz, CD_3OD) δ_{H} 7.56 (1H, s), 7.51 – 7.47 (3H, m), 6.32 (1H, s), 3.06 (3H, s), 2.47 (3H, s).

15

Example 148

6-(1H-indol-5-yl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (1H-indol-5-yl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 240; ^1H NMR (400 MHz, CD_3OD) δ_{H} 8.00 (1H, dd, $J = 1.6$ and 0.4 Hz), 7.59 (1H, td, $J = 8.4$ and 0.8 Hz), 7.47 (1H, dd, $J = 8.4$ and 1.6 Hz), 7.42 (1H, d, $J = 3.2$ Hz), 6.63 (1H, dd, $J = 3.2$ and 1.2 Hz), 6.35 (1H, s), 3.06 (3H, s).

20

25 Example 149

6-(3-chloropyridin-4-yl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (3-chloropyridin-4-yl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 236; ^1H NMR (400 MHz, CD_3OD) δ_{H} 8.83 (1H, s), 8.71 (1H, d, $J = 5.2$ Hz), 7.62 (1H, d, $J = 4.8$ Hz), 6.24 (1H, s), 3.07 (3H, s).

30

Example 150

{5-[2-amino-6-(methylamino)pyrimidin-4-yl]pyridin-2-yl}methanol.

Prepared according to general procedure 6 from [6-(hydroxymethyl)pyridin-3-yl]boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 232.

35

Example 151

4-N-cyclobutyl-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (2,3-dimethylphenyl)boronic acid

- 5 and 6-chloro-4-N-cyclobutylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 269; ^1H NMR (400 MHz, CD_3OD) δ_H 7.20 (1H, d, $J = 7.2$ Hz), 7.13 (1H, t, $J = 7.2$ Hz), 7.08 (1H, d, $J = 7.2$ Hz), 5.77 (1H, s), 4.44 (1H, br s), 2.44 – 2.36 (2H, m), 2.34 (3H, s), 2.21 (3H, s), 2.04 – 1.94 (m, 2H), 1.82 – 1.73 (m, 2H).

10 Example 152

4-N-cyclobutyl-6-[1-(4-methylbenzenesulfonyl)-1H-indol-3-yl]pyrimidine-2,4-diamine.

Prepared according to general procedure 8 from [1-(4-methylbenzenesulfonyl)-1H-indol-3-yl]boronic acid and 6-chloro-4-N-cyclobutylpyrimidine-2,4-diamine.

- 15 LCMS $[M+H]^+$ 434; ^1H NMR (400 MHz, CD_3OD) δ_H 8.39 (1H, s), 8.09 (1H, d, $J = 8.4$ Hz), 7.96 – 7.94 (2H, m), 7.84 (1H, d, $J = 8.0$ Hz), 7.50 (1H, td, $J = 7.2$ and 0.8 Hz), 7.35 (1H, td, $J = 7.2$ and 0.8 Hz), 7.41 – 7.39 (2H, m), 6.44 (1H, s), 4.66 (1H, quintet, $J = 8.4$ Hz), 2.47 – 2.41 (2H, m), 2.39 (3H, s), 2.14 – 2.04 (2H, m), 1.89 – 1.82 (2H, m).

20

Example 153

4-N-cyclopentyl-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (2,3-dimethylphenyl)boronic acid and 6-chloro-4-N-cyclopentylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 283; ^1H NMR

- 25 (400 MHz, CD_3OD) δ_H 7.19 (1H, d, $J = 7.2$ Hz), 7.13 (1H, t, $J = 7.6$ Hz), 7.08 (1H, dd, $J = 7.6$ and 1.6 Hz), 5.81 (1H, s), 4.25 (1H, br s), 2.33 (3H, s), 2.22 (3H, s), 2.06 – 2.00 (2H, m), 1.81 – 1.74 (2H, m), 1.71 – 1.63 (2H, m), 1.58 – 1.51 (2H, m).

30 Example 154

4-N-cyclopentyl-6-[1-(4-methylbenzenesulfonyl)-1H-indol-3-yl]pyrimidine-2,4-diamine.

Prepared according to general procedure 8 from [1-(4-methylbenzenesulfonyl)-1H-indol-3-yl]boronic acid and 6-chloro-4-N-cyclopentylpyrimidine-2,4-diamine.

- 35 LCMS $[M+H]^+$ 448; ^1H NMR (400 MHz, CD_3OD) δ_H 8.38 (1H, s), 8.10 (1H, d, $J =$

8.4 Hz), 7.96 – 7.94 (2H, m), 7.84 (1H, d, J = 8.0 Hz), 7.50 (1H, td, J = 7.2 and 1.2 Hz), 7.42 (1H, td, J = 7.2 and 0.8 Hz), 7.41 – 7.39 (2H, m), 6.48 (1H, s), 4.51 (1H, quintet, J = 6.8 Hz), 2.39 (3H, s), 2.14 – 2.05 (2H, m), 1.84 – 1.78 (2H, m), 1.75 – 1.66 (2H, m), 1.63 – 1.57 (2H, m).

5

Example 155

4-N-methyl-6-{1-[4-(trifluoromethyl)benzenesulfonyl]-1H-indol-3-yl}pyrimidine-2,4-diamine.

Prepared according to general procedure 8 from {1-[4-

- 10 (trifluoromethyl)benzenesulfonyl]-1H-indol-3-yl}boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 448; ^1H NMR (400 MHz, CD_3OD) δ_H 8.19 (2H, d, J = 8.4 Hz), 8.16 (1H, s), 8.08 – 8.04 (2H, m), 7.84 (2H, d, J = 8.4 Hz), 7.41 (1H, td, J = 7.6 and 0.8 Hz), 7.34 (1H, td, J = 8.0 and 0.8 Hz), 6.26 (1H, s), 2.92 (s, 3H).

15

Example 156

4-N-cyclohexyl-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (2,3-dimethylphenyl)boronic acid and 6-chloro-4-N-cyclohexylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 297; ^1H NMR (400 MHz, CD_3OD) δ_H 7.19 (1H, d, J = 7.2 Hz), 7.12 (1H, t, J = 7.6 Hz), 7.08 (1H, dd, J = 7.6 and 1.6 Hz), 5.78 (1H, s), 3.82 (1H, br s), 2.33 (3H, s), 2.21 (3H, s), 2.03 – 1.99 (2H, m), 1.83 – 1.78 (2H, m), 1.71 – 1.66 (1H, m), 1.48 – 1.37 (2H, m), 1.31 – 1.21 (3H, m).

25 Example 157

4-N-cyclohexyl-6-[1-(4-methylbenzenesulfonyl)-1H-indol-3-yl]pyrimidine-2,4-diamine.

Prepared according to general procedure 8 from [1-(4-methylbenzenesulfonyl)-1H-indol-3-yl]boronic acid and 6-chloro-4-N-cyclohexylpyrimidine-2,4-diamine.

- 30 LCMS $[M+H]^+$ 462; ^1H NMR (400 MHz, CD_3OD) δ_H 8.36 (1H, s), 8.08 (1H, d, J = 8.0 Hz), 7.95 – 7.93 (2H, m), 7.83 (1H, d, J = 8.0 Hz), 7.48 (1H, td, J = 7.2 and 0.8 Hz), 7.41 (1H, td, J = 8.0 and 1.2 Hz), 7.40 – 7.38 (2H, m), 6.46 (1H, s), 4.11 – 4.05 (1H, m), 2.38 (3H, s), 2.04 – 2.00 (2H, m), 1.86 – 1.82 (2H, m), 1.72 – 1.68 (1H, m), 1.48 – 1.26 (5H, m).

35

Example 158

6-(2,3-dimethylphenyl)-4-N-ethylpyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (2,3-dimethylphenyl)boronic acid and 6-chloro-4-N-ethylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 243; ^1H NMR (400 MHz, CD_3OD) δ_H 7.19 (1H, d, J = 7.2 Hz), 7.13 (1H, t, J = 7.6 Hz), 7.08 (1H, dd, J = 7.6 and 1.2 Hz), 5.80 (1H, s), 3.41 – 3.36 (2H, m), 2.33 (3H, s), 2.21 (3H, s), 1.23 (3H, t, J = 7.2 Hz).

Example 159

4-N-ethyl-6-[1-(4-methylbenzenesulfonyl)-1H-indol-3-yl]pyrimidine-2,4-diamine.

Prepared according to general procedure 8 from [1-(4-methylbenzenesulfonyl)-1H-indol-3-yl]boronic acid and 6-chloro-4-N-ethylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 408; ^1H NMR (400 MHz, CD_3OD) δ_H 8.12 (1H, s), 8.05 – 8.01 (2H, m), 7.87 – 7.85 (2H, m), 7.37 (1H, td, J = 7.2 and 1.2 Hz), 7.34 – 7.32 (2H, m), 7.30 (1H, td, J = 8.0 and 1.2 Hz), 6.26 (1H, s), 3.39 (2H, q, J = 7.2 Hz), 2.34 (3H, s), 1.24 (3H, t, J = 7.2 Hz).

Example 160

4-N-tert-butyl-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (2,3-dimethylphenyl)boronic acid and 4-N-tert-butyl-6-chloropyrimidine-2,4-diamine. LCMS $[M+H]^+$ 271; ^1H NMR (400 MHz, CD_3OD) δ_H 7.18 (1H, d, J = 7.2 Hz), 7.12 (1H, t, J = 7.6 Hz), 7.07 (1H, dd, J = 7.6 and 1.6 Hz), 5.81 (1H, s), 2.33 (3H, s), 2.21 (3H, s), 1.49 (9H, s).

Example 161

4-N-tert-butyl-6-[1-(4-methylbenzenesulfonyl)-1H-indol-3-yl]pyrimidine-2,4-diamine.

Prepared according to general procedure 8 from [1-(4-methylbenzenesulfonyl)-1H-indol-3-yl]boronic acid and 4-N-tert-butyl-6-chloropyrimidine-2,4-diamine.

LCMS $[M+H]^+$ 436; ^1H NMR (400 MHz, CD_3OD) δ_H 8.36 (1H, s), 8.08 (1H, d, J = 8.4 Hz), 7.95 – 7.93 (2H, m), 7.84 (1H, d, J = 7.6 Hz), 7.48 (1H, td, J = 7.2 and 1.2 Hz), 7.40 (1H, td, J = 8.4 and 1.2 Hz), 7.40 – 7.38 (2H, m), 6.52 (1H, s), 2.38 (3H, s), 1.54 (9H, s).

Example 162

6-(2,3-dimethylphenyl)-4-N-(propan-2-yl)pyrimidine-2,4-diamine.

Prepared according to general procedure 2 (2,3-dimethylphenyl)boronic acid and 6-chloro-4-N-(propan-2-yl)pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 257; ^1H NMR (400 MHz, CD_3OD) δ_H 7.36 (1H, d, $J = 7.2$ Hz), 7.25 (1H, t, $J = 7.6$ Hz), 7.19 (1H, d, $J = 7.2$ Hz), 5.96 (1H, s), 4.39 (1H, septet, $J = 6.4$ Hz), 2.37 (3H, s), 2.26 (3H, s), 1.29 (3H, s), 1.27 (3H, s).

Example 163

6-[1-(4-methylbenzenesulfonyl)-1H-indol-3-yl]-4-N-(propan-2-yl)pyrimidine-2,4-diamine.

Prepared according to general procedure 8 from [1-(4-methylbenzenesulfonyl)-1H-indol-3-yl]boronic acid and 6-chloro-4-N-(propan-2-yl)pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 422; ^1H NMR (400 MHz, CD_3OD) δ_H 8.12 (1H, s), 8.05 – 8.02 (2H, m), 7.89 – 7.86 (2H, m), 7.40 – 7.30 (4H, m), 6.25 (1H, s), 4.19 (1H, br s), 2.36 (3H, s), 1.26 (3H, s), 1.24 (3H, s).

Example 164

4-N-(cyclopropylmethyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (2,3-dimethylphenyl)boronic acid and 6-chloro-4-N-(cyclopropylmethyl)pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 269.

Example 165

4-N-(cyclopropylmethyl)-6-[1-(4-methylbenzenesulfonyl)-1H-indol-3-yl]pyrimidine-2,4-diamine.

Prepared according to general procedure 8 from [1-(4-methylbenzenesulfonyl)-1H-indol-3-yl]boronic acid and 6-chloro-4-N-(cyclopropylmethyl)pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 434; ^1H NMR (400 MHz, CD_3OD) δ_H 8.14 (1H, s), 8.06 – 8.02 (2H, m), 7.88 – 7.86 (2H, m), 7.40 – 7.30 (5H, m), 6.31 (1H, s), 3.25 (2H, d, $J = 6.8$ Hz), 1.14 – 1.11 (1H, m), 0.57 – 0.55 (2H, m), 0.30 – 0.28 (2H, m).

Example 166

4-N-[(1R)-1-cyclopropylethyl]-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (2,3-dimethylphenyl)boronic acid and 6-chloro-4-N-[(1R)-1-cyclopropylethyl]pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 283; ^1H NMR (400 MHz, CD_3OD) δ_H 7.19 (1H, d, $J = 6.8$ Hz), 7.13 (1H, t, $J = 7.6$

Hz), 7.09 (1H, dd, J = 7.6 and 1.2 Hz), 5.80 (1H, s), 3.58 (1H, br s), 2.34 (3H, s), 2.22 (3H, s), 1.28 (3H, d, J = 6.4 Hz), 0.99 – 0.92 (1H, m), 0.57 – 0.45 (2H, m), 0.44 – 0.38 (1H, m), 0.29 – 0.23 (1H, m).

5 Example 167

4-N-[(1R)-1-cyclopropylethyl]-6-[1-(4-methylbenzenesulfonyl)-1H-indol-3-yl]pyrimidine-2,4-diamine.

Prepared according to general procedure 8 from [1-(4-methylbenzenesulfonyl)-1H-indol-3-yl]boronic acid and 6-chloro-4-N-[(1R)-1-cyclopropylethyl]pyrimidine-2,4-diamine. LCMS [M+H]⁺ 448; ¹H NMR (400 MHz, CD₃OD) δ_H 8.37 (1H, s), 8.08 (1H, d, J = 8.0 Hz), 7.95 – 7.93 (2H, m), 7.84 (1H, d, J = 7.6 Hz), 7.49 (1H, dt, J = 7.6 and 1.2 Hz), 7.42 (1H, dt, J = 8.0 and 0.8 Hz), 7.40 – 7.38 (2H, m), 6.47 (1H, s), 3.78 – 3.71 (1H, m), 2.38 (3H, s), 1.33 (3H, d, J = 6.8 Hz), 1.04 – 0.99 (1H, m), 0.64 – 0.57 (1H, m), 0.56 – 0.49 (1H, m), 0.47 – 0.41 (1H, m), 0.33 – 0.27 (1H, m).

Example 168

4-N-[(1S)-1-cyclopropylethyl]-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (2,3-dimethylphenyl)boronic acid and 6-chloro-4-N-[(1S)-1-cyclopropylethyl]pyrimidine-2,4-diamine. LCMS [M+H]⁺ 283; ¹H NMR (400 MHz, CD₃OD) δ_H 7.18 (1H, d, J = 6.8 Hz), 7.11 (1H, t, J = 7.6 Hz), 7.07 (1H, dd, J = 7.6 and 1.6 Hz), 5.78 (1H, s), 3.56 (1H, br s), 2.32 (3H, s), 2.20 (3H, s), 1.27 (3H, d, J = 6.4 Hz), 0.98 – 0.91 (1H, m), 0.56 – 0.43 (2H, m), 0.42 – 0.36 (1H, m), 0.27 – 0.21 (1H, m).

Example 169

4-N-[(1S)-1-cyclopropylethyl]-6-[1-(4-methylbenzenesulfonyl)-1H-indol-3-yl]pyrimidine-2,4-diamine.

Prepared according to general procedure 8 from [1-(4-methylbenzenesulfonyl)-1H-indol-3-yl]boronic acid and 6-chloro-4-N-[(1S)-1-cyclopropylethyl]pyrimidine-2,4-diamine. LCMS [M+H]⁺ 448; ¹H NMR (400 MHz, CD₃OD) δ_H 8.37 (1H, s), 8.09 (1H, d, J = 8.4 Hz), 7.96 – 7.94 (2H, m), 7.85 (1H, d, J = 8.0 Hz), 7.49 (1H, dt, J = 7.6 and 1.2 Hz), 7.42 (1H, dt, J = 8.0 and 1.2 Hz), 7.41 – 7.39 (2H, m), 6.47 (1H, s), 3.78 – 3.71 (1H, m), 2.39 (3H, s), 1.33 (3H, d, J = 6.8 Hz), 1.05 – 0.98 (1H, m),

0.63 – 0.58 (1H, m), 0.57 – 0.50 (1H, m), 0.48 – 0.42 (1H, m), 0.33 – 0.27 (1H, m).

Example 170

5 6-(1-benzofuran-3-yl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (1-benzofuran-3-yl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 241; ^1H NMR (400 MHz, CD_3OD) δ_H 8.27 (1H, s), 8.07 (1H, dd, $J = 8.0$ and 1.2 Hz), 7.58 – 7.56 (1H, m), 7.35 (2H, dt, $J = 7.6$ and 1.2 Hz), 6.32 (1H, s), 2.95 (3H, s).

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Example 171

6-(2-chloro-5-methylphenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (2-chloro-5-methylphenyl)boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 249; ^1H NMR (400 MHz, CD_3OD) δ_H 7.35 (1H, d, $J = 8.0$ Hz), 7.28 (1H, d, $J = 2.0$ Hz), 7.23 – 7.20 (1H, m), 5.97 (1H, s), 2.92 (3H, s), 2.38 (3H, s).

15

Example 172

6-(1-benzothiophen-3-yl)-4-N-methylpyrimidine-2,4-diamine.

20 Prepared according to general procedure 2 from (1-benzothiophen-3-yl)boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 257; ^1H NMR (400 MHz, CD_3OD) δ_H 8.27 (1H, d, $J = 7.2$ Hz), 7.97 – 7.94 (1H, m), 7.92 (1H, s), 7.45 (1H, dt, $J = 7.2$ and 1.6 Hz), 7.41 (1H, dt, $J = 7.2$ and 1.6 Hz), 6.20 (1H, s), 2.95 (3H, s).

25

Example 173

2-{4-[2-amino-6-(methylamino)pyrimidin-4-yl]phenyl}propan-2-ol.

Prepared according to general procedure 2 from [4-(2-hydroxypropan-2-yl)phenyl]boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 259; ^1H NMR (400 MHz, CD_3OD) δ_H 7.82 – 7.80 (2H, m), 7.60 – 7.57 (2H, m), 6.23 (1H, s), 2.94 (3H, s), 1.58 (6H, s).

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Example 174

6-(1H-indol-4-yl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (1H-indol-4-yl)boronic acid and 6-chloro-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 240; ^1H NMR (400 MHz, CD_3OD) δ_H 7.50 – 7.48 (1H, m), 7.38 (1H, dd, $J = 7.6$ and 0.8 Hz), 7.34 (1H, d, $J = 3.2$ Hz), 7.21 (1H, t, $J = 7.6$ Hz), 6.80 (1H, dd, $J = 3.2$ and 0.8 Hz),
5 6.31 (1H, s), 2.96 (3H, s).

Example 175

4-N-cyclohexyl-6-(2,3-dichlorophenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 3 from cyclohexanamine and 4-chloro-
10 6-(2,3-dichlorophenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 337; ^1H NMR (400 MHz, CD_3OD) δ_H 7.63 – 7.61 (1H, m), 7.40 (1H, d, $J = 2.0$ Hz), 7.39 (1H, s), 5.93 (1H, s), 3.88 (1H, br s), 2.06 – 2.02 (2H, m), 1.86 – 1.81 (2H, m), 1.73 – 1.69 (1H, m), 1.50 – 1.40 (2H, m), 1.34 – 1.25 (3H, m).

15 Example 176

6-(2,3-dichlorophenyl)-4-N-(propan-2-yl)pyrimidine-2,4-diamine.

Prepared according to general procedure 3 from propan-2-amine and 4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 297; ^1H NMR (400 MHz, CD_3OD) δ_H 7.61 – 7.59 (1H, m), 7.38 (1H, d, $J = 2.0$ Hz), 7.37 (1H, s), 5.92 (1H, s),
20 s), 4.17 (1H, br s), 1.25 (3H, s), 1.24 (3H, s).

Example 177

4-N-(cyclopropylmethyl)-6-(2,3-dichlorophenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 3 from cyclopropylmethanamine and 4-
25 chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 309.

Example 178

4-N-[(1S)-1-cyclopropylethyl]-6-(2,3-dichlorophenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 3 from (1S)-1-cyclopropylethan-1-
30 amine and 4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 323; ^1H NMR (400 MHz, CD_3OD) δ_H 7.61 – 7.59 (1H, m), 7.38 (1H, d, $J = 2.0$ Hz), 7.37 (1H, s), 5.92 (1H, s), 3.59 (1H, br s), 1.28 (3H, d, $J = 6.8$ Hz), 0.99 – 0.92 (2H, m), 0.53 – 0.48 (2H, m), 0.46 – 0.38 (1H, m), 0.29 – 0.23 (1H, m).

35 Example 179

4-N-[(1R)-1-cyclopropylethyl]-6-(2,3-dichlorophenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 3 from (1R)-1-cyclopropylethan-1-amine and 4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 323; ^1H NMR (400 MHz, CD_3OD) δ_H 7.61 – 7.59 (1H, m), 7.38 (1H, d, $J = 2.0$ Hz), 7.37 (1H, s), 5.92 (1H, s), 3.59 (1H, br s), 1.28 (3H, d, $J = 6.8$ Hz), 0.99 – 0.92 (2H, m), 0.58 – 0.47 (2H, m), 0.46 – 0.38 (1H, m), 0.29 – 0.23 (1H, m).

Example 180

6-(2,3-dichlorophenyl)-4-N-(2,2-dimethylpropyl)pyrimidine-2,4-diamine.

- 10 Prepared according to general procedure 3 from 2,2-dimethylpropan-1-amine and 4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 325; ^1H NMR (400 MHz, CD_3OD) δ_H 7.61 – 7.58 (1H, m), 7.38 (1H, d, $J = 2.0$ Hz), 7.36 (1H, s), 6.01 (1H, s), 3.27 (2H, br s), 0.98 (9H, s).

15 Example 181

6-(2,3-dimethylphenyl)-4-N-(2,2-dimethylpropyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 5 from (2,3-dimethylphenyl)boronic acid and 6-chloro-4-N-(2,2-dimethylpropyl)pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 285; ^1H NMR (400 MHz, CD_3OD) δ_H 7.20 (1H, d, $J = 6.8$ Hz), 7.14 (1H, t, $J = 7.6$ Hz), 7.10 (1H, dd, $J = 7.6$ and 1.6 Hz), 5.90 (1H, s), 2.34 (3H, s), 2.22 (3H, s), 1.00 (9H, s).

Example 182

4-N-(2,2-dimethylpropyl)-6-[1-(4-methylbenzenesulfonyl)-1H-indol-3-yl]pyrimidine-2,4-diamine.

- 25 Prepared according to general procedure 8 from [1-(4-methylbenzenesulfonyl)-1H-indol-3-yl]boronic acid and 6-chloro-4-N-(2,2-dimethylpropyl)pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 450; ^1H NMR (400 MHz, CD_3OD) δ_H 8.14 (1H, s), 8.08 (1H, d, $J = 7.6$), 8.04 (1H, dt, $J = 8.0$ and 1.2 Hz), 7.90 – 7.88 (2H, m), 7.39 (1H, td, $J = 7.2$ and 1.2 Hz), 7.37 – 7.34 (2H, m), 7.33 (1H, td, $J = 7.2$ and 1.2 Hz), 6.38 (1H, s), 3.27 (2H, s), 2.37 (3H, s), 1.02 (9H, s).

Example 183

6-(5-bromo-2-methoxyphenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (5-bromo-2-methoxyphenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS [M+H]⁺ 310; ¹H NMR (400 MHz, CD₃OD) δ_H 7.72 (1H, d, J = 2.4 Hz), 7.52 (1H, dd, J = 8.8 and 2.8 Hz), 7.04 (1H, d, J = 9.2 Hz), 6.25 (1H, s), 3.87 (3H, s), 2.91 (s, 3H).

Example 184

6-(2,5-dimethylphenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (2,5-dimethylphenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS [M+H]⁺ 229; ¹H NMR (400 MHz, CD₃OD) δ_H 7.16 – 7.13 (2H, m), 7.11 (1H, s), 5.84 (1H, s), 2.92 (3H, s), 2.35 (3H, s), 2.29 (3H, s).

Example 185

4-N-methyl-6-[2-(trifluoromethyl)pyridin-3-yl]pyrimidine-2,4-diamine.

Prepared according to general procedure 6 from [2-(trifluoromethyl)pyridin-3-yl]boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS [M+H]⁺ 270.

Example 186

4-N-methyl-6-(pyrimidin-5-yl)pyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (pyrimidin-5-yl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS [M+H]⁺ 203.

Example 187

6-[4-(benzyloxy)-2-methylphenyl]-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from [4-(benzyloxy)-2-methylphenyl]boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS [M+H]⁺ 321; ¹H NMR (400 MHz, CD₃OD) δ_H 7.47 – 7.46 (2H, m), 7.41 – 7.38 (2H, m), 7.35 – 7.32 (1H, m), 7.24 (1H, d, J = 8.4 Hz), 6.92 – 6.87 (2H, m), 5.84 (1H, s), 5.14 (2H, s), 2.91 (3H, s), 2.34 (3H, s).

Example 188

6-(4-methoxy-2,5-dimethylphenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (4-methoxy-2,5-dimethylphenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS

[M+H]⁺ 259; ¹H NMR (400 MHz, CD₃OD) δ_H 7.08 (1H, s), 6.79 (1H, s), 5.83 (1H, s), 3.86 (3H, s), 2.91 (3H, s), 2.34 (3H, s), 2.19 (3H, s).

Example 189

5 4-N-methyl-6-(2,4,5-trimethylphenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (2,4,5-trimethylphenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS [M+H]⁺ 243; ¹H NMR (400 MHz, CD₃OD) δ_H 7.07 (1H, s), 7.03 (1H, s), 5.83 (1H, s), 2.91 (3H, s), 2.28 (9H, s).

10

Example 190

2-[2-amino-6-(methylamino)pyrimidin-4-yl]-4-chlorobenzonitrile.

Prepared according to general procedure 6 from (5-chloro-2-cyanophenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS [M+H]⁺ 260.

15

Example 191

6-(4,5-dichloro-2-methylphenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (4,5-dichloro-2-methylphenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS

20 [M+H]⁺ 283; ¹H NMR (400 MHz, CD₃OD) δ_H 7.62 (1H, s), 7.61 (1H, s), 6.06 (1H, s), 3.04 (3H, s), 2.36 (3H, s).

Example 192

6-(2,5-dichloro-4-methoxyphenyl)-4-N-methylpyrimidine-2,4-diamine.

25 Prepared according to general procedure 6 from (2,5-dichloro-4-methoxyphenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS [M+H]⁺ 299; ¹H NMR (400 MHz, CD₃OD) δ_H 7.52 (1H, s), 7.22 (1H, s), 6.03 (1H, s), 3.96 (3H, s), 2.92 (3H, s).

30 Example 193

6-(4-fluoro-2,5-dimethylphenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (4-fluoro-2,5-dimethylphenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS

35 [M+H]⁺ 247; ¹H NMR (400 MHz, CD₃OD) δ_H 7.16 (1H, d, J = 8.0 Hz), 6.95 (1H, d, J = 10.8 Hz), 5.83 (1H, s), 2.91 (3H, s), 2.30 (3H, s), 2.27 (3H, s).

Example 194

4-N-methyl-6-[2-methyl-5-(trifluoromethyl)phenyl]pyrimidine-2,4-diamine.

Prepared according to general procedure 6 from [2-methyl-5-

- 5 (trifluoromethyl)phenyl]boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 283; ^1H NMR (400 MHz, CD_3OD) δ_H 7.78 – 7.73 (2H, m), 7.61 (1H, d, J = 8.0 Hz), 6.08 (1H, s), 3.05 (3H, s), 2.46 (3H, s).

Example 195

- 10 6-[5-chloro-2-methyl-4-(trifluoromethyl)phenyl]-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from [5-chloro-2-methyl-4-

(trifluoromethyl)phenyl]boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-

diamine. LCMS $[M+H]^+$ 317; ^1H NMR (400 MHz, CD_3OD) δ_H 7.69 (1H, s), 7.53 (1H, s), 5.89 (1H, s), 2.93 (3H, s), 2.40 (3H, s).

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Example 196

6-[2,5-bis(trifluoromethyl)phenyl]-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from [2,5-

bis(trifluoromethyl)phenyl]boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-

- 20 diamine. LCMS $[M+H]^+$ 337; ^1H NMR (400 MHz, CD_3OD) δ_H 8.20 – 8.15 (2H, m), 8.10 (1H, s), 6.15 (1H, s), 3.08 (3H, s).

Example 197

6-(5-tert-butyl-2-methoxyphenyl)-4-N-methylpyrimidine-2,4-diamine.

- 25 Prepared according to general procedure 6 from (5-tert-butyl-2-methoxyphenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 287; ^1H NMR (400 MHz, CD_3OD) δ_H 7.64 (1H, dd, J = 8.8 and 2.4 Hz), 7.51 (1H, s), 7.17 (1H, d, J = 8.8 Hz), 6.25 (1H, s), 3.94 (3H, s), 3.05 (3H, s), 1.37 (9H, s).

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Example 198

6-[2-methoxy-5-(propan-2-yl)phenyl]-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from [2-methoxy-5-(propan-2-

yl)phenyl]boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS

- 35 $[M+H]^+$ 273; ^1H NMR (400 MHz, CD_3OD) δ_H 7.49 (1H, dd, J = 8.4 and 2.0 Hz),

7.39 (1H, s), 7.17 (1H, d, J = 8.8 Hz), 6.28 (1H, s), 3.95 (3H, s), 3.06 (3H, s), 2.98 (1H, sept, J = 6.8 Hz), 1.31 (3H, s), 1.30 (3H, s).

Example 199

5 6-[2-chloro-5-(trifluoromethyl)phenyl]-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from [2-chloro-5-(trifluoromethyl)phenyl]boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 303; ^1H NMR (400 MHz, CD_3OD) δ_H 7.87 (1H, br s), 7.82 (1H, d, J = 2.0 Hz), 7.81 (1H, s), 6.14 (1H, s), 3.03 (3H, s).

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Example 200

6-(2-fluoro-5-methylphenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (2-fluoro-5-methylphenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 233; ^1H NMR (400 MHz, CD_3OD) δ_H 7.58 (1H, dd, J = 7.2 and 2.0 Hz), 7.28 – 7.25 (1H, m), 7.10 – 7.06 (1H, m), 6.02 (1H, d, J = 1.6 Hz), 2.94 (3H, s), 2.40 (3H, s).

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Example 201

6-(5-chloro-2-methoxyphenyl)-4-N-methylpyrimidine-2,4-diamine.

20 Prepared according to general procedure 6 from (5-chloro-2-methoxyphenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 265; ^1H NMR (400 MHz, CD_3OD) δ_H 7.58 – 7.57 (1H, m), 7.56 (1H, d, J = 2.8 Hz), 7.23 (1H, d, J = 9.6 Hz), 6.27 (1H, s), 3.96 (3H, s), 3.05 (3H, s).

25 Example 202

6-(5-fluoro-2-methylphenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (5-fluoro-2-methylphenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 233; ^1H NMR (400 MHz, CD_3OD) δ_H 7.31 – 7.27 (1H, m), 7.08 – 7.04 (2H, m), 5.87 (1H, s), 2.94 (3H, s), 2.33 (3H, s).

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Example 203

6-(2,5-dimethoxyphenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (2,5-dimethoxyphenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 261; ^1H NMR

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(400 MHz, CD₃OD) δ_{H} 7.18 (1H, d, J = 3.2 Hz), 7.04 (1H, d, J = 9.2 Hz), 6.98 (1H, dd, J = 8.8 and 3.2 Hz), 6.27 (1H, s), 3.83 (6H, s), 2.93 (3H, s).

Example 204

5 6-(2-methoxy-5-methylphenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (2-methoxy-5-methylphenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS [M+H]⁺ 245; ¹H NMR (400 MHz, CD₃OD) δ_{H} 7.36 (1H, s), 7.20 (1H, d, J = 8.8 Hz), 6.98 (1H, d, J = 8.8 Hz), 6.20 (1H, s), 3.83 (3H, s), 2.91 (3H, s), 2.33 (3H, s).

10

Example 205

6-(2-chloro-5-fluorophenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (2-chloro-5-fluorophenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS [M+H]⁺ 253; ¹H NMR (400 MHz, CD₃OD) δ_{H} 7.54 – 7.50 (1H, m), 7.25 (1H, dd, J = 9.2 and 3.2 Hz), 7.19 (1H, td, J = 8.8 and 3.2 Hz), 6.01 (1H, s), 2.93 (3H, s).

15

Example 206

3-[2-amino-6-(methylamino)pyrimidin-4-yl]-4-fluorobenzonitrile.

20 Prepared according to general procedure 6 from (5-cyano-2-fluorophenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS [M+H]⁺ 244; ¹H NMR (400 MHz, CD₃OD) δ_{H} 8.26 (1H, dd, J = 6.8 and 2.0 Hz), 7.87 – 7.84 (1H, m), 7.45 – 7.40 (1H, m), 6.27 (1H, d, J = 2.0 Hz), 2.93 (3H, s).

25 Example 207

6-(2-chloro-5-methoxyphenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (2-chloro-5-methoxyphenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS [M+H]⁺ 265; ¹H NMR (400 MHz, CD₃OD) δ_{H} 7.39 (1H, d, J = 8.8 Hz), 7.02 (1H, d, J = 3.2 Hz), 6.98 (1H, dd, J = 8.8 and 3.2 Hz), 5.99 (1H, s), 3.84 (3H, s), 2.92 (3H, s).

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Example 208

6-[5-fluoro-2-(trifluoromethyl)phenyl]-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from [5-fluoro-2-(trifluoromethyl)phenyl]boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 287; ^1H NMR (400 MHz, CD_3OD) δ_H 7.87 – 7.83 (1H, m), 7.39 – 7.34 (1H, m), 7.25 (1H, dd, J = 9.2 and 2.8 Hz), 5.89 (1H, s), 2.92 (3H, s).

5

Example 209

6-(2,5-dichlorophenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (2,5-dichlorophenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 269; ^1H NMR (400 MHz, CD_3OD) δ_H 7.51 – 7.49 (2H, m), 7.42 (1H, dd, J = 8.4 and 2.4 Hz), 6.01 (1H, s), 2.92 (3H, s).

10

Example 210

6-(5-chloro-2-fluorophenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (5-chloro-2-fluorophenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 253; ^1H NMR (400 MHz, CD_3OD) δ_H 7.75 – 7.23 (1H, m), 7.69 – 7.65 (1H, m), 7.40 (1H, m), 6.31 (1H, s), 3.07 (3H, s).

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Example 211

3-[2-amino-6-(methylamino)pyrimidin-4-yl]-4-methylbenzonitrile.

Prepared according to general procedure 6 from (5-cyano-2-methylphenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 240; ^1H NMR (400 MHz, CD_3OD) δ_H 7.68 – 7.66 (2H, m), 7.48 (1H, d, J = 7.6 Hz), 5.88 (1H, s), 2.93 (3H, s), 2.44 (3H, s).

20

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Example 212

3-[2-amino-6-(methylamino)pyrimidin-4-yl]-4-methoxybenzonitrile.

Prepared according to general procedure 6 from (5-cyano-2-methoxyphenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 256; ^1H NMR (400 MHz, CD_3OD) δ_H 7.95 (1H, d, J = 2.4 Hz), 7.98 (1H, dd, J = 8.8 and 2.0 Hz), 7.27 (1H, d, J = 8.8 Hz), 6.26 (1H, s), 3.97 (3H, s), 2.92 (3H, s).

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Example 213

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6-(2-chloro-5-fluoro-4-methylphenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (2-chloro-5-fluoro-4-methylphenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS [M+H]⁺ 267; ¹H NMR (400 MHz, CD₃OD) δ_H 7.39 (1H, d, J = 6.8 Hz), 7.19 (1H, d, J = 9.6 Hz), 6.02 (1H, s), 2.92 (3H, s), 2.32 (3H, d, J = 1.6 Hz).

Example 214

6-(5-chloro-2-fluoro-4-methylphenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (5-chloro-2-fluoro-4-methylphenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS [M+H]⁺ 267; ¹H NMR (400 MHz, CD₃OD) δ_H 7.72 (1H, d, J = 6.8 Hz), 7.19 (1H, d, J = 11.2 Hz), 6.31 (1H, s), 3.05 (3H, s), 2.48 (3H, s).

Example 215

6-(2-chloro-4-fluoro-5-methylphenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (2-chloro-4-fluoro-5-methylphenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS [M+H]⁺ 267; ¹H NMR (400 MHz, CD₃OD) δ_H 7.36 (1H, d, J = 8.4 Hz), 7.23 (1H, d, J = 9.6 Hz), 5.96 (1H, s), 2.91 (3H, s), 2.29 (3H, d, J = 1.6 Hz).

Example 216

4-N-cyclopropyl-6-(4-fluoro-2,5-dimethylphenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (4-fluoro-2,5-dimethylphenyl)boronic acid and 6-chloro-4-N-cyclopropylpyrimidine-2,4-diamine.

LCMS [M+H]⁺ 273; ¹H NMR (400 MHz, CD₃OD) δ_H 7.19 (1H, d, J = 8.0 Hz), 6.97 (1H, d, J = 10.4 Hz), 6.03 (1H, s), 2.63 (1H, br s), 2.33 (3H, s), 2.28 (3H, s), 0.84 – 0.79 (2H, m), 0.60 – 0.56 (2H, m).

Example 217

4-N-cyclopropyl-6-(4-methoxy-2,5-dimethylphenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (4-methoxy-2,5-dimethylphenyl)boronic acid and 6-chloro-4-N-cyclopropylpyrimidine-2,4-diamine. LCMS [M+H]⁺ 285.

Example 218

4-N-cyclopropyl-6-(2,5-dimethylphenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (2,5-dimethylphenyl)boronic acid and 6-chloro-4-N-cyclopropylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 255; ^1H NMR (400 MHz, CD_3OD) δ_H 7.30 – 7.28 (2H, m), 7.23 (1H, s), 6.00 (1H, s), 3.06 (1H, br s), 2.40 (3H, s), 2.36 (3H, s), 0.93 – 0.88 (2H, m), 0.69 – 0.66 (2H, m).

Example 219

6-(5-chloro-2-methylphenyl)-4-N-cyclopropylpyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (5-chloro-2-

methylphenyl)boronic acid and 6-chloro-4-N-cyclopropylpyrimidine-2,4-diamine.

LCMS $[M+H]^+$ 275; ^1H NMR (400 MHz, CD_3OD) δ_H 7.33 – 7.27 (3H, m), 6.05 (1H, s), 2.65 (1H, br s), 0.84 – 0.79 (2H, m), 0.60 – 0.56 (2H, m).

Example 220

6-(5-chloro-2-methylphenyl)-4-N-cyclobutylpyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (5-chloro-2-

methylphenyl)boronic acid and 6-chloro-4-N-cyclobutylpyrimidine-2,4-diamine.

LCMS $[M+H]^+$ 289; ^1H NMR (400 MHz, CD_3OD) δ_H 7.33 – 7.26 (3H, m), 5.81 (1H, s), 4.45 (1H, br s), 2.44 – 2.37 (2H, m), 2.32 (3H, s), 2.05 – 1.95 (2H, m), 1.83 – 1.74 (2H, m).

Example 221

6-(5-chloro-2-methylphenyl)-4-N-ethylpyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (5-chloro-2-

methylphenyl)boronic acid and 6-chloro-4-N-ethylpyrimidine-2,4-diamine. LCMS

$[M+H]^+$ 263; ^1H NMR (400 MHz, CD_3OD) δ_H 7.51 – 7.46 (2H, m), 7.41 (1H, d, J = 8.4 Hz), 6.05 (1H, s), 3.57 (2H, q, J = 6.8 Hz), 2.37 (3H, s), 1.28 (3H, t, J = 7.2 Hz).

Example 222

6-(5-chloro-2-methylphenyl)-4-N-[2-(4-chlorophenyl)ethyl]pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (5-chloro-2-

methylphenyl)boronic acid and 6-chloro-4-N-[2-(4-chlorophenyl)ethyl]pyrimidine-

2,4-diamine. LCMS $[M+H]^+$ 374; ^1H NMR (400 MHz, CD_3OD) δ_H 7.32 – 7.26 (7H, m), 5.81 (1H, s), 3.64 – 3.60 (2H, m), 2.92 (2H, t, J = 7.6 Hz), 2.31 (3H, s).

Example 223

4-N-[2-(4-chlorophenyl)ethyl]-6-(4-fluoro-2,5-dimethylphenyl)pyrimidine-2,4-diamine.

- 5 Prepared according to general procedure 2 from (4-fluoro-2,5-dimethylphenyl)boronic acid and 6-chloro-4-N-[2-(4-chlorophenyl)ethyl]pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 371; ^1H NMR (400 MHz, CD_3OD) δ_H 7.32 – 7.26 (4H, m), 7.14 (1H, d, J = 8.0 Hz), 6.94 (1H, d, J = 10.8 Hz), 5.79 (1H, s), 3.63 – 3.59 (2H, m), 2.92 (2H, t, J = 7.2 Hz), 2.30 (3H, s),
10 2.27 (3H, s).

Example 224

4-N-[2-(4-chlorophenyl)ethyl]-6-(2,5-dimethylphenyl)pyrimidine-2,4-diamine.

- Prepared according to general procedure 2 from (2,5-dimethylphenyl)boronic acid
15 and 6-chloro-4-N-[2-(4-chlorophenyl)ethyl]pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 353; ^1H NMR (400 MHz, CD_3OD) δ_H 7.32 – 7.26 (4H, m), 7.16 – 7.09 (3H, m), 5.80 (1H, s), 3.61 (2H, t, J = 6.4 Hz), 2.92 (2H, t, J = 7.2 Hz), 2.35 (3H, s), 2.28 (3H, s).

20 Example 225

1-(3-[(2-amino-6-(quinolin-5-yl)pyrimidin-4-yl)amino]propyl)pyrrolidin-2-one.

- Prepared according to general procedure 2 from (quinolin-5-yl)boronic acid and
1-{3-[(2-amino-6-chloropyrimidin-4-yl)amino]propyl}pyrrolidin-2-one. LCMS $[M+H]^+$
25 363; ^1H NMR (400 MHz, CD_3OD) δ_H 8.90 (1H, dd, J = 4.0 and 1.6 Hz), 8.64 (1H, d, J = 8.8 Hz), 8.12 (1H, d, J = 8.4 Hz), 7.88 – 7.84 (1H, m), 7.71 (1H, d, J = 7.2 Hz), 7.59 – 7.56 (1H, m), 6.07 (1H, s), 3.53 (2H, t, J = 6.8 Hz), 3.42 (4H, t, J = 6.8 Hz), 2.42 (2H, t, J = 8.0 Hz), 2.12 – 2.05 (2H, m), 1.93 – 1.86 (2H, m).

Example 226

- 30 6-(2-chloro-3-methylphenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 3 from methanamine and 4-chloro-6-(2-chloro-3-methylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 249; ^1H NMR (400 MHz, CD_3OD) δ_H 7.56 – 7.54 (1H, m), 7.42 – 7.37 (2H, m), 6.11 (1H, s), 3.05 (3H, s),
2.49 (3H, s).

35

Example 227

6-(2-chloro-3-methylphenyl)-4-N-cyclopropylpyrimidine-2,4-diamine.

Prepared according to general procedure 3 from cyclopropanamine and 4-chloro-

6-(2-chloro-3-methylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 275; ^1H NMR (400

5 MHz, CD_3OD) δ_H 7.56 (1H, d, $J = 5.6$ Hz), 7.42 – 7.39 (2H, m), 6.07 (1H, s), 3.09 (1H, br s), 2.50 (3H, s), 0.92 – 0.90 (2H, m), 0.68 (2H, br s).

Example 228

6-(2-chloro-3-methylphenyl)-4-N-[2-(4-chlorophenyl)ethyl]pyrimidine-2,4-diamine.

10 Prepared according to general procedure 3 from 2-(4-chlorophenyl)ethan-1-amine and 4-chloro-6-(2-chloro-3-methylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 373; ^1H NMR (400 MHz, CD_3OD) δ_H 7.57 – 7.55 (1H, m), 7.41 (1H, t, $J = 7.6$ Hz), 7.37 (1H, dd, $J = 8.0$ and 2.0 Hz), 7.34 – 7.28 (4H, m), 6.08 (1H, s), 3.79 (2H, t, $J = 7.2$ Hz), 2.97 (2H, t, $J = 7.2$ Hz), 2.49 (3H, s).

15

Example 229

1-(3-[[2-amino-6-(2-chloro-3-methylphenyl)pyrimidin-4-yl]amino}propyl)pyrrolidin-2-one.

Prepared according to general procedure 3 from 1-(3-aminopropyl)pyrrolidin-2-

20 one and 4-chloro-6-(2-chloro-3-methylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 360; ^1H NMR (400 MHz, CD_3OD) δ_H 7.57 – 7.55 (1H, m), 7.44 – 7.38 (2H, m), 6.13 (1H, s), 3.55 (2H, t, $J = 5.6$ Hz), 3.52 (2H, t, $J = 7.2$ Hz), 3.41 (2H, t, $J = 6.8$ Hz), 2.49 (3H, s), 2.42 (2H, t, $J = 8.0$ Hz), 2.09 (2H, quintet, $J = 7.6$ Hz), 1.92 (2H, quintet, $J = 7.2$ Hz).

25

Example 230

4-N-cyclopropyl-6-(1H-indol-4-yl)pyrimidine-2,4-diamine.

Prepared according to general procedure 3 from cyclopropanamine and 4-chloro-

6-(1H-indol-4-yl)pyrimidin-2-amine. LCMS $[M+H]^+$ 266; ^1H NMR (400 MHz,

30 CD_3OD) δ_H 7.67 (1H, d, $J = 7.6$ Hz), 7.50 (1H, s), 7.33 (2H, d, $J = 7.2$ Hz), 6.71 (1H, s), 6.43 (1H, s), 3.10 (1H, br s), 0.92 (2H, br s), 0.69 (2H, br s).

Example 231

4-N-[2-(4-chlorophenyl)ethyl]-6-(1H-indol-4-yl)pyrimidine-2,4-diamine.

Prepared according to general procedure 3 from 2-(4-chlorophenyl)ethan-1-amine and 4-chloro-6-(1H-indol-4-yl)pyrimidin-2-amine. LCMS $[M+H]^+$ 364; ^1H NMR (400 MHz, CD_3OD) δ_H 7.67 – 7.66 (1H, m), 7.52 – 7.46 (1H, m), 7.35 – 7.29 (6H, m), 6.86 (1H, s), 6.44 (1H, s), 3.80 (2H, t, $J = 7.2$ Hz), 2.95 (2H, t, $J = 6.8$ Hz).

Example 232

4-N-cyclopropyl-6-(quinolin-5-yl)pyrimidine-2,4-diamine.

Prepared according to general procedure 3 from cyclopropanamine and 4-chloro-6-(quinolin-5-yl)pyrimidin-2-amine. LCMS $[M+H]^+$ 278; ^1H NMR (400 MHz, CD_3OD) δ_H 8.91 (1H, dd, $J = 4$ and 1.6 Hz), 8.66 (1H, d, $J = 8.4$ Hz), 8.14 (1H, d, $J = 8.4$ Hz), 7.89 – 7.85 (1H, m), 7.74 (1H, d, $J = 6.8$ Hz), 7.59 – 7.56 (1H, m), 6.26 (1H, s), 2.69 (1H, br s), 0.85 – 0.80 (2H, m), 0.62 – 0.59 (2H, m).

Example 233

(2E)-3-{4-[2-amino-6-(methylamino)pyrimidin-4-yl]phenyl}prop-2-enoic acid.

Prepared according to general procedure 6 from (2E)-3-[4-(dihydroxyboranyl)phenyl]prop-2-enoic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 271.

Example 234

tert-butyl 3-({[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}methyl)-azetidine-1-carboxylate.

Prepared according to general procedure 3 from tert-butyl 3-(aminomethyl)azetidine-1-carboxylate and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 384; ^1H NMR (400 MHz, CD_3OD) δ_H 7.19 (1H, d, $J = 7.6$ Hz), 7.12 (1H, t, $J = 7.6$ Hz), 7.07 (1H, d, $J = 7.6$ Hz), 5.82 (s, 1H), 4.05 – 4.00 (2H, m), 3.73 – 3.69 (2H, m), 3.60 – 3.59 (2H, m), 2.92 – 2.82 (1H, m), 2.33 (3H, s), 2.21 (3H, s), 1.45 (9H, s).

Example 235

4-N-cyclopropyl-6-(1H-indol-5-yl)pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from (1H-indol-5-yl)boronic acid and 6-chloro-4-N-cyclopropylpyrimidine-2,4-diamine. LCMS $[M+H]^+$ 266.

Example 236

1-(3-[[2-amino-6-(1H-indol-5-yl)pyrimidin-4-yl]amino]propyl)pyrrolidin-2-one.

Prepared according to general procedure 2 from (2,3-dimethylphenyl)boronic acid and 1-{3-[(2-amino-6-chloropyrimidin-4-yl)amino]propyl}pyrrolidin-2-one.

- 5 [M+H]⁺ 351; ¹H NMR (400 MHz, CD₃OD) δ_H 8.02 (1H, d, J = 1.6 Hz), 7.59 (1H, d, J = 8.4 Hz), 7.48 (1H, dd, J = 8.4 and 2.0 Hz), 7.42 (1H, d, J = 3.2 Hz), 6.64 (1H, d, J = 3.2 Hz), 6.37 (1H, s), 3.57 – 3.51 (4H, m), 3.42 (2H, t, J = 7.2 Hz), 2.43 (2H, t, J = 8.0 Hz), 2.10 (2H, quintet, J = 8.4 Hz), 1.93 (2H, quintet, J = 7.2 Hz).

10 Example 237

tert-Butyl 4-((2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl)amino)piperidine-1-carboxylate.

Prepared according to general procedure 3 from 4-chloro-6-(3-chloro-2-methylphenyl)pyrimidin-2-amine and tert-butyl 4-aminopiperidine-1-carboxylate.

- 15 LCMS [M+H]⁺ 398; ¹H NMR (400 MHz, CD₃OD) δ_H 7.19 (1H, d, J = 6.8 Hz), 7.13 (1H, t, J = 7.6 Hz), 7.08 (1H, dd, J = 7.2 and 0.8 Hz), 5.82 (1H, s), 4.07 – 4.05 (2H, m), 2.99 (2H, m), 2.33 (3H, s), 2.22 (3H, s), 2.03 – 1.99 (2H, s), 1.49 (9H, s), 1.42 – 1.39 (2H, m).

20 Example 238

Ethyl 4-((2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl)amino)piperidine-1-carboxylate.

Prepared according to general procedure 3 from 4-chloro-6-(3-chloro-2-methylphenyl)pyrimidin-2-amine and ethyl 4-aminopiperidine-1-carboxylate.

- 25 LCMS [M+H]⁺ 370; ¹H NMR (400 MHz, CD₃OD) δ_H 7.19 (1H, d, J = 7.2 Hz), 7.11 (1H, t, J = 7.2 Hz), 7.08 (1H, d, J = 7.6 Hz), 5.82 (1H, s), 4.15 (2H, q, J = 7.2 Hz), 4.15 – 4.09 (3H, m), 3.07 – 2.98 (2H, m), 2.33 (3H, s), 2.21 (3H, s), 2.04 – 2.01 (2H, m), 1.48 – 1.39 (2H, m), 1.29 (4H, t, J = 7.2 Hz).

30 Example 239

tert-Butyl (3-((2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl)amino)-2,2-dimethylpropyl)carbamate.

Prepared according to general procedure 3 from 4-chloro-6-(3-chloro-2-methylphenyl)pyrimidin-2-amine and tert-butyl N-(3-amino-2,2-

- 35 dimethylpropyl)carbamate. LCMS [M+H]⁺ 400.

Example 240

6-(5-chloro-4-methoxy-2-methylphenyl)-4-N-methylpyrimidine-2,4-diamine.

Prepared according to general procedure 6 from (5-chloro-4-methoxy-2-methylphenyl)boronic acid and 6-iodo-4-N-methylpyrimidine-2,4-diamine. LCMS [M+H]⁺ 279.

Example 241

6-(3-chloro-2-methylphenyl)-4-N-[(1R)-1-phenylethyl]pyrimidine-2,4-diamine.

4-Chloro-6-(3-chloro-2-methylphenyl)pyrimidin-2-amine (25 mg, 0,098 mmol) and (+)-1-phenylethan-1-amine (0,050 mL) were stirred neat at 150°C for 1 hour. The crude material was dissolved in MeOH (2 mL) and purified by preparative HPLC to give the desired product. LCMS [M+H]⁺ 339; ¹H NMR (400 MHz, DMSO-d₆) δ_H ppm 9.25 (1 H, d, J=8.08 Hz) 7.62 - 7.71 (1 H, m) 7.24 - 7.47 (7 H, m) 6.23 (0.1 H, s) 6.09 (0.9 H, s) 5.35 (1 H, quin, J=7.26 Hz) 2.31 (2.7 H, s) 2.13 (0.3 H, s) 1.46 - 1.57 (3 H, m).

Example 242

6-(3-chloro-2-methylphenyl)-4-N-(2-phenylpropan-2-yl)pyrimidine-2,4-diamine.

4-Chloro-6-(3-chloro-2-methylphenyl)pyrimidin-2-amine (25 mg, 0,098 mmol) and 2-phenylpropan-2-amine (0,050 mL) were stirred neat at 150°C for 24 hours. The crude material was dissolved in MeOH (2 mL) and purified by preparative HPLC to give the desired product. LCMS [M+H]⁺ 353; ¹H NMR (400 MHz, DMSO-d₆) δ_H ppm 12.45 (1 H, br. s.) 8.96 (1 H, br. s.) 7.12 - 7.79 (8 H, m) 6.22 (1 H, s) 2.31 (3 H, s) 1.79 (6 H, br. s.)

Example 243

6-(3-chloro-2-methylphenyl)-4-N-[1-(1H-indol-3-yl)propan-2-yl]pyrimidine-2,4-diamine.

4-Chloro-6-(3-chloro-2-methylphenyl)pyrimidin-2-amine (25 mg, 0,098 mmol) and 1-(1H-indol-3-yl)propan-2-amine (0,050 mL) were stirred neat at 150°C for 1 hour. The crude material was dissolved in MeOH (2 mL) and purified by preparative HPLC to give the desired product. LCMS [M+H]⁺ 392; ¹H NMR (400 MHz, DMSO-d₆) δ_H ppm 12.34 (1 H, br. s.) 10.90 (0.9 H, s) 10.85 (0.1 H, br. s.) 8.79 (0.9 H, d, J=7.83 Hz) 8.63 (0.1 H, d, J=9.09 Hz) 7.66 (0.9 H, dd, J=7.20, 2.15 Hz) 7.62 (0.1

H, d, J=7.58 Hz) 7.54 (1 H, d, J=7.83 Hz) 7.28 - 7.43 (3 H, m) 7.20 (0.9 H, d, J=2.27 Hz) 6.95 - 7.13 (2 H, m) 6.89 - 6.95 (0.1 H, m) 5.99 (0.9 H, s) 5.93 (0.1 H, s) 4.39 - 4.50 (1 H, m) 2.86 - 3.03 (2 H, m) 2.30 (2.7 H, s) 2.14 (0.3 H, s) 1.27 (0.3 H, d, J=6.32 Hz) 1.20 (2.7 H, d, J=6.57 Hz).

5

Example 244

4-N-{bicyclo[2.2.1]heptan-2-yl}-6-(3-chloro-2-methylphenyl)pyrimidine-2,4-diamine.

4-Chloro-6-(3-chloro-2-methylphenyl)pyrimidin-2-amine (25 mg, 0,098 mmol) and
10 bicyclo[2.2.1]heptan-2-amine (0,050 mL) were stirred neat at 150°C for 1 hour.
The crude material was dissolved in MeOH (~2 mL) and purified by preparative HPLC to give the desired product. LCMS [M+H]⁺ 329; ¹H NMR (400 MHz, DMSO-d₆) δ_H ppm 8.66 (1 H, br. s.) 7.62 - 7.69 (1 H, m) 7.35 - 7.44 (2 H, m) 5.99 (1 H, s) 3.87 (1 H, br. s.) 2.30 (3 H, s) 2.27 - 2.35 (1 H, m) 2.24 (1 H, d, J=3.28 Hz) 1.70 -
15 1.80 (1 H, m) 1.33 - 1.60 (4 H, m) 1.09 - 1.26 (3 H, m)

Example 245

6-(3-chloro-2-methylphenyl)-4-N-ethylpyrimidine-2,4-diamine.

4-Chloro-6-(3-chloro-2-methylphenyl)pyrimidin-2-amine (25 mg, 0,098
20 mmol), 70% ethanamine (0,050 mL) and n-butanol (2 mL) were stirred in a sealed tube at 120°C for 8 hours. The solvent was removed in vacuo and the crude material was dissolved in MeOH (2 mL) and purified by preparative HPLC to give the desired product. LCMS [M+H]⁺ 263; ¹H NMR (400 MHz, DMSO-d₆) δ_H ppm 12.49 (1 H, br. s.) 8.86 (0.9 H, t, J=5.18 Hz) 8.63 - 8.73 (0.1 H, m) 7.60 -
25 7.70 (1 H, m) 7.34 - 7.45 (2 H, m) 6.34 (0.1 H, br. s.) 6.02 (0.9 H, s) 3.23 - 3.58 (2 H, m) 2.33 (0.3 H, s) 2.30 (2.7 H, s) 1.18 (2.7 H, t, J=7.20 Hz) 1.08 - 1.14 (0.3 H, m)

Example 246

6-(3-chloro-2-methylphenyl)-4-N-(propan-2-yl)pyrimidine-2,4-diamine.
30 4-Chloro-6-(3-chloro-2-methylphenyl)pyrimidin-2-amine (25 mg, 0,098 mmol), propan-2-amine (0,050 mL) and n-butanol (2 mL) were stirred in a sealed tube at 120°C for 8 hours. The solvent was removed in vacuo and the crude material was dissolved in MeOH (2 mL) and purified by preparative HPLC to give
35 the desired product. LCMS [M+H]⁺ 277.

Example 247

4-N-[2-(2-chlorophenoxy)ethyl]-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.

- 4-Chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (13 mg, 0,054 mmol) and 1-(2-aminoethoxy)-2-chlorobenzene (18 mg, 0,11 mmol) were stirred neat at 150°C for 1 h. The crude material was dissolved in MeOH (1 mL) and purified by preparative HPLC to give the desired product. LCMS [M+H]⁺ 369.

Example 248

- 4-N-[2-(5-chloro-1H-1,3-benzodiazol-2-yl)ethyl]-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.

- 4-Chloro-6-(3-chloro-2-methylphenyl)pyrimidin-2-amine (23 mg, 0,10 mmol), 2-(5-chloro-1H-1,3-benzodiazol-2-yl)ethan-1-amine (20 mg, 0,10 mmol), Et₃N (0,040 mL, 0,30 mmol) and 1-butanol (0,20 mL) were stirred at 100°C for 20 hours. MeOH (1 mL) was added and the mixture was purified by preparative HPLC to give the desired product. LCMS [M+H]⁺ 393.

Example 249

- 4-N-[2-(2,5-dimethyl-1H-indol-3-yl)ethyl]-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.

- 4-Chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (12 mg, 0,050 mmol) and 2-(2,5-dimethyl-1H-indol-3-yl)ethan-1-amine (0,020 mL) were stirred neat at 150°C for 1 hour. The crude material was dissolved in MeOH (1 mL) and purified by preparative HPLC to give the desired product. LCMS [M+H]⁺ 386; ¹H NMR (400 MHz, DMSO-d₆) δ ppm 12.30 (1 H, br. s.) 10.65 (0.9 H, s) 10.60 (0.1 H, s) 8.82 (0.9 H, t, J=5.56 Hz) 8.56 - 8.67 (0.1 H, m) 7.06 - 7.41 (5 H, m) 6.70 - 6.85 (1 H, m) 5.97 (0.9 H, s) 5.76 (0.1 H, s) 3.58 (1.8 H, q, J=6.65 Hz) 3.48 (0.2 H, d, J=6.32 Hz) 2.93 (0.8 H, t, J=7.07 Hz) 2.80 - 2.89 (0.2 H, m) 2.23 - 2.38 (9 H, m) 2.17 (2.7 H, s) 2.06 (0.3 H, s)

Example 250

6-(2,3-dimethylphenyl)-4-N-[2-(pyridin-3-yloxy)propyl]pyrimidine-2,4-diamine.

- 4-Chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (12 mg, 0,050 mmol) and 3-[(1-aminopropan-2-yl)oxy]pyridine (15 mg, 0,10 mmol) were stirred neat at 150°C for

1 h. The crude material was dissolved in MeOH (1 mL) and purified by preparative HPLC to give the desired product. LCMS $[M+H]^+$ 350.

Example 251

- 5 6-(2,3-dimethylphenyl)-4-N-(1H-indazol-5-ylmethyl)pyrimidine-2,4-diamine.
4-Chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (12 mg, 0,050 mmol), 1H-indazol-5-ylmethanamine (15 mg, 0,10 mmol), Et₃N (0.040 mL, 0,30 mmol) and 1-butanol (0,20 mL) were stirred at 100°C for 20 hours. MeOH (1 mL) was added and the mixture was purified by preparative HPLC to give the desired product.
10 LCMS $[M+H]^+$ 345.

Example 252

- 6-(2,3-dimethylphenyl)-4-N-(1H-indazol-6-ylmethyl)pyrimidine-2,4-diamine.
4-Chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (12 mg, 0,050 mmol), 1H-indazol-6-ylmethanamine (15 mg, 0,10 mmol), Et₃N (0.040 mL, 0,30 mmol) and
15 1-butanol (0,20 mL) were stirred at 100°C for 20 h. MeOH (1 mL) was added and the mixture was purified by preparative HPLC to give the desired product. LCMS $[M+H]^+$ 345

20 Example 253

- 6-(2,3-dimethylphenyl)-4-N-[(2-methoxypyridin-4-yl)methyl]pyrimidine-2,4-diamine.
4-Chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (12 mg, 0,050 mmol), (2-methoxypyridin-4-yl)methanamine (14 mg, 0,10 mmol), Et₃N (0,040 mL, 0,30
25 mmol) and 1-butanol (0,20 mL) were stirred at 100°C for 20 hours. MeOH (1 mL) was added and the mixture was purified by preparative HPLC to give the desired product. LCMS $[M+H]^+$ 336.

Example 254

- 30 4-N-[(5-chloropyrazin-2-yl)methyl]-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.
4-Chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (12 mg, 0,050 mmol), (5-chloropyrazin-2-yl)methanamine (14 mg, 0,10 mmol), Et₃N (0,040 mL, 0,30 mmol) and 1-butanol (0,20 mL) were stirred at 100°C for 20 hours. MeOH (1 mL) was added and the mixture was purified by preparative HPLC to give the desired
35 product. LCMS $[M+H]^+$ 341.

Example 255

6-(2,3-dimethylphenyl)-4-N-{imidazo[1,2-a]pyridin-2-ylmethyl}pyrimidine-2,4-diamine.

- 5 4-Chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (12 mg, 0,050 mmol), imidazo[1,2-a]pyridin-2-ylmethanamine (14 mg, 0,10 mmol), Et₃N (0,040 mL, 0,30 mmol) and 1-butanol (0,20 mL) were stirred at 100°C for 20 hours. MeOH (1 mL) was added and the mixture was purified by preparative HPLC to give the desired product. LCMS [M+H]⁺ 345.

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Example 256

tert-butyl 4-{4-[2-amino-6-(methylamino)pyrimidin-4-yl]-2-(methoxymethyl)phenoxy-methyl}piperidine-1-carboxylate.

- A mixture of 6-chloro-4-N-methylpyrimidine-2,4-diamine (24 mg, 0.15 mmol), tert-butyl 4-[4-(dimethoxyboranyl)-2-(methoxymethyl)phenoxy-methyl]piperidine-1-carboxylate (67 mg, 0.17 mmol), potassium carbonate (41 mg, 0.30 mmol) and palladium tetrakis(triphenylphosphine)palladium (0) (9 mg, 0.008 mmol) in 1,4-dioxane (5 mL) and water (1.5 mL) was heated in a sealed tube at 90°C overnight. The reaction mixture was concentrated and purified by preparative HPLC. LCMS [M+H]⁺ 458.

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Example 257

6-[3-(methoxymethyl)-4-(piperidin-4-ylmethoxy)phenyl]-4-N-methylpyrimidine-2,4-diamine hydrochloride.

- 25 A solution of tert-butyl 4-{4-[2-amino-6-(methylamino)pyrimidin-4-yl]-2-(methoxymethyl)-phenoxy-methyl}piperidine-1-carboxylate (45 mg, 0.10 mmol; Example 256) in methanol (3 mL) was treated with 4M HCl in 1,4-dioxane (1 mL). The mixture was stirred at r.t. for 3 h, concentrated and dried in vacuo to give the desired product. LCMS [M+H]⁺ 358.

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Example 258

3-[2-amino-6-(methylamino)pyrimidin-4-yl]-2-methylbenzonitrile.

- A mixture of 6-chloro-4-N-methylpyrimidine-2,4-diamine (24 mg, 0.15 mmol), (3-cyano-2-methylphenyl)boronic acid (29 mg, 0.18 mmol), potassium carbonate (41 mg, 0.30 mmol) and palladium tetrakis(triphenylphosphine)palladium (0) (9 mg,

35

0.008 mmol) in 1,4-dioxane (3 mL) and water (1 mL) was heated in a sealed tube at 90°C overnight. The reaction mixture was concentrated and purified by preparative HPLC. LCMS [M+H]⁺ 240.

5 Example 259

6-(4-methoxy-2,3-dimethylphenyl)-4-N-methylpyrimidine-2,4-diamine.

A mixture of 6-chloro-4-N-methylpyrimidine-2,4-diamine (24 mg, 0.15 mmol), (4-methoxy-2,3-dimethylphenyl)boronic acid (32 mg, 0.18 mmol), potassium carbonate (41 mg, 0.30 mmol) and tetrakis(triphenylphosphine)palladium (0) (9 mg, 0.008 mmol) in 1,4-dioxane (3 mL) and water (1 mL) was heated in a sealed tube at 90°C overnight. The reaction mixture was concentrated and purified by preparative HPLC. LCMS [M+H]⁺ 259.

Example 260

15 6-(4-fluoro-2,3-dimethylphenyl)-4-N-methylpyrimidine-2,4-diamine.

A mixture of 6-chloro-4-N-methylpyrimidine-2,4-diamine (24 mg, 0.15 mmol), (4-fluoro-2,3-dimethylphenyl)boronic acid (30 mg, 0.18 mmol), potassium carbonate (41 mg, 0.30 mmol) and tetrakis(triphenylphosphine)palladium (0) (9 mg, 0.008 mmol) in 1,4-dioxane (3 mL) and water (1 mL) was heated in a sealed tube at 90°C overnight. The reaction mixture was concentrated and purified by preparative HPLC. LCMS [M+H]⁺ 247.

Example 261

6-(2,3-dihydro-1-benzofuran-7-yl)-4-N-methylpyrimidine-2,4-diamine.

25 A mixture of 6-chloro-4-N-methylpyrimidine-2,4-diamine (24 mg, 0.15 mmol), (2,3-dihydro-1-benzofuran-7-yl)boronic acid (30 mg, 0.18 mmol), potassium carbonate (41 mg, 0.30 mmol) and tetrakis(triphenylphosphine)palladium (0) (9 mg, 0.008 mmol) in 1,4-dioxane (3 mL) and water (1 mL) was heated in a sealed tube at 90°C overnight. The reaction mixture was concentrated and purified by preparative HPLC. LCMS [M+H]⁺ 243.

Example 262

4-N-methyl-6-[2-methyl-5-(morpholine-4-sulfonyl)phenyl]pyrimidine-2,4-diamine.

35 A mixture of 6-chloro-4-N-methylpyrimidine-2,4-diamine (24 mg, 0.15 mmol), [2-methyl-5-(morpholine-4-sulfonyl)phenyl]boronic acid (51 mg, 0.18 mmol),

potassium carbonate (41 mg, 0.30 mmol) and tetrakis(triphenylphosphine)-palladium (0) (9 mg, 0.008 mmol) in 1,4-dioxane (3 mL) and water (1 mL) was heated in a sealed tube at 90°C overnight. The reaction mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 364.

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Example 263

4-N-[2-(4-chlorophenyl)ethyl]-6-(2,3-dichlorophenyl)pyrimidine-2,4-diamine.

A mixture of 4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine (28 mg, 0.10 mmol), 2-(4-chlorophenyl)ethan-1-amine (22 mg, 0.14 mmol) and Hünig's base (36 μ L, 0.20 mmol) in n-butanol (2 mL) was heated in a sealed tube at 85°C overnight. The reaction mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 393. ^1H NMR (400 MHz, DMSO- d_6) δ_H ppm 12.56 (br. s., 1 H), 8.90 (br. s., 1 H), 7.83 - 7.89 (m, 1 H), 7.51 - 7.59 (m, 2 H), 7.35 - 7.41 (m, 2 H), 7.28 - 7.34 (m, 2 H), 6.11 (s, 1 H), 3.63 (q, J=6.4 Hz, 2 H), 2.89 (t, J=7.1 Hz, 2 H).

15

Example 264

4-N-[2-(4-chlorophenyl)ethyl]-6-(2-methylphenyl)pyrimidine-2,4-diamine.

A mixture of 6-chloro-4-N-[2-(4-chlorophenyl)ethyl]pyrimidine-2,4-diamine (34 mg, 0.12 mmol), (2-methylphenyl)boronic acid (20 mg, 0.14 mmol), potassium carbonate (33 mg, 0.24 mmol) and palladium tetrakis(triphenylphosphine)-palladium (0) (7 mg, 0.006 mmol) in 1,4-dioxane/water (4 mL; 4:1) was heated in a sealed tube at 90°C overnight. The reaction mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 339.

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Example 265

4-N-[2-(4-chlorophenyl)ethyl]-6-[3-(trifluoromethyl)phenyl]pyrimidine-2,4-diamine.

A mixture of 6-chloro-4-N-[2-(4-chlorophenyl)ethyl]pyrimidine-2,4-diamine (34 mg, 0.12 mmol), [3-(trifluoromethyl)phenyl]boronic acid (27 mg, 0.14 mmol), potassium carbonate (33 mg, 0.24 mmol) and palladium tetrakis(triphenylphosphine)palladium (0) (7 mg, 0.006 mmol) in 1,4-dioxane/water (4 mL; 4:1) was heated in a sealed tube at 90°C overnight. The reaction mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 393.

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Example 266

4-N-[2-(4-chlorophenyl)ethyl]-6-(quinolin-5-yl)pyrimidine-2,4-diamine.

- A mixture of 6-chloro-4-N-[2-(4-chlorophenyl)ethyl]pyrimidine-2,4-diamine (34 mg, 0.12 mmol), (quinolin-5-yl)boronic acid (25 mg, 0.14 mmol), potassium carbonate (33 mg, 0.24 mmol) and palladium tetrakis(triphenylphosphine)palladium (0) (7 mg, 0.006 mmol) in 1,4-dioxane/water (4 mL; 4:1) was heated in a sealed tube at 90°C overnight. The reaction mixture was concentrated and purified by preparative HPLC. LCMS [M+H]⁺ 376.

10 Example 267

4-N-[2-(4-chlorophenyl)cyclopropyl]-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.

- A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (28 mg, 0.12 mmol), 2-(4-chlorophenyl)cyclopropan-1-amine (43 mg, 0.26 mmol) and Hünig's base (90 µL, 0.52 mmol) in n-butanol (2 mL) was heated in a sealed tube at 85°C overnight. The reaction mixture was concentrated and purified by preparative HPLC. LCMS [M+H]⁺ 365.

Example 268

- 20 6-(2,3-dimethylphenyl)-4-N-[2-(pyridin-3-yl)ethyl]pyrimidine-2,4-diamine.

- A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (28 mg, 0.12 mmol), 2-(pyridin-3-yl)ethan-1-amine (21 mg, 0.17 mmol) and Hünig's base (42 µL, 0.24 mmol) in n-butanol (2 mL) was heated in a sealed tube at 85°C overnight. The reaction mixture was concentrated and purified by preparative HPLC. LCMS [M+H]⁺ 320.

Example 269

3-(2-[[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino]ethyl)phenol.

- A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (28 mg, 0.12 mmol), 3-(2-aminoethyl)phenol (23 mg, 0.17 mmol) and Hünig's base (42 µL, 0.24 mmol) in n-butanol (2 mL) was heated in a sealed tube at 85°C overnight. The reaction mixture was concentrated and purified by preparative HPLC. LCMS [M+H]⁺ 335.

35 Example 270

6-(2,3-dimethylphenyl)-4-N-[3-(morpholin-4-yl)propyl]pyrimidine-2,4-diamine.

A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (28 mg, 0.12 mmol), 3-(morpholin-4-yl)propan-1-amine (24 mg, 0.17 mmol) and Hünig's base (42 μ L, 0.24 mmol) in n-butanol (2 mL) was heated in a sealed tube at 85°C overnight. The reaction mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 342.

Example 271

tert-butyl N-(2-[[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino]ethyl)-carbamate.

A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (28 mg, 0.12 mmol), tert-butyl N-(2-aminoethyl)carbamate (27 mg, 0.17 mmol) and Hünig's base (42 μ L, 0.24 mmol) in n-butanol (2 mL) was heated in a sealed tube at 85°C overnight. The reaction mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 358.

Example 272

N-(2-[[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino]ethyl)acetamide.

A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (28 mg, 0.12 mmol), N-(2-aminoethyl)acetamide (17 mg, 0.17 mmol) and Hünig's base (42 μ L, 0.24 mmol) in n-butanol (2 mL) was heated in a sealed tube at 85°C overnight. The reaction mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 300.

Example 273

benzyl N-(2-[[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino]ethyl)-carbamate.

A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (28 mg, 0.12 mmol), benzyl N-(2-aminoethyl)carbamate hydrochloride (39 mg, 0.17 mmol) and Hünig's base (42 μ L, 0.24 mmol) in n-butanol (2 mL) was heated in a sealed tube at 85°C overnight. The reaction mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 392.

Example 274

tert-butyl N-(2-[[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino]ethyl)-N-methylcarbamate.

- 5 A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (28 mg, 0.12 mmol), tert-butyl N-(2-aminoethyl)-N-methylcarbamate (29 mg, 0.17 mmol) and Hünig's base (42 μ L, 0.24 mmol) in n-butanol (2 mL) was heated in a sealed tube at 85°C overnight. The reaction mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 372.

Example 275

- 10 tert-butyl N-(3-[[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino]propyl)-carbamate.

- A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (28 mg, 0.12 mmol), tert-butyl N-(3-aminopropyl)carbamate (29 mg, 0.17 mmol) and Hünig's base (42 μ L, 0.24 mmol) in n-butanol (2 mL) was heated in a sealed tube at 85°C
15 overnight. The reaction mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 372.

Example 276

- 20 6-(2,3-dimethylphenyl)-4-N-[3-(5-methyl-1H-pyrazol-3-yl)propyl]pyrimidine-2,4-diamine.

- A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (28 mg, 0.12 mmol), 3-(5-methyl-1H-pyrazol-4-yl)propan-1-amine (23 mg, 0.17 mmol) and Hünig's base (42 μ L, 0.24 mmol) in n-butanol (2 mL) was heated in a sealed tube at 85°C overnight. The reaction mixture was concentrated and purified by
25 preparative HPLC. LCMS $[M+H]^+$ 337.

Example 277

- 3-[[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino]-1-(morpholin-4-yl)propan-1-one.
- 30 A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (23 mg, 0.10 mmol), 3-amino-1-(morpholin-4-yl)propan-1-one (22 mg, 0.14 mmol) and Hünig's base (35 μ L, 0.20 mmol) in n-butanol (1.5 mL) was heated in a sealed tube at 85°C overnight. The reaction mixture was concentrated and purified by preparative HPLC.
- 35 LCMS $[M+H]^+$ 356.

Example 278

4-N-[(4-benzylmorpholin-2-yl)methyl]-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.

- 5 A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (23 mg, 0.10 mmol), (4-benzylmorpholin-2-yl)methanamine (29 mg, 0.14 mmol) and Hünig's base (35 μ L, 0.20 mmol) in n-butanol (1.5 mL) was heated in a sealed tube at 85°C overnight. The reaction mixture was concentrated and purified by preparative HPLC.
- 10 LCMS $[M+H]^+$ 404.

Example 279

6-(2,3-dimethylphenyl)-4-N-[(4-methanesulfonylphenyl)methyl]pyrimidine-2,4-diamine.

- 15 A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (23 mg, 0.10 mmol), (4-methanesulfonylphenyl)methanamine hydrochloride (31 mg, 0.14 mmol) and Hünig's base (35 μ L, 0.20 mmol) in n-butanol (1.5 mL) was heated in a sealed tube at 85°C overnight. The reaction mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 383.

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Example 280

6-(2,3-dimethylphenyl)-4-N-[[4-(4-methylpiperazin-1-yl)phenyl]methyl]pyrimidine-2,4-diamine.

- A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (23 mg, 0.10 mmol), [4-(4-methylpiperazin-1-yl)phenyl]methanamine (29 mg, 0.14 mmol) and Hünig's base (35 μ L, 0.20 mmol) in n-butanol (1.5 mL) was heated in a sealed tube at 85°C overnight. The reaction mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 403.

30 Example 281

4-N-[(3S)-1-azabicyclo[2.2.2]octan-3-yl]-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.

- A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (23 mg, 0.10 mmol), (S)-quinuclidin-3-amine hydrochloride (29 mg, 0.14 mmol) and Hünig's base (35 μ L, 0.20 mmol) in n-butanol (1.5 mL) was heated in a sealed tube at
- 35

85°C overnight. The reaction mixture was concentrated and purified by preparative HPLC. LCMS [M+H]⁺ 324.

Example 282

- 5 tert-butyl 2-({[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}methyl)-pyrrolidine-1-carboxylate.

A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (23 mg, 0.10 mmol), tert-butyl 2-(aminomethyl)pyrrolidine-1-carboxylate (28 mg, 0.14 mmol) and Hünig's base (35 µL, 0.20 mmol) in n-butanol (1.5 mL) was heated in a sealed tube at 85°C overnight. The reaction mixture was concentrated and purified by preparative HPLC. LCMS [M+H]⁺ 398.

Example 283

- 15 tert-butyl 4-({[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}methyl)-piperidine-1-carboxylate.

A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (23 mg, 0.10 mmol), tert-butyl 4-(aminomethyl)piperidine-1-carboxylate (30 mg, 0.14 mmol) and Hünig's base (35 µL, 0.20 mmol) in n-butanol (1.5 mL) was heated in a sealed tube at 85°C overnight. The reaction mixture was concentrated and purified by preparative HPLC. LCMS [M+H]⁺ 412.

Example 284

- 1-(3-({[2-amino-6-(2,3-dichlorophenyl)pyrimidin-4-yl]amino}propyl)pyrrolidin-2-one. A mixture of 4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine (19 mg, 0.070 mmol) and 1-(3-aminopropyl)pyrrolidin-2-one (49 µL, 0.35 mmol) in n-butanol (1 mL) was heated in a sealed tube at 110°C overnight. The reaction mixture was concentrated and purified by preparative HPLC. LCMS [M+H]⁺ 380.

Example 285

- 30 1-(3-({[2-amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-yl]amino}propyl)pyrrolidin-2-one. A mixture of 4-chloro-6-(3-chloro-2-methylphenyl)pyrimidin-2-amine (19 mg, 0.076 mmol) and 1-(3-aminopropyl)pyrrolidin-2-one (53 µL, 0.38 mmol) in n-butanol (1 mL) was heated in a sealed tube at 110°C overnight. The reaction mixture was concentrated and purified by preparative HPLC. LCMS [M+H]⁺ 360.

Example 286

1-(3-[(2-amino-6-(4-fluoro-2,3-dimethylphenyl)pyrimidin-4-yl)amino]propyl)pyrrolidin-2-one.

- 5 A mixture of 1-(3-[(2-amino-6-chloropyrimidin-4-yl)amino]propyl)pyrrolidin-2-one (27 mg, 0.10 mmol), (4-fluoro-2,3-dimethylphenyl)boronic acid (18 mg, 0.11 mmol), potassium carbonate (28 mg, 0.20 mmol) and palladium tetrakis(triphenylphosphine)palladium (0) (6 mg, 0.005 mmol) in 1,4-dioxane (4 mL) and water (1 mL) was heated in a sealed tube at 95°C for 2 h. The reaction
10 mixture was concentrated and purified by preparative HPLC. LCMS [M+H]⁺ 358.

Example 287

1-(3-[(2-amino-6-(4-methoxy-2,3-dimethylphenyl)pyrimidin-4-yl)amino]propyl)pyrrolidin-2-one.

- 15 A mixture of 1-(3-[(2-amino-6-chloropyrimidin-4-yl)amino]propyl)pyrrolidin-2-one (27 mg, 0.10 mmol), (4-methoxy-2,3-dimethylphenyl)boronic acid (20 mg, 0.11 mmol), potassium carbonate (28 mg, 0.20 mmol) and palladium tetrakis(triphenylphosphine)palladium (0) (6 mg, 0.005 mmol) in 1,4-dioxane (4 mL) and water (1 mL) was heated in a sealed tube at 95°C for 2 h. The reaction
20 mixture was concentrated and purified by preparative HPLC. LCMS [M+H]⁺ 370.

Example 288

1-(3-[(2-amino-6-(4-methyl-1H-indazol-5-yl)pyrimidin-4-yl)amino]propyl)pyrrolidin-2-one.

- 25 A mixture of 1-(3-[(2-amino-6-chloropyrimidin-4-yl)amino]propyl)pyrrolidin-2-one (27 mg, 0.10 mmol), (4-methyl-1H-indazol-5-yl)boronic acid (19 mg, 0.11 mmol), potassium carbonate (28 mg, 0.20 mmol) and palladium tetrakis(triphenylphosphine)palladium (0) (6 mg, 0.005 mmol) in 1,4-dioxane (4 mL) and water (1 mL) was heated in a sealed tube at 95°C for 2 h. The reaction
30 mixture was concentrated and purified by preparative HPLC. LCMS [M+H]⁺ 366.

Example 289

1-[3-({2-amino-6-[2-methyl-5-(morpholine-4-sulfonyl)phenyl]pyrimidin-4-yl)amino]propyl]pyrrolidin-2-one.

A mixture of 1-{3-[(2-amino-6-chloropyrimidin-4-yl)amino]propyl}pyrrolidin-2-one (27 mg, 0.10 mmol), [2-methyl-5-(morpholine-4-sulfonyl)phenyl]boronic acid (31 mg, 0.11 mmol), potassium carbonate (28 mg, 0.20 mmol) and palladium tetrakis(triphenylphosphine)palladium (0) (6 mg, 0.005 mmol) in 1,4-dioxane (4 mL) and water (1 mL) was heated in a sealed tube at 95°C for 2 h. The reaction mixture was concentrated and purified by preparative HPLC. LCMS [M+H]⁺ 475.

Example 290

1-(3-{[2-amino-6-(2,3-dihydro-1-benzofuran-7-yl)pyrimidin-4-yl]amino}propyl)pyrrolidin-2-one.

A mixture of 1-{3-[(2-amino-6-chloropyrimidin-4-yl)amino]propyl}pyrrolidin-2-one (27 mg, 0.10 mmol), (2,3-dihydro-1-benzofuran-7-yl)boronic acid (18 mg, 0.11 mmol), potassium carbonate (28 mg, 0.20 mmol) and palladium tetrakis(triphenylphosphine)palladium (0) (6 mg, 0.005 mmol) in 1,4-dioxane (4 mL) and water (1 mL) was heated in a sealed tube at 95°C for 2 h. The reaction mixture was concentrated and purified by preparative HPLC. LCMS [M+H]⁺ 354.

Example 291

1-(3-{[2-amino-6-(2,5-dimethylphenyl)pyrimidin-4-yl]amino}propyl)pyrrolidin-2-one.
A mixture of 1-{3-[(2-amino-6-chloropyrimidin-4-yl)amino]propyl}pyrrolidin-2-one (27 mg, 0.10 mmol), (2,5-dimethylphenyl)boronic acid (17 mg, 0.11 mmol), potassium carbonate (28 mg, 0.20 mmol) and palladium tetrakis(triphenylphosphine)palladium (0) (6 mg, 0.005 mmol) in 1,4-dioxane (4 mL) and water (1 mL) was heated in a sealed tube at 95°C for 2 h. The reaction mixture was concentrated and purified by preparative HPLC. LCMS [M+H]⁺ 340.

Example 292

1-(3-{[2-amino-6-(5-chloro-2-methylphenyl)pyrimidin-4-yl]amino}propyl)pyrrolidin-2-one.
A mixture of 1-{3-[(2-amino-6-chloropyrimidin-4-yl)amino]propyl}pyrrolidin-2-one (27 mg, 0.10 mmol), (5-chloro-2-methylphenyl)boronic acid (19 mg, 0.11 mmol), potassium carbonate (28 mg, 0.20 mmol) and palladium tetrakis(triphenylphosphine)palladium (0) (6 mg, 0.005 mmol) in 1,4-dioxane (4 mL) and water (1 mL) was heated in a sealed tube at 95°C for 2 h. The reaction mixture was concentrated and purified by preparative HPLC. LCMS [M+H]⁺ 360.

Example 293

1-[3-({2-amino-6-[2-(trifluoromethyl)phenyl]pyrimidin-4-yl}amino)propyl]pyrrolidin-2-one.

- 5 A mixture of 1-{3-[(2-amino-6-chloropyrimidin-4-yl)amino]propyl}pyrrolidin-2-one (27 mg, 0.10 mmol), [2-(trifluoromethyl)phenyl]boronic acid (21 mg, 0.11 mmol), potassium carbonate (28 mg, 0.20 mmol) and palladium tetrakis-(triphenylphosphine)palladium (0) (6 mg, 0.005 mmol) in 1,4-dioxane (4 mL) and water (1 mL) was heated in a sealed tube at 95°C for 2 h. The reaction mixture
10 was concentrated and purified by preparative HPLC. LCMS [M+H]⁺ 380.

Example 294

1-(3-[(2-amino-6-(1H-indol-4-yl)pyrimidin-4-yl)amino]propyl)pyrrolidin-2-one.

- A mixture of 1-{3-[(2-amino-6-chloropyrimidin-4-yl)amino]propyl}pyrrolidin-2-one
15 (27 mg, 0.10 mmol), (1H-indol-4-yl)boronic acid (18 mg, 0.11 mmol), potassium carbonate (28 mg, 0.20 mmol) and palladium tetrakis(triphenylphosphine)-palladium (0) (6 mg, 0.005 mmol) in 1,4-dioxane (4 mL) and water (1 mL) was heated in a sealed tube at 95°C for 2 h. The reaction mixture was concentrated and purified by preparative HPLC. LCMS [M+H]⁺ 351.

20

Example 295

4-N-[[1-(4-chlorophenyl)cyclopropyl]methyl]-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.

- A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (47 mg, 0.20
25 mmol), [1-(4-chlorophenyl)cyclopropyl]methanamine hydrochloride (65 mg, 0.30 mmol) and Hünig's base (70 µL, 0.40 mmol) in n-butanol (1.5 mL) was heated in a sealed tube at 130°C overnight. The reaction mixture was concentrated and purified by preparative HPLC. LCMS [M+H]⁺ 379.

- 30 Example 296

4-(2-[(2-amino-6-(2,3-dichlorophenyl)pyrimidin-4-yl]amino)ethyl)benzene-1-sulfonamide.

- A mixture of 4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine (41 mg, 0.15
mmol), 4-(2-aminoethyl)benzene-1-sulfonamide (45 mg, 0.23 mmol) and Hünig's
35 base (39 µL, 0.23 mmol) in n-butanol (2 mL) was heated in a sealed tube at 90°C

for 48 h. The reaction mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 438.

Example 297

5 4-(2-[[2-amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-yl]amino]ethyl)benzene-1-sulfonamide.

A mixture of 4-chloro-6-(3-chloro-2-methylphenyl)pyrimidin-2-amine (38 mg, 0.15 mmol), 4-(2-aminoethyl)benzene-1-sulfonamide (45 mg, 0.23 mmol) and Hünig's base (39 μ L, 0.23 mmol) in n-butanol (2 mL) was heated in a sealed tube at 90°C
10 for 48 h. The reaction mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 418. ^1H NMR (400 MHz, DMSO- d_6) δ_{H} ppm 12.33 (br. s., 1 H), 8.89 (br. s., 1 H), 7.77 (d, $J=8.1$ Hz, 2 H), 7.64 - 7.68 (m, 1 H), 7.48 (d, $J=8.1$ Hz, 2 H), 7.37 - 7.41 (m, 2 H), 7.32 (s, 2 H), 6.03 (s, 1 H), 3.67 (q, $J=6.7$ Hz, 2 H), 2.98 (t, $J=7.1$ Hz, 2 H), 2.30 (s, 3 H).

15

Example 298

4-N-(Adamantan-1-yl)-6-(2,3-dichlorophenyl)pyrimidine-2,4-diamine.

A mixture of the 4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine (25 mg) and adamantylamine (50 mg) was heated at 150°C for 1 h. The mixture was cooled,
20 diluted in methanol then purified by preparative HPLC. LCMS $[M+H]^+$ 389.

Example 299

6-(2,3-dichlorophenyl)-4-N-[(1R,2R,3R,5S)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl]pyrimidine-2,4-diamine.

25

A mixture of 4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine (25 mg) and (1R,2R,3R,5S)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-amine (50 mg) was heated at 150°C for 1h. The mixture was cooled, diluted in methanol then purified by
30 preparative HPLC. LCMS $[M+H]^+$ 391.

Example 300

6-(2,3-Dichlorophenyl)-4-N-({3-[(4-methylpiperidin-1-yl)methyl]phenyl}methyl)-pyrimidine-2,4-diamine.

35 A mixture of 4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine (25 mg) and {3-[(4-

methylpiperidin-1-yl)methyl]phenyl]methanamine (50 mg) was heated at 150°C for 1 h. The mixture was cooled, diluted in methanol and then purified by preparative HPLC. LCMS [M+H]⁺ 456.

5 Example 301

4-(2-[[2-Amino-6-(2,3-dichlorophenyl)pyrimidin-4-yl]amino]ethyl)phenol.

A mixture of 4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine (25 mg) and 4-(2-aminoethyl)phenol (50 mg) was heated at 150°C for 1 h. The mixture was cooled, diluted in methanol then purified by preparative HPLC. LCMS [M+H]⁺ 375.

10

Example 302

Ethyl 4-[[2-amino-6-(2,3-dichlorophenyl)pyrimidin-4-yl]amino]piperidine-1-carboxylate.

A mixture of 4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine (25 mg) and ethyl

15 4-aminopiperidine-1-carboxylate (50 mg) was heated at 150°C for 1 h. The mixture was cooled, diluted in methanol then purified by preparative HPLC. LCMS [M+H]⁺ 410.

Example 303

20 N-(4-[[2-Amino-6-(2,3-dichlorophenyl)pyrimidin-4-yl]amino]butyl)acetamide.

A solution of 4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine (25 mg; 0.1 mmol) in n-BuOH (1.0 ml) was heated at 130°C with N-(4-aminobutyl)acetamide (1 eq.) and triethylamine (1 eq). After 18 h the reaction was halted and evaporated. The residue was purified by preparative HPLC. LCMS [M+H]⁺ 368.

25

Example 304

6-(2,3-Dichlorophenyl)-4-N-{tricyclo[3.3.1.0^{3,7}]nonan-3-yl}pyrimidine-2,4-diamine.

A solution of 4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine (25 mg; 0.1 mmol) in n-BuOH (1.0 ml) was heated at 130°C with tricyclo[3.3.1.0^{3,7}]nonan-3-amine (1

30 eq) and triethylamine (1 eq). After 18 h the reaction was halted and evaporated. The residue was purified by preparative HPLC. LCMS [M+H]⁺ 375.

Example 305

6-(2,3-Dichlorophenyl)-4-N-[[4-(1,2,3-thiadiazol-4-yl)phenyl]methyl]pyrimidine-2,4-

35 diamine.

A solution of 4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine (25 mg; 0.1 mmol) in n-BuOH (1.0 ml) was heated at 130°C with [4-(1,2,3-thiadiazol-4-yl)phenyl]methanamine (1 eq) and triethylamine (1 eq). After 18 h the reaction was halted and evaporated. The residue was purified by preparative HPLC.

5 LCMS $[M+H]^+$ 429.

Example 306

4-N-[2-(1-Benzylpiperidin-4-yl)ethyl]-6-(2,3-dichlorophenyl)pyrimidine-2,4-diamine.

10 A solution of 4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine (25 mg; 0.1 mmol) in n-BuOH (1.0 ml) was heated at 130°C with 2-(1-benzylpiperidin-4-yl)ethan-1-amine (1 eq) and triethylamine (1 eq). After 18 h the reaction was halted and evaporated. The residue was purified by preparative HPLC. LCMS $[M+H]^+$ 456.

15 Example 307

6-(2,3-Dichlorophenyl)-4-N-(2,3-dihydro-1,4-benzodioxin-2-ylmethyl)pyrimidine-2,4-diamine.

A solution of 4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine (25 mg; 0.1 mmol) in n-BuOH (1.0 ml) was heated at 130 degrees with 2,3-dihydro-1,4-benzodioxin-

20 2-ylmethanamine (1 eq) and triethylamine (1 eq). After 18 h the reaction was halted and evaporated. The residue was purified by preparative HPLC. LCMS $[M+H]^+$ 403.

Example 308

25 N-{3-[2-amino-6-(methylamino)pyrimidin-4-yl]phenyl}-3-hydroxypyridine-2-carboxamide.

Equimolar quantities of 3-hydroxypyridine-2-carboxylic acid (0.24 mmol) and 6-(3-aminophenyl)-4-N-methylpyrimidine-2,4-diamine were dissolved in 2 ml DMF followed by addition of hydroxybenzotriazole (1.0 eq) and N,N'-

30 dicyclohexylcarbodiimide (1.5 eq). The solution was stirred at rt overnight. The mixture was then filtrated and purified by preparative HPLC.

LCMS $[M+H]^+$ 337; ^1H NMR (400 MHz, DMSO- d_6) δ_{H} ppm 12.15 (1 H, br. s.), 11.17 (1 H, s), 8.86 (1 H, m, $J=5.05$ Hz), 8.25 - 8.35 (2 H, m), 8.03 (1 H, dd, $J=8.08$, 1.26 Hz), 7.59 - 7.68 (2 H, m), 7.52 (2 H, dd, $J=8.46$, 1.39 Hz), 6.36 (1 H, s), 2.95 (3 H, d, $J=4.80$ Hz).

Example 309

N-{3-[2-Amino-6-(methylamino)pyrimidin-4-yl]phenyl}prop-2-enamide.

To a stirred suspension of 6-(3-aminophenyl)-4-N-methyl-pyrimidine-2,4-diamine
5 (0.29 mmol) and triethylamine (1.5 eq.) in acetonitrile (2 mL) at 0 °C was slowly
added prop-2-enoyl chloride (1.0 eq.). The mixture was allowed to warm to rt and
stirred for 3 h. The mixture was concentrated and purified by preparative HPLC.
LCMS [M+H]⁺ 270; ¹H NMR (400 MHz, DMSO-d₆) δ_H ppm 10.35 (1 H, s), 8.23 (1
H, t, J=1.89 Hz), 7.79 (1 H, d, J=8.08 Hz), 7.56 - 7.69 (4 H, m), 7.34 - 7.52 (4 H,
10 m), 6.88 (1 H, s), 6.84 (1 H, s), 6.18 (1 H, s), 5.98 (2 H, s), 2.80 (3 H, d, J=4.80
Hz).

Example 310

(2E)-N-{3-[2-Amino-6-(methylamino)pyrimidin-4-yl]phenyl}-3-phenylprop-2-
15 enamide.

To a suspension of the 6-(3-aminophenyl)-4-N-methyl-pyrimidine-2,4-diamine
(0.25 mmol) and triethylamine (1.5 eq.) in acetonitrile (2 mL) at 0 °C was added
drop wise, with stirring, the (E)-3-phenylprop-2-enoyl chloride (1.0 eq.). The
mixture was allowed to warm to rt, and stirred for 3 h. The mixture was
20 concentrated and purified by preparative HPLC. LCMS [M+H]⁺ 346; ¹H NMR (400
MHz, DMSO-d₆) δ_H ppm 10.35 (s, 1 H), 8.23 (t, J=1.89 Hz, 1 H), 7.79 (d, J=8.08
Hz, 1 H), 7.56 - 7.69 (m, 4 H), 7.34 - 7.52 (m, 4 H), 6.88 (s, 1 H), 6.84 (s, 1 H),
6.18 (s, 1 H), 5.98 (s, 2 H), 2.80 (d, J=4.80 Hz, 3 H).

25 Example 311

N-{3-[2-Amino-6-(methylamino)pyrimidin-4-yl]-2-methylphenyl}prop-2-enamide.

To a suspension of 6-(3-amino-2-methyl-phenyl)-4-N-methyl-pyrimidine-2,4-
diamine (0.39 mmol) and triethylamine (1.5 eq.) in acetonitrile (3 ml) at 0 °C was
added drop wise, with stirring, prop-2-enoyl chloride (1.0 eq.). The mixture was
30 allowed to warm to rt, and stirred for 3 h. The mixture was concentrated and
purified by preparative HPLC. LCMS [M+H]⁺ 284; ¹H NMR (400 MHz, DMSO-d₆)
δ_H ppm 9.57 (1 H, s), 7.41 (1 H, d, J=7.58 Hz), 7.20 (1 H, t, J=7.83 Hz), 7.10 (1 H,
d, J=6.82 Hz), 6.83 (1 H, br. s.), 6.54 (1 H, dd, J=17.05, 10.23 Hz), 6.25 (1 H, dd,
J=17.05, 2.15 Hz), 5.97 (2 H, s), 5.73 - 5.78 (1 H, m), 5.71 (1 H, s), 2.77 (3 H, d,
35 J=4.55 Hz), 2.14 (3 H, s).

Example 312

(2E)-N-{3-[2-Amino-6-(methylamino)pyrimidin-4-yl]phenyl}-4-(dimethylamino)but-2-enamide.

- 5 To a solution of 6-(3-aminophenyl)-4-N-methylpyrimidine-2,4-diamine (0.29 mol) in acetonitrile (4 mL) was added successively (E)-4-(dimethylamino)but-2-enoic acid; hydrochloride (1.0 eq.), triethylamine (3.0 eq.) and n-propanephosphonic acid anhydride (T3P, 2.0 eq.). The resulting mixture was stirred at rt overnight. The solution was then filtrated and purified by preparative HPLC. LCMS [M+H]⁺
10 327; ¹H NMR (400 MHz, DMSO-d₆) δ_H ppm 10.17 (1 H, s), 8.20 (1 H, t, J=1.77 Hz), 7.71 (1 H, d, J=8.08 Hz), 7.58 (1 H, d, J=7.83 Hz), 7.36 (1 H, t, J=7.83 Hz), 6.81 - 6.96 (1 H, m), 6.70 - 6.80 (1 H, m), 6.28 (1 H, dt, J=15.35, 1.55 Hz), 6.16 (1 H, s), 5.97 (2 H, s), 3.06 (2 H, dd, J=6.06, 1.52 Hz), 2.79 (3 H, d, J=4.80 Hz), 2.18 (6 H, s).

15

Example 313

N-{3-[2-amino-6-(methylamino)pyrimidin-4-yl]phenyl}ethene-1-sulfonamide.

- To a suspension of 6-(3-aminophenyl)-4-N-methyl-pyrimidine-2,4-diamine (0.20 mmol) and triethylamine (1.1 eq.) in acetonitrile (1.5 mL) at -60 °C was added
20 drop wise, with stirring, ethenesulfonyl chloride (0.9 eq.) in 0.5 ml acetonitrile. The mixture was allowed to warm to rt, and stirred for 2 h. The solution was then filtrated and purified by preparative HPLC. LCMS [M+H]⁺ 306; ¹H NMR (400 MHz, DMSO-d₆) δ_H ppm 11.98 (1 H, br. s.), 10.38 (1 H, br. s.), 8.79 (1 H, br. s.), 7.31 - 7.60 (4 H, m), 6.85 (1 H, dd, J=16.42, 9.85 Hz), 6.25 (1 H, s), 6.18 (1 H, d, J=16.42 Hz), 6.08 (1 H, d, J=9.85 Hz), 2.93 (3 H, d, J=4.80 Hz).

25

Example 314

N-{3-[2-Amino-6-(methylamino)pyrimidin-4-yl]phenyl}prop-2-ynamide.

- To a solution of 6-(3-aminophenyl)-4-N-methyl-pyrimidine-2,4-diamine (0.30 mol) in acetonitrile (5 mL) at 0 °C was added successively prop-2-ynoic acid (1.0 eq.),
30 triethylamine (2.0 eq.) and n-propanephosphonic acid anhydride (T3P, 1.7 eq.). The resulting mixture was stirred at rt overnight. The solution was then filtrated and purified by preparative HPLC. LCMS [M+H]⁺ 268; ¹H NMR (400 MHz, DMSO-d₆) δ_H ppm 8.19 (1 H, br. s.), 7.84 (1 H, d, J=7.83 Hz), 7.65 (1 H, d, J=7.83 Hz),

7.46 (1 H, d, J=13.39 Hz), 7.38 (1 H, t, J=7.83 Hz), 7.00 (1 H, d, J=13.89 Hz), 6.28 (1 H, br. s.), 5.97 (2 H, s), 2.78 (3 H, d, J=4.55 Hz).

Example 315

5 N-{3-[2-Amino-6-(methylamino)pyrimidin-4-yl]phenyl}-2-oxopropanamide.

To a solution of 6-(3-aminophenyl)-4-N-methyl-pyrimidine-2,4-diamine (0.39 mol) in acetonitrile (4 mL) was added successively pyruvic acid (1.0 eq.), triethylamine (2.5 eq.) and n-propanephosphonic acid anhydride (T3P, 2.0 eq.). The resulting mixture was stirred at rt overnight. The solution was then filtrated and purified by
10 preparative HPLC. LCMS [M+H]⁺ 286.

Example 316

N-{3-[2-Amino-6-(methylamino)pyrimidin-4-yl]phenyl}-2-oxo-2-phenylacetamide.

To a solution of 6-(3-aminophenyl)-4-N-methyl-pyrimidine-2,4-diamine (0.42 mol)
15 in acetonitrile (4 mL) was added successively 2-oxo-2-phenyl-acetic acid (0.9 eq.), triethylamine (2.5 eq.) and n-propanephosphonic acid anhydride (T3P, 2.0 eq.). The resulting mixture was stirred at rt overnight. The mixture was concentrated and purified by preparative HPLC. LCMS [M+H]⁺ 348; ¹H NMR (400 MHz, DMSO-d₆) δ_H ppm 8.30 - 8.36 (1 H, m), 8.00 - 8.11 (2 H, m), 7.66 - 7.84 (3
20 H, m), 7.59 - 7.66 (2 H, m), 7.45 (1 H, t, J=7.96 Hz), 6.90 (1 H, br. s.), 6.19 (1 H, s), 6.01 (2 H, s), 2.80 (3 H, d, J=4.80 Hz).

Example 317

N-{4-[2-Amino-6-(methylamino)pyrimidin-4-yl]phenyl}prop-2-enamide.

25 To a suspension of 6-(4-aminophenyl)-4-N-methyl-pyrimidine-2,4-diamine (0.29 mmol) and triethylamine (1.5 eq.) in tetrahydrofuran (2 ml) at 0 °C was added drop wise, with stirring, prop-2-enoyl chloride (1.0 eq.). The mixture was allowed to warm to rt, and stirred for 3 h. The mixture was concentrated and purified by preparative HPLC. LCMS [M+H]⁺ 270; ¹H NMR (400 MHz, DMSO-d₆) δ_H ppm
30 10.28 (1 H, s), 7.89 (2 H, d, J=8.8 Hz), 7.58 - 7.75 (2 H, m), 6.76 (1 H, br. s.), 6.40 - 6.49 (1 H, m), 6.24 - 6.30 (1 H, m), 6.17 (1 H, s), 5.94 (2 H, s), 5.58 - 5.80 (1 H, m), 2.79 (3 H, d, J=4.8 Hz).

Example 318

35 N-({4-[2-Amino-6-(methylamino)pyrimidin-4-yl]phenyl}methyl)prop-2-enamide.

To a suspension of 6-[4-(aminomethyl)phenyl]-4-N-methyl-pyrimidine-2,4-diamine (0.29 mmol) and triethylamine (1.5 eq.) in tetrahydrofuran (2 ml) at 0 °C was added drop wise, with stirring, prop-2-enoyl chloride (1.0 eq.). The mixture was allowed to warm to rt and stirred for 3 h. The mixture was concentrated and
5 purified by preparative HPLC. LCMS [M+H]⁺ 284.

Example 319

N-({3-[2-Amino-6-(methylamino)pyrimidin-4-yl]phenyl}methyl)prop-2-enamide.
To a suspension of 6-[3-(aminomethyl)phenyl]-4-N-methyl-pyrimidine-2,4-diamine
10 (0.16 mmol) and triethylamine (1.5 eq.) acetonitrile (4 mL) at 0 °C was added drop wise, with stirring, prop-2-enoyl chloride (1.0 eq.). The mixture was allowed to warm to room temperature, and stirred for 3 h. The mixture was concentrated and purified by preparative HPLC. LCMS [M+H]⁺ 284.

15 Example 320

N-{3-[2-Amino-6-(ethylamino)pyrimidin-4-yl]-4-methylphenyl}prop-2-enamide.
To a suspension of 6-(5-amino-2-methyl-phenyl)-4-N-methyl-pyrimidine-2,4-diamine (0.48 mmol) and triethylamine (1.7 eq.) in acetonitrile (3 mL) at 0 °C was added drop wise, with stirring, prop-2-enoyl chloride (1.0 eq.). The mixture was
20 allowed to warm to rt and stirred for 3 h. The mixture was concentrated and purified by preparative HPLC. LCMS [M+H]⁺ 284; ¹H NMR (400 MHz, DMSO-d₆) δ_H ppm 10.10 (1 H, s), 7.46 - 7.75 (2 H, m), 7.16 (1 H, d, J=8.34 Hz), 6.80 (1 H, br. s.), 6.37 - 6.46 (1 H, m), 6.23 (1 H, dd, J=17.05, 2.15 Hz), 5.95 (2 H, s), 5.62 - 5.84 (2 H, m), 2.77 (3 H, d, J=4.55 Hz), 2.27 (3 H, s).

25

Example 321

N-{3-[2-Amino-6-(methylamino)pyrimidin-4-yl]phenyl}-5-chloro-2-hydroxybenzamide.
Equimolar quantities of 5-chloro-2-hydroxy-benzoic acid and 6-(3-aminophenyl)-
30 4-N-methyl-pyrimidine-2,4-diamine (0.24 mmol) were dissolved in DMF (2 mL) followed by adding hydroxybenzotriazole (1.0 eq) and N,N'-dicyclohexylcarbodiimide (1.5 eq). The solution was stirred under rt overnight. The mixture was then filtrated and purified by preparative HPLC. LCMS [M+H]⁺ 370; ¹H NMR (400 MHz, DMSO-d₆) δ_H ppm 15.10 (1 H, br. s), 8.08 - 8.16 (1 H, m), 7.86 (1 H, d, J=7.58 Hz), 7.64 (1 H, d, J=3.03 Hz), 7.49 (1 H, d, J=7.33 Hz), 7.32 (1 H, t,
35

J=7.96 Hz), 6.93 (1 H, dd, J=8.84, 3.03 Hz), 6.78 - 6.89 (1 H, m), 6.40 (1 H, d, J=8.84 Hz), 6.20 (1 H, s), 6.03 (2 H, s), 2.80 (3 H, d, J=4.55 Hz).

Example 322

- 5 N-{3-[2-Amino-6-(methylamino)pyrimidin-4-yl]phenyl}-2-hydroxyacetamide.
Equimolar quantities of 2-hydroxyacetic acid and 6-(3-aminophenyl)-4-N-methylpyrimidine-2,4-diamine (0.24 mmol) were dissolved in 2 ml DMF followed by adding hydroxybenzotriazole (1.0 eq) in 1 mL DMF and N,N'-dicyclohexylcarbodiimide (1.5 eq, dissolved in xylene). The solution was stirred under room
10 temperature overnight. The mixture was then filtrated and purified by preparative. LCMS [M+H]⁺ 274; ¹H NMR (400 MHz, DMSO-d₆) δ_H ppm 12.06 (1 H, br. s.), 9.75 - 10.10 (1 H, m), 8.83 (1 H, d, J=4.55 Hz), 8.22 (1 H, s), 7.84 (1 H, d, J=9.35 Hz), 7.54 (1 H, t, J=7.96 Hz), 7.40 (1 H, d, J=8.08 Hz), 6.30 (1 H, s), 5.61 - 5.97 (1 H, m), 4.03 (2 H, s), 2.94 (3 H, d, J=4.80 Hz).

15

Example 323

- N-{3-[2-Amino-6-(methylamino)pyrimidin-4-yl]phenyl}-2-(4-chlorophenyl)-2-hydroxyacetamide.
Equimolar quantities of 6-(3-aminophenyl)-4-N-methylpyrimidine-2,4-diamine
20 (0.24 mmol) and 2-(4-chlorophenyl)-2-hydroxyacetic acid were dissolved in 2 ml DMF followed by adding hydroxybenzotriazole (1.0 eq) in 1 mL DMF and N,N'-dicyclohexylcarbodiimide (1.5 eq.; as a solution in xylene). The solution was stirred at rt overnight. The mixture was then filtrated and purified by preparative HPLC. LCMS [M+H]⁺ 384; ¹H NMR (400 MHz, DMSO-d₆) δ_H ppm 10.05 (1 H, s),
25 8.22 (1 H, t, J=1.89 Hz), 7.69 (1 H, d, J=8.59 Hz), 7.59 (1 H, d, J=6.57 Hz), 7.52 - 7.57 (2 H, m), 7.40 - 7.45 (2 H, m), 7.34 (1 H, t, J=7.96 Hz), 6.85 (1 H, br. s.), 6.14 (1 H, s), 6.04 (2 H, br. s.), 5.97 (1 H, s), 5.14 (1 H, s), 2.78 (3 H, d, J=4.80 Hz).

Example 324

- N-{3-[2-Amino-6-(methylamino)pyrimidin-4-yl]phenyl}-2-hydroxy-2-phenylacetamide.
Equimolar quantities of 2-hydroxy-2-phenylacetic acid and 6-(3-aminophenyl)-4-N-methylpyrimidine-2,4-diamine (0.24 mmol) were dissolved in DMF (2 mL)
35 followed by adding hydroxybenzotriazole (1.0 eq) in DMF (1 mL) and N,N'-

dicyclohexylcarbodiimide (1.5 eq, dissolved in xylene). The solution was stirred under rt overnight. The mixture was then filtrated and purified by preparative HPLC. LCMS [M+H]⁺ 350; ¹H NMR (400 MHz, DMSO-d₆) δ_H ppm 11.86 (1 H, br. s.), 10.25 (2 H, s), 8.25 (1 H, s), 7.85 (1 H, d, J=8.59 Hz), 7.48 - 7.63 (3 H, m),
5 7.26 - 7.46 (4 H, m), 6.56 (1 H, d, J=4.29 Hz), 6.28 (1 H, s), 5.15 (1 H, d, J=3.79 Hz), 2.93 (3 H, d, J=4.80 Hz).

Example 325

N-{3-[2-Amino-6-(methylamino)pyrimidin-4-yl]phenyl}-4-oxo-4-(pyrrolidin-1-yl)butanamide.
10

Equimolar quantities of 4-oxo-4-pyrrolidin-1-yl-butanolic acid and 6-(3-amino-phenyl)-4-N-methyl-pyrimidine-2,4-diamine (0.24 mmol) were dissolved in DMF (2 mL) followed by adding hydroxybenzotriazole (1.0 eq) in DMF (1 mL) and N,N'-dicyclohexylcarbodiimide (1.5 eq, dissolved in xylene). The solution was stirred at
15 rt overnight. The mixture was then filtrated and purified by preparative HPLC. LCMS [M+H]⁺ 369.

Example 326

N-{3-[2-Amino-6-(methylamino)pyrimidin-4-yl]phenyl}-2-hydroxybenzamide.
20 Equimolar quantities of 2-hydroxybenzoic acid and 6-(3-aminophenyl)-4-N-methyl-pyrimidine-2,4-diamine (0.24 mmol) were dissolved in MeCN (2 mL) followed by adding N,N'-dicyclohexylcarbodiimide (1.25 eq). The solution was stirred at rt overnight. The mixture was then filtrated and purified by preparative HPLC. LCMS [M+H]⁺ 336.

25

Example 327

1-{4-[2-Amino-6-(methylamino)pyrimidin-4-yl]phenyl}-2,2,2-trifluoroethan-1-one.
Tetrakis(triphenylphosphine)palladium (0) (5 mol%) was added to a stirred mixture of 6-chloro-4-N-methylpyrimidine-2,4-diamine (0.25 mmol), [4-
30 (trifluoroacetyl)phenyl]boronic ester (1.3 eq.), sodium carbonate (3.2 eq.), dioxane (2 mL) and water (0.5 mL) in a tube. The tube was sealed and the reaction was heated at 90°C for 5 hours. The mixture was then filtrated and purified by preparative HPLC. LCMS [M+H]⁺ 297.

35 Example 328

6-[3-(Aminomethyl)phenyl]-4-N-methylpyrimidine-2,4-diamine.

Tetrakis(triphenylphosphine)palladium (0) (5 mol%) was added to a stirred mixture of 6-chloro-4-N-methylpyrimidine-2,4-diamine (2.00 mmol), [3-(aminomethyl)phenyl]boronic acid (1.3 eq.), sodium carbonate (3.2 eq.), dioxane (4 mL) and water (1 mL) in a tube. The tube was sealed and the reaction was heated at 90°C overnight. The solvent were removed in vacuum and to the remaining solid was added ethyl acetate and washed with water. The organic phase was dried over magnesium sulfate. The crude material was then purified by flash chromatography (0→15 % MeOH/DCM) to give the title compound.

LCMS [M+H]⁺ 230; ¹H NMR (400 MHz, DMSO-d₆) δ_H ppm 7.90 (1 H, s), 7.75 (1 H, d, J=6.32 Hz), 7.35 - 7.42 (3 H, m), 6.82 (1 H, br. S), 6.21 (1 H, s), 5.98 (2 H, s), 3.79 (2 H, s), 2.79 (3 H, d, J=4.80 Hz).

Example 329

6-[4-(Aminomethyl)phenyl]-4-N-methylpyrimidine-2,4-diamine.

Tetrakis(triphenylphosphine)palladium (0) (5 mol%) was added to a stirred mixture of 6-chloro-4-N-methylpyrimidine-2,4-diamine (1.00 mmol), [4-(aminomethyl)phenyl]boronic acid (1.3 eq.), sodium carbonate (4.2 eq.), dioxane (4 ml) and water (1 ml) in a tube. The tube was sealed and the reaction was heated at 90°C overnight. The solvent were removed in vacuum and to the remaining solid was added ethyl acetate and washed with water. The organic phase was dried over magnesium sulfate. The crude material was then purified by flash chromatography (0→15 % MeOH/DCM) to give the title compound.

LCMS [M+H]⁺ 230; ¹H NMR (400 MHz, DMSO-d₆) δ_H ppm 7.86 (2 H, d, J=7.58 Hz), 7.38 (2 H, d, J=8.59 Hz), 6.19 (1 H, s), 5.96 (2 H, s), 3.76 (2 H, s), 2.79 (3 H, d, J=4.80 Hz).

Example 330

4-(2-([2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}ethyl)benzene-1-sulfonamide.

A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (0.12 mmol), 4-(2-aminoethyl)benzene-1-sulfonamide (0.9 eq.) and triethylamine (1.5 eq.) in acetonitrile/ethanol/methanol 5:3:2 (1 mL) was heated in a sealed tube at 95°C overnight. Methanol was added, and the mixture was filtered and purified by preparative HPLC. LCMS [M+H]⁺ 398; ¹H NMR (400 MHz, DMSO-d₆) δ_H ppm

12.28 (1 H, br. s.), 8.87 (1 H, br. s.), 7.77 (2 H, d, J=8.34 Hz), 7.48 (2 H, d, J=8.34 Hz), 7.37 (1 H, d, J=7.33 Hz), 7.32 (2 H, s), 7.23 - 7.28 (1 H, m), 7.18 - 7.23 (1 H, m), 5.99 (1 H, s), 3.67 (2 H, q, J=6.82 Hz), 2.98 (2 H, t, J=7.20 Hz), 2.31 (3 H, s), 2.17 (3 H, s).

5

Example 331

6-(2,3-Dimethylphenyl)-4-N-[2-(4-methanesulfonylphenyl)ethyl]pyrimidine-2,4-diamine.

A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (0.15 mmol), 2-(4-methanesulfonylphenyl)ethan-1-amine (1.2 eq.) and N,N-diisopropylethylamine (2.25 eq.) in n-butanol (0.3 mL) was heated in a sealed tube at 110°C overnight. Methanol was added and the mixture was filtered and purified by preparative HPLC. LCMS [M+H]⁺ 397.

15 Example 332

6-(2,3-Dimethylphenyl)-4-N-[2-(5-methyl-1H-1,2,4-triazol-3-yl)ethyl]pyrimidine-2,4-diamine.

A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (0.15 mmol), 2-(5-methyl-1H-1,2,4-triazol-3-yl)ethan-1-amine (0.9 eq.) and triethylamine (1.5 eq.) in acetonitrile/ethanol/methanol 5:3:2 (1 mL) was heated in a sealed tube at 95°C overnight. Methanol was added, and the mixture was filtered and purified by preparative HPLC. LCMS [M+H]⁺ 324.

Example 333

25 4-(2-[[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino]ethyl)benzonitrile.

A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (0.15 mmol), 4-(2-aminoethyl)benzonitrile (1.2 eq.) and N,N-diisopropylethylamine (2.25 eq.) in n-butanol (0.3 mL) was heated in a sealed tube at 110°C overnight. Methanol was added, and the mixture was filtered and purified by preparative HPLC. LCMS [M+H]⁺ 344; ¹H NMR (400 MHz, DMSO-d₆) δ_H ppm 12.36 (1 H, br. s.), 8.87 (1 H, t, J=5.31 Hz), 7.80 (2 H, d, J=8.08 Hz), 7.51 (2 H, d, J=8.34 Hz), 7.37 (1 H, d, J=7.33 Hz), 7.23 - 7.28 (1 H, m), 7.16 - 7.22 (1 H, m), 5.98 (1 H, s), 3.67 (2 H, q, J=6.65 Hz), 2.99 (2 H, t, J=7.20 Hz), 2.31 (3 H, s), 2.17 (3 H, s).

35 Example 334

6-(2,3-Dimethylphenyl)-4-N-[2-(pyridin-4-yl)ethyl]pyrimidine-2,4-diamine.

A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (0.15 mmol), 2-(pyridin-4-yl)ethan-1-amine (1.2 eq.) and N,N-diisopropylethylamine (1.25 eq.) in n-butanol (0.3 ml) was heated in a sealed tube at 110°C overnight. Methanol was added, and the mixture was filtered and purified by preparative HPLC. LCMS [M+H]⁺ 320; ¹H NMR (400 MHz, DMSO-d₆) δ_H ppm 12.45 (1 H, br. s.), 8.93 (1 H, t, J=5.56 Hz), 8.76 (2 H, d, J=6.32 Hz), 7.80 (2 H, d, J=6.32 Hz), 7.37 (1 H, d, J=7.33 Hz), 7.25 (1 H, t, J=7.58 Hz), 7.17 - 7.21 (1 H, m), 5.99 (1 H, s), 3.68 - 3.83 (2 H, m), 3.13 (2 H, t, J=7.07 Hz), 2.31 (3 H, s), 2.17 (3 H, s).

10

Example 335

4-(2-([2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino)ethoxy)benzonitrile.

A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (0.15 mmol), 4-(2-aminoethoxy)benzonitrile (1.2 eq.) and N,N-diisopropylethylamine (1.25 eq.) in n-butanol (0.3 mL) was heated in a sealed tube at 110°C overnight. Methanol was added, and the mixture was filtered and purified by preparative HPLC. LCMS [M+H]⁺ 360; ¹H NMR (400 MHz, DMSO-d₆) δ_H ppm 12.37 (1 H, br. s.), 9.02 (1 H, t, J=5.31 Hz), 7.77 - 7.83 (2 H, m), 7.37 (1 H, d, J=7.33 Hz), 7.23 - 7.29 (1 H, m), 7.18 - 7.22 (1 H, m), 7.12 - 7.18 (2 H, m), 6.06 (1 H, s), 4.29 (2 H, t, J=5.43 Hz), 3.82 (2 H, q, J=5.22 Hz), 2.31 (3 H, s), 2.17 (3 H, s).

20

Example 336

4-([2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino)methyl)benzene-1-sulfonamide.

A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (0.08 mmol), 4-(aminomethyl)benzene-1-sulfonamide (0.9 eq.) and triethylamine (1.5 eq.) in acetonitrile/ethanol/methanol 5:3:2 (1 mL) was heated in a sealed tube at 95°C overnight. Methanol was added, and the mixture was filtered and purified by preparative HPLC. LCMS [M+H]⁺ 384; ¹H NMR (400 MHz, DMSO-d₆) δ_H ppm 7.74 - 7.81 (2 H, m), 7.49 - 7.54 (2 H, m), 7.46 (1 H, t, J=5.68 Hz), 7.30 (2 H, s), 7.12 - 7.21 (1 H, m), 7.01 - 7.12 (2 H, m), 6.00 (2 H, s), 5.76 (1 H, br. s.), 4.57 (2 H, br. s.), 2.26 (3 H, s), 2.15 (3 H, s).

30

Example 337

1-(2-([2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino)ethyl)-1,2-dihydropyridin-2-one.

A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (0.11 mmol), 1-(2-aminoethyl)-1,2-dihydropyridin-2-one (0.9 eq.) and triethylamine (1.5 eq.) in
5 acetonitrile/ethanol/methanol 5:3:2 (1 mL) was heated in a sealed tube at 95°C overnight. Methanol was added, and the mixture was filtered and purified by preparative HPLC. LCMS [M+H]⁺ 336.

Example 338

10 3-([2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino)methyl)-1,2-dihydropyridin-2-one.

A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (0.11 mmol), 3-(aminomethyl)-1,2-dihydropyridin-2-one (0.9 eq.) and triethylamine (1.5 eq.) in
15 acetonitrile/ethanol/methanol 5:3:2 (1 mL) was heated in a sealed tube at 95°C overnight. Methanol was added, and the mixture was filtered and purified by preparative HPLC. LCMS [M+H]⁺ 322.

Example 339

20 6-(3-([2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino)propyl)-5H,6H,7H-pyrrolo[3,4-b]pyridin-5-one.

A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (0.12 mmol), 6-(3-aminopropyl)-5H,6H,7H-pyrrolo[3,4-b]pyridin-5-one (0.9 eq.) and triethylamine (1.5 eq.) in acetonitrile/ethanol/methanol 5:3:2 (1 mL) was heated in a sealed
25 tube at 95°C overnight. Methanol was added, and the mixture was filtered and purified by preparative HPLC. LCMS [M+H]⁺ 389.

Example 340

6-([2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino)methyl)pyridin-3-ol.
A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (0.08 mmol), 6-(aminomethyl)pyridin-3-ol hydrochloride (0.9 eq.) and triethylamine (2.5 eq.) in
30 acetonitrile/ethanol/methanol 5:3:2 (1 mL) was heated in a sealed tube at 95°C overnight. Methanol was added, and the mixture was filtered and purified by preparative HPLC. LCMS [M+H]⁺ 322.

35 Example 341

4-N-[2-(3-Chlorophenyl)ethyl]-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 9 from 2-(3-chlorophenyl)ethan-1-amine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 353; ^1H NMR (400 MHz, $CDCl_3$) δ_H ppm 2.24 (s, 3 H) 2.31 (s, 3 H) 2.88 (t, $J=7.07$ Hz, 2 H) 3.56 (d, $J=5.81$ Hz, 2 H) 4.86 - 5.12 (m, 3 H) 5.79 (s, 1 H) 7.07 - 7.15 (m, 3 H) 7.17 (q, $J=4.04$ Hz, 1 H) 7.20 - 7.26 (m, 3 H).

Example 342

6-(2,3-Dimethylphenyl)-4-N-[3-(1H-imidazol-1-yl)propyl]pyrimidine-2,4-diamine.

Prepared according to general procedure 9 from 3-(1H-imidazol-1-yl)propan-1-amine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 323; ^1H NMR (400 MHz, CD_3OD) δ_H ppm 2.11 (t, $J=6.82$ Hz, 2 H) 2.20 (s, 3 H) 2.32 (s, 3 H) 3.38 (br. s., 2 H) 4.13 (t, $J=6.95$ Hz, 2 H) 5.82 (s, 1 H) 6.98 (br. s., 1 H) 7.05 - 7.23 (m, 4 H) 7.69 (br. s., 1 H).

Example 343

4-N-[2-(4-Chlorophenyl)propyl]-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 9 from 2-(4-chlorophenyl)propan-1-amine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 367; ^1H NMR (400 MHz, $CDCl_3$) δ_H ppm 1.31 (d, $J=7.07$ Hz, 3 H) 2.23 (s, 3 H) 2.31 (s, 3 H) 2.97 - 3.09 (m, 1 H) 3.28 - 3.40 (m, 1 H) 3.46 - 3.66 (m, 1 H) 4.74 (br. s., 1 H) 4.95 (br. s., 2 H) 5.74 (s, 1 H) 7.09 - 7.14 (m, 2 H) 7.14 - 7.19 (m, 3 H) 7.28 - 7.33 (m, 2 H).

Example 344

6-(2,3-Dimethylphenyl)-4-N-[2-(4-fluorophenyl)ethyl]pyrimidine-2,4-diamine.

Prepared according to general procedure 9 from 2-(4-fluorophenyl)ethan-1-amine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 337; ^1H NMR (400 MHz, $CDCl_3$) δ_H ppm 2.23 (s, 3 H) 2.29 - 2.34 (m, 3 H) 2.89 - 2.96 (m, 3 H) 3.49 - 3.60 (m, 1 H) 3.76 (d, $J=6.06$ Hz, 3 H) 5.77 (s, 4 H) 7.00 - 7.07 (m, 3 H) 7.08 - 7.12 (m, 2 H) 7.13 - 7.22 (m, 5 H) 7.28 - 7.32 (m, 1 H).

Example 345

6-(2,3-Dimethylphenyl)-4-N-[2-(4-methoxyphenyl)-2-(pyrrolidin-1-yl)ethyl]pyrimidine-2,4-diamine.

Prepared according to general procedure 9 from 2-(4-methoxyphenyl)-2-(pyrrolidin-1-yl)ethan-1-amine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 418; ^1H NMR (400 MHz, $CDCl_3$) δ_H ppm 1.74 - 1.81 (m, 4 H) 2.22 (s, 3 H) 2.30 (s, 3 H) 2.46 - 2.69 (m, 5 H) 3.49 (br. s., 2 H) 3.81 (s, 3 H)
5 4.88 (br. s., 2 H) 5.04 - 5.18 (m, 1 H) 5.74 (s, 1 H) 6.85 - 6.90 (m, 2 H) 7.09 - 7.12 (m, 2 H) 7.13 - 7.17 (m, 1 H) 7.24 - 7.29 (m, 2 H).

Example 346

10 4-N-[[4-(Dimethylamino)phenyl]methyl]-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 9 from 4-(aminomethyl)-N,N-dimethylaniline and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 348.

15

Example 347

4-N-[2-(Benzenesulfonyl)ethyl]-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 9 from 2-(benzenesulfonyl)ethan-1-amine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 383;
20 ^1H NMR (400 MHz, $CDCl_3$) δ_H ppm 2.22 (s, 3 H) 2.31 (s, 3 H) 3.41 - 3.46 (m, 2 H) 3.86 (q, $J=6.06$ Hz, 2 H) 5.10 (br. s., 2 H) 5.41 - 5.53 (m, 1 H) 5.76 (s, 1 H) 7.07 - 7.16 (m, 2 H) 7.16 - 7.20 (m, 1 H) 7.57 - 7.63 (m, 2 H) 7.66 - 7.71 (m, 1 H) 7.92 - 7.97 (m, 2 H),

25 Example 348

6-(2,3-Dimethylphenyl)-4-N-[[1-(4-fluorophenyl)-1H-pyrazol-4-yl]methyl]pyrimidine-2,4-diamine.

Prepared according to general procedure 9 from [1-(4-fluorophenyl)-1H-pyrazol-4-yl]methanamine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS
30 $[M+H]^+$ 389; ^1H NMR (400 MHz, $CDCl_3$) δ_H ppm 2.22 (s, 3 H) 2.29 (s, 3 H) 4.47 (d, $J=5.31$ Hz, 2 H) 5.11 - 5.41 (m, 3 H) 5.85 (s, 1 H) 7.10 - 7.19 (m, 5 H) 7.59 - 7.65 (m, 2 H) 7.68 (s, 1 H) 7.85 (s, 1 H)

Example 349

6-(2,3-dimethylphenyl)-4-N-{2-[5-(pyridin-4-yl)-1H-1,2,4-triazol-3-yl]ethyl}pyrimidine-2,4-diamine.

Prepared according to general procedure 9 from 2-[5-(pyridin-4-yl)-1H-1,2,4-triazol-3-yl]ethan-1-amine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine.

5 LCMS $[M+H]^+$ 387.

Example 350

6-(2,3-Dimethylphenyl)-4-N-[[1-(pyrimidin-2-yl)piperidin-3-yl]methyl]pyrimidine-2,4-diamine.

10 Prepared according to general procedure 9 from [1-(pyrimidin-2-yl)piperidin-3-yl]methanamine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 390; ^1H NMR (400 MHz, $CDCl_3$) δ_H ppm 1.41 (m, 1 H) 1.48 - 1.60 (m, 1 H) 1.75 (m, 1 H) 1.85 - 1.98 (m, 2 H) 2.24 (s, 3 H) 2.31 (s, 3 H) 3.13 - 3.48 (m, 4 H) 4.15 - 4.24 (m, 1 H) 4.30 (m, 1 H) 5.11 (br. s., 2 H) 5.39 (br. s., 1 H) 5.82 (s, 1 H)
15 6.45 (t, $J=4.80$ Hz, 1 H) 7.10 - 7.19 (m, 3 H) 8.28 - 8.31 (d, $J=4.80$ Hz, 2 H).

Example 351

6-(2,3-Dimethylphenyl)-4-N-[2-(6-methoxy-1H-1,3-benzodiazol-2-yl)ethyl]pyrimidine-2,4-diamine.

20 Prepared according to general procedure 9 from 2-(6-methoxy-1H-1,3-benzodiazol-2-yl)ethan-1-amine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 389; ^1H NMR (400 MHz, $CDCl_3$) δ_H ppm 2.16 (s, 3 H) 2.24 (s, 3 H) 3.12 (t, $J=6.19$ Hz, 2 H) 3.81 (s, 3 H) 3.82 - 3.90 (m, 2 H) 5.11 - 5.43 (m, 2 H) 5.79 (s, 1 H) 5.88 (br. s., 1 H) 6.85 (dd, $J=8.72$, 2.40 Hz, 1 H) 7.01 (d, $J=8.08$
25 Hz, 2 H) 7.05 (t, $J=7.58$ Hz, 1 H) 7.12 (d, $J=6.82$ Hz, 1 H) 7.40 (d, $J=8.59$ Hz, 1 H).

Example 352

6-(2,3-Dimethylphenyl)-4-N-[2-(4-methyl-1,3-thiazol-5-yl)ethyl]pyrimidine-2,4-diamine.

30 Prepared according to general procedure 9 from 2-(4-methyl-1,3-thiazol-5-yl)ethan-1-amine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 340; ^1H NMR (400 MHz, $CDCl_3$) δ_H ppm 2.23 (s, 3 H) 2.30 (s, 3 H) 2.40 (s, 3 H) 3.07 (t, $J=6.82$ Hz, 2 H) 3.56 (q, $J=6.48$ Hz, 2 H) 5.01 (br. s., 3 H) 5.79 (s, 1
35 H) 7.11 - 7.14 (m, 2 H) 7.17 (q, $J=4.55$ Hz, 1 H) 8.59 (s, 1 H).

Example 353

4-N-[(3-Cyclopropyl-1H-pyrazol-5-yl)methyl]-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.

- 5 Prepared according to general procedure 9 from (3-cyclopropyl-1H-pyrazol-5-yl)methanamine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS [M+H]⁺ 335; ¹H NMR (400 MHz, CD₃OD) δ_H ppm 0.63 - 0.71 (m, 2 H) 0.93 (br. d, J=7.33 Hz, 2 H) 1.83 - 1.93 (m, 1 H) 2.18 (s, 3 H) 2.31 (s, 3 H) 4.50 (br. s., 2 H) 5.86 (s, 1 H) 5.92 (s, 1 H) 7.03 - 7.22 (m, 3 H).

10

Example 354

4-N-[3-(3,5-Dimethyl-1H-pyrazol-1-yl)propyl]-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.

- 15 Prepared according to general procedure 9 from 3-(3,5-dimethyl-1H-pyrazol-1-yl)propan-1-amine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS [M+H]⁺ 351; ¹H NMR (400 MHz, CDCl₃) δ_H ppm 2.05 (quin, J=6.44 Hz, 2 H) 2.20 (s, 3 H) 2.21 (d, J=0.51 Hz, 3 H) 2.23 (s, 3 H) 2.31 (s, 3 H) 3.28 - 3.38 (m, 2 H) 4.07 (t, J=6.57 Hz, 2 H) 5.00 (br. s., 2 H) 5.36 (br. s., 1 H) 5.74 (s, 1 H) 5.78 (s, 1 H) 7.10 - 7.14 (m, 2 H) 7.16 (q, J=4.29 Hz, 1 H).

20

Example 355

6-(2,3-Dimethylphenyl)-4-N-[[1-(pyridin-2-yl)piperidin-3-yl]methyl]pyrimidine-2,4-diamine.

- 25 Prepared according to general procedure 9 from [1-(pyridin-2-yl)piperidin-3-yl]methanamine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS [M+H]⁺ 389; ¹H NMR (400 MHz, CDCl₃) δ_H ppm 1.28 - 1.40 (m, 1 H) 1.53 - 1.67 (m, 1 H) 1.73 - 1.83 (m, 1 H) 1.88 - 2.00 (m, 2 H) 2.24 (s, 3 H) 2.31 (s, 3 H) 3.00 (br. t, J=11.40 Hz, 1H) 3.09 (ddd, J=12.95, 10.04, 3.28 Hz, 1 H) 3.17 - 3.40 (m, 2 H) 3.91 (dt, J=12.88, 4.29 Hz, 1 H) 4.10 (dd, J=12.88, 3.03 Hz, 1 H) 4.99 (br. s., 2 H) 5.31 (d, J=2.02 Hz, 1 H) 5.83 (s, 1 H) 6.57 (ddd, J=7.07, 4.93, 0.88 Hz, 1 H) 6.62 - 6.67 (m, 1 H) 7.12 - 7.19 (m, 3 H) 7.45 (ddd, J=8.91, 7.01, 2.02 Hz, 1 H) 8.16 (ddd, J=4.93, 2.02, 0.88 Hz, 1 H).

30

Example 356

6-(2,3-Dimethylphenyl)-4-N-[(2-phenyl-2H-1,2,3-triazol-4-yl)methyl]pyrimidine-2,4-diamine.

Prepared according to general procedure 9 from (2-phenyl-2H-1,2,3-triazol-4-yl)methanamine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS

5 [M+H]⁺ 372; ¹H NMR (400 MHz, CDCl₃) δ_H ppm 2.21 (s, 3 H) 2.28 (s, 3 H) 4.67 (br d, J=5.31 Hz, 2 H) 5.17 (br. s., 2 H) 5.58 - 5.70 (m, 1 H) 5.87 (s, 1 H) 7.08 - 7.18 (m, 3 H) 7.32 - 7.38 (m, 1 H) 7.45 - 7.51 (m, 2 H) 7.74 (s, 1 H) 8.01 - 8.06 (m, 2 H).

10 Example 357

N-(3-[[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}propyl)-4-chlorobenzene-1-sulfonamide.

Prepared according to general procedure 10 from 4-chlorobenzene-1-sulfonyl chloride and 4-N-(3-aminopropyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.

15 LCMS [M+H]⁺ 446; ¹H NMR (400 MHz, CDCl₃) δ_H ppm 1.72 (quin, J=6.06 Hz, 2 H) 2.21 (s, 3 H) 2.30 (s, 3 H) 2.90 (d, J=5.05 Hz, 2 H) 3.49 (q, J=6.32 Hz, 2 H) 3.44 - 3.52 (m, 2 H) 5.33 - 5.43 (m, 1 H) 5.57 (br. s., 2 H) 5.78 (s, 1 H) 7.05 - 7.09 (m, 1 H) 7.09 - 7.13 (m, 1 H) 7.16 - 7.20 (m, 1 H) 7.41 - 7.46 (m, 2 H) 7.79 - 7.84 (m, 2 H).

20

Example 358

3-(3-[[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}propyl)-1-(4-chlorophenyl)urea.

Prepared according to general procedure 11 from 1-chloro-4-isocyanatobenzene

25 and 4-N-(3-aminopropyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine. LCMS [M+H]⁺ 425; ¹H NMR (400 MHz, CD₃OD) δ_H ppm 1.85 (t, J=6.69 Hz, 2 H) 2.23 (s, 3 H) 2.34 (s, 3 H) 3.28 (overlap with methanol) 3.50 - 3.61 (m, 2 H) 5.97 (s, 1 H) 7.15 (s, 1 H) 7.17 - 7.25 (m, 3 H) 7.28 - 7.37 (m, 3 H).

30 Example 359

N-(3-[[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}propyl)-3,5-dimethyl-1,2-oxazole-4-sulfonamide.

Prepared according to general procedure 10 from dimethyl-1,2-oxazole-4-sulfonyl chloride and 4-N-(3-aminopropyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.

35 LCMS [M+H]⁺ 431; ¹H NMR (400 MHz, CDCl₃) δ_H ppm 1.79 (br. quin, J=6.0 Hz, 2

H) 2.23 (s, 3 H) 2.30 (s, 3 H) 2.42 (s, 3 H) 2.64 (s, 3 H) 3.01 (br. q, J=5.90 Hz, 2 H) 3.53 (br. q, J=6.00 Hz, 2 H) 5.89 (s, 1 H) 7.05 - 7.13 (m, 2 H) 7.18 - 7.21 (m, 1 H).

5 Example 360

N-(3-([2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino)propyl)-2-(dimethylamino)acetamide.

In a vial 4-N-(3-aminopropyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine (10 mg, 0.037 mmol) and 2-(dimethylamino)acetyl chloride hydrochloride (50 mg, 0.32 mmol) were suspended in DCM (1.0 ml), then Et₃N (0.013 ml, 0.092 mmol) was added. The resulting reaction mixture was stirred at r.t. for 1 h. Then MeOH was added and the mixture was stirred 30 min after which the mixture was concentrated and purified by preparative HPLC. LCMS [M+H]⁺ 357; ¹H NMR (400 MHz, CDCl₃) δ_H ppm 1.70 - 1.78 (m, 2 H) 2.28 (s, 3 H) 2.31 (s, 3 H) 2.35 (s, 6 H) 3.06 (s, 2 H) 3.34 - 3.41 (m, 2 H) 3.48 - 3.55 (m, 2 H) 5.85 (s, 1 H) 7.12 - 7.16 (m, 2 H) 7.17 - 7.22 (m, 1 H).

Example 361

3-(3-([2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino)propyl)-1-(2,6-dichloropyridin-4-yl)urea.

Prepared according to general procedure 11 from 2,6-dichloro-4-isocyanatopyridine and 4-N-(3-aminopropyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine. LCMS [M+H]⁺ 460; ¹H NMR (400 MHz, CDCl₃) δ_H ppm 1.86 (br. quint, J=6.7 Hz, 2 H) 2.24 (s, 3 H) 2.34 (s, 3 H) 3.30 - 3.34 (m [overlap w MeOH], 2H) 3.55 (br. s., 3 H) 5.98 (s, 1 H) 7.11 - 7.24 (m, 2 H) 7.27 - 7.33 (m, 1 H) 7.46 (s, 2 H).

Example 362

3-(3-([2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino)propyl)-1-(3,4-difluorophenyl)urea.

Prepared according to general procedure 11 from 1,2-difluoro-4-isocyanatobenzene and 4-N-(3-aminopropyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine. LCMS [M+H]⁺ 427; ¹H NMR (400 MHz, CDCl₃) δ_H ppm 1.81 - 1.89 (m, 2 H) 2.24 (s, 3 H) 2.34 (s, 3 H) 3.25 - 3.30 (m [overlap w MeOH], 2H) 3.55 (br.

s., 2 H) 5.98 (s, 1 H) 6.94 - 7.01 (m, 1 H) 7.06 - 7.17 (m, 2 H) 7.17 - 7.23 (m, 1 H) 7.27 - 7.33 (m, 1 H) 7.45 - 7.54 (m, 1 H).

Example 363

5 N-[3-(3-[[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino]propoxy)phenyl]acetamide.

Prepared according to general procedure 9 from N-[3-(3-aminopropoxy)phenyl]acetamide and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS [M+H]⁺ 406; ¹H NMR (400 MHz, DMSO-d₆) δ_H ppm 1.96 (t, J=6.32 Hz, 2 H) 2.02 (s, 3 H) 2.15 (s, 3 H) 2.25 (s, 3 H) 4.00 (t, J=6.32 Hz, 2 H) 5.70 (s, 1 H) 5.92 (br. s., 2 H) 6.61 (dd, J=8.46, 1.64 Hz, 1 H) 6.85 - 6.99 (m, 1 H) 6.99 - 7.10 (m, 3 H) 7.11 - 7.19 (m, 2 H) 7.31 (s, 1 H) 9.88 (s, 1 H). A signal from one of the CH₂-groups is overlapping with solvent peaks and is not observed by NMR.

15 Example 364

6-(2,3-Dimethylphenyl)-4-N-[(2-methyl-1H-indol-5-yl)methyl]pyrimidine-2,4-diamine.

Prepared according to general procedure 9 from (2-methyl-1H-indol-5-yl)methanamine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS [M+H]⁺ 358; ¹H NMR (400 MHz, CDCl₃) δ_H ppm 2.22 (s, 3 H) 2.29 (s, 3 H) 2.45 (d, J=0.76 Hz, 3 H) 4.57 (br. s., 2 H) 5.16 - 5.32 (m, 2 H) 5.85 (s, 1 H) 6.18 - 6.21 (m, 1 H) 7.05 - 7.15 (m, 3 H) 7.15 - 7.19 (m, 1 H) 7.24 - 7.28 (m, 1 H) 7.47 (s, 1 H) 7.97 (br. s., 1 H).

25 Example 365

4-N-[2-(3,5-Dimethyl-1H-pyrazol-1-yl)ethyl]-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 9 from 2-(3,5-dimethyl-1H-pyrazol-1-yl)ethan-1-amine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS [M+H]⁺ 337; ¹H NMR (400 MHz, CDCl₃) δ_H ppm 2.17 (d, J=0.51 Hz, 3 H) 2.18 (s, 3 H) 2.21 (s, 3 H) 2.29 (s, 3 H) 2.51 - 2.63 (m, 1 H) 3.68 - 3.76 (m, 2 H) 4.13 (t, J=5.56 Hz, 2 H) 5.03 (s, 2 H) 5.37 - 5.47 (m, 1 H) 5.71 (s, 1 H) 5.77 (s, 1 H) 7.07 - 7.12 (m, 2 H) 7.12 - 7.17 (m, 1 H).

35 Example 366

6-(2,3-Dimethylphenyl)-4-N-[4-(pyrrolidin-1-yl)butyl]pyrimidine-2,4-diamine.

Prepared according to general procedure 9 from 4-(pyrrolidin-1-yl)butan-1-amine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 340; ^1H NMR (400 MHz, $CDCl_3$) δ_H ppm 1.60 - 1.73 (m, 4 H) 1.78 - 1.86 (m, 4 H) 2.24 (s, 3 H) 2.31 (s, 3 H) 2.49 - 2.60 (m, 6 H) 3.31 (br. s., 2 H) 4.79 (s, 2 H) 5.46 - 5.58 (m, 1 H) 5.78 (s, 1 H) 7.09 - 7.18 (m, 3 H).

Example 367

N-(3-[[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}propyl)-3-bromobenzamide.

4-N-(3-aminopropyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine (1.0 eq) was dissolved in THF (0.50 mL) and NMP (0.050 mL), then Et_3N (1.5 eq) and 3-bromobenzoyl chloride (1.2 eq) were added. The resulting reaction mixture was stirred at rt overnight. The mixture was then concentrated and purified by column chromatography. LCMS $[M+H]^+$ 454; ^1H NMR (400 MHz, $CDCl_3$) δ_H ppm 1.80 - 1.89 (m, 2 H) 2.23 (s, 3 H) 2.30 (s, 3 H) 2.37 - 2.59 (m, 1 H) 3.47 - 3.58 (m, 4 H) 5.14 (br. s., 2 H) 5.55 - 5.69 (m, 1 H) 5.85 (s, 1 H) 7.07 - 7.13 (m, 2 H) 7.17 (dd, $J=6.19, 2.91$ Hz, 1 H) 7.31 (t, $J=7.83$ Hz, 1 H) 7.63 (ddd, $J=7.89, 1.96, 1.01$ Hz, 1 H) 7.75 (dd, $J=7.83, 1.01$ Hz, 1 H) 7.98 (t, $J=1.77$ Hz, 1 H).

Example 368

N-(3-[[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}propyl)benzamide.

In a vial 4-N-(3-aminopropyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine (1.0 eq) was dissolved in NMP (0.050 mL) and THF (0.50 mL), then Et_3N (1.5 eq) and benzoyl chloride (1.0 eq) were added. The resulting reaction mixture was stirred at rt for 1 h. The mixture was then concentrated and purified by column chromatography. LCMS $[M+H]^+$ 376; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.86 (t, $J=6.06$ Hz, 2 H) 2.22 (s, 3 H) 2.29 (s, 3 H) 3.54 (dt, $J=12.32, 6.09$ Hz, 4 H) 5.36 - 5.54 (m, 1 H) 5.89 (s, 1 H) 6.14 - 6.31 (m, 1 H) 7.06 - 7.13 (m, 2 H) 7.16 - 7.20 (m, 1 H) 7.40 - 7.46 (m, 2 H) 7.47 - 7.53 (m, 1 H) 7.80 - 7.85 (m, 2 H).

Example 369

1-(3-[[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}propyl)-3-(propan-2-yl)urea.

Prepared according to general procedure 11 from 2-isocyanatopropane and 4-N-(3-aminopropyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 357; ^1H NMR (400 MHz, $CDCl_3$) δ_H ppm 1.12 (d, $J=6.57$ Hz, 6 H) 1.78 (t, $J=6.69$ Hz, 2 H) 2.24 (s, 3 H) 2.35 (s, 3 H) 3.20 (t, $J=6.82$ Hz, 2 H) 3.45 - 3.57 (m, 2 H) 3.74 - 3.85 (m, 1 H) 5.97 (s, 1 H) 7.19 (d, $J=14.65$ Hz, 2 H) 7.30 (s, 1 H).

Example 370

tert-Butyl N-(4-[[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino]butyl)-carbamate.

Prepared according to general procedure 9 from tert-butyl N-(4-aminobutyl)carbamate. LCMS $[M+H]^+$ 386; ^1H NMR (400 MHz, $CDCl_3$) δ_H ppm 1.45 (s, 9 H) 1.54 - 1.72 (m, 6 H) 2.24 - 2.28 (m, 3 H) 2.31 (s, 3 H) 3.20 (d, $J=6.32$ Hz, 3 H) 3.33 - 3.43 (m, 2 H) 4.79 - 4.91 (m, 1 H) 5.79 - 5.83 (m, 1 H) 7.14 (s, 2 H) 7.16 - 7.21 (m, 1 H).

Example 371

tert-Butyl N-(5-[[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino]pentyl)-carbamate.

Step 1: 4-N-(5-Aminopentyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine was prepared according to general procedure 9 from pentane-1,5-diamine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine.

Step 2: 4-N-(5-Aminopentyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine (15 mg, 0.028 mmol) and tert-butoxycarbonyl tert-butyl carbonate (7.2 mg, 0.033 mmol) were dissolved in THF (0.50 mL). Then Et_3N (0.011 mL, 0.085 mmol) was added and the resulting mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated and purified by column chromatography (0→5% in DCM) to afford tert-butyl N-[5-[[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino]pentyl]carbamate. LCMS $[M+H]^+$ 400; ^1H NMR (400 MHz, $CDCl_3$) δ_H ppm 1.35 - 1.47 (m, 11 H) 1.52 (d, $J=7.07$ Hz, 2 H) 1.58 - 1.68 (m, 2 H) 2.24 (s, 3 H) 2.29 (s, 3 H) 3.13 (d, $J=6.06$ Hz, 2 H) 3.26 - 3.37 (m, 2 H) 4.58 - 4.68 (m, 1 H) 5.89 (s, 1 H) 7.11 (d, $J=4.80$ Hz, 2 H) 7.18 (d, $J=4.80$ Hz, 1 H).

Example 372

tert-Butyl N-(2-[[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino]cyclohexyl)-carbamate.

Step 1: 4-N-(2-Aminocyclohexyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine was prepared according to general procedure 9 from cyclohexane-1,2-diamine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine.

Step 2: 4-N-(2-Aminocyclohexyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine (15 mg, 0.028 mmol) and tert-butoxycarbonyl tert-butyl carbonate (7.0 mg, 0.032 mmol) were dissolved in THF (0.50 mL). Then Et₃N (0.0050 mL, 0.036 mmol) was added and the resulting mixture was stirred at rt for 16 h. The reaction mixture was concentrated and purified by column chromatography (0→5% in DCM) to afford tert-butyl N-[2-[[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino]cyclohexyl]carbamate. LCMS [M+H]⁺ 412; NMR: mixture of cis- and trans-diastereomers: ¹H NMR (400 MHz, CDCl₃) δ_H ppm 1.16 - 1.37 (m, 6 H) 1.38 - 1.42 (m, 18 H) 1.53 (br. s., 6 H) 1.79 (br. s., 4 H) 2.00 - 2.08 (m, 1 H) 2.18 - 2.23 (m, 1 H) 2.25 (d, J=3.79 Hz, 6 H) 2.31 (s, 6 H) 3.40 - 3.51 (m, 1 H) 3.62 - 3.75 (m, 1 H) 3.83 - 3.92 (m, 1 H) 3.97 - 4.10 (m, 1 H) 4.80 - 4.93 (m, 1 H) 4.97 - 5.10 (m, 1 H) 5.15 - 5.37 (m, 2 H) 5.43 - 5.67 (m, 2 H) 5.75 (s, 1 H) 5.83 (s, 1 H) 7.09 - 7.15 (m, 4 H) 7.16 - 7.21 (m, 2 H).

Example 373

tert-Butyl N-(1-[[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino]-2-methylpropan-2-yl)carbamate.

Step 1: 4-N-(2-Amino-2-methyl-propyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine was prepared according to general procedure 9 from 2-methylpropane-1,2-diamine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine.

Step 2: 4-N-(2-Amino-2-methylpropyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine (15 mg, 0.029 mmol) and tert-butoxycarbonyl tert-butyl carbonate (7.8 mg, 0.036 mmol) were dissolved in THF (0.50 mL). Then Et₃N (0.0061 mL, 0.044 mmol) was added and the resulting mixture was stirred at rt for 16 h. The reaction mixture was concentrated and purified by column chromatography (0→5% in DCM) to afford tert-butyl N-[2-[[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino]-1,1-dimethyl-ethyl]carbamate. LCMS [M+H]⁺ 386; ¹H NMR (400 MHz, CDCl₃) δ_H ppm 1.34 (s, 6 H) 1.43 (s, 9 H) 2.26 (s, 3 H) 2.31 (s, 3 H) 3.53 (d,

J=5.81 Hz, 2 H) 5.14 - 5.47 (m, 2 H) 5.87 (s, 1 H) 7.10 - 7.16 (m, 2 H) 7.18 (d, J=3.28 Hz, 1 H).

Example 374

- 5 N-(3-{[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}propyl)-3-cyanobenzene-1-sulfonamide.

Prepared according to general procedure 10 from 3-cyanobenzene-1-sulfonyl chloride and 4-N-(3-aminopropyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.

- LCMS [M+H]⁺ 437; ¹H NMR (400 MHz, CDCl₃) δ_H ppm 1.70 - 1.82 (m, 4 H) 2.23 (s, 3 H) 2.31 (s, 3 H) 2.98 (d, J=5.31 Hz, 2 H) 3.54 (d, J=5.81 Hz, 2 H) 4.71 - 4.80 (m, 1 H) 5.29 (br. s., 2 H) 5.76 (s, 1 H) 7.07 - 7.21 (m, 3 H) 7.59 - 7.65 (m, 1 H) 7.82 (dt, J=7.64, 1.36 Hz, 1 H) 8.14 (dq, J=7.96, 0.97 Hz, 1 H) 8.18 - 8.21 (m, 1 H).

- 15 Example 375

N-(3-{[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}propyl)-4-methanesulfonylbenzene-1-sulfonamide.

Prepared according to general procedure 10 from 4-methanesulfonylbenzene-1-sulfonyl chloride and 4-N-(3-aminopropyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-

- 20 diamine. LCMS [M+H]⁺ 490; ¹H NMR (400 MHz, CDCl₃) δ_H ppm 1.73 - 1.80 (m, 2 H) 2.23 (s, 3 H) 2.32 (s, 3 H) 2.95 - 3.01 (m, 2 H) 3.08 (s, 3 H) 3.51 - 3.58 (m, 2 H) 4.69 - 4.77 (m, 1 H) 5.31 (s, 2 H) 5.77 (s, 1 H) 7.08 - 7.21 (m, 3 H) 8.09 (q, J=8.76 Hz, 4 H).

- 25 Example 376

N-(3-{[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}propyl)benzene-sulfonamide.

Prepared according to general procedure 10 from benzenesulfonyl chloride and 4-N-(3-aminopropyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine. LCMS [M+H]⁺

- 30 412; ¹H NMR (400 MHz, CDCl₃) δ ppm 1.72 (dt, J=12.06, 5.97 Hz, 2 H) 1.76 - 1.89 (m, 1 H) 2.22 (s, 3 H) 2.31 (s, 3 H) 2.93 (q, J=6.15 Hz, 2 H) 3.49 (q, J=6.40 Hz, 2 H) 4.70 - 4.82 (m, 1 H) 5.28 (br. s., 2 H) 5.72 - 5.74 (m, 1 H) 7.08 - 7.15 (m, 2 H) 7.16 - 7.20 (m, 1 H) 7.45 - 7.51 (m, 2 H) 7.52 - 7.57 (m, 1 H) 7.87 - 7.92 (m, 2 H).

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Example 377

N-(3-[[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino]-2,2-dimethylpropyl)-3-fluorobenzene-1-sulfonamide.

Step 1: tert-butyl N-(3-[[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino]-2,2-dimethylpropyl)carbamate (prepared in example 239) (180 mg, 0.45 mmol) was dissolved in trifluoroacetic acid (2 ml) and stirred at reflux for 1 h. The TFA was evaporated and the crude residue was purified by silica gel chromatography using a gradient of 2-30% MeOH [containing 1 v/v% NH₄OH] in DCM which afforded 4-N-(3-amino-2,2-dimethyl-propyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine (110 mg, 0.37 mmol). LCMS [M+H]⁺ 300.

Step 2: N-(3-[[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino]-2,2-dimethylpropyl)-3-fluorobenzene-1-sulfonamide was prepared according to general procedure 10 from 3-fluorobenzene-1-sulfonyl chloride and 4-N-(3-amino-2,2-dimethyl-propyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine (prepared in step 1) . LCMS [M+H]⁺ 458; ¹H NMR (400 MHz, CDCl₃) δ_H ppm 0.92 (s, 6 H) 2.16 - 2.20 (m, 3 H) 2.29 (s, 3 H) 2.69 (d, J=7.07 Hz, 2 H) 3.38 (d, J=6.82 Hz, 2 H) 5.91 (s, 1 H) 6.53 (s, 1 H) 7.04 - 7.08 (m, 1 H) 7.09 - 7.15 (m, 1 H) 7.23 - 7.30 (m, 1 H) 7.38 - 7.45 (m, 1 H) 7.46 - 7.56 (m, 2 H) 7.64 (d, J=7.83 Hz, 1 H).

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Example 378

N-(3-[[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino]-2,2-dimethylpropyl)-4-(morpholine-4-sulfonyl)benzene-1-sulfonamide.

Step 1: tert-butyl N-(3-[[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino]-2,2-dimethylpropyl)carbamate (prepared in example 239) (180 mg, 0.45 mmol) was dissolved in trifluoroacetic acid (2 ml) and stirred at reflux for 1 h. The TFA was evaporated and the crude residue was purified by silica gel chromatography using a gradient of 2-30% MeOH [containing 1 v/v% NH₄OH] in DCM which afforded 4-N-(3-amino-2,2-dimethyl-propyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine (110 mg, 0.37 mmol). LCMS [M+H]⁺ 300.

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Step 2: N-(3-[[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino]-2,2-dimethylpropyl)-4-(morpholine-4-sulfonyl)benzene-1-sulfonamide was prepared according to general procedure 10 from 4-(morpholine-4-sulfonyl)benzene-1-sulfonyl chloride and 4-N-(3-amino-2,2-dimethyl-propyl)-6-(2,3-dimethyl-

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phenyl)pyrimidine-2,4-diamine (prepared in step 1 above). LCMS $[M+H]^+$ 589; ^1H NMR (400 MHz, $CDCl_3$) δ_H ppm 0.92 (s, 6 H) 2.18 (d, $J=0.51$ Hz, 3 H) 2.28 (s, 3 H) 2.71 (d, $J=6.82$ Hz, 2 H) 2.99 - 3.06 (m, 4 H) 3.38 (d, $J=6.82$ Hz, 2 H) 3.70 - 3.78 (m, 4 H) 5.93 (s, 1 H) 6.94 (s, 1 H) 7.03 - 7.08 (m, 1 H) 7.09 - 7.15 (m, 1 H) 7.25 (d, $J=7.58$ Hz, 1 H) 7.42 (s, 1 H) 7.87 (d, $J=8.59$ Hz, 2 H) 8.02 (d, $J=8.59$ Hz, 2 H).

Example 379

6-(2,3-Dimethylphenyl)-4-N-(prop-2-en-1-yl)pyrimidine-2,4-diamine.
Prepared according to general procedure 9 from prop-2-en-1-amine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 255; ^1H NMR (400 MHz, $CDCl_3$) δ_H ppm 2.23 (s, 3 H) 2.31 (s, 3 H) 3.92 (br. s., 2 H) 4.95 (br. s., 3 H) 5.18 (dq, $J=10.23$, 1.47 Hz, 1 H) 5.26 (dq, $J=17.18$, 1.60 Hz, 1 H) 5.81 (s, 1 H) 5.85 - 5.96 (m, 1 H) 7.10 - 7.15 (m, 2 H) 7.15 - 7.19 (m, 1 H).

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Example 380

1-(3-([2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino)propyl)imidazolidin-2-one.
Prepared according to general procedure 9 from 1-(3-aminopropyl)imidazolidin-2-one and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 341.

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Example 381

N-(3-([2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino)propyl)-3-fluorobenzene-1-sulfonamide.
Prepared according to general procedure 9 from 3-fluorobenzene-1-sulfonyl chloride and 4-N-(3-aminopropyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 430.

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Example 382

N-{4-[(3-([2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino)propyl)sulfamoyl]-phenyl}acetamide.
Prepared according to general procedure 10 from 4-acetamidobenzene-1-sulfonyl chloride and 4-N-(3-aminopropyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 469.

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Example 383

N-(3-[[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}propyl)methanesulfonamide.

- Prepared according to general procedure 10 from methanesulfonyl chloride and
5 4-N-(3-aminopropyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine. LCMS [M+H]⁺
350.

Example 384

- N-(2-[[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}ethyl)-3-
10 fluorobenzene-1-sulfonamide.

Prepared according to general procedure 10 from 3-fluorobenzene-1-sulfonyl
chloride and 4-N-(2-aminoethyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.
LCMS [M+H]⁺ 416.

- 15 Example 385

N-(2-[[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}ethyl)-4-
methoxybenzene-1-sulfonamide.

Prepared according to general procedure 10 from 4-methoxybenzene-1-sulfonyl
chloride and 4-N-(2-aminoethyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.

- 20 LCMS [M+H]⁺ 428.

Example 386

6-(2,3-Dimethylphenyl)-4-N-(prop-2-yn-1-yl)pyrimidine-2,4-diamine.

- Prepared according to general procedure 9 from prop-2-yn-1-amine and 4-chloro-
25 6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS [M+H]⁺ 253.

Example 387

2-[[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}acetamide.

- Prepared according to general procedure 9 from 2-aminoacetamide and 4-chloro-
30 6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS [M+H]⁺ 272.

Example 388

N-(3-[[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}propyl)-4,5-
dichlorothiophene-2-sulfonamide.

Prepared according to general procedure 10 from 4,5-dichlorothiophene-2-sulfonyl chloride and 4-N-(3-aminopropyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 486.

5 Example 389

N-(3-([2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino)propyl)-5-chloro-1,3-dimethyl-1H-pyrazole-4-sulfonamide.

Prepared according to general procedure 10 from 5-chloro-1,3-dimethyl-1H-pyrazole-4-sulfonyl chloride and 4-N-(3-aminopropyl)-6-(2,3-dimethylphenyl)-
10 pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 464.

Example 390

2-([2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino)acetonitrile.

Prepared according to general procedure 9 from 2-aminoacetonitrile and 4-
15 chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 254.

Example 391

N-(3-([2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino)propyl)-1,2-dimethyl-1H-imidazole-4-sulfonamide.

20 Prepared according to general procedure 10 from 1,2-dimethyl-1H-imidazole-4-sulfonyl chloride and 4-N-(3-aminopropyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 430; ^1H NMR (400 MHz, CD_3OD) δ_H ppm 7.69 (s, 2 H), 7.33 - 7.38 (m, 1 H), 7.21 - 7.27 (m, 1 H), 7.16 - 7.20 (m, 1 H), 6.00 (s, 1 H), 3.71 (s, 3 H), 3.58 (s, 2 H), 3.06 (s, 2 H), 2.45 (s, 3 H), 2.36 (s, 3 H), 2.25 (s, 3 H), 1.80
25 - 1.90 (m, 2 H).

Example 392

N-(2-([2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino)ethyl)-5-chloro-1,3-dimethyl-1H-pyrazole-4-sulfonamide.

30 Prepared according to general procedure 10 from 5-chloro-1,3-dimethyl-1H-pyrazole-4-sulfonyl chloride and 4-N-(2-aminoethyl)-6-(2,3-dimethylphenyl)-pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 450.

Example 393

4-N-{2-[(1,3-Benzoxazol-2-yl)amino]ethyl}-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 12 from 2-chloro-1,3-benzoxazole and 4-N-(2-aminoethyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine. LCMS

5 [M+H]⁺ 375.

Example 394

6-(2,3-Dimethylphenyl)-4-N-(4-phenylbutan-2-yl)pyrimidine-2,4-diamine.

Prepared according to general procedure 9 from 4-phenylbutan-2-amine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS [M+H]⁺ 347.

10

Example 395

4-N-(2,2-Dimethyloxan-4-yl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 9 from 2,2-dimethyloxan-4-amine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS [M+H]⁺ 327.

15

Example 396

Ethyl 2-[[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino]acetate.

Prepared according to general procedure 9 from ethyl 2-aminoacetate and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS [M+H]⁺ 301.

20

Example 397

6-[(2-[[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino]ethyl)amino]pyridine-3-carbonitrile.

Prepared according to general procedure 12 from 6-chloropyridine-3-carbonitrile and 4-N-(2-aminoethyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine. LCMS [M+H]⁺ 360; ¹H NMR (400 MHz, CD₃OD) δ_H ppm 8.32 - 8.34 (m, 1 H), 7.59 - 7.64 (m, 1 H), 7.34 - 7.38 (m, 1 H), 7.22 - 7.27 (m, 2 H), 7.15 - 7.18 (m, 1 H), 6.55 - 6.59 (m, 1 H), 5.97 (s, 1 H), 3.72 - 3.77 (m, 3 H), 3.66 - 3.71 (m, 3 H), 2.36 (s, 4 H), 2.24 (s, 3 H).

30

Example 398

4-N-{2-[(3-Bromo-1,2,4-thiadiazol-5-yl)amino]ethyl}-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 12 from 3-bromo-5-chloro-1,2,4-thiadiazole and 4-N-(2-aminoethyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 420.

5 Example 399

6-(2,3-Dimethylphenyl)-4-N-[(5-methyl-4H-1,2,4-triazol-3-yl)methyl]pyrimidine-2,4-diamine.

Prepared according to general procedure 9 from (5-methyl-4H-1,2,4-triazol-3-yl)methanamine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS

10 $[M+H]^+$ 310; ^1H NMR (400 MHz, CD_3OD) δ_H ppm 7.37 - 7.41 (m, 1 H), 7.25 - 7.30 (m, 1 H), 7.20 - 7.24 (m, 1 H), 6.12 (s, 1 H), 4.79 (s, 2 H), 2.47 (s, 3 H), 2.38 (s, 3 H), 2.29 (s, 3 H).

Example 400

15 6-(2,3-Dimethylphenyl)-4-N-{2-[5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl]ethyl}pyrimidine-2,4-diamine.

Prepared according to general procedure 9 from 2-[5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl]ethan-1-amine and 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine. LCMS $[M+H]^+$ 405.

20

Example 401

N-(2-[[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino]ethyl)-4-methanesulfonylbenzene-1-sulfonamide.

Prepared according to general procedure 10 from 4-methanesulfonylbenzene-1-

25 sulfonyl chloride and 4-N-(2-aminoethyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 476; ^1H NMR (400 MHz, CD_3OD) δ_H ppm 8.10 - 8.14 (m, 3 H), 8.05 - 8.09 (m, 3 H), 7.16 - 7.20 (m, 1 H), 7.09 - 7.14 (m, 1 H), 7.05 - 7.08 (m, 1H), 5.73 - 5.76 (m, 1 H), 3.42 - 3.49 (m, 2 H), 3.14 (s, 6 H), 2.31 (s, 4 H), 2.18 (s, 3 H).

30

Example 402

N-(3-[[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino]propyl)-3-methanesulfonylbenzene-1-sulfonamide.

Prepared according to general procedure 10 from 3-methanesulfonylbenzene-1-

35 sulfonyl chloride and 4-N-(3-aminopropyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-

diamine. LCMS $[M+H]^+$ 490; ^1H NMR (400 MHz, $CDCl_3$) δ_H ppm 8.43 - 8.45 (m, 1 H), 8.18 (ddd, $J=7.8, 1.8, 1.0$ Hz, 3 H), 8.11 (ddd, $J=7.8, 1.8, 1.0$ Hz, 3 H), 7.67 - 7.73 (m, 1 H), 7.15 - 7.19 (m, 1 H), 7.09 - 7.13 (m, 1 H), 7.08 (d, $J=2.0$ Hz, 1 H), 5.74 (s, 1 H), 5.31 (br. s., 2 H), 4.82 - 5.00 (m, 1 H), 3.50 (d, $J=5.8$ Hz, 2 H), 3.09 (s, 3 H), 2.94 (d, $J=4.0$ Hz, 2 H), 2.29 (s, 3 H), 2.20 (s, 3 H), 1.71 (t, $J=5.8$ Hz, 2 H).

Example 403

N-(3-[[2-Amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}propyl)-2-methanesulfonylbenzene-1-sulfonamide.

Prepared according to general procedure 10 from 2-methanesulfonylbenzene-1-sulfonyl chloride and 4-N-(3-aminopropyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine. LCMS $[M+H]^+$ 490; ^1H NMR (400 MHz, CD_3OD) δ_H ppm 8.20 - 8.33 (m, 3 H), 8.10 - 8.17 (m, 1 H), 7.84 - 7.90 (m, 5 H), 7.68 - 7.80 (m, 3 H), 7.16 - 7.21 (m, 3H), 7.12 (s, 3 H), 7.08 (d, $J=1.5$ Hz, 3 H), 5.74 (s, 3 H), 3.46 (s, 3 H), 3.43 (s, 8 H), 3.32 - 3.36 (m, 3 H), 3.07 (t, $J=6.7$ Hz, 5 H), 2.31 (s, 8 H), 2.19 (s, 3 H), 1.66 (t, $J=6.7$ Hz, 5 H).

Example 404

6-(2,3-Dimethylphenyl)-4-N-[2-(4-methanesulfonylphenyl)ethyl]pyrimidine-2,4-diamine.

A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (0.15 mmol), 2-(4-methylsulfonylphenyl)ethanamine (1.2 eq.) and N,N-diisopropylethylamine (2.25 eq.) in n-butanol (0.3 mL) was heated in a sealed tube at 110°C overnight.

Methanol was added and the mixture was filtered and purified by preparative HPLC. LCMS $[M+H]^+$ 397.

Example 405

6-(2,3-Dimethylphenyl)-4-N-[2-(4-methanesulfonylphenyl)ethyl]pyrimidine-2,4-diamine.

A mixture of 4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine (0.08 mmol), 2-(4-methylthiazol-5-yl)ethanamine; dihydrobromide (1.2 eq.) and N,N-diisopropylethylamine (4.25 eq.) in n-butanol (0.3 ml) was heated in a sealed tube at 110°C overnight. Methanol was added and the mixture was filtered and purified by preparative HPLC. LCMS $[M+H]^+$ 380.

Example 406

6-(2,3-Dimethylphenyl)-4-N-[2-(4-methanesulfonylphenyl)ethyl]pyrimidine-2,4-diamine.

- 5 A mixture of 4-chloro-6-(3-chloro-2-methyl-phenyl)pyrimidin-2-amine (0.14 mmol), 2-(4-methylthiazol-5-yl)ethanamine; dihydrobromide (1.2 eq.) and N,N-diisopropylethylamine (4.25 eq.) in n-butanol (0.3 mL) was heated in a sealed tube at 110°C overnight. Methanol was added and the mixture was filtered and purified by preparative HPLC. LCMS [M+H]⁺ 360.

10

Example 407

6-(2,3-Dimethylphenyl)-4-N-[2-(4-methanesulfonylphenyl)ethyl]pyrimidine-2,4-diamine.

- 15 A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (0.13 mmol), [2-(difluoromethyl)-4-pyridyl]methanamine; hydrochloride (1.2 eq.) and N,N-diisopropylethylamine (3.25 eq.) in n-butanol (0.3 mL) was heated in a sealed tube at 110°C overnight. Methanol was added and the mixture was filtered and purified by preparative HPLC. LCMS [M+H]⁺ 356.

20 Example 408

6-(2,3-Dimethylphenyl)-4-N-[2-(4-methanesulfonylphenyl)ethyl]pyrimidine-2,4-diamine.

- 25 A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (0.13 mmol), 2-(1H-imidazol-4-yl)ethanamine; dihydrochloride (1.2 eq.) and N,N-diisopropylethylamine (3.25 eq.) in n-butanol (0.3 mL) was heated in a sealed tube at 110°C overnight. Methanol was added and the mixture was filtered and purified by preparative HPLC. LCMS [M+H]⁺ 309.

Example 409

- 30 6-(2,3-Dimethylphenyl)-4-N-[2-(4-methanesulfonylphenyl)ethyl]pyrimidine-2,4-diamine.

- A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (0.13 mmol), 3-(1H-benzimidazol-2-yl)propan-1-amine (1.2 eq.) and N,N-diisopropylethylamine (3.25 eq.) in n-butanol (0.3 mL) was heated in a sealed tube at 110°C overnight.
- 35 Methanol was added and the mixture was filtered and purified by preparative

HPLC. LCMS $[M+H]^+$ 373.

Example 410

6-(2,3-Dimethylphenyl)-4-N-[2-(4-methanesulfonylphenyl)ethyl]pyrimidine-2,4-diamine.

A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (0.14 mmol), (1-methylbenzimidazol-2-yl)methanamine (1.2 eq.) and N,N-diisopropylethylamine (1.25 eq.) in n-butanol (0.3 mL) was heated in a sealed tube at 110°C overnight. Methanol was added and the mixture was filtered and purified by preparative HPLC. LCMS $[M+H]^+$ 359.

Example 411

6-(2,3-Dimethylphenyl)-4-N-[2-(4-methanesulfonylphenyl)ethyl]pyrimidine-2,4-diamine.

A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (0.13 mmol), (2-phenylthiazol-5-yl)methanamine hydrochloride (1.2 eq.) and N,N-diisopropylethylamine (2.25 eq.) in n-butanol (0.3 mL) was heated in a sealed tube at 110°C overnight. Methanol was added and the mixture was filtered and purified by preparative HPLC. LCMS $[M+H]^+$ 388.

Example 412

6-(3-chloro-2-methylphenyl)-4-N-[2-(5-methyl-1H-1,2,4-triazol-3-yl)ethyl]pyrimidine-2,4-diamine.

A mixture 4-chloro-6-(3-chloro-2-methyl-phenyl)pyrimidin-2-amine (0.14 mmol), 2-(5-methyl-1H-1,2,4-triazol-3-yl)ethanamine hydrochloride (1.2 eq.) and N,N-diisopropylethylamine (3.25 eq.) in n-butanol (0.3 mL) was heated in a sealed tube at 110°C overnight. Methanol was added and the mixture was filtered and purified by preparative HPLC. LCMS $[M+H]^+$ 344.

Example 413

6-(2,3-dichlorophenyl)-4-N-[2-(5-methyl-1H-1,2,4-triazol-3-yl)ethyl]pyrimidine-2,4-diamine.

A mixture of 4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine (0.13 mmol), 2-(5-methyl-1H-1,2,4-triazol-3-yl)ethanamine hydrochloride (1.0 eq.) and N,N-diisopropylethylamine (3.25 eq.) in n-butanol (0.3 mL) was heated in a sealed

tube at 110°C overnight. Methanol was added and the mixture was filtered and purified by preparative HPLC. LCMS [M+H]⁺ 364.

Example 414

5 4-(2-[[2-amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-yl]amino}ethyl)-N,N-dimethylbenzene-1-sulfonamide.

A mixture of 4-chloro-6-(3-chloro-2-methyl-phenyl)pyrimidin-2-amine (0.14 mmol), 4-(2-aminoethyl)-N,N-dimethyl-benzenesulfonamide (1.0 eq.) and N,N-diisopropylethylamine (2.25 eq.) in n-butanol (0.3 mL) was heated in a sealed
10 tube at 110°C overnight. Methanol was added and the mixture was filtered and purified by preparative HPLC. LCMS [M+H]⁺ 446.

Example 415

15 4-(2-[[2-amino-6-(2,3-dichlorophenyl)pyrimidin-4-yl]amino}ethyl)-N,N-dimethylbenzene-1-sulfonamide.

A mixture of 4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine (0.13 mmol), 4-(2-aminoethyl)-N,N-dimethyl-benzenesulfonamide (1.0 eq.) and N,N-diisopropylethylamine (2.25 eq.) in n-butanol (0.3 mL) was heated in a sealed tube at 110°C overnight. Methanol was added and the mixture was filtered and purified by
20 preparative HPLC. LCMS [M+H]⁺ 466.

Example 416

4-(2-[[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}ethyl)-N,N-dimethylbenzene-1-sulfonamide.

25 A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (0.15 mmol), 4-(2-aminoethyl)-N,N-dimethyl-benzenesulfonamide (1.0 eq.) and N,N-diisopropylethylamine (2.25 eq.) in n-butanol (0.3 mL) was heated in a sealed tube at 110°C overnight. Methanol was added and the mixture was filtered and purified by preparative HPLC. LCMS [M+H]⁺ 426.

30

Example 417

4-N-{1-[(4-Chlorophenyl)methyl]cyclopropyl}-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.

A mixture of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (47 mg, 0.20
35 mmol), 1-[(4-chlorophenyl)methyl]cyclopropan-1-amine hydrochloride (52 mg,

0.24 mmol) and triethylamine (50 μ L, 0.36 mmol) in n-butanol (3 mL) was heated in a sealed tube at 130°C overnight. The reaction mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 379.

5 Example 418

4-N-Cyclopropyl-6-(2,3,4-trichlorophenyl)pyrimidine-2,4-diamine.

A mixture of 4-chloro-6-(2,3,4-trichlorophenyl)pyrimidin-2-amine (21 mg, 0.050 mmol), cyclopropanamine (25 μ L, 0.36 mmol) and triethylamine (25 μ L, 0.18 mmol) in n-butanol (1.5 mL) was heated in a sealed tube at 90°C overnight. The reaction mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 329.

Example 419

4-N-[2-(4-Chlorophenyl)ethyl]-6-(2,3,4-trichlorophenyl)pyrimidine-2,4-diamine.

15 A mixture of 4-chloro-6-(2,3,4-trichlorophenyl)pyrimidin-2-amine (21 mg, 0.050 mmol), 2-(4-chlorophenyl)ethan-1-amine (30 μ L, 0.24 mmol) and triethylamine (25 μ L, 0.18 mmol) in n-butanol (1.5 mL) was heated in a sealed tube at 90°C overnight. The reaction mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 427.

20

Example 420

6-(2,3-dimethylphenyl)-4-N-($^2H_3$)methylpyrimidine-2,4-diamine.

A solution of 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine (0.15 mmol) and d_3 -methanamine hydrochloride (70 mg; 1 mmol) and triethylamine (101 mg; 1 mmol) in n-BuOH (2.0 mL) was heated at 95 °C overnight. The reaction mixture was concentrated and purified by preparative HPLC. LCMS $[M+H]^+$ 232.

Example 421

6-(2,3-dichlorophenyl)-4-N-($^2H_3$)methylpyrimidine-2,4-diamine.

30 A solution of 4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine (0.15 mmol) and d_3 -methanamine hydrochloride (70 mg; 1 mmol) and triethylamine (101 mg; 1 mmol) in n-BuOH (2.0 mL) was heated at 95 °C overnight. The reaction mixture was concentrated and purified by preparative HPLC to afford the product. LCMS $[M+H]^+$ 272.

35

Example 422

6-(2-chloro-3-methylphenyl)-4-N-(²H₃)methylpyrimidine-2,4-diamine.

A solution of 4-chloro-6-(2-chloro-3-methylphenyl)pyrimidin-2-amine (0.15 mmol) and d₃-methanamine hydrochloride (70 mg; 1 mmol) and triethylamine (101 mg; 1 mmol) in n-BuOH (2.0 mL) was heated at 95 °C overnight. The reaction mixture was concentrated and purified by preparative HPLC to afford the product. LCMS [M+H]⁺ 252.

Example 423

4-N-[2-(4-Chlorophenyl)ethyl]-6-(1H-pyrrol-2-yl)pyrimidine-2,4-diamine.

Prepared according to general procedure 10 from 6-chloro-4-N-[2-(4-chlorophenyl)ethyl]pyrimidine-2,4-diamine and (1-tert-butoxycarbonylpyrrol-2-yl)boronic acid. The t-butoxycarbonyl group was removed during work-up. LCMS [M+H]⁺ 314; ¹H NMR (400 MHz, CD₃OD) δ_H ppm 7.29 - 7.33 (m, 5 H), 7.27 (s, 2 H), 7.10 - 7.13 (m, 1 H), 6.88 - 6.92 (m, 1 H), 6.33 - 6.37 (m, 1 H), 6.12 (s, 1 H), 3.70 - 3.76 (m, 2 H), 2.91 - 2.96 (m, 2 H).

Example 424

N-(4-[[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino]butyl)-4-methanesulfonylbenzene-1-sulfonamide.

Prepared according to general procedure 10 from 4-(methylsulfonyl)benzenesulfonyl chloride and 4-N-(4-aminobutyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine. LCMS [M+H]⁺ 504; ¹H NMR (400 MHz, CD₃OD) δ_H ppm 8.12 - 8.17 (m, 2 H), 8.06 - 8.10 (m, 2 H), 7.16 - 7.20 (m, 1 H), 7.09 - 7.14 (m, 1 H), 7.05 - 7.09 (m, 1 H), 5.76 - 5.79 (m, 1 H), 3.18 (s, 3 H), 2.94 - 2.99 (m, 2 H), 2.31 (s, 3 H), 2.19 (s, 3 H), 1.50 - 1.66 (m, 4 H).

Example 425

4-(2-[[2-amino-6-(4-fluoro-2,3-dimethylphenyl)pyrimidin-4-yl]amino]ethyl)benzene-1-sulfonamide.

Prepared according to general procedure 2 from 4-[2-[(2-amino-6-chloropyrimidin-4-yl)amino]ethyl]benzenesulfonamide and 4-fluoro-2,3-dimethylbenzeneboronic acid. LCMS [M+H]⁺ 416; ¹H NMR (400 MHz, CD₃OD) δ_H ppm 7.81 - 7.85 (m, 2 H), 7.44 (d, J=8.6 Hz, 2 H), 7.07 (dd, J=8.5, 5.9 Hz, 1 H), 6.92 (t,

J=8.8 Hz, 1 H), 5.75 (s, 1 H), 3.63 (br. s., 2 H), 2.99 (t, J=7.2 Hz, 2 H), 2.20 - 2.23 (m, 6 H).

Example 426

5 4-(2-[[2-amino-6-(3-cyano-2-methylphenyl)pyrimidin-4-yl]amino]ethyl)benzene-1-sulfonamide.

Prepared according to general procedure 2 from 4-[2-[(2-amino-6-chloro-pyrimidin-4-yl)amino]ethyl]benzenesulfonamide and 3-cyano-2-methyl-benzene-
boronic acid. LCMS [M+H]⁺ 409; ¹H NMR (400 MHz, CD₃OD) δ_H ppm 7.80 - 7.86
10 (m, 2 H), 7.70 (dd, J=7.8, 1.3 Hz, 1 H), 7.53 (d, J=6.8 Hz, 1 H), 7.37 - 7.47 (m, 3 H), 5.80 (s, 1 H), 3.65 (br. s., 2 H), 3.00 (t, J=7.2 Hz, 2 H), 2.49 (s, 3 H).

Example 427

15 4-(2-[[2-amino-6-(5-chloro-2-methylphenyl)pyrimidin-4-yl]amino]ethyl)benzene-1-sulfonamide.

Prepared according to general procedure 2 from 4-[2-[(2-amino-6-chloro-pyrimidin-4-yl)amino]ethyl]benzenesulfonamide and 5-chloro-2-methyl-benzeneboronic acid. LCMS [M+H]⁺ 418; ¹H NMR (400 MHz, CD₃OD) δ_H ppm
7.81 - 7.85 (m, 2 H), 7.44 (d, J=8.3 Hz, 2 H), 7.21 - 7.29 (m, 3 H), 5.80 (s, 1 H),
20 3.64 (br. s., 2 H), 2.99 (t, J=7.2 Hz, 2 H), 2.28 (s, 3 H).

Example 428

4-(2-[[2-amino-6-(3,4-dichloro-2-methylphenyl)pyrimidin-4-yl]amino]ethyl)benzene-1-sulfonamide.
25 Prepared according to general procedure 2 from 4-[2-[(2-amino-6-chloro-pyrimidin-4-yl)amino]ethyl]benzenesulfonamide and 3,4-dichloro-2-methyl-benzeneboronic acid. LCMS [M+H]⁺ 452; ¹H NMR (400 MHz, CDCl₃) δ_H ppm 7.88
(d, J=8.3 Hz, 2 H), 7.38 (d, J=8.3 Hz, 2 H), 7.33 - 7.36 (m, 1 H), 7.15 (s, 1 H),
5.73 (s, 1 H), 4.87 (s, 2 H), 4.81 - 4.84 (m, 2 H), 4.70 - 4.77 (m, 1 H), 3.61 - 3.69
30 (m, 2 H), 3.01 (s, 2 H), 2.41 (s, 3 H).

Example 429

6-(3-chloro-2-methylphenyl)-4-N-(prop-2-yn-1-yl)pyrimidine-2,4-diamine.
Prepared according to general procedure 7 from propargylamine and 4-chloro-6-
35 (3-chloro-2-methyl-phenyl)pyrimidin-2-amine. LCMS [M+H]⁺ 273; ¹H NMR (400

MHz, CD₃OD) δ_{H} ppm 7.40 - 7.43 (m, 1 H), 7.21 (s, 2 H), 5.85 - 5.88 (m, 1 H), 4.13 - 4.18 (m, 2 H), 2.59 (s, 1 H), 2.33 (s, 3 H).

Example 430

- 5 6-(4-fluoro-2,3-dimethylphenyl)-4-N-[2-(4-methanesulfonylphenyl)ethyl]pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from 6-chloro-4-N-[2-(4-methylsulfonylphenyl)ethyl]pyrimidine-2,4-diamine and 4-fluoro-2,3-dimethylbenzeneboronic acid. LCMS $[\text{M}+\text{H}]^+$ 415; ¹H NMR (400 MHz, CD₃OD) δ_{H} ppm
10 7.88 (s, 2 H), 7.53 - 7.58 (m, 2 H), 7.06 - 7.11 (m, 1 H), 6.91 - 6.97 (m, 1 H), 5.76 (s, 1 H), 3.64 - 3.72 (m, 2 H), 3.11 (s, 3 H), 3.02 - 3.08 (m, 2 H), 2.22 - 2.25 (m, 6 H).

Example 431

- 15 6-(3,4-dichloro-2-methylphenyl)-4-N-[2-(4-methanesulfonylphenyl)ethyl]pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from 6-chloro-4-N-[2-(4-methylsulfonylphenyl)ethyl]pyrimidine-2,4-diamine and 3,4-dichloro-2-methylbenzeneboronic acid. LCMS $[\text{M}+\text{H}]^+$ 451; ¹H NMR (400 MHz, CD₃OD) δ_{H} ppm
20 7.89 (d, J=8.6 Hz, 2 H), 7.57 (s, 2 H), 7.43 - 7.46 (m, 1 H), 7.17 - 7.21 (m, 1 H), 5.78 (s, 1 H), 3.63 - 3.75 (m, 2 H), 3.11 (s, 3 H), 3.03 - 3.08 (m, 2 H), 2.39 (s, 3 H).

Example 432

- 25 4-(2-[[2-amino-6-(4-chloro-2-methylphenyl)pyrimidin-4-yl]amino]ethyl)benzene-1-sulfonamide.

Prepared according to general procedure 2 from 4-[2-[(2-amino-6-chloropyrimidin-4-yl)amino]ethyl]benzenesulfonamide and 4-chloro-2-methylbenzeneboronic acid. LCMS $[\text{M}+\text{H}]^+$ 418; ¹H NMR (400 MHz, CD₃OD) δ_{H} ppm
30 (m, 2 H), 7.42 - 7.46 (m, 2 H), 7.27 - 7.28 (m, 1 H), 7.23 (d, J=1.3 Hz, 2 H), 5.78 (s, 1 H), 3.63 (br. s., 2 H), 2.99 (t, J=7.1 Hz, 2 H), 2.30 (d, J=0.8 Hz, 3 H).

Example 433

- 35 4-(2-[[2-amino-6-(2-chloro-4-fluorophenyl)pyrimidin-4-yl]amino]ethyl)benzene-1-sulfonamide.

Prepared according to general procedure 2 from 4-[2-[(2-amino-6-chloro-pyrimidin-4-yl)amino]ethyl]benzenesulfonamide and 2-chloro-4-fluoro-benzene-boronic acid. LCMS $[M+H]^+$ 422.

5 Example 434

4-(2-[[2-amino-6-(2,3,4-trifluorophenyl)pyrimidin-4-yl]amino]ethyl)benzene-1-sulfonamide.

Prepared according to general procedure 2 from 4-[2-[(2-amino-6-chloro-pyrimidin-4-yl)amino]ethyl]benzenesulfonamide and 2,3,4-trifluorobenzeneboronic
10 acid. LCMS $[M+H]^+$ 424.

Example 435

4-(2-[[2-amino-6-(4-fluoro-3-methylphenyl)pyrimidin-4-yl]amino]ethyl)benzene-1-sulfonamide.

15 Prepared according to general procedure 2 from 4-[2-[(2-amino-6-chloro-pyrimidin-4-yl)amino]ethyl]benzenesulfonamide and 4-fluoro-3-methyl-benzene-boronic acid. LCMS $[M+H]^+$ 402; ^1H NMR (400 MHz, CD_3OD) δ_H ppm 7.80 - 7.85 (m, 2 H), 7.67 - 7.72 (m, 1 H), 7.59 - 7.65 (m, 1 H), 7.41 - 7.46 (m, 2 H), 7.07 (dd, $J=9.6, 8.6$ Hz, 1 H), 6.12 (s, 1 H), 3.64 (t, $J=7.2$ Hz, 2 H), 2.99 (t, $J=7.1$ Hz, 2 H),
20 2.31 (d, $J=2.0$ Hz, 3 H).

Example 436

4-N-cyclopropyl-6-(4-fluoro-2,3-dimethylphenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 2 from 6-chloro-4-N-cyclopropyl-pyrimidine-2,4-diamine and 4-fluoro-2,3-dimethyl-benzeneboronic acid. LCMS
25 $[M+H]^+$ 273; ^1H NMR (400 MHz, CD_3OD) δ_H ppm 7.08 - 7.15 (m, 1 H), 6.90 - 6.98 (m, 1 H), 5.90 - 6.07 (m, 1 H), 2.53 - 2.66 (m, 1 H), 2.21 - 2.26 (m, 6 H), 0.78 (dd, $J=7.1, 2.0$ Hz, 2 H), 0.54 (dd, $J=3.7, 1.9$ Hz, 2 H).

30 Example 437

3-[2-amino-6-(cyclopropylamino)pyrimidin-4-yl]-2-methylbenzonitrile.

Prepared according to general procedure 2 from 6-chloro-4-N-cyclopropyl-pyrimidine-2,4-diamine and 3-cyano-2-methyl-benzeneboronic acid. LCMS
 $[M+H]^+$ 266; ^1H NMR (400 MHz, CD_3OD) δ_H ppm 7.73 - 7.77 (m, 1 H), 7.58 - 7.63

(m, 1 H), 7.42 - 7.48 (m, 1 H), 5.91 - 6.17 (m, 1 H), 2.59 - 2.70 (m, 1 H), 2.54 (s, 3 H), 0.81 (d, J=4.8 Hz, 2 H), 0.54 - 0.59 (m, 2 H).

Example 438

- 5 6-(2,3-dichlorophenyl)-4-N-(prop-2-yn-1-yl)pyrimidine-2,4-diamine.

Prepared according to general procedure 9 from 4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine and propargyl amine. LCMS [M+H]⁺ 293.

Example 439

- 10 4-(2-[[2-amino-6-(4-fluoro-2,5-dimethylphenyl)pyrimidin-4-yl]amino]ethyl)benzene-1-sulfonamide.

Prepared according to general procedure 9 from 4-chloro-6-(4-fluoro-2,5-dimethyl-phenyl)pyrimidin-2-amine and 2-(4-sulfamoylphenyl)ethylammonium chloride. LCMS [M+H]⁺ 416.

15

Example 440

4-N-[2-(3,5-dimethyl-1H-pyrazol-4-yl)ethyl]-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 9 from 4-chloro-6-(2,3-

- 20 dimethylphenyl)pyrimidin-2-amine and 2-(3,5-dimethyl-1H-pyrazol-1-ium-4-yl)ethylammonium dichloride. [M+H]⁺ 337; ¹H NMR (400 MHz, CD₃OD) δ_H ppm 7.34 (s, 1 H), 7.21 - 7.26 (m, 1 H), 7.18 (dd, J=1.0, 0.5 Hz, 1 H), 6.00 (s, 1 H), 3.70 (t, J=6.8 Hz, 2 H), 2.83 (t, J=6.9 Hz, 2 H), 2.39 (s, 6 H), 2.35 (s, 3 H), 2.24 (s, 3 H).

25

Example 441

4-N-{2-[(6-chloropyridazin-3-yl)amino]ethyl}-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.

Prepared according to general procedure 12 from 4-N-(2-aminoethyl)-6-(2,3-

- 30 dimethylphenyl)pyrimidine-2,4-diamine and 3,6-dichloropyridazine. [M+H]⁺ 370.

Example 442

2-[(2-[[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino]ethyl)amino]pyridine-4-carbonitrile.

Prepared according to general procedure 12 from 4-N-(2-aminoethyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine and 2-chloropyridine-4-carbonitrile. LCMS $[M+H]^+$ 360.

5 Example 443

6-[(2-{[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}ethyl)amino]pyridine-3-sulfonamide.

Prepared according to general procedure 12 from 4-N-(2-aminoethyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine and 6-chloropyridine-3-sulfonamide.

10 LCMS $[M+H]^+$ 414.

Example 444

1-N-(3-{[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}propyl)benzene-1,4-disulfonamide.

15 Prepared according to general procedure 10 from 4-N-(4-aminopropyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine and 4-(aminosulfonyl)benzenesulfonyl chloride. LCMS $[M+H]^+$ 491; ^1H NMR (400 MHz, CD_3OD) δ_{H} ppm 8.04 - 8.08 (m, 2 H), 7.98 - 8.02 (m, 2 H), 7.28 (d, $J=7.1$ Hz, 1 H), 7.16 - 7.22 (m, 1 H), 7.15 (d, $J=1.5$ Hz, 1 H), 5.91 (s, 1 H), 3.48 (d, $J=1.5$ Hz, 2 H), 2.98 (t, $J=6.8$ Hz, 2 H), 2.34
20 (s, 3 H), 2.22 (s, 3 H), 1.78 (t, $J=6.8$ Hz, 2 H).

Example 445

6-(2,3-dichlorophenyl)-4-N-[2-(4-methanesulfonylphenyl)ethyl]pyrimidine-2,4-diamine.

25 Prepared according to general procedure 2 from 6-chloro-4-N-[2-(4-methylsulfonylphenyl)ethyl]pyrimidine-2,4-diamine and 2,3-dichlorobenzene-boronic acid. LCMS $[M+H]^+$ 437; ^1H NMR (400 MHz, CD_3OD) δ_{H} ppm 7.90 (d, $J=8.6$ Hz, 2 H), 7.78 (t, $J=4.9$ Hz, 1 H), 7.56 (d, $J=8.6$ Hz, 2 H), 7.49 (dd, $J=4.9$, 0.6 Hz, 2 H), 6.08 (s, 1 H), 3.84 (s, 2 H), 3.06 - 3.11 (m, 5 H).

30

Example 446

6-(2,3-dimethylphenyl)-4-N-[1-(1H-pyrazol-1-yl)propan-2-yl]pyrimidine-2,4-diamine.

Prepared according to general procedure 9 from 4-chloro-6-(2,3-dimethylphenyl)-pyrimidin-2-amine and 1-pyrazol-1-ylpropan-2-amine. LCMS $[M+H]^+$ 323; ^1H NMR

35

(400 MHz, CDCl₃) δ_H ppm 7.71 (d, J=7.8 Hz, 1 H), 7.57 (d, J=1.8 Hz, 1 H), 7.51 (d, J=2.3 Hz, 1 H), 7.24 (d, J=7.3 Hz, 1 H), 7.12 (t, J=7.6 Hz, 1 H), 7.04 - 7.08 (m, 1 H), 6.30 (t, J=2.3 Hz, 1 H), 5.85 (s, 1 H), 4.65 - 4.75 (m, 1 H), 4.34 - 4.41 (m, 1 H), 4.23 (dd, J=14.1, 6.3 Hz, 1 H), 2.29 (s, 3 H), 2.18 (s, 3 H), 1.16 (d, J=6.8 Hz, 3 H).

Example 447

6-(2,3-dimethylphenyl)-4-N-{2-[(3-methoxyphenyl)amino]ethyl}pyrimidine-2,4-diamine.

- 10 Prepared according to general procedure 9 from 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine and N'-(3-methoxyphenyl)ethane-1,2-diamine. LCMS [M+H]⁺ 364; ¹H NMR (400 MHz, CDCl₃) δ_H ppm 7.18 - 7.26 (m, 1 H), 7.01 - 7.07 (m, 1 H), 6.96 - 7.00 (m, 1 H), 6.95 (t, J=2.0 Hz, 1 H), 6.84 (d, J=7.8 Hz, 1 H), 6.76 (dd, J=8.3, 2.0 Hz, 1 H), 5.91 (s, 1 H), 3.82 (d, J=4.8 Hz, 2 H), 3.75 (s, 3 H), 3.48 (br. s., 2 H), 2.24 (s, 3 H), 2.10 (s, 3 H).

Example 448

6-(2,3-dimethylphenyl)-4-N-{2-[(3-fluoro-4-methylphenyl)amino]ethyl}pyrimidine-2,4-diamine.

- 20 Step 1: A vial was charged with 2-fluoro-4-iodo-1-methyl-benzene (240 mg, 1.0 mmol), ethane-1,2-diamine (0.20 mL, 3.0 mmol), CuCl (9.9 mg, 0.10 mmol), and KOH (110 mg, 2.0 mmol). The vial was then flushed with nitrogen and sealed. The mixture was stirred at r.t. for 16 h, thereafter the mixture was extracted with EtOAc. The combined organic phases were dried, concentrated and purified by column chromatography to afford N'-(3-fluoro-4-methyl-phenyl)ethane-1,2-diamine.

- 30 Step 2: A mixture of 6-(2,3-dimethylphenyl)-4-chloropyrimidin-2-amine (30 mg, 0.13 mmol), N'-(3-fluoro-4-methyl-phenyl)ethane-1,2-diamine (20 mg, 0.12 mmol), and diisopropylethylamine (0.040 mL, 0.23 mmol) in 2-propanol (0.50 mL) was heated in a sealed tube at 150 °C for 30 min in a microwave reactor. The reaction mixture was then concentrated and purified by preparative HPLC. LCMS [M+H]⁺ 366; ¹H NMR (400 MHz, CD₃OD) δ_H ppm 7.33 - 7.37 (m, 1 H), 7.21 - 7.27 (m, 1 H), 7.15 - 7.18 (m, 1 H), 6.93 - 6.99 (m, 1 H), 6.38 - 6.45 (m, 2 H), 5.99 (s, 1 H), 3.72 (s, 2 H), 3.39 (s, 2 H), 2.36 (s, 3 H), 2.24 (s, 3 H), 2.11 (d, J=1.5 Hz, 3 H).

Example 449

4-N-{2-[(3,4-dichlorophenyl)amino]ethyl}-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.

- 5 Prepared according to general procedure 9 from 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine and N'-(3,4-dichlorophenyl)ethane-1,2-diamine. LCMS [M+H]⁺ 402; ¹H NMR (400 MHz, CD₃OD) δ_H ppm 7.33 - 7.37 (m, 1 H), 7.24 (s, 1 H), 7.18 (m, 2 H), 6.76 (d, J=2.8 Hz, 1 H), 6.57 (dd, J=8.8, 2.8 Hz, 1 H), 5.97 (s, 3 H), 3.69 - 3.73 (m, 2 H), 3.37 - 3.42 (m, 2 H), 2.35 (s, 3 H), 2.23 (s, 3 H).

10

Example 450

4-N-{2-[(5-chloropyridin-2-yl)amino]ethyl}-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.

- 15 Prepared according to general procedure 9 from 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine and N'-(5-chloro-2-pyridyl)ethane-1,2-diamine. LCMS [M+H]⁺ 369; ¹H NMR (400 MHz, CDCl₃) δ_H ppm 7.61 - 7.69 (m, 2 H), 7.30 (d, J=7.6 Hz, 1 H), 7.10 - 7.22 (m, 3 H), 6.17 (br. s., 1 H), 3.71 (br. s., 4 H), 2.33 (s, 3 H), 2.24 (s, 3 H).

20 Example 451

4-N-{2-[(5-bromopyridin-2-yl)amino]ethyl}-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine.

- 25 Prepared according to general procedure 9 from 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine and N'-(5-bromo-2-pyridyl)ethane-1,2-diamine. LCMS [M+H]⁺ 413; ¹H NMR (400 MHz, CD₃OD) δ_H ppm 8.07 (dd, J=2.3, 0.8 Hz, 1 H), 7.86 (dd, J=9.3, 2.3 Hz, 2 H), 7.33 - 7.37 (m, 2 H), 7.24 (t, J=7.6 Hz, 1 H), 7.15 - 7.19 (m, 1 H), 6.90 (dd, J=9.5, 0.6 Hz, 1 H), 6.03 (s, 1 H), 3.77 - 3.82 (m, 2 H), 3.64 - 3.69 (m, 2 H), 2.35 (s, 3 H), 2.24 (s, 3 H).

30 Example 452

4-[(2-{[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}ethyl)amino]benzene-1-sulfonamide.

- 35 Prepared according to general procedure 9 from 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine and 4-(2-aminoethylamino)benzene-sulfonamide. LCMS [M+H]⁺ 413; ¹H NMR (400 MHz, CD₃OD) δ_H ppm 7.64 (d,

J=9.1 Hz, 2 H), 7.33 - 7.37 (m, 1 H), 7.24 (s, 1 H), 7.15 - 7.19 (m, 1 H), 6.70 (d, J=9.1 Hz, 2 H), 6.00 (s, 1 H), 3.72 - 3.77 (m, 2 H), 3.45 - 3.50 (m, 2 H), 2.35 (s, 3 H), 2.24 (s, 3 H).

5 Example 453

4-N-[2-(4-chlorophenyl)ethyl]-6-(dimethyl-1,2-oxazol-4-yl)pyrimidine-2,4-diamine.
Prepared according to general procedure 2 from 6-chloro-4-N-[2-(4-chlorophenyl)ethyl]pyrimidine-2,4-diamine and (3,5-dimethylisoxazol-4-yl)boronic acid. LCMS [M+H]⁺ 344.

10

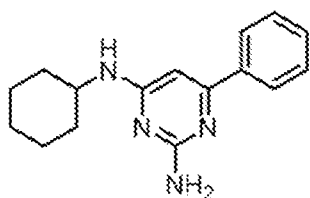
Example 454

6-(2,3-dimethylphenyl)-4-N-{2-[(pyridin-3-yl)amino]ethyl}pyrimidine-2,4-diamine.

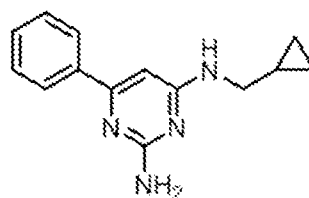
Prepared according to general procedure 9 from 4-chloro-6-(2,3-dimethylphenyl)pyrimidin-2-amine and N'-(3-pyridyl)ethane-1,2-diamine. LCMS

15 [M+H]⁺ 335; ¹H NMR (400 MHz, CD₃OD) δ_H ppm 8.10 - 8.12 (m, 1 H), 7.97 - 8.00 (m, 1 H), 7.72 - 7.80 (m, 2 H), 7.34 - 7.38 (m, 1 H), 7.22 - 7.27 (m, 1 H), 7.19 (dd, J=1.0, 0.5 Hz, 1 H), 6.04 (s, 1 H), 3.75 - 3.80 (m, 2 H), 3.54 (t, J=6.2 Hz, 2 H), 2.36 (s, 3 H), 2.25 (s, 3 H).

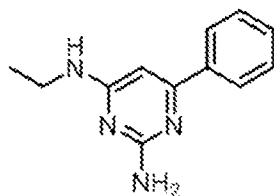
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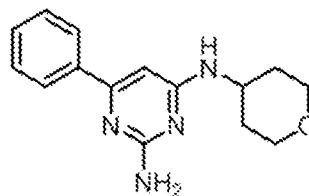
Example 1



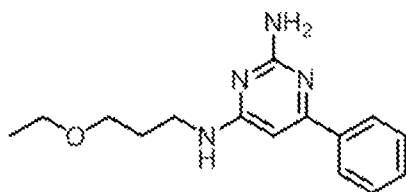
Example 6



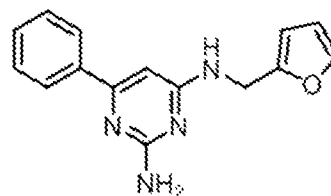
Example 2



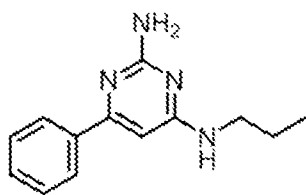
Example 7



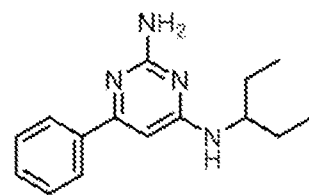
Example 3



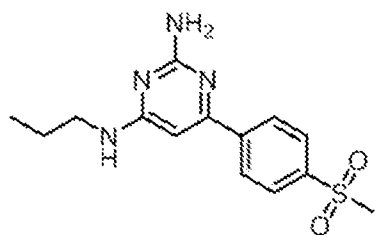
Example 8



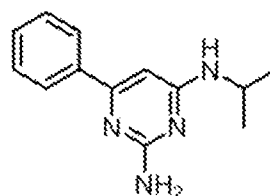
Example 4



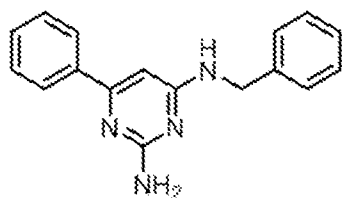
Example 9



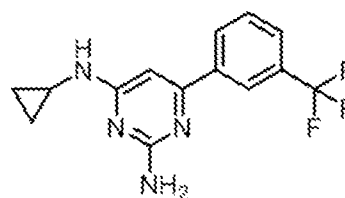
Example 5



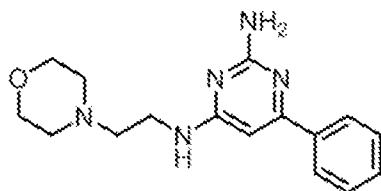
Example 10



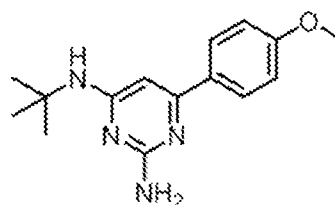
Example 11



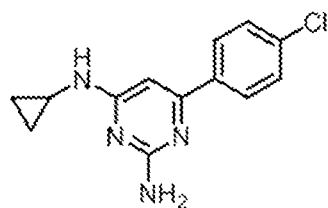
Example 16



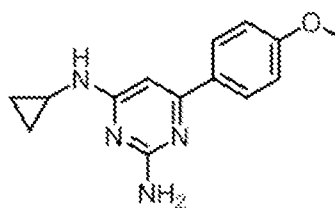
Example 12



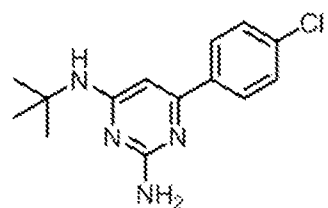
Example 17



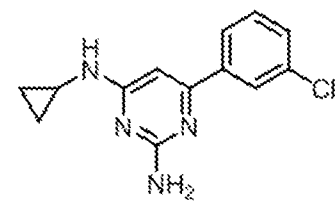
Example 13



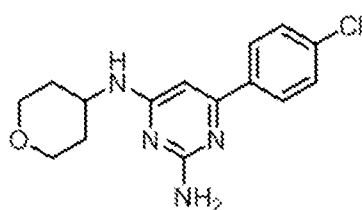
Example 18



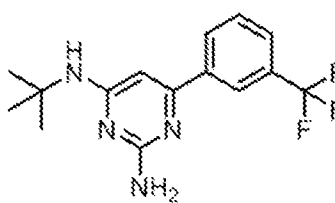
Example 14



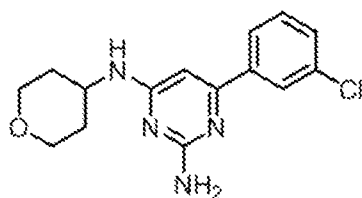
Example 19



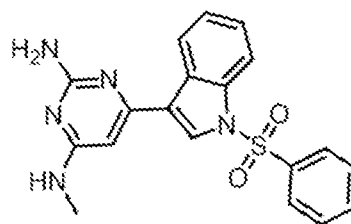
Example 15



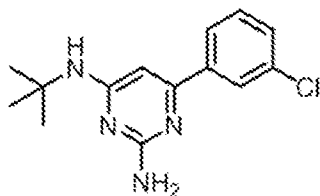
Example 20



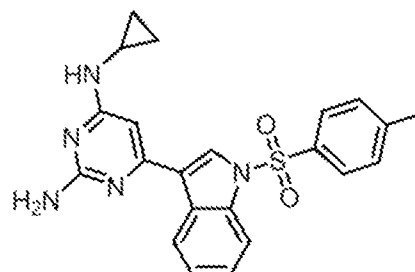
Example 21



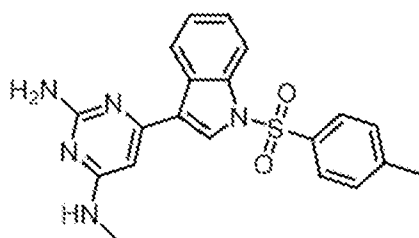
Example 26



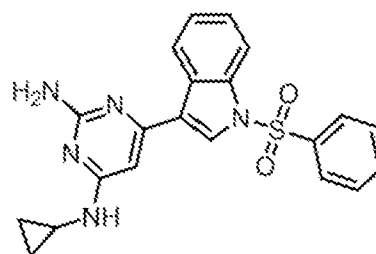
Example 22



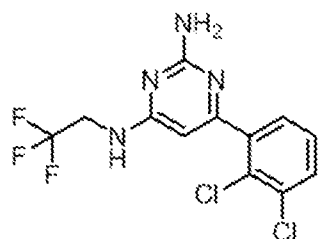
Example 27



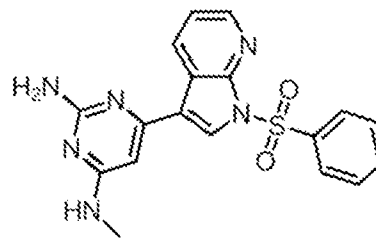
Example 23



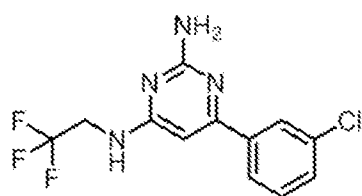
Example 28



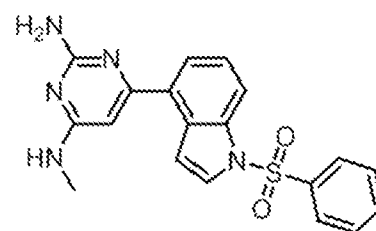
Example 24



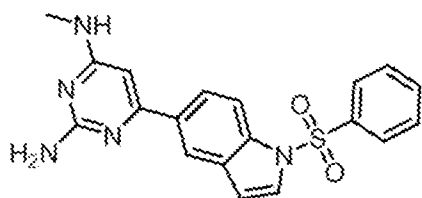
Example 29



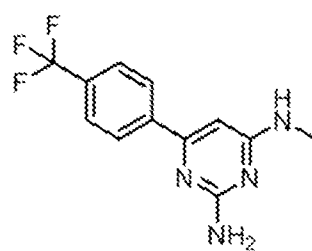
Example 25



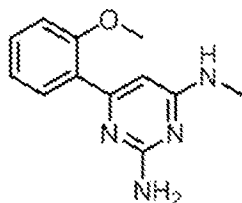
Example 30



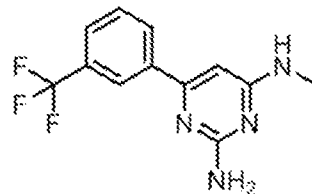
Example 31



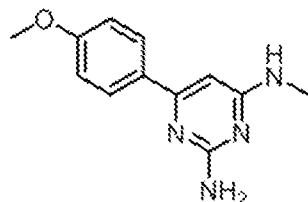
Example 36



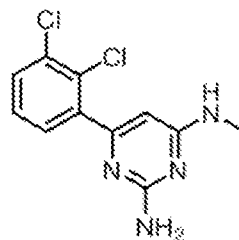
Example 32



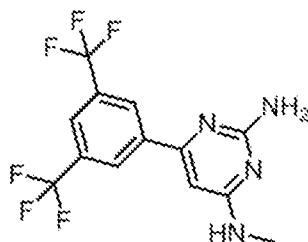
Example 37



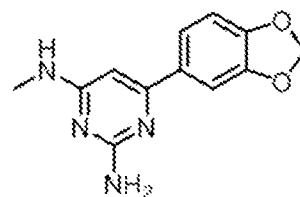
Example 33



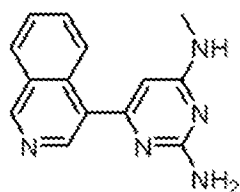
Example 38



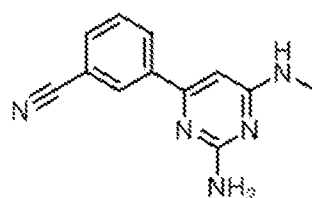
Example 34



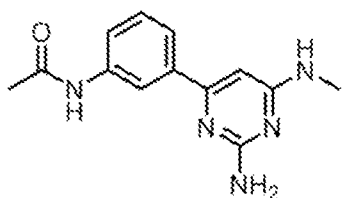
Example 39



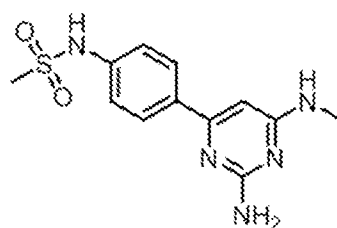
Example 35



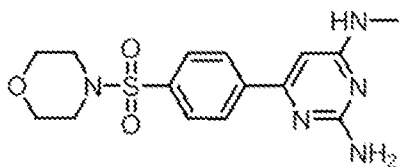
Example 40



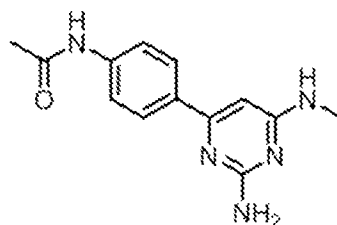
Example 41



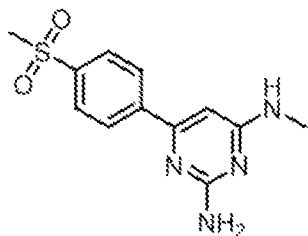
Example 46



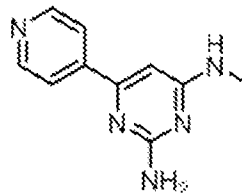
Example 42



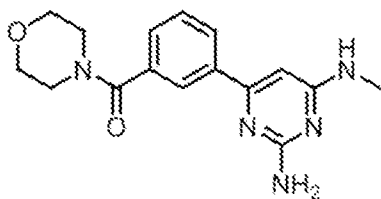
Example 47



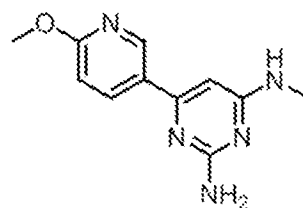
Example 43



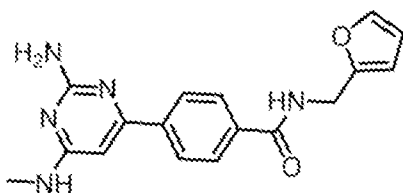
Example 48



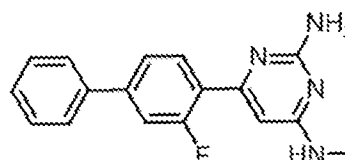
Example 44



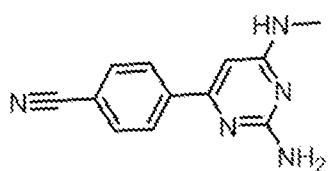
Example 49



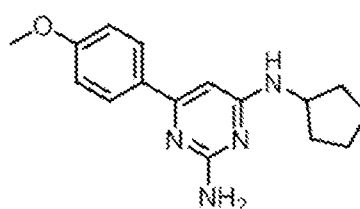
Example 45



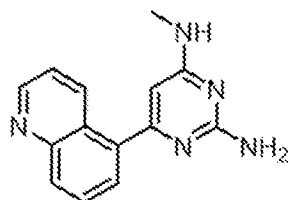
Example 50



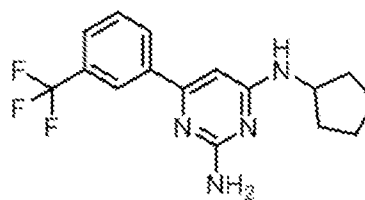
Example 51



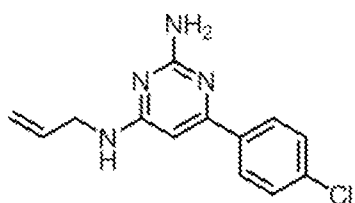
Example 56



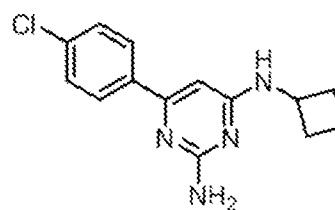
Example 52



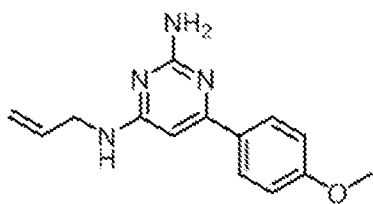
Example 57



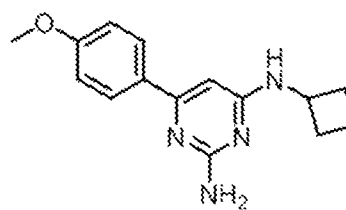
Example 53



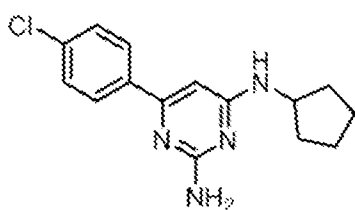
Example 58



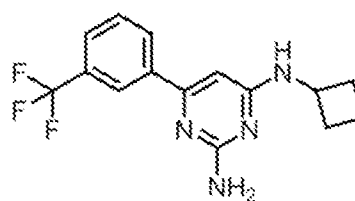
Example 54



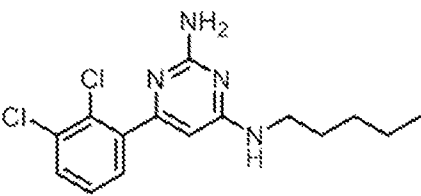
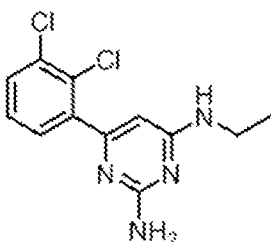
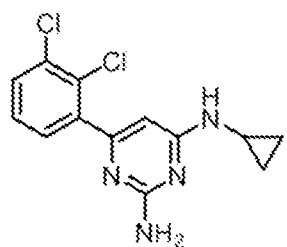
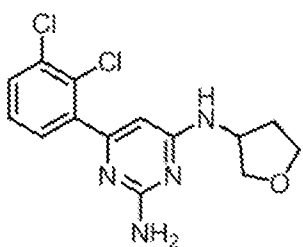
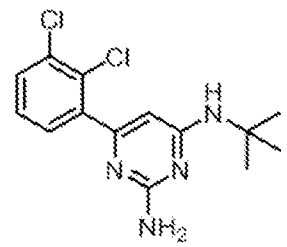
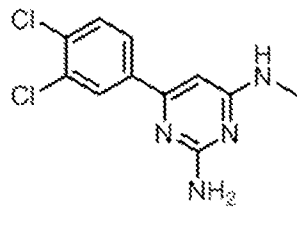
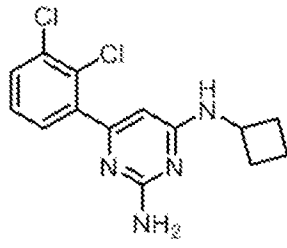
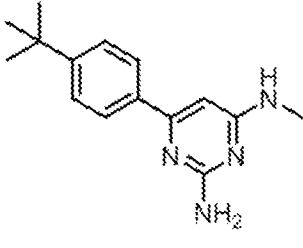
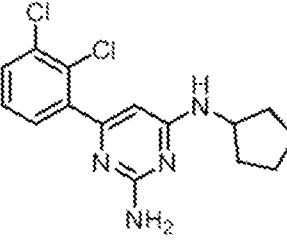
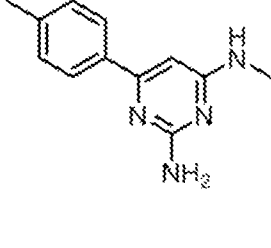
Example 59

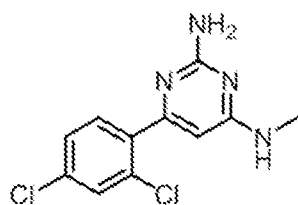


Example 55

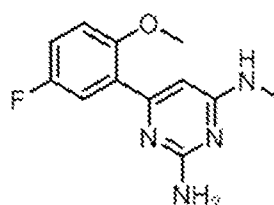


Example 60

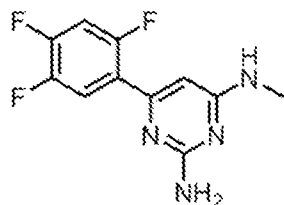
 Example 61	 Example 66
 Example 62	 Example 67
 Example 63	 Example 68
 Example 64	 Example 69
 Example 65	 Example 70



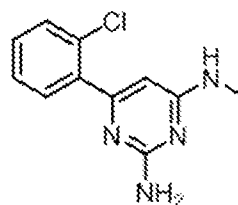
Example 71



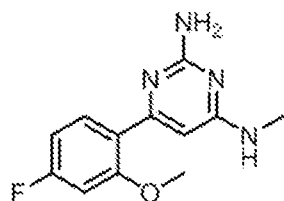
Example 76



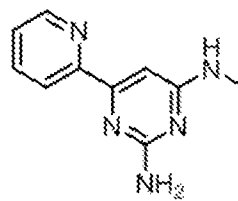
Example 72



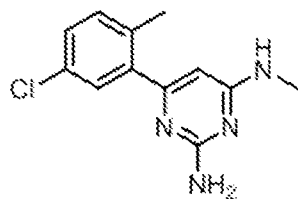
Example 77



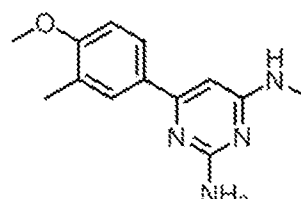
Example 73



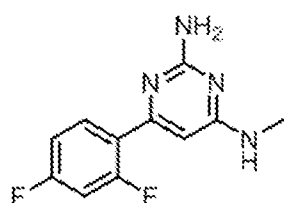
Example 78



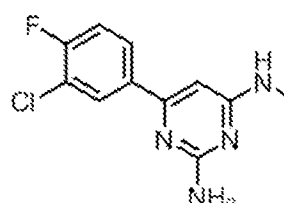
Example 74



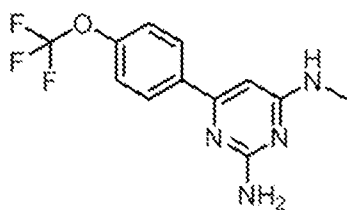
Example 79



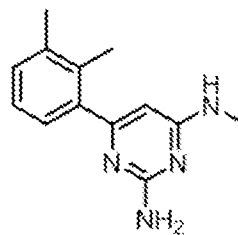
Example 75



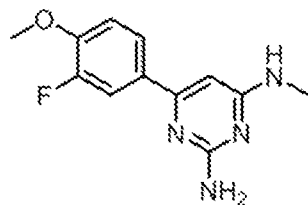
Example 80



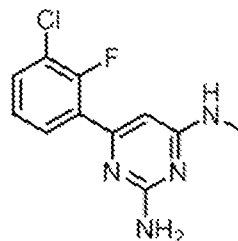
Example 81



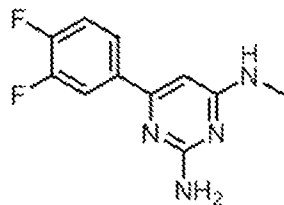
Example 86



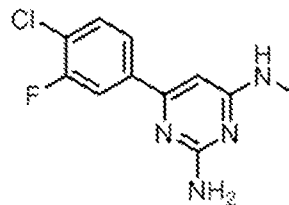
Example 82



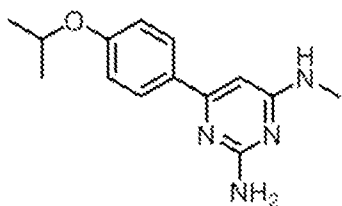
Example 87



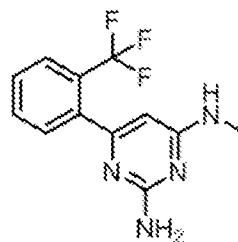
Example 83



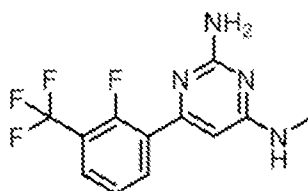
Example 88



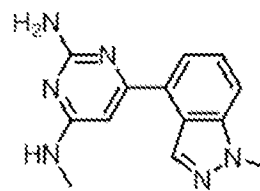
Example 84



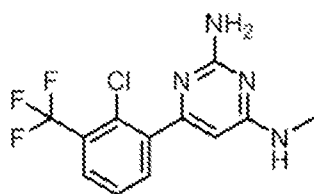
Example 89



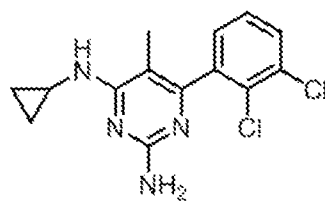
Example 85



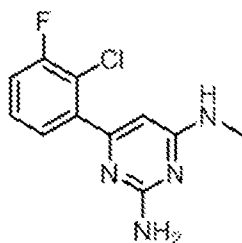
Example 90



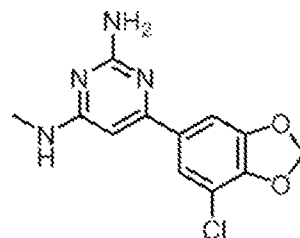
Example 91



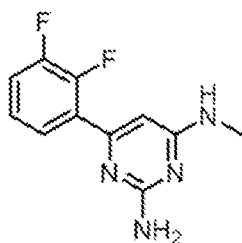
Example 96



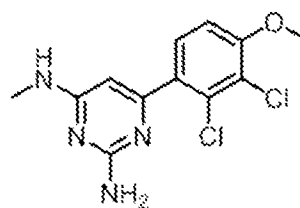
Example 92



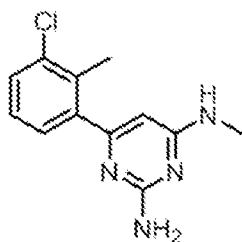
Example 97



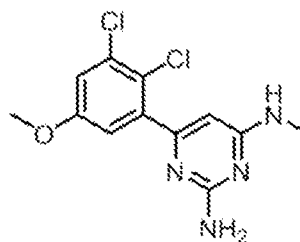
Example 93



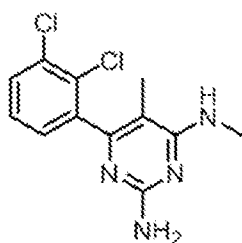
Example 98



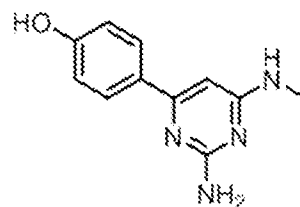
Example 94



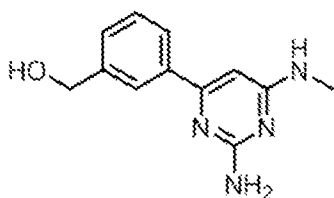
Example 99



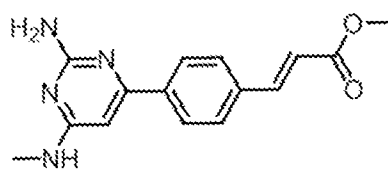
Example 95



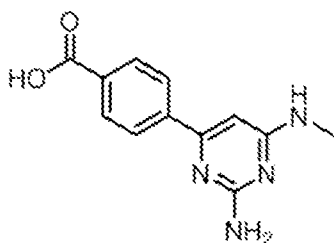
Example 100



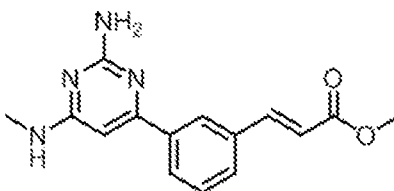
Example 101



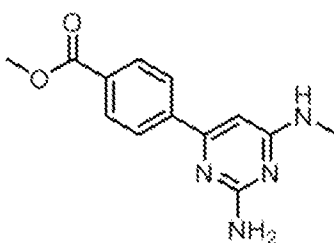
Example 106



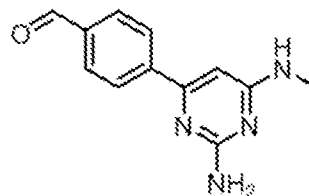
Example 102



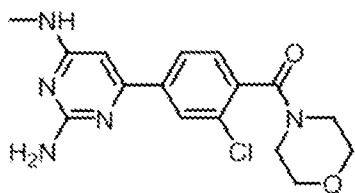
Example 107



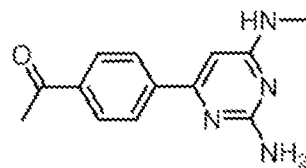
Example 103



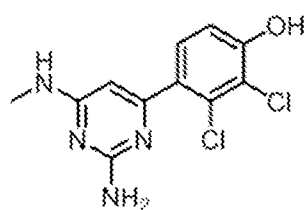
Example 108



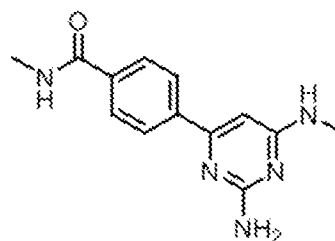
Example 104



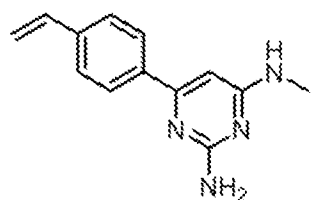
Example 109



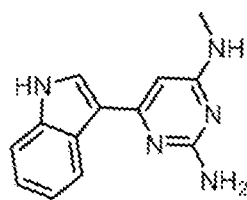
Example 105



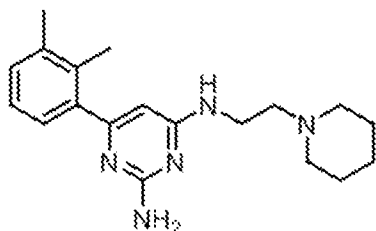
Example 110



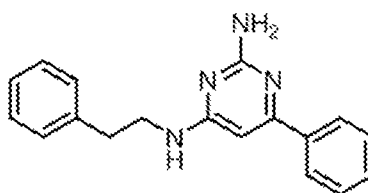
Example 111



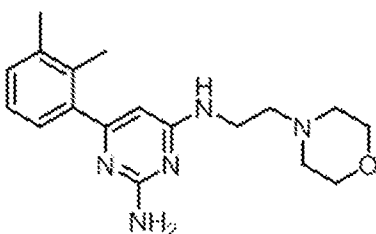
Example 116



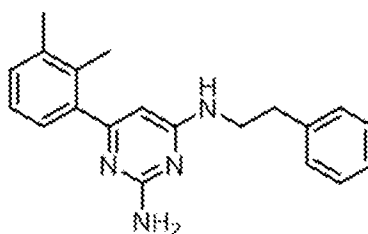
Example 112



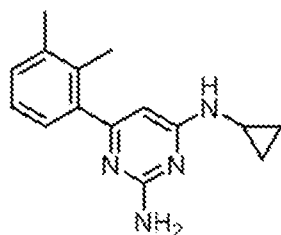
Example 117



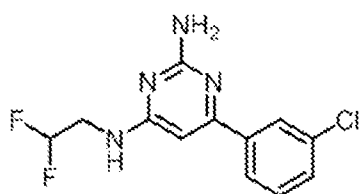
Example 113



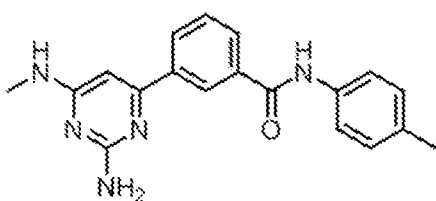
Example 118



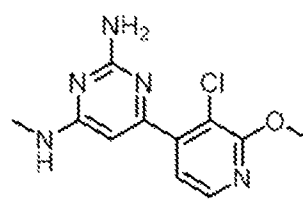
Example 114



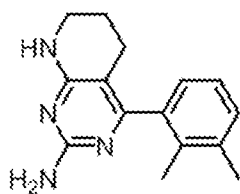
Example 119



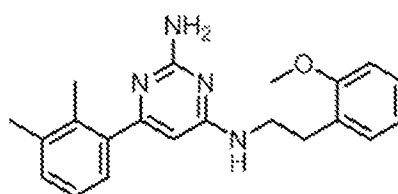
Example 115



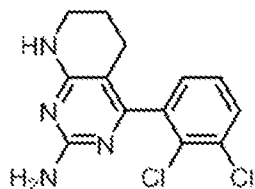
Example 120



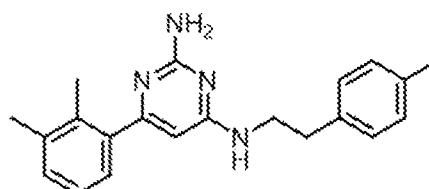
Example 121



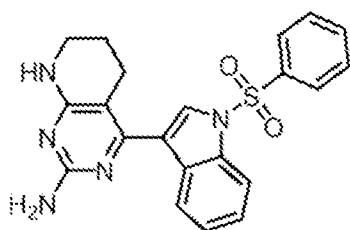
Example 126



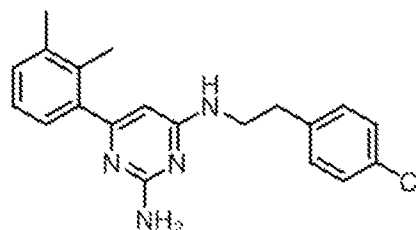
Example 122



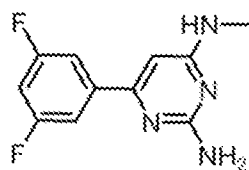
Example 127



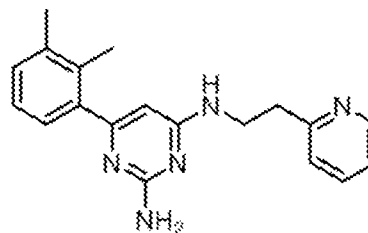
Example 123



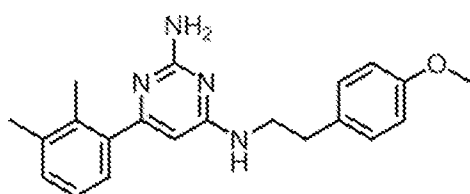
Example 128



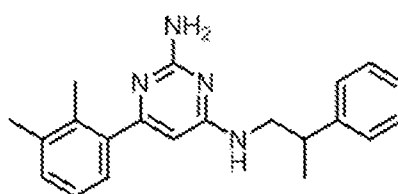
Example 124



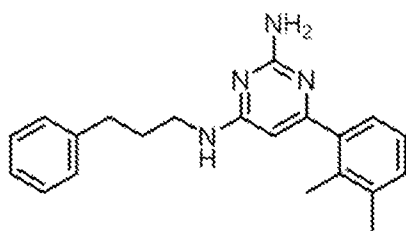
Example 129



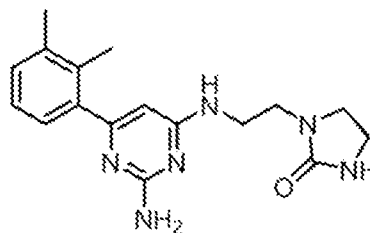
Example 125



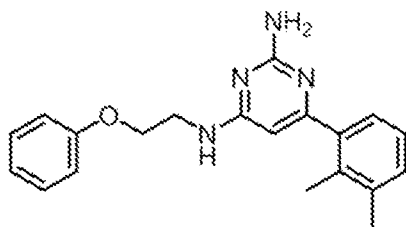
Example 130



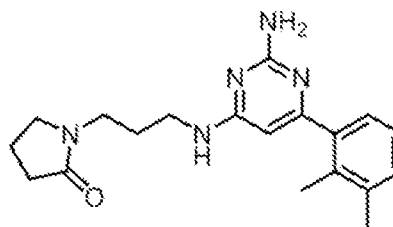
Example 131



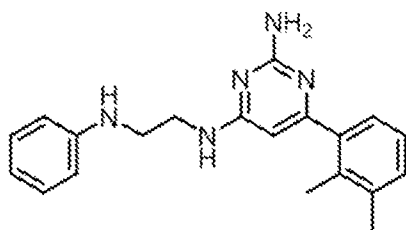
Example 136



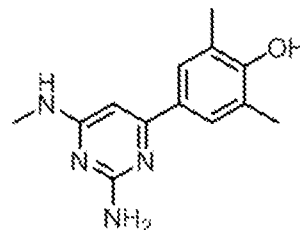
Example 132



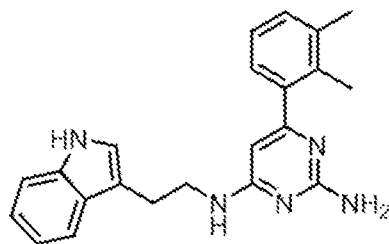
Example 137



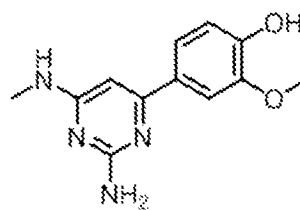
Example 133



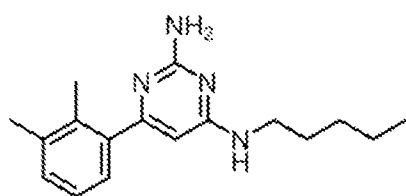
Example 138



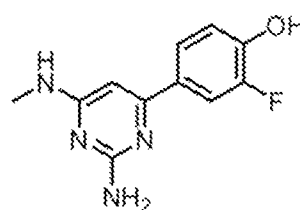
Example 134



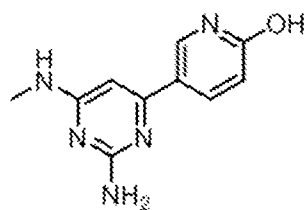
Example 139



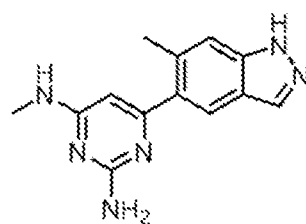
Example 135



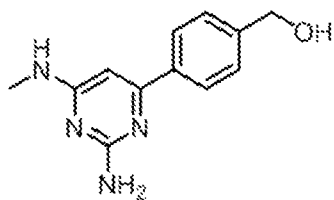
Example 140



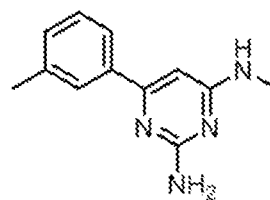
Example 141



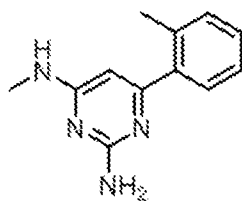
Example 146



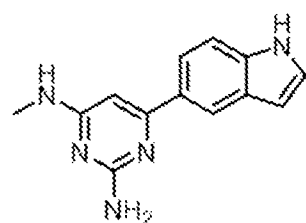
Example 142



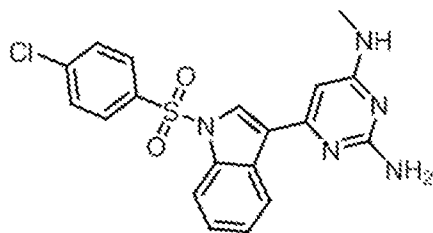
Example 147



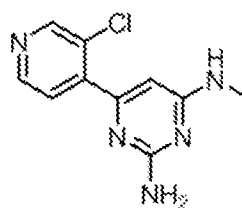
Example 143



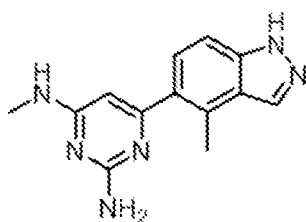
Example 148



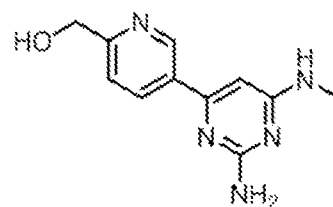
Example 144



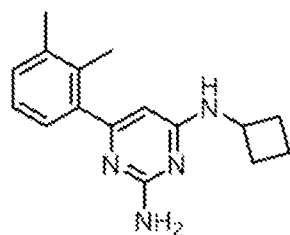
Example 149



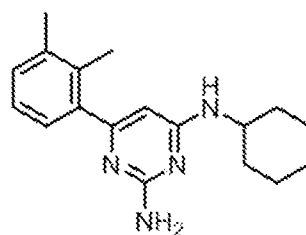
Example 145



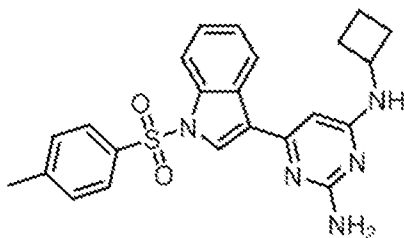
Example 150



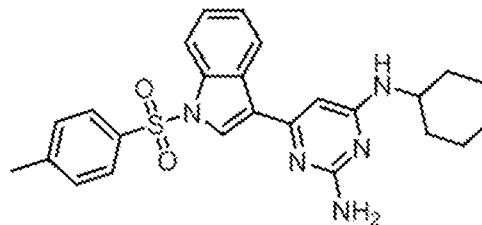
Example 151



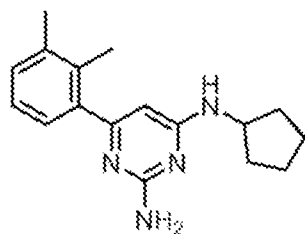
Example 156



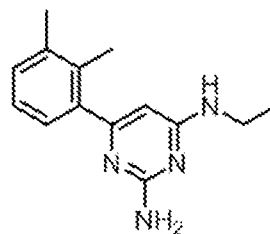
Example 152



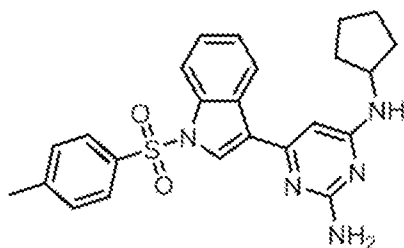
Example 157



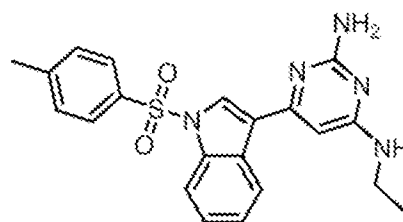
Example 153



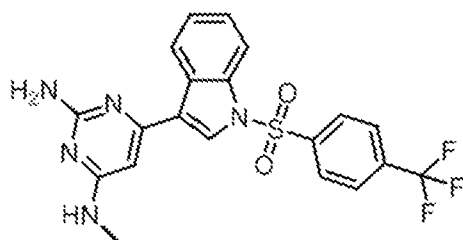
Example 158



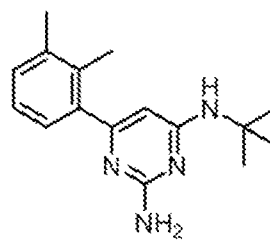
Example 154



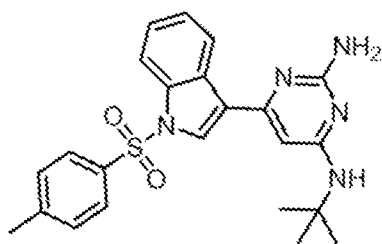
Example 159



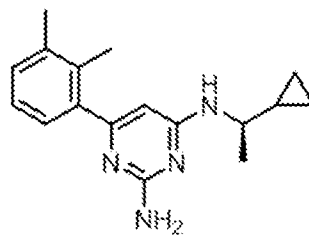
Example 155



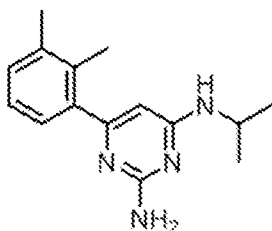
Example 160



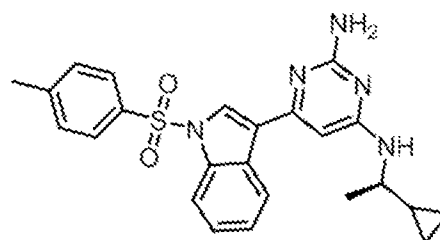
Example 161



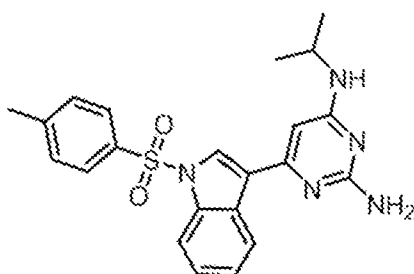
Example 166



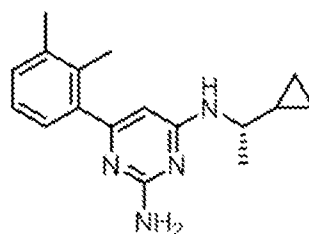
Example 162



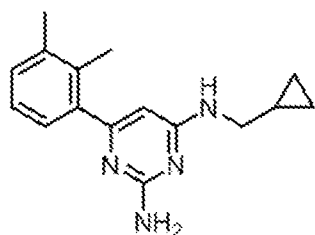
Example 167



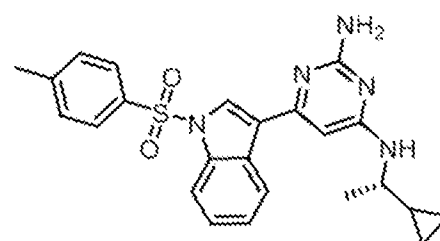
Example 163



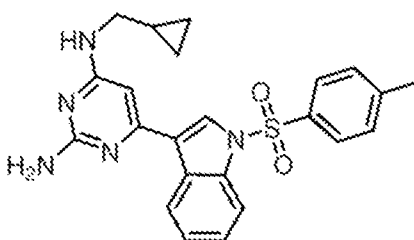
Example 168



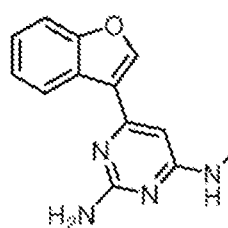
Example 164



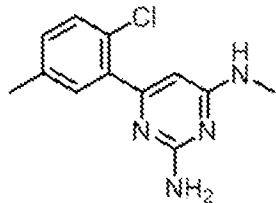
Example 169



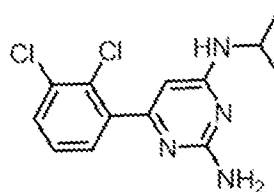
Example 165



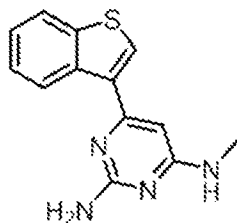
Example 170



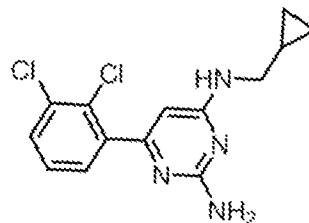
Example 171



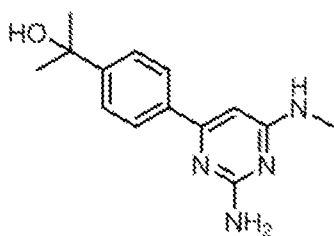
Example 176



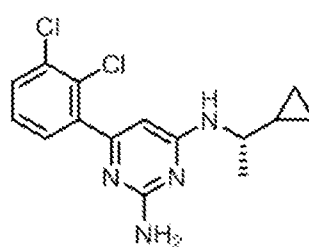
Example 172



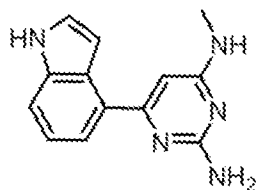
Example 177



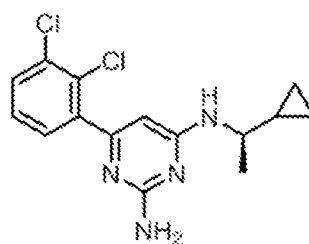
Example 173



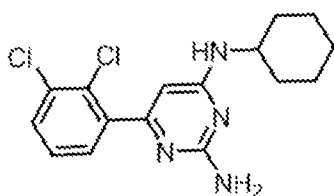
Example 178



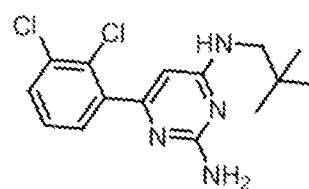
Example 174



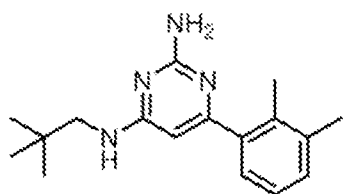
Example 179



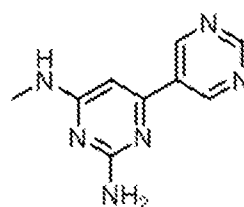
Example 175



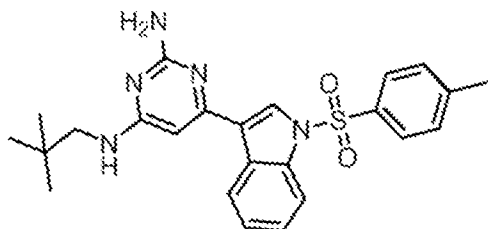
Example 180



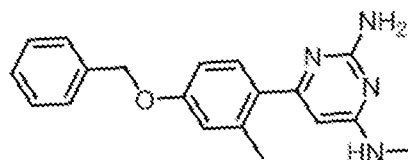
Example 181



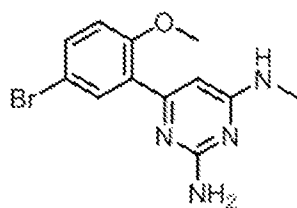
Example 186



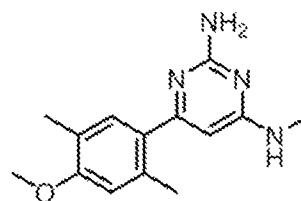
Example 182



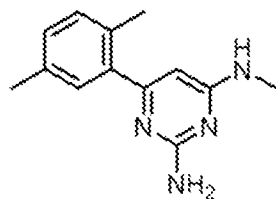
Example 187



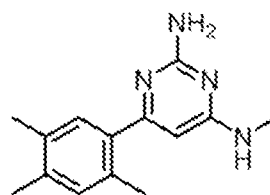
Example 183



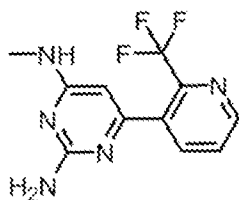
Example 188



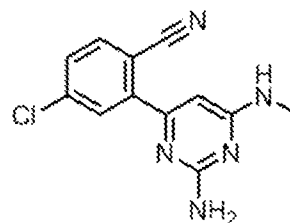
Example 184



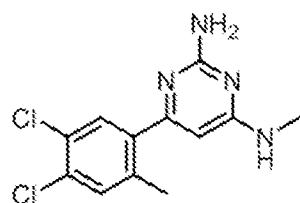
Example 189



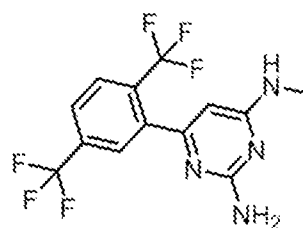
Example 185



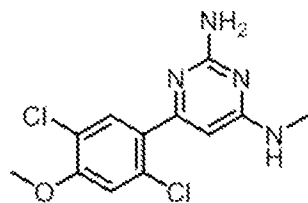
Example 190



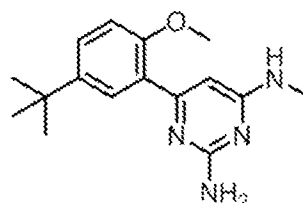
Example 191



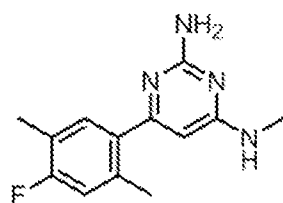
Example 196



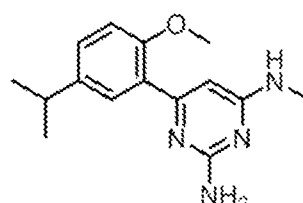
Example 192



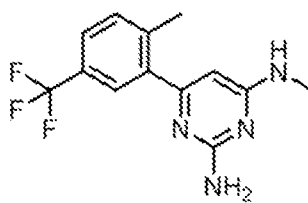
Example 197



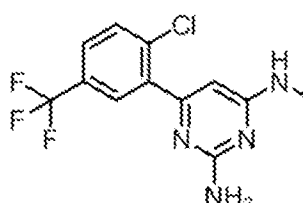
Example 193



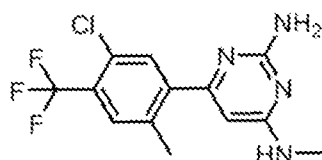
Example 198



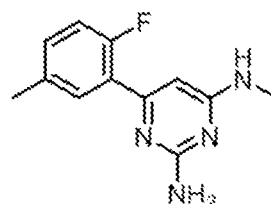
Example 194



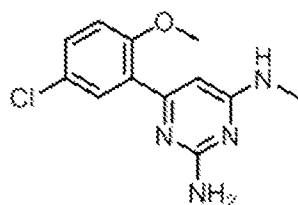
Example 199



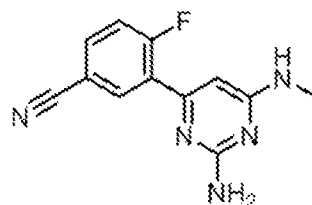
Example 195



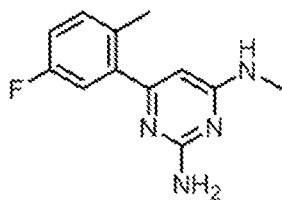
Example 200



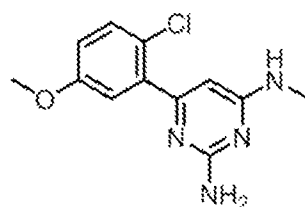
Example 201



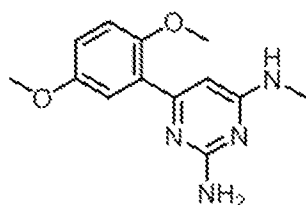
Example 206



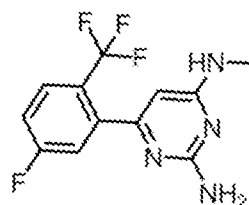
Example 202



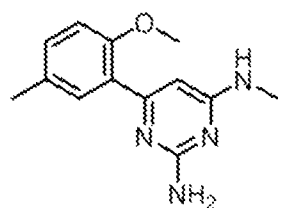
Example 207



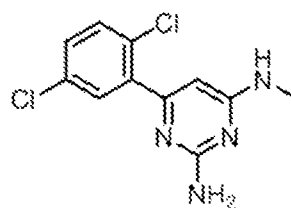
Example 203



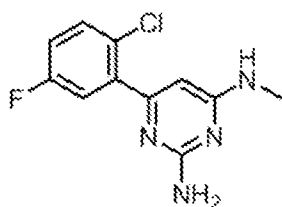
Example 208



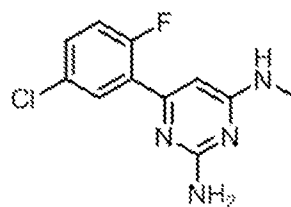
Example 204



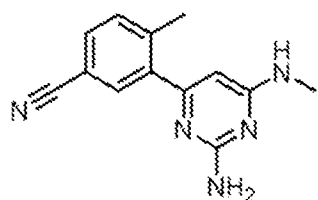
Example 209



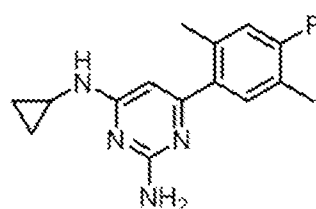
Example 205



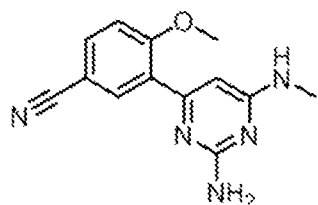
Example 210



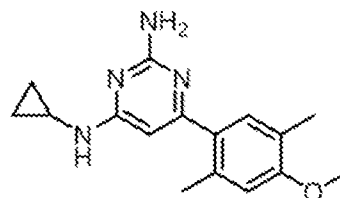
Example 211



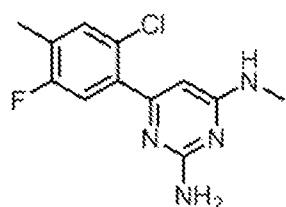
Example 216



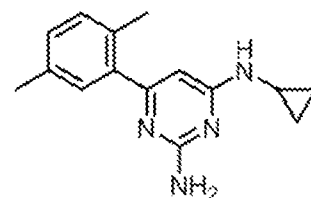
Example 212



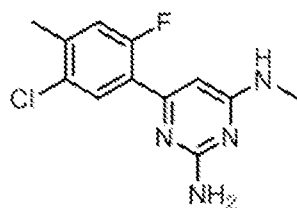
Example 217



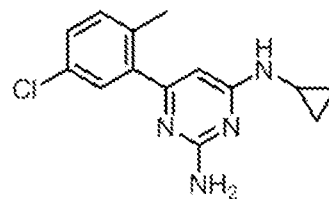
Example 213



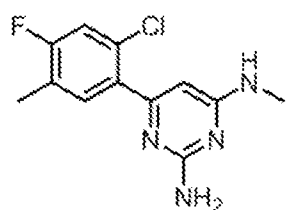
Example 218



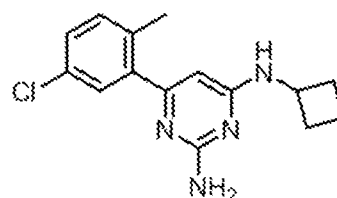
Example 214



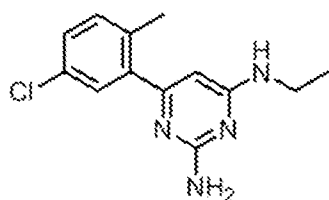
Example 219



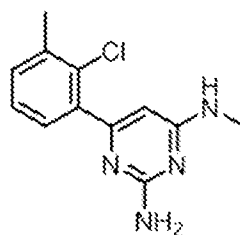
Example 215



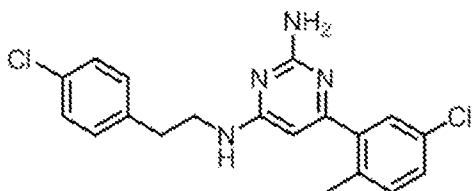
Example 220



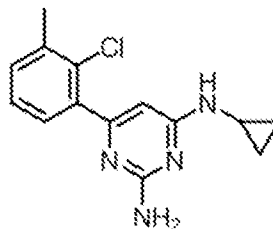
Example 221



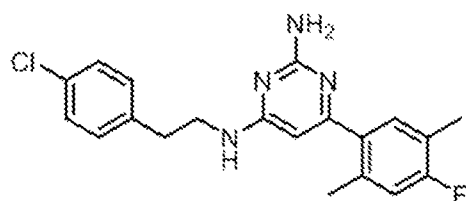
Example 226



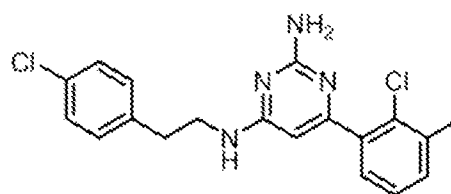
Example 222



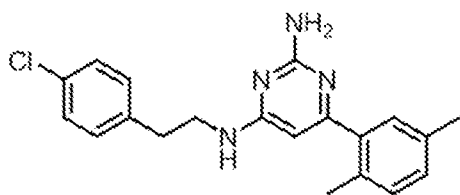
Example 227



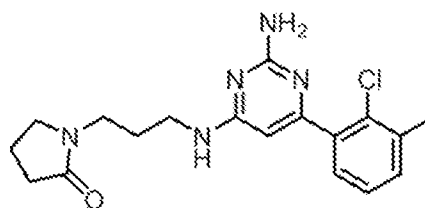
Example 223



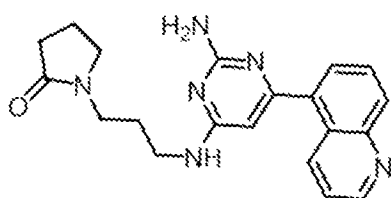
Example 228



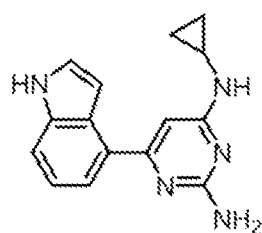
Example 224



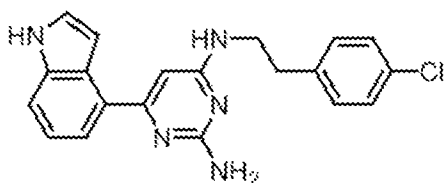
Example 229



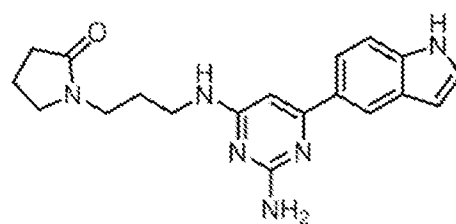
Example 225



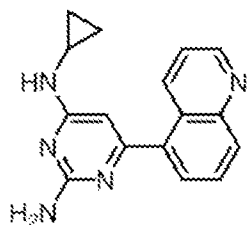
Example 230



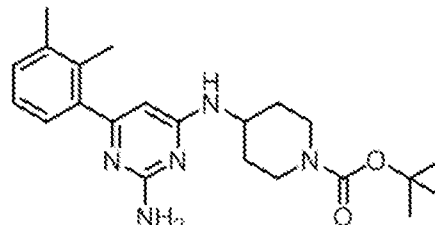
Example 231



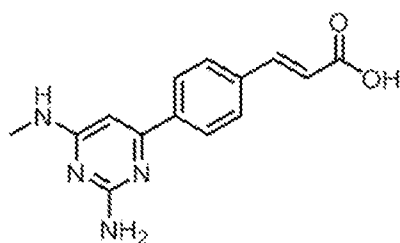
Example 236



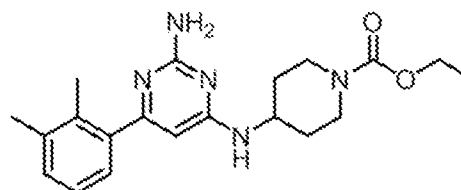
Example 232



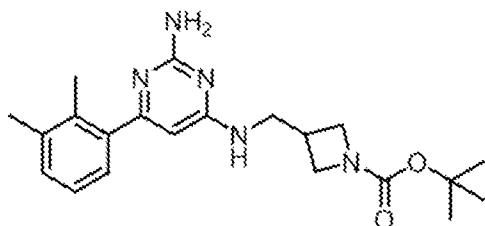
Example 237



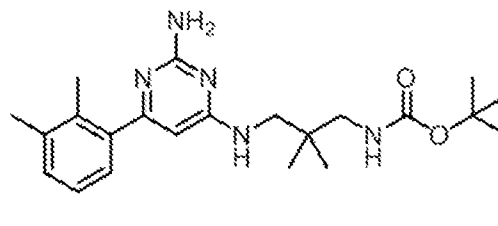
Example 233



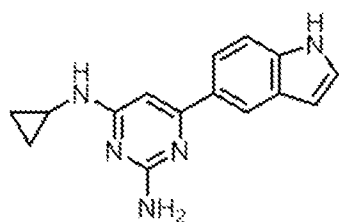
Example 238



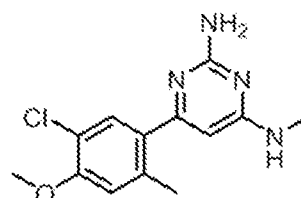
Example 234



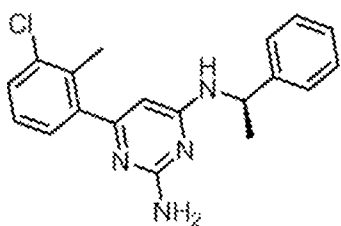
Example 239



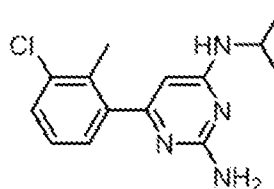
Example 235



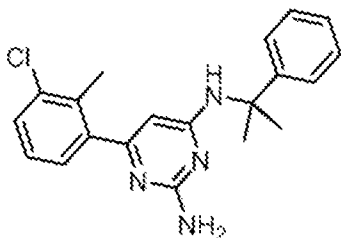
Example 240



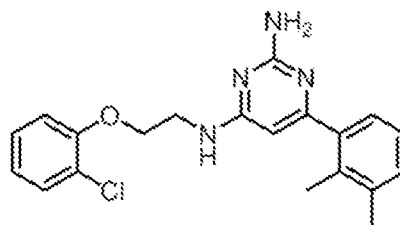
Example 241



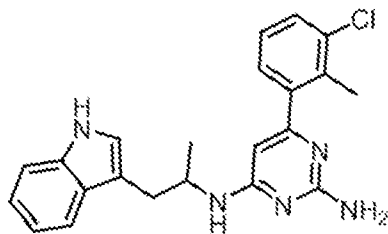
Example 246



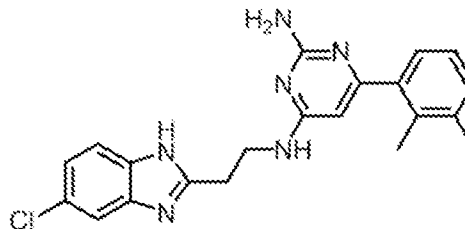
Example 242



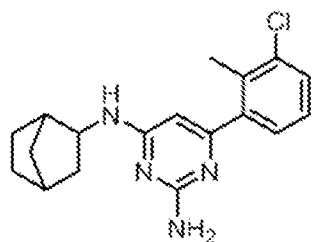
Example 247



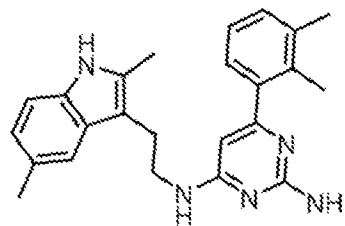
Example 243



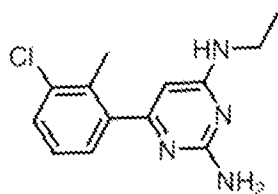
Example 248



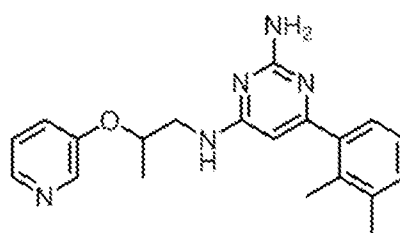
Example 244



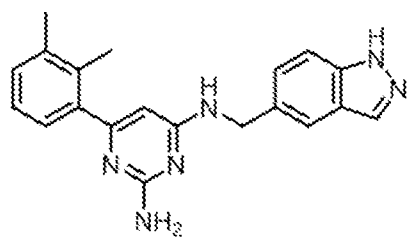
Example 249



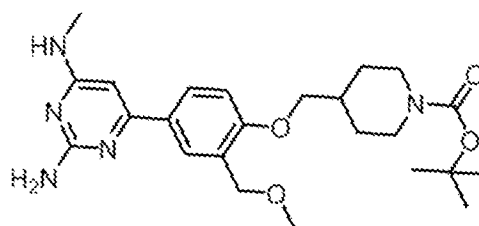
Example 245



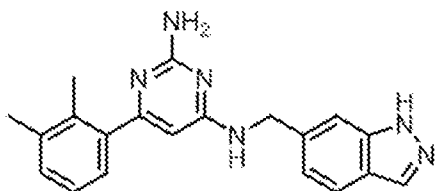
Example 250



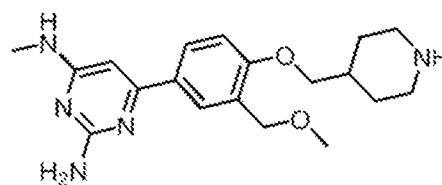
Example 251



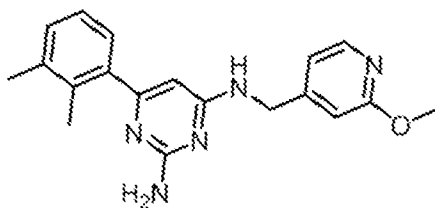
Example 256



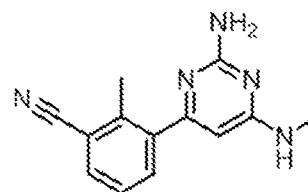
Example 252



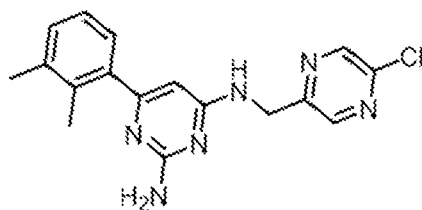
Example 257



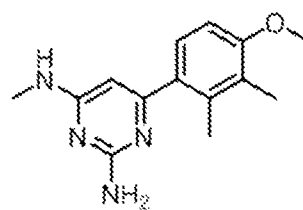
Example 253



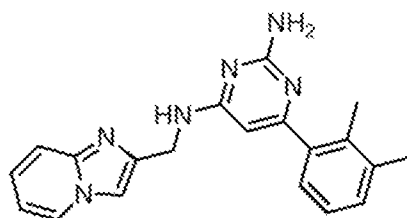
Example 258



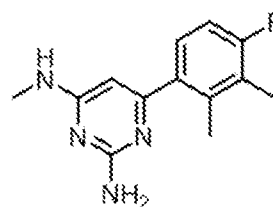
Example 254



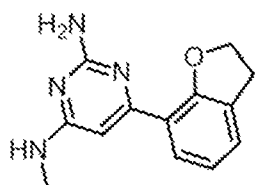
Example 259



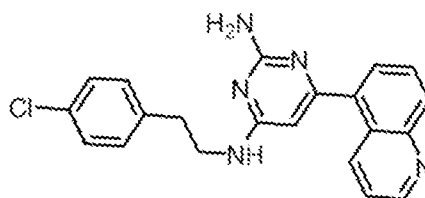
Example 255



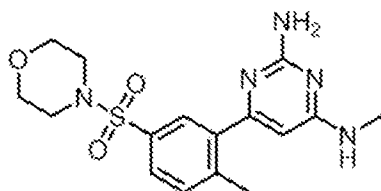
Example 260



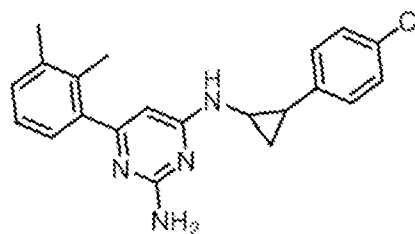
Example 261



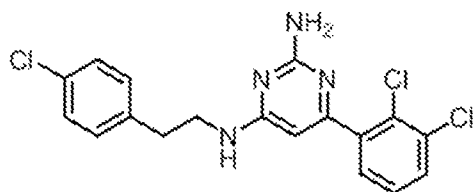
Example 266



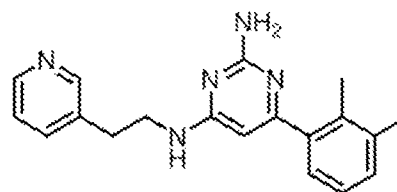
Example 262



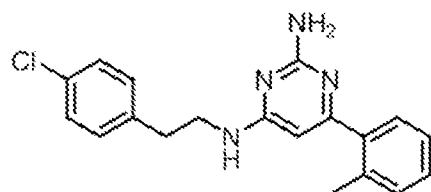
Example 267



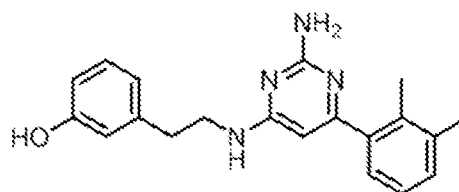
Example 263



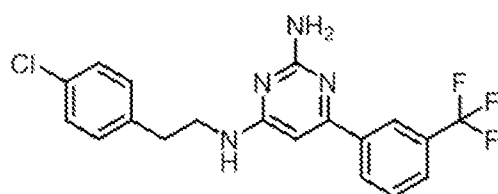
Example 268



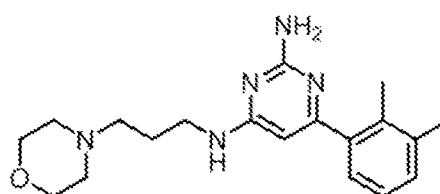
Example 264



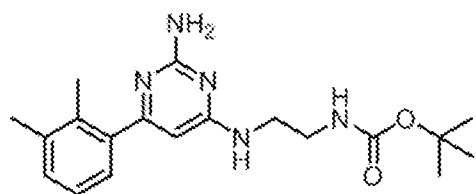
Example 269



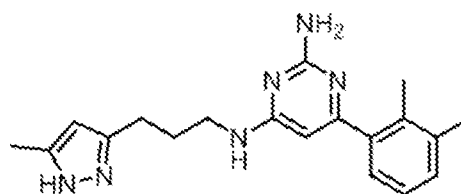
Example 265



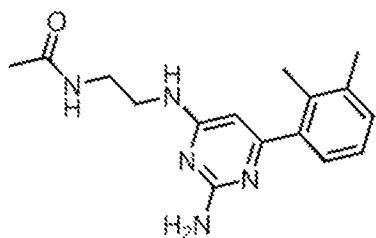
Example 270



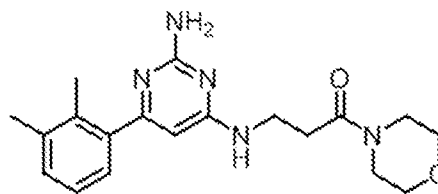
Example 271



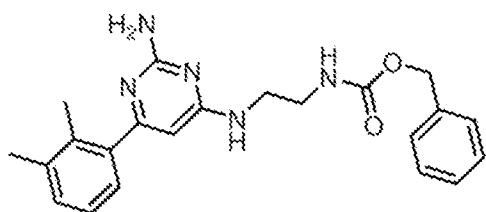
Example 276



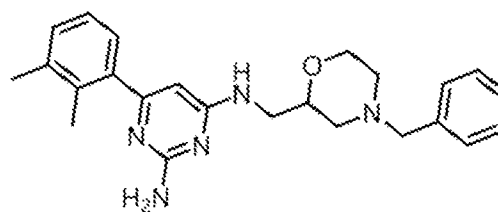
Example 272



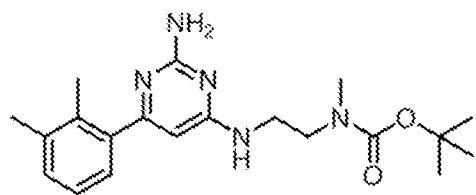
Example 277



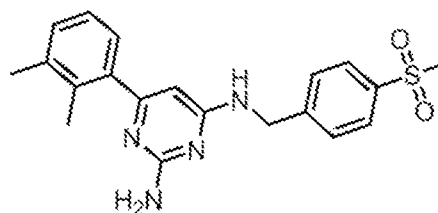
Example 273



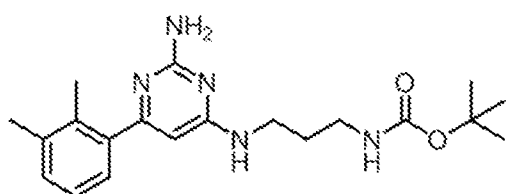
Example 278



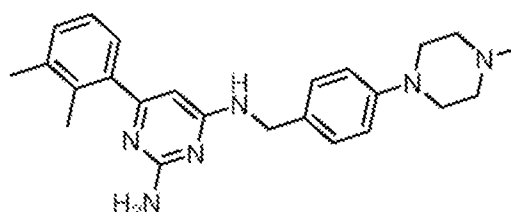
Example 274



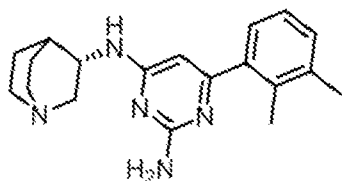
Example 279



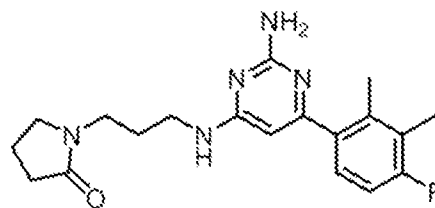
Example 275



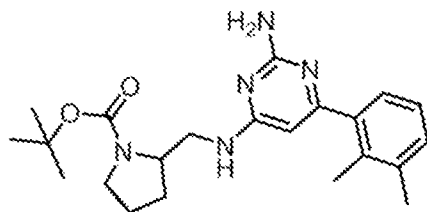
Example 280



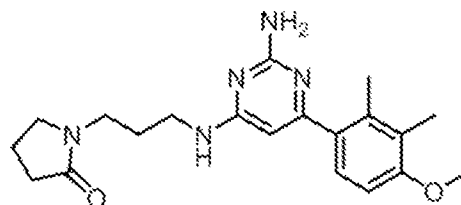
Example 281



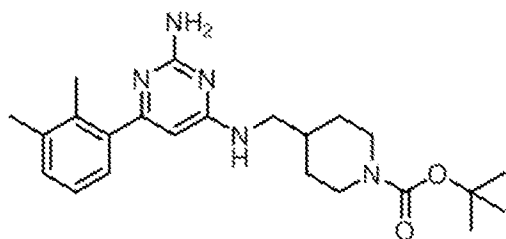
Example 286



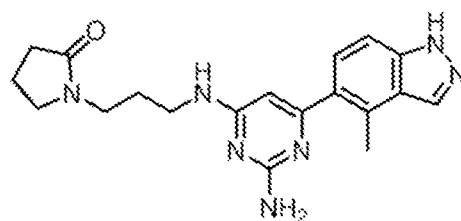
Example 282



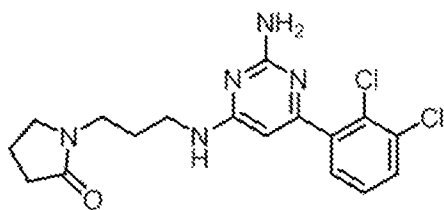
Example 287



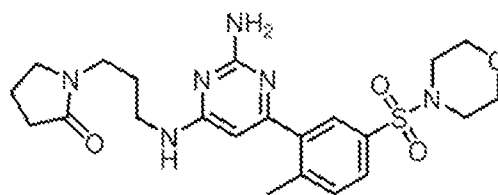
Example 283



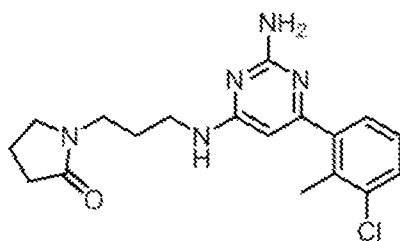
Example 288



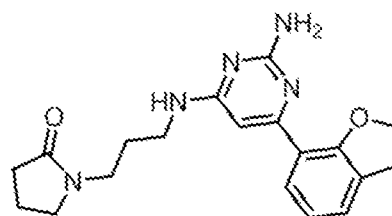
Example 284



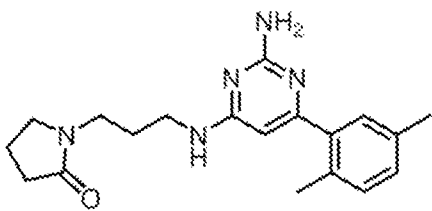
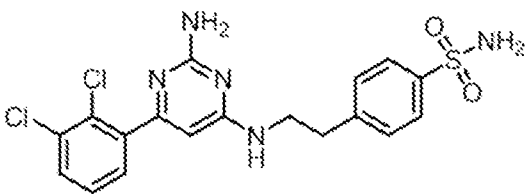
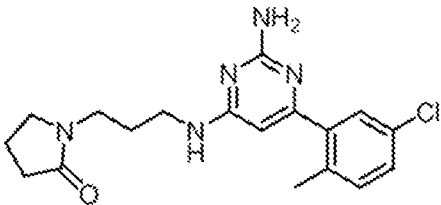
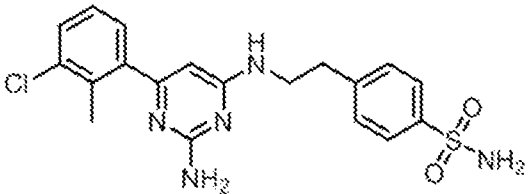
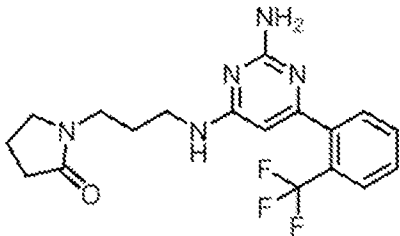
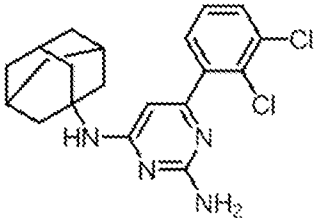
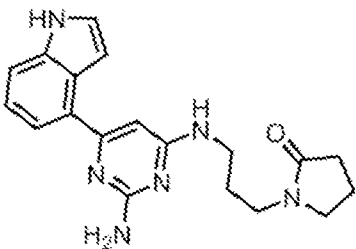
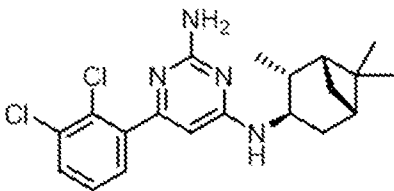
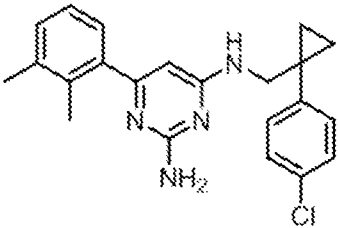
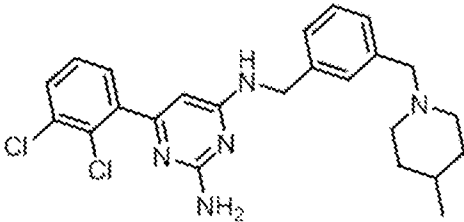
Example 289

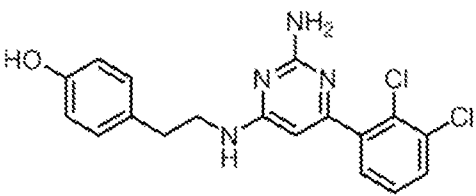
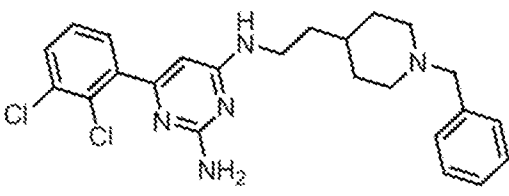
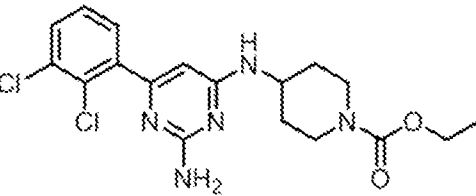
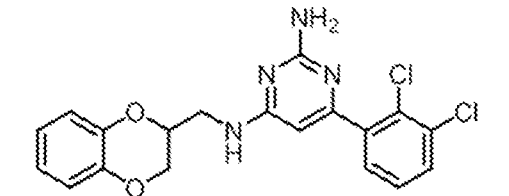
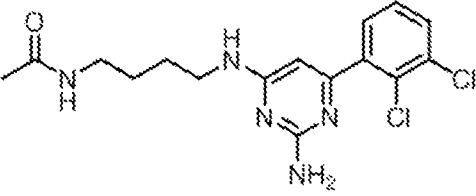
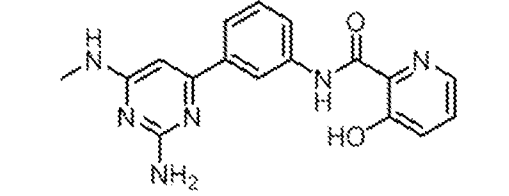
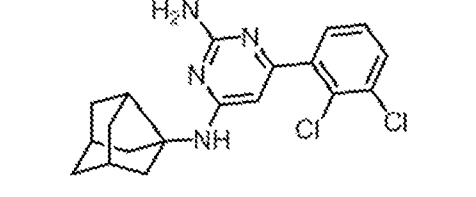
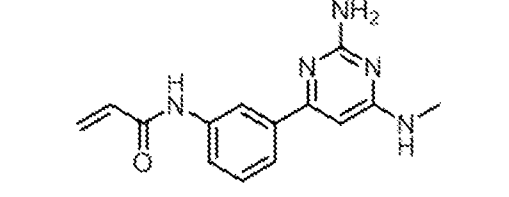
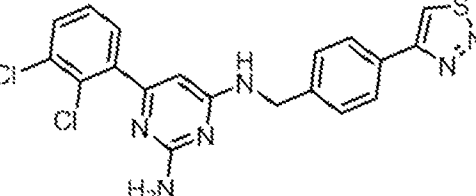
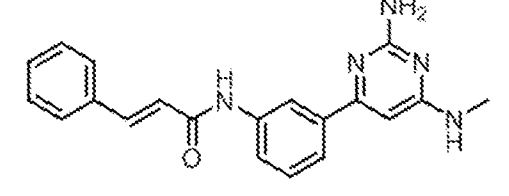


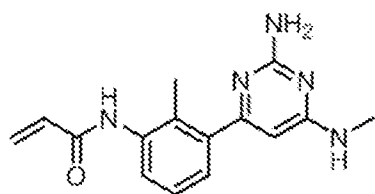
Example 285



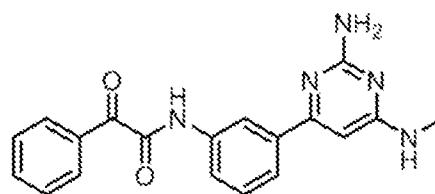
Example 290

	
Example 291	Example 296
	
Example 292	Example 297
	
Example 293	Example 298
	
Example 294	Example 299
	
Example 295	Example 300

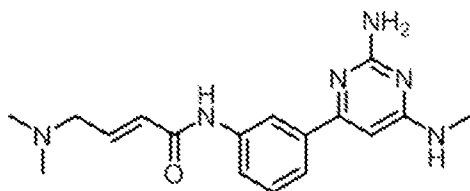
	
Example 301	Example 306
	
Example 302	Example 307
	
Example 303	Example 308
	
Example 304	Example 309
	
Example 305	Example 310



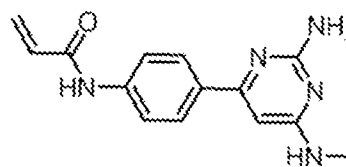
Example 311



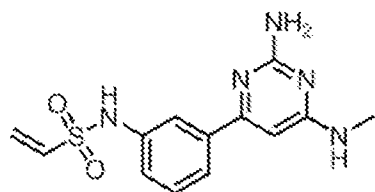
Example 316



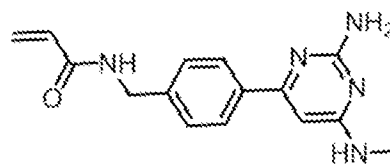
Example 312



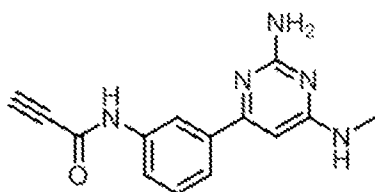
Example 317



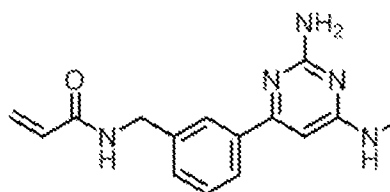
Example 313



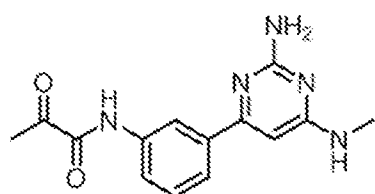
Example 318



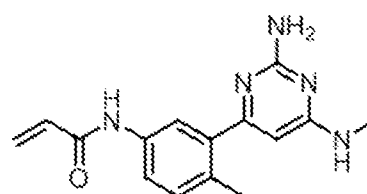
Example 314



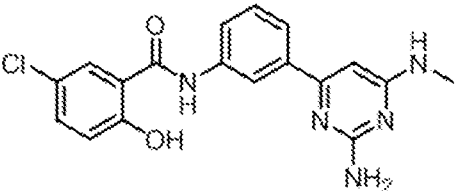
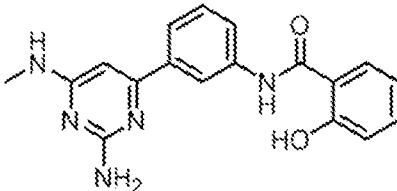
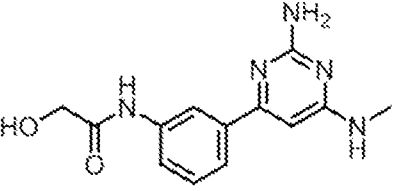
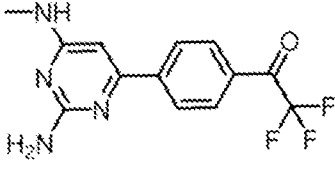
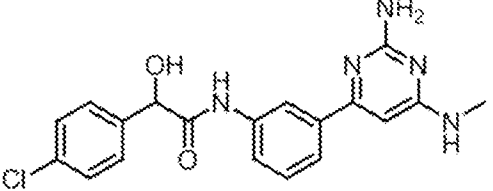
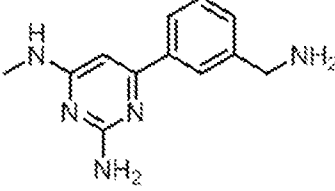
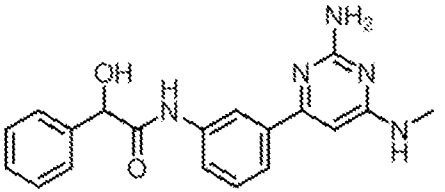
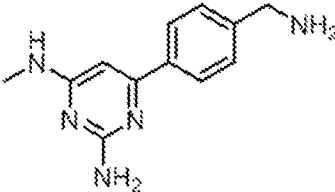
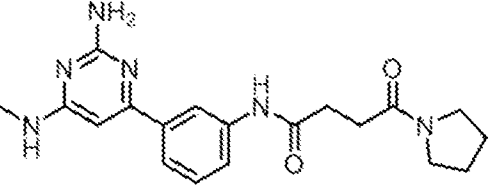
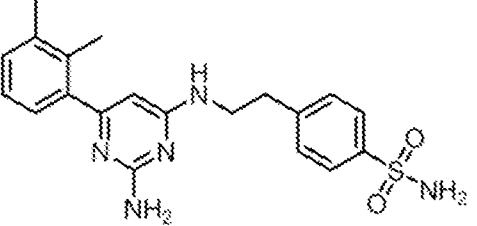
Example 319

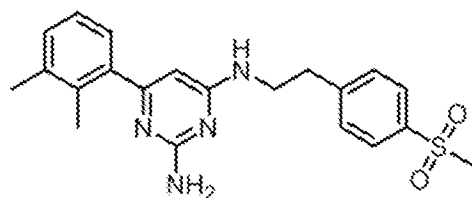


Example 315

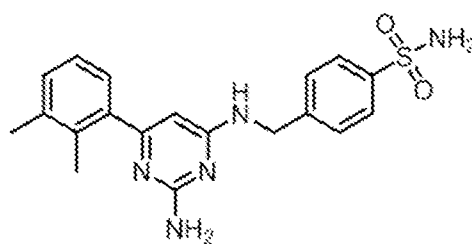


Example 320

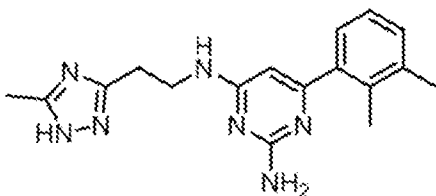
	
Example 321	Example 326
	
Example 322	Example 327
	
Example 323	Example 328
	
Example 324	Example 329
	
Example 325	Example 330



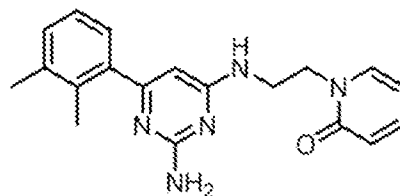
Example 331



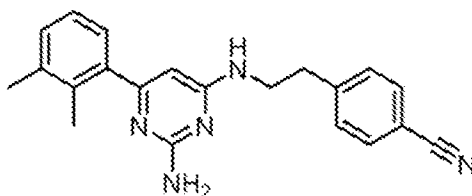
Example 336



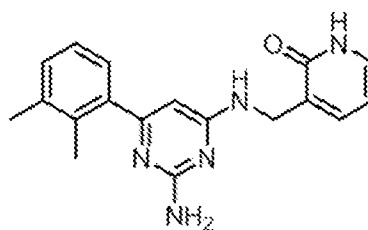
Example 332



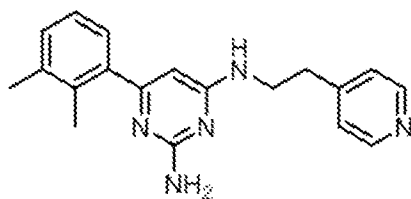
Example 337



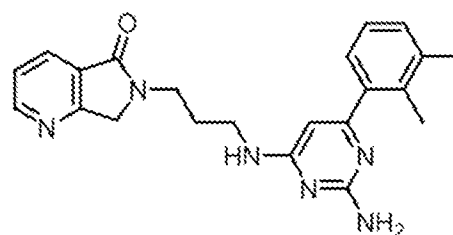
Example 333



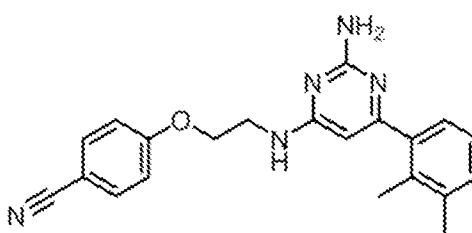
Example 338



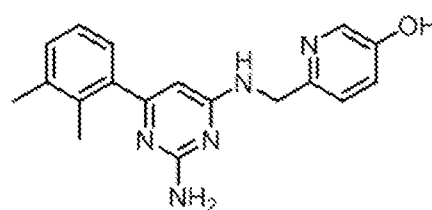
Example 334



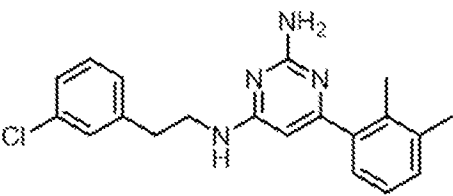
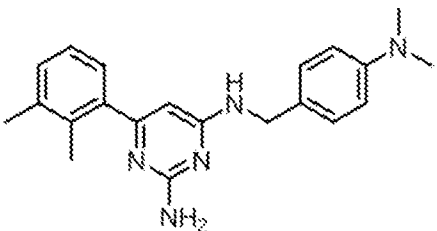
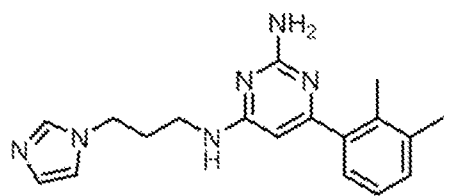
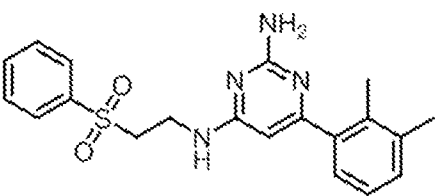
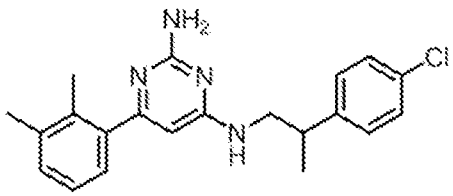
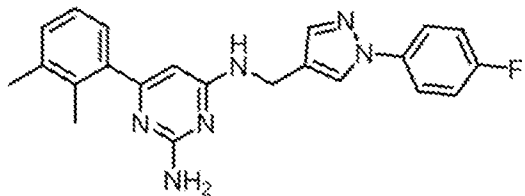
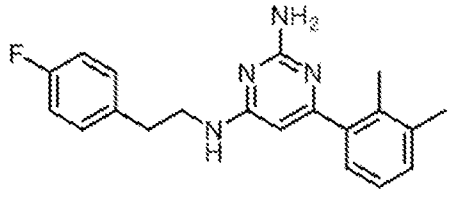
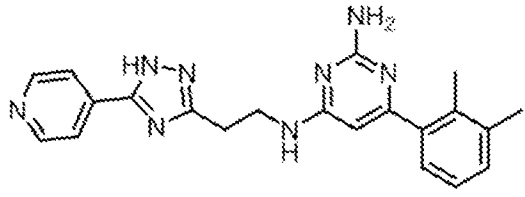
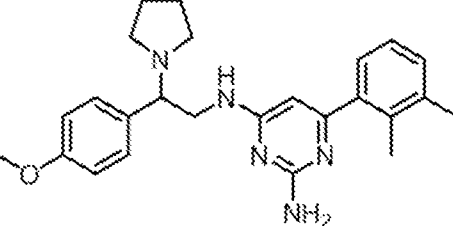
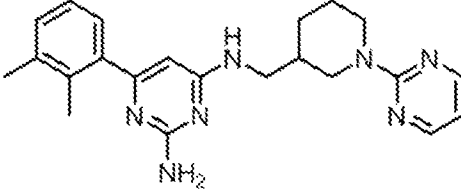
Example 339

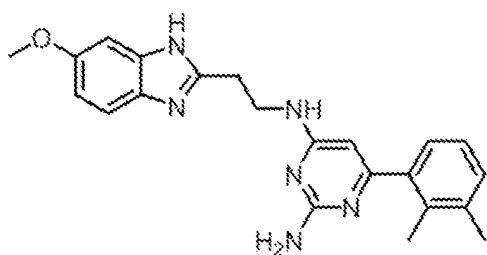


Example 335

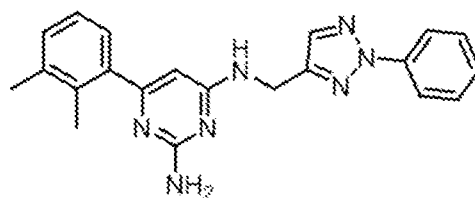


Example 340

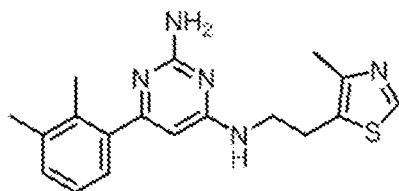
 Example 341	 Example 346
 Example 342	 Example 347
 Example 343	 Example 348
 Example 344	 Example 349
 Example 345	 Example 350



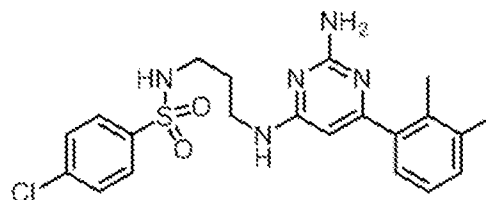
Example 351



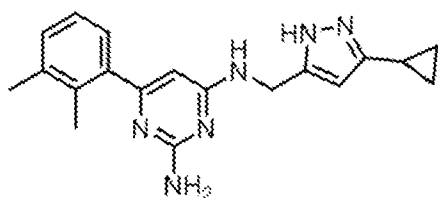
Example 356



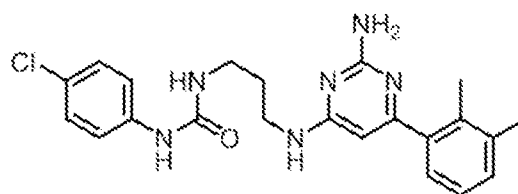
Example 352



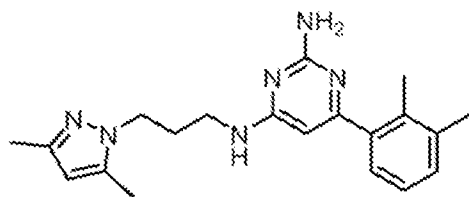
Example 357



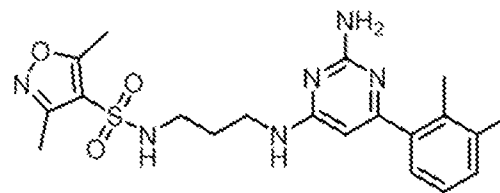
Example 353



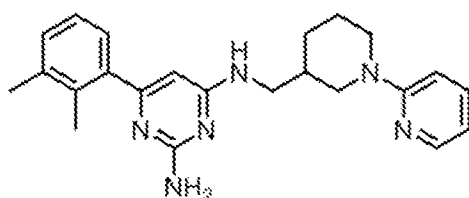
Example 358



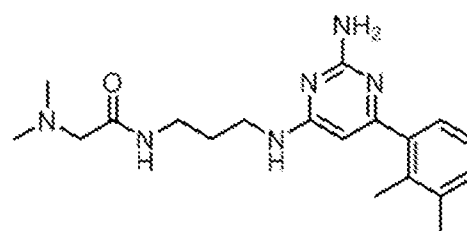
Example 354



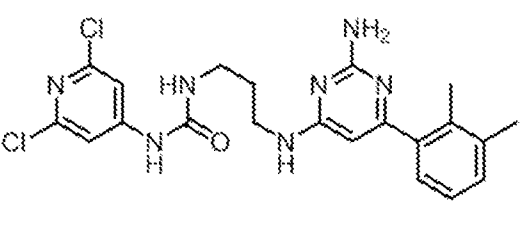
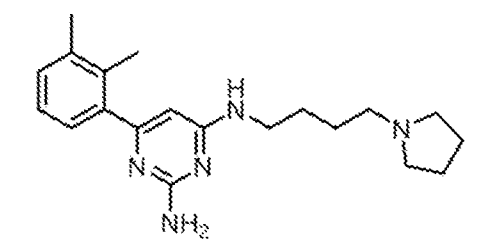
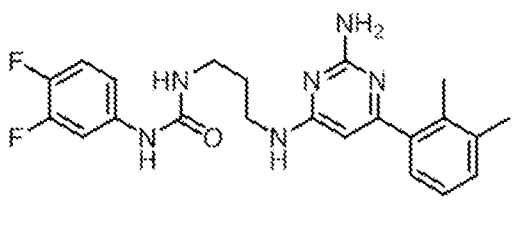
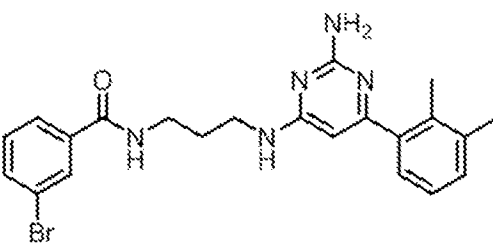
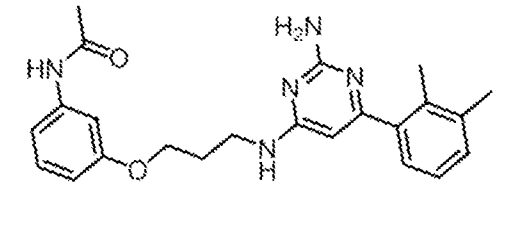
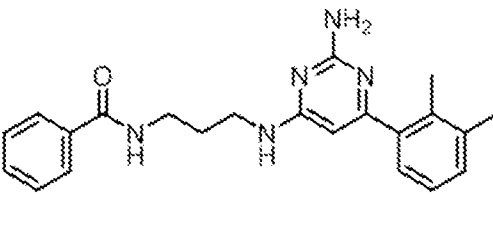
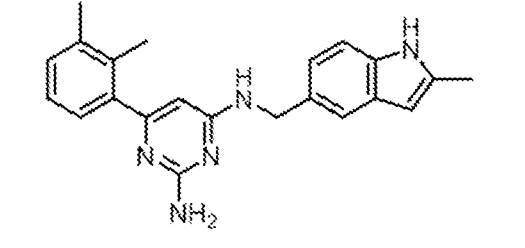
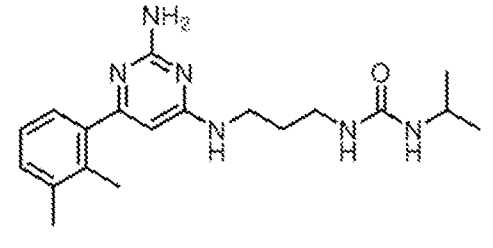
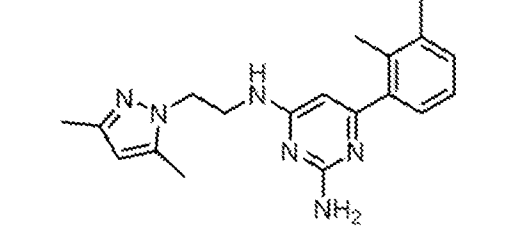
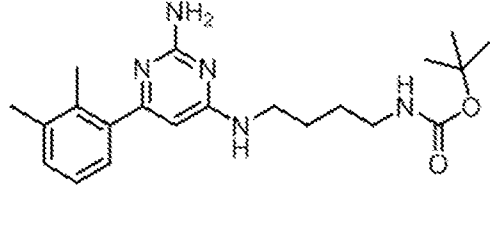
Example 359

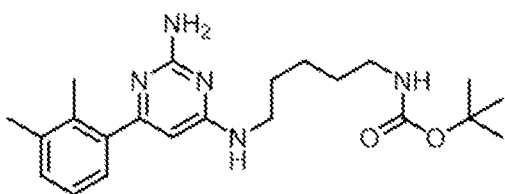


Example 355

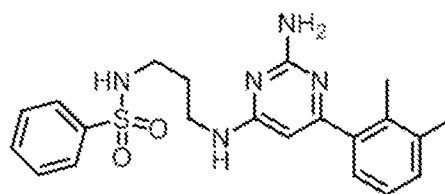


Example 360

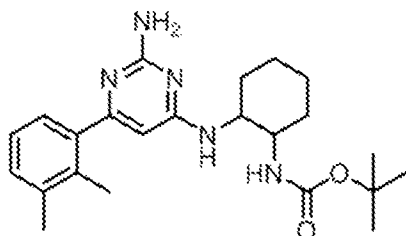
	
Example 361	Example 366
	
Example 362	Example 367
	
Example 363	Example 368
	
Example 364	Example 369
	
Example 365	Example 370



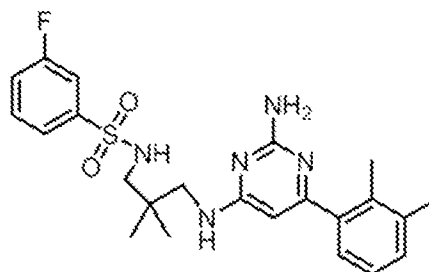
Example 371



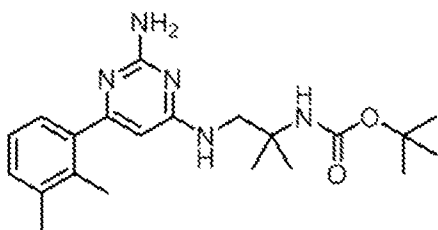
Example 376



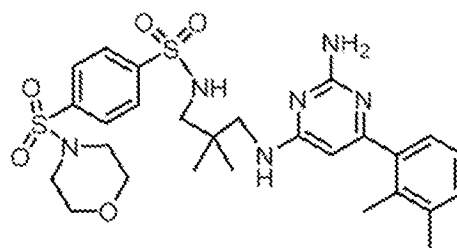
Example 372



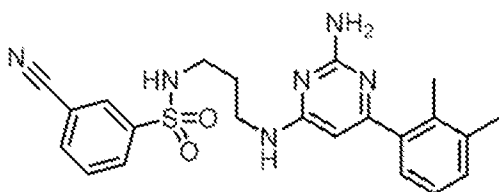
Example 377



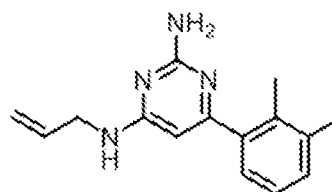
Example 373



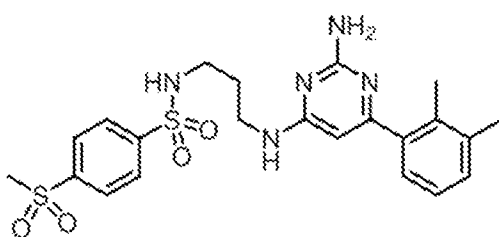
Example 378



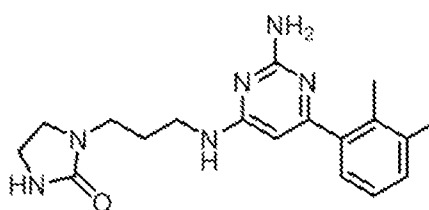
Example 374



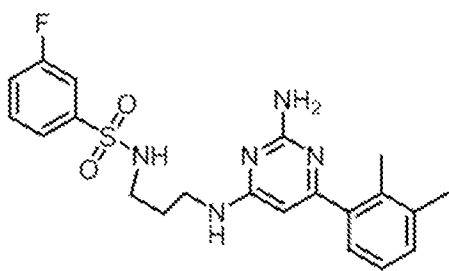
Example 379



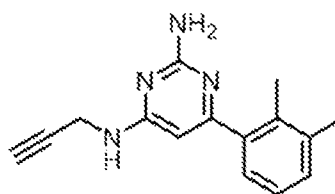
Example 375



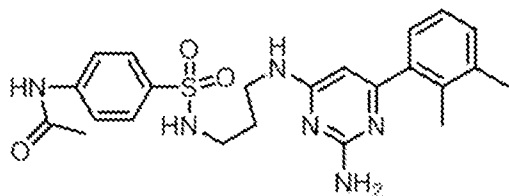
Example 380



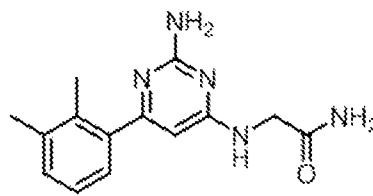
Example 381



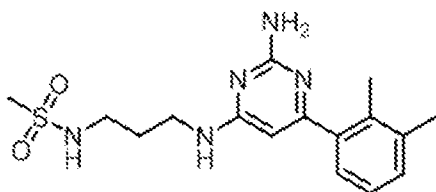
Example 386



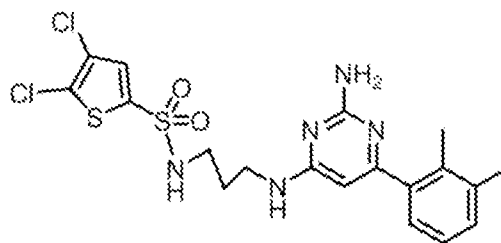
Example 382



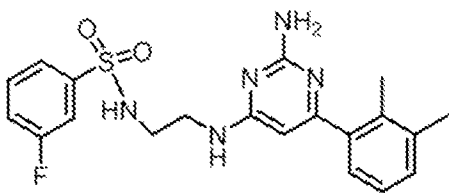
Example 387



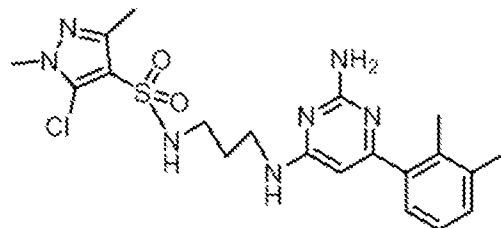
Example 383



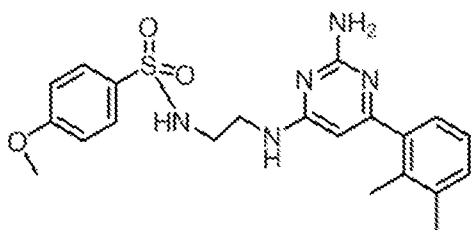
Example 388



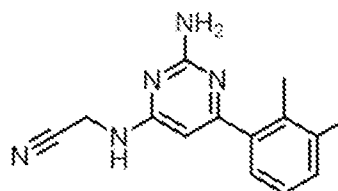
Example 384



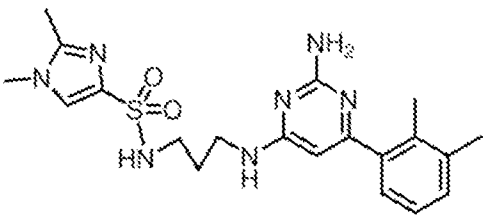
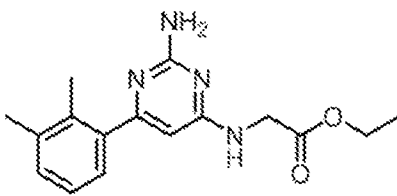
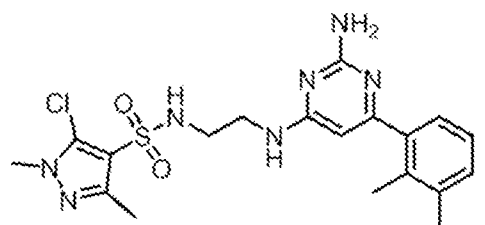
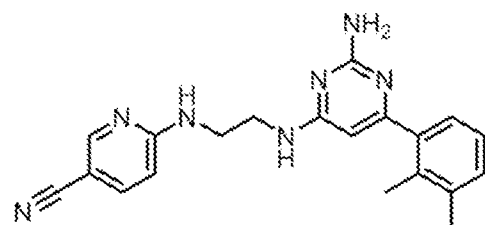
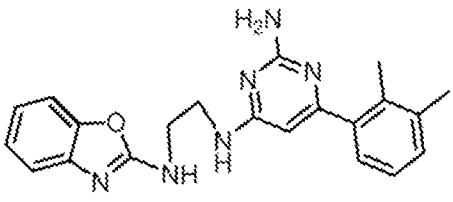
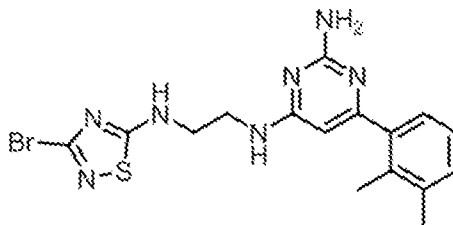
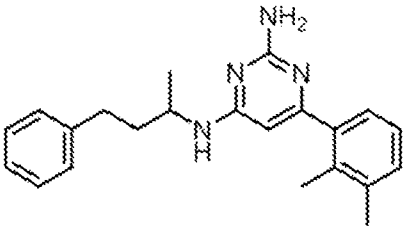
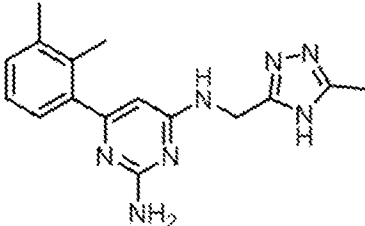
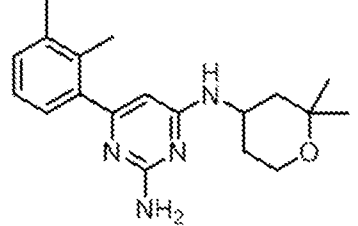
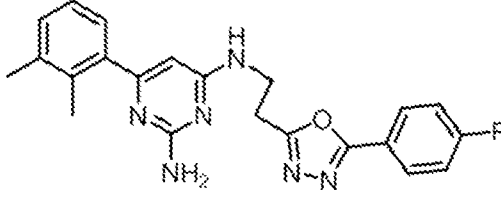
Example 389

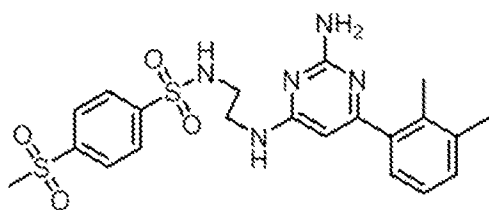


Example 385

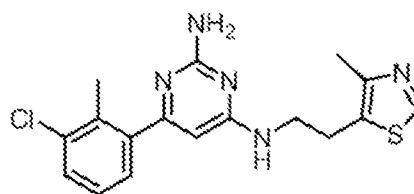


Example 390

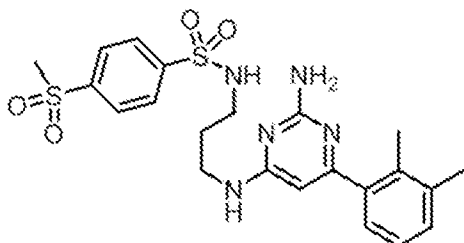
 <p>Example 391</p>	 <p>Example 396</p>
 <p>Example 392</p>	 <p>Example 397</p>
 <p>Example 393</p>	 <p>Example 398</p>
 <p>Example 394</p>	 <p>Example 399</p>
 <p>Example 395</p>	 <p>Example 400</p>



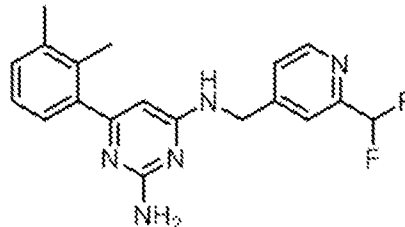
Example 401



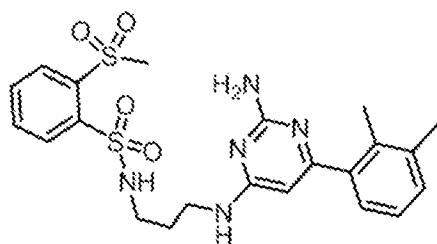
Example 406



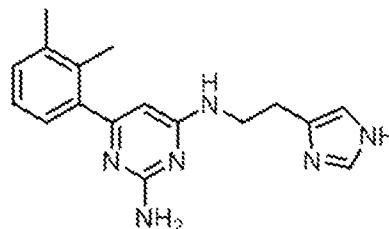
Example 402



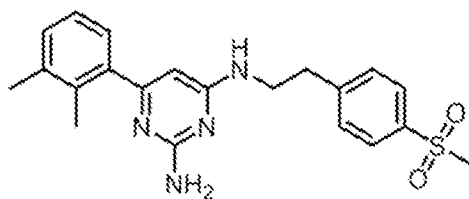
Example 407



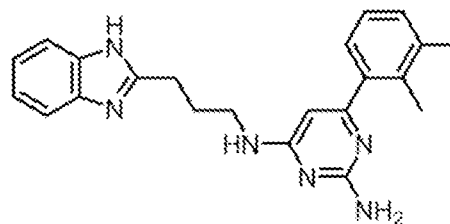
Example 403



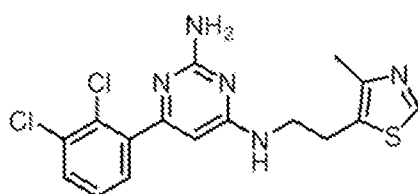
Example 408



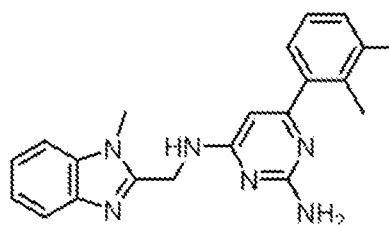
Example 404



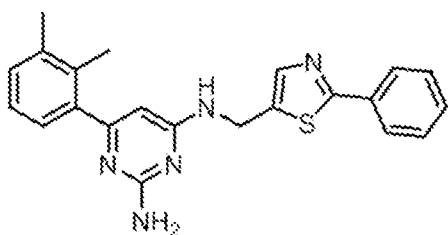
Example 409



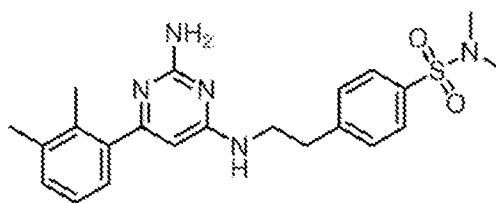
Example 405



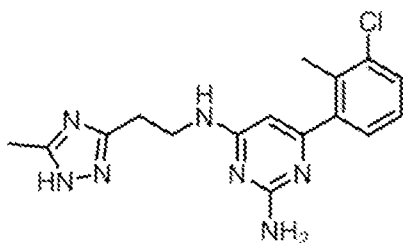
Example 410



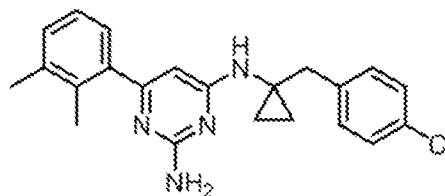
Example 411



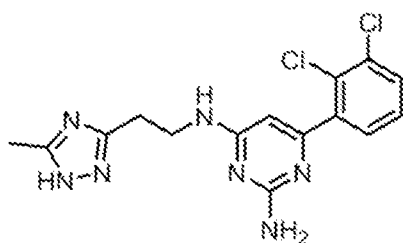
Example 416



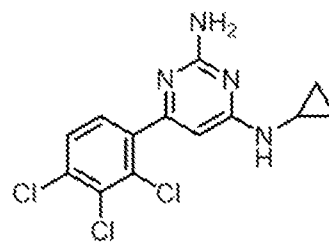
Example 412



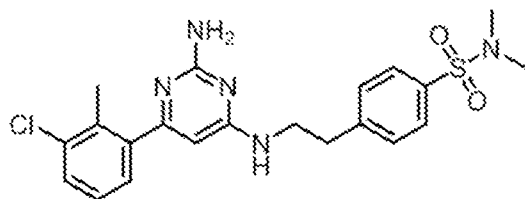
Example 417



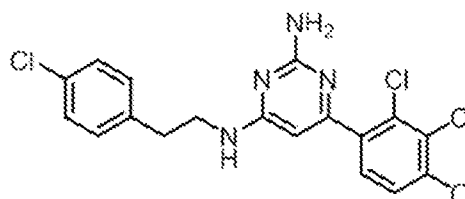
Example 413



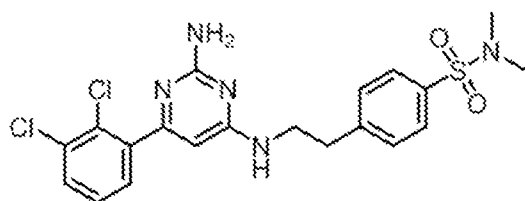
Example 418



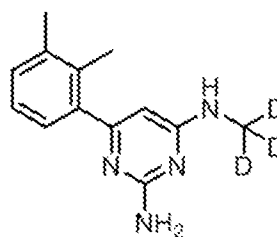
Example 414



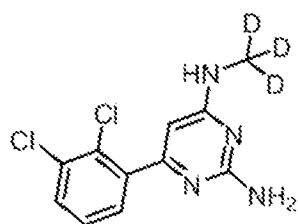
Example 419



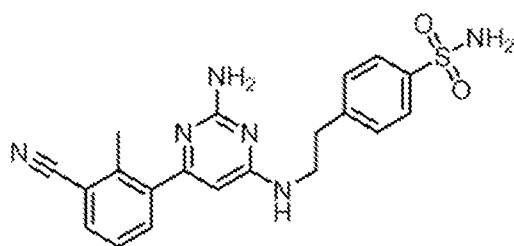
Example 415



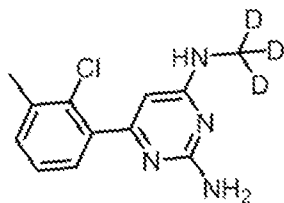
Example 420



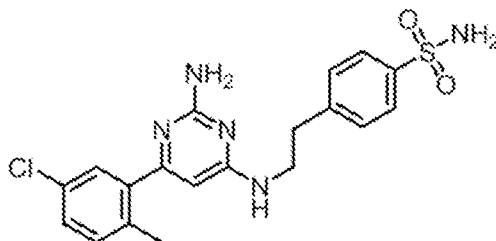
Example 421



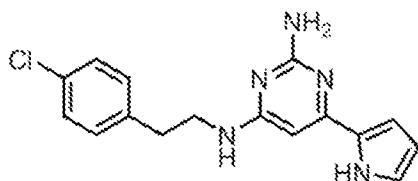
Example 426



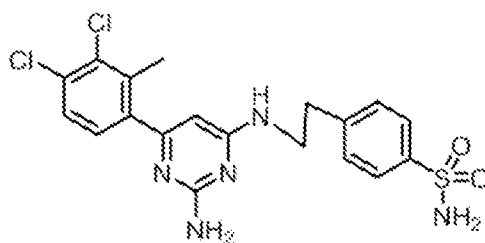
Example 422



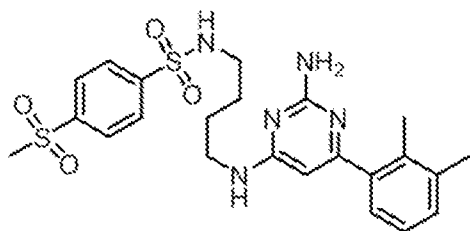
Example 427



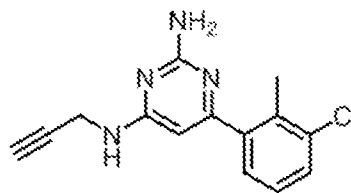
Example 423



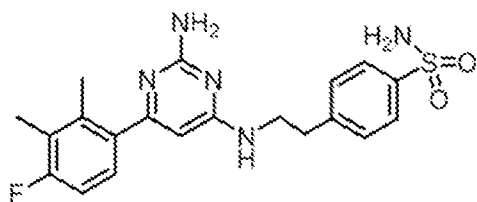
Example 428



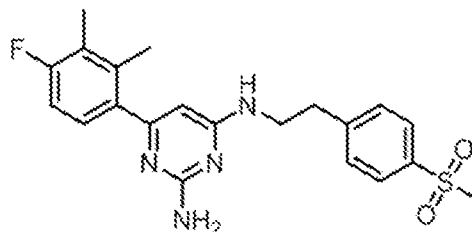
Example 424



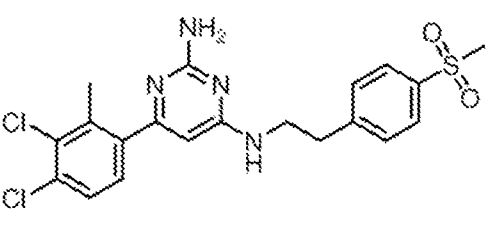
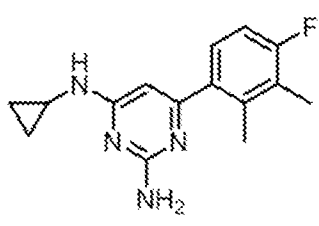
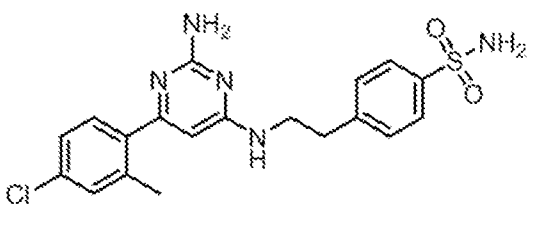
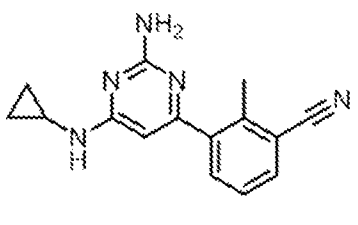
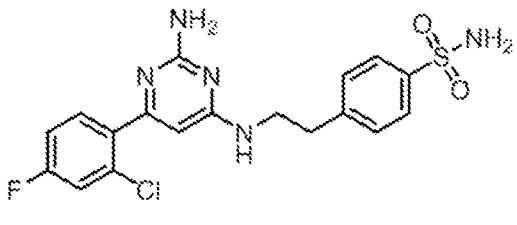
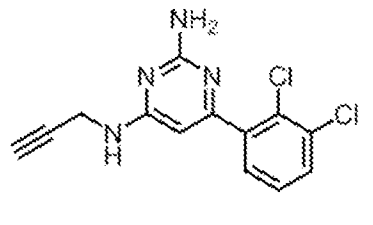
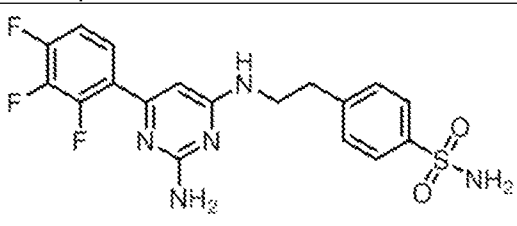
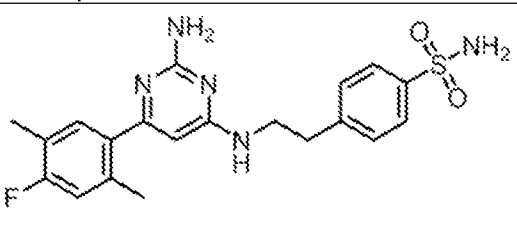
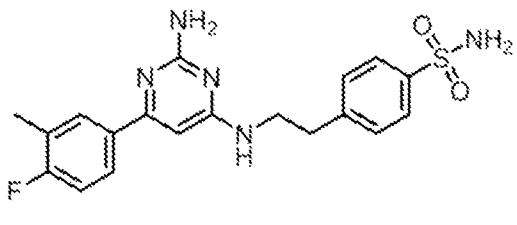
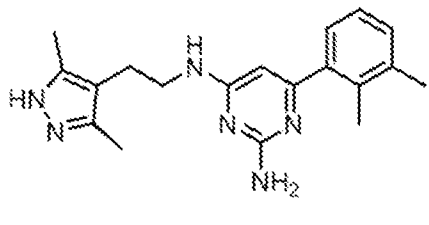
Example 429

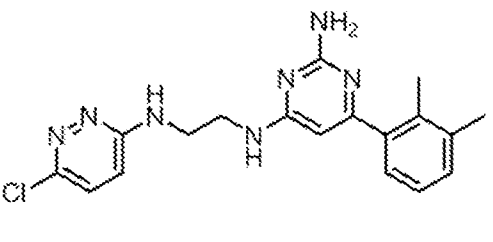
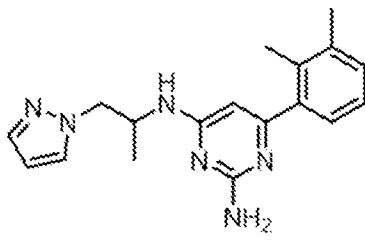
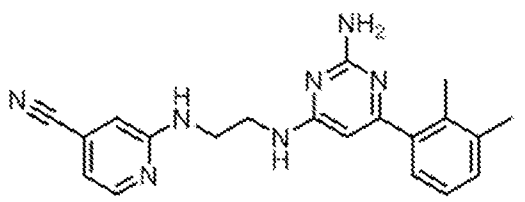
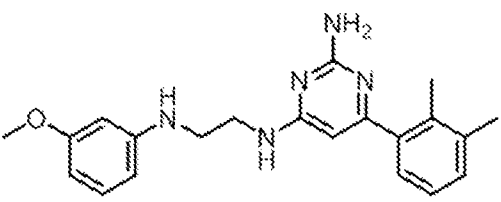
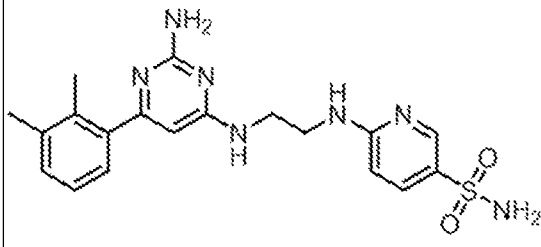
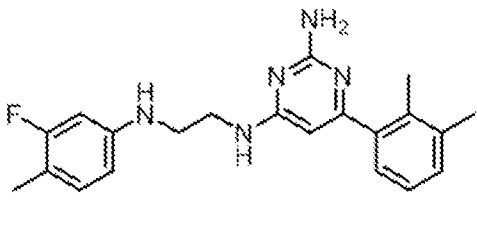
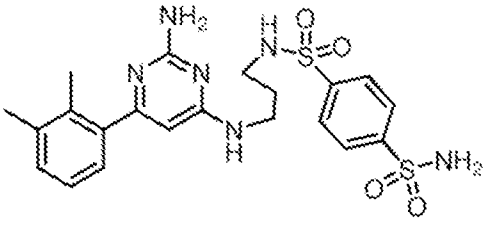
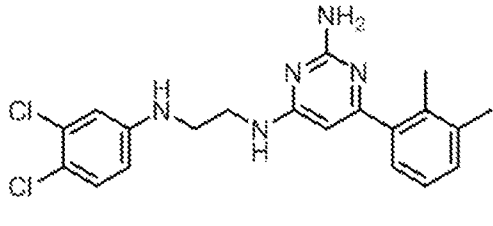
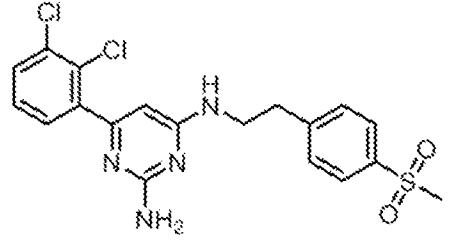
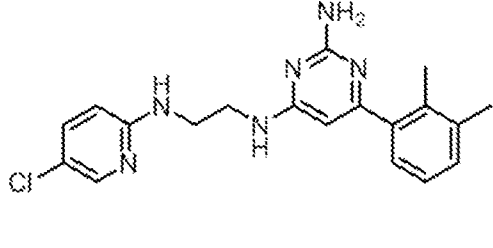


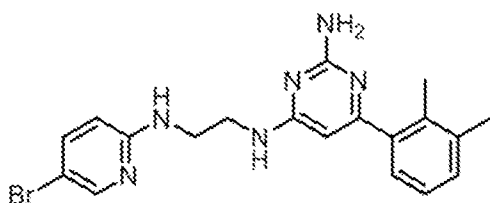
Example 425



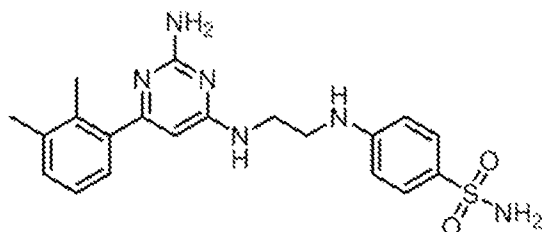
Example 430

	
Example 431	Example 436
	
Example 432	Example 437
	
Example 433	Example 438
	
Example 434	Example 439
	
Example 435	Example 440

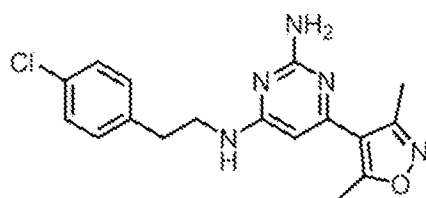
 <p>Chemical structure of Example 441: A pyrazole ring substituted with a chlorine atom at the 4-position and an amino group at the 3-position. The pyrazole is connected via a 1,3-bis(2-amino-4-methylphenyl)propan-2-ylidene group to another pyrazole ring, which is further substituted with an amino group at the 3-position and a 2,4-dimethylphenyl group at the 4-position.</p>	 <p>Chemical structure of Example 446: A pyrazole ring substituted with an amino group at the 3-position and a 2,4-dimethylphenyl group at the 4-position. The pyrazole is connected via a 1,3-bis(2-amino-4-methylphenyl)propan-2-ylidene group to another pyrazole ring, which is further substituted with an amino group at the 3-position and a 2,4-dimethylphenyl group at the 4-position.</p>
Example 441	Example 446
 <p>Chemical structure of Example 442: A pyrazole ring substituted with a cyano group at the 4-position and an amino group at the 3-position. The pyrazole is connected via a 1,3-bis(2-amino-4-methylphenyl)propan-2-ylidene group to another pyrazole ring, which is further substituted with an amino group at the 3-position and a 2,4-dimethylphenyl group at the 4-position.</p>	 <p>Chemical structure of Example 447: A pyrazole ring substituted with a methoxy group at the 4-position and an amino group at the 3-position. The pyrazole is connected via a 1,3-bis(2-amino-4-methylphenyl)propan-2-ylidene group to another pyrazole ring, which is further substituted with an amino group at the 3-position and a 2,4-dimethylphenyl group at the 4-position.</p>
Example 442	Example 447
 <p>Chemical structure of Example 443: A pyrazole ring substituted with an amino group at the 3-position and a 2,4-dimethylphenyl group at the 4-position. The pyrazole is connected via a 1,3-bis(2-amino-4-methylphenyl)propan-2-ylidene group to another pyrazole ring, which is further substituted with an amino group at the 3-position and a 2,4-dimethylphenyl group at the 4-position.</p>	 <p>Chemical structure of Example 448: A pyrazole ring substituted with a fluorine atom at the 4-position and an amino group at the 3-position. The pyrazole is connected via a 1,3-bis(2-amino-4-methylphenyl)propan-2-ylidene group to another pyrazole ring, which is further substituted with an amino group at the 3-position and a 2,4-dimethylphenyl group at the 4-position.</p>
Example 443	Example 448
 <p>Chemical structure of Example 444: A pyrazole ring substituted with an amino group at the 3-position and a 2,4-dimethylphenyl group at the 4-position. The pyrazole is connected via a 1,3-bis(2-amino-4-methylphenyl)propan-2-ylidene group to another pyrazole ring, which is further substituted with an amino group at the 3-position and a 2,4-dimethylphenyl group at the 4-position.</p>	 <p>Chemical structure of Example 449: A pyrazole ring substituted with a chlorine atom at the 4-position and an amino group at the 3-position. The pyrazole is connected via a 1,3-bis(2-amino-4-methylphenyl)propan-2-ylidene group to another pyrazole ring, which is further substituted with an amino group at the 3-position and a 2,4-dimethylphenyl group at the 4-position.</p>
Example 444	Example 449
 <p>Chemical structure of Example 445: A pyrazole ring substituted with a chlorine atom at the 4-position and an amino group at the 3-position. The pyrazole is connected via a 1,3-bis(2-amino-4-methylphenyl)propan-2-ylidene group to another pyrazole ring, which is further substituted with an amino group at the 3-position and a 2,4-dimethylphenyl group at the 4-position.</p>	 <p>Chemical structure of Example 450: A pyrazole ring substituted with an amino group at the 3-position and a 2,4-dimethylphenyl group at the 4-position. The pyrazole is connected via a 1,3-bis(2-amino-4-methylphenyl)propan-2-ylidene group to another pyrazole ring, which is further substituted with an amino group at the 3-position and a 2,4-dimethylphenyl group at the 4-position.</p>
Example 445	Example 450



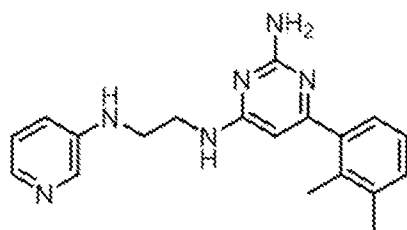
Example 451



Example 452



Example 453



Example 454

Biological Examples

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Biological Example 1

MTH1 enzymatic assay and IC50 value determination

MTH1 catalyzes the hydrolysis of dGTP to dGMP and PPi. By coupling the reaction to pyrophosphatase added in excess PPi is converted to Pi that can be

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detected by using the malachite green assay reagent. Briefly, for IC₅₀ value determination the compound to be analyzed is diluted in assay buffer in a 1:3 dilution series generating 12 different compound concentrations giving a final DMSO concentration of 1% in the assay well. MTH1 diluted in assay buffer (100 mM Tris-acetate, 40 mM NaCl, 10 mM magnesium acetate, 1 mM DTT and 0.005% Tween 20) fortified with *E.coli* pyrophosphatase (0.8 U/ml) is added to a final concentration of 4.8 nM. dGTP diluted in assay buffer is added to a final concentration of 100 μM. The reaction mixture is incubated with shaking for 15 minutes at 22°C. To 100 μl reaction mixture is 25 μl Malachite green assay reagent (0.095% Malachite green in 17% H₂SO₄, 1.5% Ammonium molybdate, 0.17% Tween 20) added followed by incubation with shaking for 15 minutes at 22°C. The absorbance of the assay plate is read at 630 nm using an EnVision Multilabel plate reader. The IC₅₀ value is determined by fitting a dose response curve to the data points using nonlinear regression analysis and the equation $Y = \text{Bottom} + (\text{Top} - \text{Bottom}) / (1 + 10^{((\text{LogIC}_{50} - X) * \text{HillSlope}))}$, where Y is the read absorbance at 630 nm and X is log[compound].

Using this approach the following representative IC₅₀ values were derived.

Examples – 4, 6, 11, 18, 31, 32, 35, 36, 40, 43, 44, 46, 51, 52, 55, 56, 57, 59, 64, 65, 66, 67, 72, 73, 74, 77, 79, 80, 81, 85, 87, 89, 90, 93, 97, 98, 101, 103, 105, 108, 110, 111, 115, 120, 126, 127, 129, 131, 132, 135, 141, 142, 144, 146, 148, 149, 151, 159, 164, 165, 168, 171, 173, 174, 175, 192, 197, 198, 201, 202, 203, 208, 209, 210, 211, 213, 215, 219, 220, 222, 226, 227, 228, 230, 231, 232, 244, 245, 246, 249, 252, 254, 256, 257, 259, 260, 264, 266, 267, 269, 273, 275, 276, 282, 295, 296, 300, 301, 304, 308, 312, 313, 315, 316, 317, 322, 323, 324, 326, 327, 329, 330, 331, 333, 334, 335, 336, 343, 346, 348, 349, 350, 351, 359, 361, 363, 367, 374, 376, 379, 381, 386, 389, 391, 397, 402, 403, 404, 405, 406, 408, 409, 411, 415, 416, 418, 419, 420, 422, 424, 426, 428, 429, 430, 432, 434, 436, 439, 443, 444, 445, 447, 451, 453, 454 had IC₅₀'s of less than 200 nM

30

Examples – 3, 8, 9, 10, 17, 22, 24, 25, 42, 45, 54, 60, 95, 96, 102, 113, 117, 119, 150, 154, 157, 160, 162, 169, 178, 186, 199, 212, 225, 229, 236, 238, 241, 242, 255, 265, 270, 272, 278, 284, 285, 286, 287, 288, 290, 291, 292, 293, 294, 298, 302, 306, 318, 319, 320, 339, 340, 347, 353, 354, 358, 360, 365, 366, 368, 369,

373, 377, 378, 380, 383, 384, 387, 390, 392, 395, 410, 413, 423, 446 had IC₅₀'s of between 200 nM and 2 µM

5 Examples – 5, 12, 14, 15, 20, 21, 78, 112, 161, 166, 167, 179, 180, 181, 182, 237, 277, 281, 289, 299, 345, 372, 396, 399 had IC₅₀'s of between 2 µM and 10 µM

Biological example 2: MTH1 siRNA knock down and cell survival

Cells were cultivated in suitable medium supplemented with 10% FBS and 10
10 U/ml PeSt. On day 1, cells were seeded at approximately 30% confluency in 6-well plates in complete medium. The day after, the medium was aspirated and fresh medium without antibiotics was added. The cells were transfected with All-stars Non-targeting RNA (NT RNA, Qiagen) and MTH1 siRNA (5'-CGACGACAGCUACUGGUUU-3') and Interferin (Polyplus) according to the
15 manufacturer's protocol. On day 5, cells were either trypsinized, counted and re-seeded for clonogenic outgrowth on 10-cm plates at 500 cells/plate or washed with PBS and scraped in lysis buffer (10 mM Hepes pH 7.1, 50 mM NaCl, 0.3 M sucrose, 0.1 mM EDTA, 0.5% Triton X100, 1 mM DTT and 1x protease inhib, cocktail (Pierce)) and processed for Western blot. Blots were stained with anti-
20 MTH1 antibody (rabbit polyclonal, HPA, KTH, Sweden) and anti-tubulin (mouse monoclonal, Sigma Aldrich). After additional 7-10 days, survival plates were fixed/stained with 4% methylene blue in MeOH and colonies were counted manually. Figure 1 shows the effect on cell survival following MTH1 siRNA depletion in various human cancer and normal cell lines.

25

Biological example 3: Cell survival assay

Cells are cultured in DMEM GlutaMAX™ or other suitable cell medium and plated in cell culture dishes (100 mm x 20 mm) (500 cells/dish) and incubated in 5% CO₂ at 37 °C. After 5 hours of incubation cells are treated with compound at various
30 concentrations and left in the incubator for 7-14 days dependent on cell line. Clonogenic survival is measured by fixating and staining the cells with methylene blue (4 g/L in methanol) and number of colonies are counted and compared to vehicle treated dishes. Figure 2 shows how an MTH1 inhibitor reduces cell survival in various cancer cell lines, with less effect on normal immortalised cells
35 (VH10 and BJ hTERT).

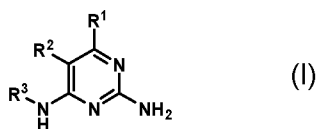
Biological example 4: Cell viability assay

Cells are seeded into 96 well plates (1500 cells/well) in DMEM GlutaMAX™ or other suitable media dependent on cell line and incubated overnight in 5% CO₂,
5 37 °C. Thereafter cells are treated with compound or vehicle and left in incubator for 3 days until staining with resazurin. Cells are incubated in resazurin (diluted in suitable media) at 37 °C for 2 hours before measuring the fluorescence.

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Claims

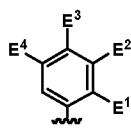
1. A compound of formula I,



5

or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, wherein:

10 R^1 represents heteroaryl connected to the pyrimidine of formula I via a carbon atom of the heteroaryl ring, which heteroaryl ring is optionally substituted by one or more substituents selected from Y^1 , $-C_{1-6}$ alkyl optionally substituted by one or more Y^2 and heterocycloalkyl optionally substituted by one or more Y^3 ; or aryl represented by



15 E^1 represents hydrogen, Y^{1a} , $-C_{1-6}$ alkyl optionally substituted by one or more Y^2 or heterocycloalkyl optionally substituted by one or more Y^3 ;

E^2 represents hydrogen, Y^{1b} , $-C_{1-6}$ alkyl optionally substituted by one or more Y^2 or heterocycloalkyl optionally substituted by one or more Y^3 ;

20 E^3 and E^4 each independently represents hydrogen, Y^1 , $-C_{1-6}$ alkyl optionally substituted by one or more Y^2 or heterocycloalkyl optionally substituted by one or more Y^3 ;

R^2 represents hydrogen, halogen, $-CN$, $-C_{1-12}$ alkyl optionally substituted by one or more Z^1 , or heterocycloalkyl optionally substituted by one or more Z^2 ;

25

R^3 represents $-C_{1-12}$ alkyl optionally substituted by one or more Z^1 or heterocycloalkyl optionally substituted by one or more Z^2 ; or

30 R^2 and R^3 are linked together to form, along with the atoms to which they are attached, a 5- to 8-membered non-aromatic ring, wherein the link formed by R^2 and R^3 is optionally substituted by one or more substituents selected from Z^3 and

-C₁₋₉alkyl optionally substituted by one or more Z⁴;

each Y¹ independently represents halogen, -CN, -C(O)R^a, -C(O)N(R^b)R^c,
 -C(O)OR^d, -N(R^e)R^f, -N(R^g)C(O)R^h, -N(Rⁱ)C(O)OR^j, -N(R^k)C(O)N(R^l)R^m, -NO₂,
 5 -N(Rⁿ)S(O)₂R^o, -OR^p, -OC(O)R^q, -OS(O)₂R^r, -S(O)_mR^s, -S(O)₂N(R^t)R^u,
 heterocycloalkyl optionally substituted by one or more substituents selected from
 W², aryl optionally substituted by one or more substituents selected from W³ or
 heteroaryl optionally substituted by one or more substituents selected from W³;

10 Y^{1a} represents halogen, -CN, -C(O)R^a, -C(O)N(R^b)R^c, -C(O)OR^d, -N(R^e)R^f,
 -N(R^g)C(O)R^h, -N(Rⁱ)C(O)OR^j, -N(R^k)C(O)N(R^l)R^m, -NO₂, -N(Rⁿ)S(O)₂R^o,
 -OR^{px}, -OC(O)R^q, -OS(O)₂R^r, -S(O)_mR^s, -S(O)₂N(R^t)R^u, heterocycloalkyl optionally
 substituted by one or more substituents selected from W², aryl optionally
 substituted by one or more substituents selected from W³ or heteroaryl optionally
 15 substituted by one or more substituents selected from W³;

Y^{1b} represents halogen, -CN, -C(O)R^a, -C(O)N(R^b)R^c, -C(O)OR^d, -N(R^e)R^f,
 -N(R^g)C(O)R^h, -N(Rⁱ)C(O)OR^j, -N(R^k)C(O)N(R^l)R^m, -NO₂, -N(Rⁿ)S(O)₂R^o,
 -OR^{py}, -OC(O)R^q, -OS(O)₂R^r, -S(O)_mR^s, -S(O)₂N(R^t)R^u, heterocycloalkyl optionally
 20 substituted by one or more substituents selected from W², aryl optionally
 substituted by one or more substituents selected from W³ or heteroaryl optionally
 substituted by one or more substituents selected from W³;

each R^a, R^b, R^c, R^d, R^e, R^g, R^h, Rⁱ, R^k, R^l, R^m, Rⁿ, R^p, R^q, R^s, R^t and R^u
 25 independently represents hydrogen, -C₁₋₆ alkyl optionally substituted by one or
 more substituents selected from W¹, heterocycloalkyl optionally substituted by
 one or more substituents selected from W², aryl optionally substituted by one or
 more substituents selected from W³, or heteroaryl optionally substituted by one or
 more substituents selected from W³; or

30 any two R^b and R^c, R^e and R^f, R^l and R^m and/or R^t and R^u are linked together to
 form, along with the nitrogen atom to which they are attached, a 3- to 8-
 membered monocyclic or bicyclic ring, which ring optionally contains one or two
 further heteroatoms and which ring optionally is substituted by one or more

substituents selected from W^2 , C_{1-3} alkyl optionally substituted by one or more substituents selected from W^1 , and =O;

- each R^f , R^j , R^o , R^r and R^{px} independently represents C_{1-6} alkyl optionally substituted by one or more substituents selected from W^1 , heterocycloalkyl optionally substituted by one or more substituents selected from W^2 , aryl optionally substituted by one or more substituents selected from W^3 or heteroaryl optionally substituted by one or more substituents selected from W^3 ;
- 10 R^{py} represents hydrogen, $-C_{2-6}$ alkyl optionally substituted by one or more substituents selected from W^1 , heterocycloalkyl optionally substituted by one or more substituents selected from W^2 , aryl optionally substituted by one or more substituents selected from W^3 , or heteroaryl optionally substituted by one or more substituents selected from W^3 ;

- 15 each Y^2 independently represents halogen, $-CN$, $-C(O)R^{b1}$, $-C(O)N(R^{c1})R^{d1}$, $-C(O)OR^{e1}$, $-N(R^{f1})R^{g1}$, $-N(R^{h1})C(O)R^{i1}$, $-N(R^{j1})C(O)OR^{k1}$, $-N(R^{l1})C(O)N(R^{m1})R^{n1}$, $-N(R^{o1})S(O)_2R^{p1}$, $-OR^{q1}$, $-OC(O)R^{r1}$, $-OS(O)_2R^{s1}$, $-S(O)_mR^{t1}$, $-S(O)_2N(R^{u1})R^{v1}$, heterocycloalkyl optionally substituted by one or more substituents selected from W^1 , aryl optionally substituted by one or more substituents selected from W^2 , heteroaryl optionally substituted by one or more substituents selected from W^2 , or =O;

- 25 each Y^3 independently represents halogen, $-R^{a1}$, $-CN$, $-C(O)R^{b1}$, $-C(O)N(R^{c1})R^{d1}$, $-C(O)OR^{e1}$, $-N(R^{f1})R^{g1}$, $-N(R^{h1})C(O)R^{i1}$, $-N(R^{j1})C(O)OR^{k1}$, $-N(R^{l1})C(O)N(R^{m1})R^{n1}$, $-N(R^{o1})S(O)_2R^{p1}$, $-OR^{q1}$, $-OC(O)R^{r1}$, $-OS(O)_2R^{s1}$, $-S(O)_mR^{t1}$, $-S(O)_2N(R^{u1})R^{v1}$, heterocycloalkyl optionally substituted by one or more substituents selected from W^1 , aryl optionally substituted by one or more substituents selected from W^2 , heteroaryl optionally substituted by one or more substituents selected from W^2 , or =O;
- 30

- each R^{a1} , R^{b1} , R^{c1} , R^{d1} , R^{e1} , R^{f1} , R^{h1} , R^{i1} , R^{j1} , R^{l1} , R^{m1} , R^{n1} , R^{o1} , R^{q1} , R^{r1} , R^{t1} , R^{u1} and R^{v1} independently represents hydrogen, C_{1-6} alkyl optionally substituted by one or more substituents selected from W^1 , heterocycloalkyl optionally substituted by one or more substituents selected from W^2 , aryl optionally substituted by one
- 35

or more substituents selected from W^3 , or heteroaryl optionally substituted by one or more substituents selected from W^3 ; or

any two R^{c1} and R^{d1} , R^{f1} and R^{g1} , R^{m1} and R^{n1} and/or R^{u1} and R^{v1} are linked together to form, along with the nitrogen atom to which they are attached, a 3- to 8-membered monocyclic or bicyclic ring, which ring optionally contains one or two heteroatoms and which ring optionally is substituted by one or more substituents selected from W^2 , C_{1-3} alkyl optionally substituted by one or more substituents selected from W^1 , and $=O$;

10

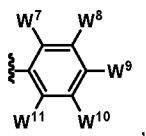
each R^{g1} , R^{k1} , R^{p1} and R^{s1} independently represents $-C_{1-6}$ alkyl optionally substituted by one or more substituents selected from W^1 , heterocycloalkyl optionally substituted by one or more substituents selected from W^2 , aryl optionally substituted by one or more substituents selected from W^3 , or heteroaryl optionally substituted by one or more substituents selected from W^3 ;

15

each Z^1 independently represents halogen, $-CN$, $-C(O)R^{b2}$, $-C(O)N(R^{c2})R^{d2}$, $-C(O)OR^{e2}$, $-N(R^{f2})R^{g2}$, $-N(R^{h2})C(O)R^{i2}$, $-N(R^{j2})C(O)OR^{k2}$, $-N(R^{l2})C(O)N(R^{m2})R^{n2}$, $-N(R^{o2})S(O)_2R^{p2}$, $-OR^{q2}$, $-OC(O)R^{r2}$, $-OS(O)_2R^{s2}$, $-S(O)_mR^{l2}$, $-S(O)_2N(R^{u2})R^{v2}$,

20

heterocycloalkyl optionally substituted by one or more substituents selected from W^5 , aryl represented by



heteroaryl having 1 to 3 nitrogen atoms, one oxygen atom and/or one sulfur atom and optionally substituted by one or more substituents selected from W^6 , or $=O$;

25

each Z^2 and Z^3 independently represents halogen, $-R^{a2}$, $-CN$, $-C(O)R^{b2}$, $-C(O)N(R^{c2})R^{d2}$, $-C(O)OR^{e2}$, $-N(R^{f2})R^{g2}$, $-N(R^{h2})C(O)R^{i2}$, $-N(R^{j2})C(O)OR^{k2}$, $-N(R^{l2})C(O)N(R^{m2})R^{n2}$, $-N(R^{o2})S(O)_2R^{p2}$, $-OR^{q2}$, $-OC(O)R^{r2}$, $-OS(O)_2R^{s2}$, $-S(O)_mR^{l2}$, $-S(O)_2N(R^{u2})R^{v2}$, heterocycloalkyl optionally substituted by one or more

30

substituents selected from W^5 , aryl optionally substituted by one or more substituents selected from W^6 , or heteroaryl optionally substituted by one or more substituents selected from W^6 ;

each Z^4 independently represents halogen, $-\text{CN}$, $-\text{C}(\text{O})\text{R}^{b2}$, $-\text{C}(\text{O})\text{N}(\text{R}^{c2})\text{R}^{d2}$,
 $-\text{C}(\text{O})\text{OR}^{e2}$, $-\text{N}(\text{R}^{f2})\text{R}^{g2}$, $-\text{N}(\text{R}^{h2})\text{C}(\text{O})\text{R}^{i2}$, $-\text{N}(\text{R}^{j2})\text{C}(\text{O})\text{OR}^{k2}$, $-\text{N}(\text{R}^{l2})\text{C}(\text{O})\text{N}(\text{R}^{m2})\text{R}^{n2}$,
 $-\text{N}(\text{R}^{o2})\text{S}(\text{O})_2\text{R}^{p2}$, $-\text{OR}^{q2}$, $-\text{OC}(\text{O})\text{R}^{r2}$, $-\text{OS}(\text{O})_2\text{R}^{s2}$, $-\text{S}(\text{O})_m\text{R}^{l2}$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{u2})\text{R}^{v2}$,
heterocycloalkyl optionally substituted by one or more substituents selected from
5 W^5 , aryl optionally substituted by one or more substituents selected from W^6 ,
heteroaryl optionally substituted by one or more substituents selected from W^6 , or
 $=\text{O}$;

each R^{a2} , R^{b2} , R^{c2} , R^{d2} , R^{e2} , R^{f2} , R^{h2} , R^{i2} , R^{j2} , R^{l2} , R^{m2} , R^{n2} , R^{o2} , R^{r2} , R^{t2} , R^{u2} and
10 R^{v2} independently represents hydrogen, C_{1-6} alkyl optionally substituted by one or
more substituents selected from W^4 , heterocycloalkyl optionally substituted by
one or more substituents selected from W^5 , aryl optionally substituted by one or
more substituents selected from W^6 , or heteroaryl optionally substituted by one or
more substituents selected from W^6 ; or

15 any two R^{c2} and R^{d2} , R^{f2} and R^{g2} , R^{m2} and R^{n2} and/or R^{u2} and R^{v2} are linked
together to form, along with the nitrogen atom to which they are attached, a 3- to
8-membered monocyclic or bicyclic ring, which ring optionally contains one or two
heteroatoms and which ring optionally is substituted by one or more substituents
20 selected from W^5 , C_{1-3} alkyl optionally substituted by one or more substituents
selected from W^4), and $=\text{O}$;

each R^{g2} , R^{k2} , R^{p2} , R^{q2} and R^{s2} independently represents C_{1-6} alkyl optionally
substituted by one or more substituents selected from W^4 , heterocycloalkyl
25 optionally substituted by one or more substituents selected from W^5 , aryl
optionally substituted by one or more substituents selected from W^6 , or heteroaryl
optionally substituted by one or more substituents selected from W^6 ;

each W^1 and W^4 independently represents halogen, $-\text{CN}$, $-\text{N}(\text{R}^{f3})\text{R}^{g3}$,
30 $-\text{N}(\text{R}^{h3})\text{C}(\text{O})\text{R}^{i3}$, $-\text{N}(\text{R}^{j3})\text{C}(\text{O})\text{OR}^{k3}$, $-\text{N}(\text{R}^{l3})\text{C}(\text{O})\text{N}(\text{R}^{m3})\text{R}^{n3}$, $-\text{N}(\text{R}^{o3})\text{S}(\text{O})_2\text{R}^{p3}$, $-\text{OR}^{q3}$,
 $-\text{OC}(\text{O})\text{R}^{r3}$, $-\text{OS}(\text{O})_2\text{R}^{s3}$, $-\text{S}(\text{O})_m\text{R}^{t3}$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{u3})\text{R}^{v3}$, heterocycloalkyl optionally
substituted by one or more substituents selected from G^1 , aryl optionally
substituted by one or more substituents selected from G^2 , heteroaryl optionally
substituted by one or more substituents selected from G^2 , or $=\text{O}$;

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each W^2 , W^3 , W^5 and W^6 independently represents halogen, $-R^{a3}$, $-\text{CN}$, $-\text{C}(\text{O})\text{R}^{b3}$, $-\text{C}(\text{O})\text{N}(\text{R}^{c3})\text{R}^{d3}$, $-\text{C}(\text{O})\text{OR}^{e3}$, $-\text{N}(\text{R}^{f3})\text{R}^{g3}$, $-\text{N}(\text{R}^{h3})\text{C}(\text{O})\text{R}^{i3}$, $-\text{N}(\text{R}^{j3})\text{C}(\text{O})\text{OR}^{k3}$, $-\text{N}(\text{R}^{l3})\text{C}(\text{O})\text{N}(\text{R}^{m3})\text{R}^{n3}$, $-\text{N}(\text{R}^{o3})\text{S}(\text{O})_2\text{R}^{p3}$, $-\text{OR}^{q3}$, $-\text{OC}(\text{O})\text{R}^{r3}$, $-\text{OS}(\text{O})_2\text{R}^{s3}$, $-\text{S}(\text{O})_m\text{R}^{t3}$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{u3})\text{R}^{v3}$, heterocycloalkyl optionally substituted by one or more

5 substituents selected from G^1 , aryl optionally substituted by one or more substituents selected from G^2 , heteroaryl (optionally substituted by one or more substituents selected from G^2 , or $=\text{O}$;

each W^7 , W^8 , W^{10} and W^{11} independently represents hydrogen, halogen, $-R^{a3}$, $-\text{CN}$, $-\text{C}(\text{O})\text{R}^{b3}$, $-\text{C}(\text{O})\text{N}(\text{R}^{c3})\text{R}^{d3}$, $-\text{C}(\text{O})\text{OR}^{e3}$, $-\text{N}(\text{R}^{f3})\text{R}^{g3}$, $-\text{N}(\text{R}^{h3})\text{C}(\text{O})\text{R}^{i3}$, $-\text{N}(\text{R}^{j3})\text{C}(\text{O})\text{OR}^{k3}$, $-\text{N}(\text{R}^{l3})\text{C}(\text{O})\text{N}(\text{R}^{m3})\text{R}^{n3}$, $-\text{N}(\text{R}^{o3})\text{S}(\text{O})_2\text{R}^{p3}$, $-\text{OR}^{q3}$, $-\text{OC}(\text{O})\text{R}^{r3}$, $-\text{OS}(\text{O})_2\text{R}^{s3}$, $-\text{S}(\text{O})_m\text{R}^{t3}$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{u3})\text{R}^{v3}$, heterocycloalkyl optionally substituted by one or more substituents selected from G^1 , aryl optionally substituted by one or more substituents selected from G^2 , or heteroaryl optionally substituted by one or

10 more substituents selected from G^2 ;

15 more substituents selected from G^2 ;

W^9 represents hydrogen, halogen, $-R^{a3}$, $-\text{CN}$, $-\text{C}(\text{O})\text{R}^{b3}$, $-\text{C}(\text{O})\text{N}(\text{R}^{c3})\text{R}^{d3}$, $-\text{C}(\text{O})\text{OR}^{e3}$, $-\text{N}(\text{R}^{f3})\text{R}^{g3}$, $-\text{N}(\text{R}^{h3})\text{C}(\text{O})\text{R}^{i3}$, $-\text{N}(\text{R}^{j3})\text{C}(\text{O})\text{OR}^{k3}$, $-\text{N}(\text{R}^{l3})\text{C}(\text{O})\text{N}(\text{R}^{m3})\text{R}^{n3}$, $-\text{N}(\text{R}^{o3})\text{S}(\text{O})_2\text{R}^{p3}$, $-\text{OR}^{q3x}$, $-\text{OC}(\text{O})\text{R}^{r3}$, $-\text{OS}(\text{O})_2\text{R}^{s3}$, $-\text{S}(\text{O})_m\text{R}^{t3}$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{u3})\text{R}^{v3}$,

20 heterocycloalkyl optionally substituted by one or more substituents selected from G^1 , aryl optionally substituted by one or more substituents selected from G^2 , or heteroaryl optionally substituted by one or more substituents selected from G^2 ;

each R^{a3} , R^{b3} , R^{c3} , R^{d3} , R^{e3} , R^{f3} , R^{h3} , R^{i3} , R^{j3} , R^{l3} , R^{m3} , R^{n3} , R^{o3} , R^{q3} , R^{r3} , R^{t3} , R^{u3} and R^{v3} independently represents hydrogen or C_{1-6} alkyl optionally substituted by one or more G^3 ; or

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any two R^{c3} and R^{d3} , R^{f3} and R^{g3} , R^{m3} and R^{n3} and/or R^{u3} and R^{v3} are linked together to form, along with the nitrogen atom to which they are attached, a 4- to

30 6-membered ring, which ring optionally contains one heteroatom and which ring optionally is substituted by one or more G^2 ;

each R^{g3} , R^{k3} , R^{p3} , R^{q3} and R^{s3} independently represents C_{1-6} alkyl optionally substituted by one or more G^3 ;

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R^{q3x} represents C_{2-6} alkyl optionally substituted by one or more G^3 ;

each G^1 and G^2 independently represents halogen, $-R^{a4}$, $-\text{CN}$, $-\text{C}(\text{O})R^{b4}$,
 $-\text{C}(\text{O})N(R^{c4})R^{d4}$, $-\text{C}(\text{O})OR^{e4}$, $-N(R^{f4})R^{g4}$, $-N(R^{h4})\text{C}(\text{O})R^{i4}$, $-N(R^{j4})\text{C}(\text{O})OR^{k4}$,
 5 $-N(R^{l4})\text{C}(\text{O})N(R^{m4})R^{n4}$, $-N(R^{o4})\text{S}(\text{O})_2R^{p4}$, $-\text{OR}^{q4}$, $-\text{OC}(\text{O})R^{r4}$, $-\text{OS}(\text{O})_2R^{s4}$, $-\text{S}(\text{O})_mR^{t4}$,
 $-\text{S}(\text{O})_2N(R^{u4})R^{v4}$, or $=\text{O}$;

G^3 represents halogen, $-\text{CN}$, $-\text{C}(\text{O})R^{b4}$, $-\text{C}(\text{O})N(R^{c4})R^{d4}$, $-\text{C}(\text{O})OR^{e4}$, $-N(R^{f4})R^{g4}$,
 $-N(R^{h4})\text{C}(\text{O})R^{i4}$, $-N(R^{j4})\text{C}(\text{O})OR^{k4}$, $-N(R^{l4})\text{C}(\text{O})N(R^{m4})R^{n4}$, $-N(R^{o4})\text{S}(\text{O})_2R^{p4}$, $-\text{OR}^{q4}$,
 10 $-\text{OC}(\text{O})R^{r4}$, $-\text{OS}(\text{O})_2R^{s4}$, $-\text{S}(\text{O})_mR^{t4}$, $-\text{S}(\text{O})_2N(R^{u4})R^{v4}$, or $=\text{O}$;

each R^{a4} , R^{b4} , R^{c4} , R^{d4} , R^{e4} , R^{f4} , R^{h4} , R^{i4} , R^{j4} , R^{l4} , R^{m4} , R^{n4} , R^{o4} , R^{q4} , R^{r4} , R^{t4} , R^{u4}
 and R^{v4} independently represents hydrogen or C_{1-6} alkyl optionally substituted by
 one or more $-\text{F}$; or

15 any two R^{c4} and R^{d4} , R^{f4} and R^{g4} , R^{m4} and R^{n4} and/or R^{u4} and R^{v4} are linked
 together to form, along with the nitrogen atom to which they are attached, a 3- to
 6-membered ring, which ring optionally substituted by one or more $-\text{F}$, $-\text{CH}_3$,
 $-\text{CH}_2\text{CH}_3$, $-\text{CHF}_2$, $-\text{CF}_3$, $-\text{CH}_2\text{CF}_3$, or $=\text{O}$;

20 each R^{g4} , R^{k4} , R^{p4} and R^{s4} independently represent C_{1-6} alkyl optionally
 substituted by one or more $-\text{F}$;

each m independently represents 0, 1 or 2;

25 provided that the compound is not
 6-(3-pyridinyl)- N^4 -[[4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]methyl]-2,4-
 pyrimidinediamine,
 6-(3-pyridinyl)- N^4 -[[5-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]-2-pyridinyl]methyl]-
 30 2,4-pyrimidinediamine,
 6-(3-pyridinyl)- N^4 -[[5-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]-2-pyridinyl]-
 methyl]-2,4-pyrimidinediamine or
 N^4 -[2-(1-aziridinyl)ethyl]-5-fluoro-6-phenyl-2,4-pyrimidinediamine.

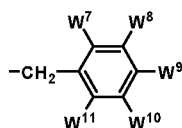
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2. A compound for use as claimed in Claim 1, wherein:
 R^2 represents hydrogen, halogen, -CN or -C₁₋₁₂alkyl optionally substituted by one or more Z^1 ; and
 R^3 represents -C₁₋₁₂alkyl optionally substituted by one or more Z^1 or
 5 heterocycloalkyl optionally substituted by one or more Z^2 .

3. A compound for use as claimed in Claim 2, wherein:
 R^2 represents hydrogen, -CN or -C₁₋₃alkyl optionally substituted by one or more -F; and
 10 R^3 represents -C₂₋₆alkyl optionally substituted by one or more Z^1 or heterocycloalkyl optionally substituted by one or more Z^2 .

4. A compound for use as claimed in Claim 3, wherein:
 R^2 represents hydrogen; and
 15 R^3 represents a -C₃₋₆alkyl or a heterocycloalkyl selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclopropylethyl, cyclobutylethyl, cyclopropylpropyl, oxetanyl, tetrahydrofuryl, tetrahydropyranyl, azetidiny, pyrrolidinyl, piperidinyl, piperazinyl or morpholinyl wherein the C₃₋₆alkyl is optionally substituted by one or more Z^1
 20 and the heterocycloalkyl is optionally substituted by one or more Z^2 .

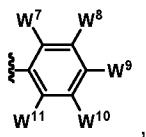
5. A compound for use as claimed in Claim 2, wherein:
 R^2 represents hydrogen and R^3 represents



- 25 or heteroaryl (having 1 to 3 nitrogen atoms, one oxygen atom and/or one sulfur atom and optionally substituted by one or more substituents selected from W^3).

6. A compound for use as claimed in any one of Claims 1 to 5 wherein:
 Z^1 represents -F, -CN, -C(O) R^{b2} , -C(O) $N(R^{c2})R^{d2}$, -C(O) OR^{e2} , - $N(R^{f2})R^{g2}$,
 30 - $N(R^{h2})C(O)R^{i2}$, - $N(R^{j2})C(O)OR^{k2}$, - $N(R^{l2})C(O)N(R^{m2})R^{n2}$, - $N(R^{o2})S(O)_2R^{p2}$, - OR^{q2} ,
 - $S(O)_mR^{l2}$, - $S(O)_2N(R^{u2})R^{v2}$, heterocycloalkyl selected from dihydropyridinyl, morpholinyl, piperazinyl, piperidinyl and pyrrolidinyl which heterocycloalkyl is

optionally substituted by one or more substituents selected from W^5 , aryl represented by



heteroaryl selected from benzimidazolyl, benzodioxinyl, benzoxazolyl, furanyl,

- 5 imidazolyl, imidazopyridinyl, indolyl, isoquinolinyl, oxadiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridyl, pyrrolopyridinyl, quinolinyl, thiazolyl, thiophenyl and triazolyl, which heteroaryl is optionally substituted by one or more substituents selected from W^6 ;

- 10 Z^2 represents $-F$, $-R^{a2}$, $-C(O)N(R^{c2})R^{d2}$, $-N(R^{f2})R^{g2}$, $-N(R^{h2})C(O)R^{i2}$, $-N(R^{j2})C(O)OR^{k2}$, $-N(R^{l2})C(O)N(R^{m2})R^{n2}$, $-N(R^{o2})S(O)_2R^{p2}$, $-OR^{q2}$, $-S(O)_mR^{t2}$, $-S(O)_2N(R^{u2})R^{v2}$, heterocycloalkyl optionally substituted by one or more substituents selected from W^5 , aryl optionally substituted by one or more substituents selected from W^6 , or heteroaryl optionally substituted by one or more substituents selected from W^6 ;

each W^7 , W^{10} and W^{11} independently represents hydrogen, halogen, $-R^{a3}$ or $-CN$; and

- one of W^8 and W^9 represents hydrogen, halogen, $-R^{a3}$ or $-CN$ and the other represents halogen, $-R^{a3}$, $-CN$, $-C(O)R^{b3}$, $-C(O)N(R^{c3})R^{d3}$, $-C(O)OR^{e3}$, $-N(R^{f3})R^{g3}$,
 20 $-N(R^{h3})C(O)R^{i3}$, $-N(R^{j3})C(O)OR^{k3}$, $-N(R^{l3})C(O)N(R^{m3})R^{n3}$, $-N(R^{o3})S(O)_2R^{p3}$, $-OR^{q3x}$, $-OC(O)R^{r3}$, $-OS(O)_2R^{s3}$, $-S(O)_mR^{t3}$, $-S(O)_2N(R^{u3})R^{v3}$, heterocycloalkyl optionally substituted by one or more substituents selected from G^1 , aryl optionally substituted by one or more substituents selected from G^2 , or heteroaryl optionally substituted by one or more substituents selected from G^2 .

25

7. A compound for use as claimed in Claim 2, wherein:

R^2 represents hydrogen; and

R^3 represents $-C_{1-2}$ alkyl optionally substituted with one or more $-F$.

- 30 8. A compound for use as claimed in Claim 1, wherein:

R^2 and R^3 are linked together to form, along with the atoms to which they are attached, a 5- to 6-membered non-aromatic ring, wherein the link formed by R^2

and R^3 is optionally substituted by one or more substituents selected from Z^3 and/or $-C_{1-9}$ alkyl optionally substituted by one or more Z^4 .

9. A compound for use as claimed in Claim 8, wherein:

- 5 Z^3 is not present or is selected from $-F$, $-R^{a2}$, $-C(O)N(R^{c2})R^{d2}$, $-N(R^{f2})R^{g2}$, $-N(R^{h2})C(O)R^{i2}$, $-N(R^{j2})C(O)OR^{k2}$, $-N(R^{l2})C(O)N(R^{m2})R^{n2}$, $-N(R^{o2})S(O)_2R^{p2}$, $-OR^{q2}$, $-S(O)_mR^{i2}$, $-S(O)_2N(R^{u2})R^{v2}$, heterocycloalkyl optionally substituted by one or more substituents selected from W^5 , aryl optionally substituted by one or more substituents selected from W^6 , or heteroaryl optionally substituted by one or more substituents selected from W^6 ; and/or
- 10 Z^4 is not present or is selected from $-F$, $-C(O)N(R^{c2})R^{d2}$, $-N(R^{f2})R^{g2}$, $-N(R^{h2})C(O)R^{i2}$, $-N(R^{j2})C(O)OR^{k2}$, $-N(R^{l2})C(O)N(R^{m2})R^{n2}$, $-N(R^{o2})S(O)_2R^{p2}$, $-OR^{q2}$, $-S(O)_mR^{i2}$, $-S(O)_2N(R^{u2})R^{v2}$, heterocycloalkyl optionally substituted by one or more substituents selected from W^5 , aryl optionally substituted by one or more substituents selected from W^6 , or heteroaryl optionally substituted by one or more substituents selected from W^6 .
- 15

10. A compound for use as claimed in any one of Claims 1 to 9 wherein:

- E^1 is Y^{1a} or $-C_{1-6}$ alkyl optionally substituted by one or more Y^2 and at least one of
- 20 E^2 , E^3 and E^4 represents Y^{1b} , $-C_{1-6}$ alkyl optionally substituted by one or more Y^2 .

11. A compound for use as claimed in any one of Claims 1 to 10 wherein:

- Y^1 independently represents halogen, $-CN$, $-C(O)R^a$, $-C(O)N(R^b)R^c$, $-C(O)OR^d$, $-N(R^e)R^f$, $-N(R^g)C(O)R^h$, $-N(R^i)C(O)OR^j$, $-N(R^k)C(O)N(R^l)R^m$, $-NO_2$, $-N(R^n)S(O)_2R^o$,
- 25 $-OC(O)R^q$, $-OS(O)_2R^r$, $-S(O)_mR^s$ or $-S(O)_2N(R^t)R^u$;
- Y^{1a} represents halogen, $-CN$, $-C(O)R^a$, $-C(O)N(R^b)R^c$, $-C(O)OR^d$, $-N(R^e)R^f$, $-N(R^g)C(O)R^h$, $-N(R^i)C(O)OR^j$, $-N(R^k)C(O)N(R^l)R^m$, $-NO_2$, $-N(R^n)S(O)_2R^o$, $-OC(O)R^q$, $-OS(O)_2R^r$, $-S(O)_mR^s$ or $-S(O)_2N(R^t)R^u$; and
- Y^{1b} represents halogen, $-CN$, $-C(O)R^a$, $-C(O)N(R^b)R^c$, $-C(O)OR^d$, $-N(R^e)R^f$,
- 30 $-N(R^g)C(O)R^h$, $-N(R^i)C(O)OR^j$, $-N(R^k)C(O)N(R^l)R^m$, $-NO_2$, $-N(R^n)S(O)_2R^o$, $-OC(O)R^q$, $-OS(O)_2R^r$, $-S(O)_mR^s$ or $-S(O)_2N(R^t)R^u$.

12. A compound for use as claimed in Claim 11 wherein:

- 35 E^1 , E^3 and E^4 represent hydrogen and

- E^2 represents $-\text{CH}=\text{CHC}(\text{O})\text{OCH}_3$, $-\text{CH}_2\text{NH}_2$, $-\text{CH}_2\text{N}(\text{H})\text{C}(\text{O})\text{CH}=\text{CH}_2$, $-\text{CH}_2\text{OH}$, $-\text{N}(\text{H})\text{C}(\text{O})\text{CH}=\text{CH}_2$, $-\text{N}(\text{H})\text{C}(\text{O})\text{CH}=\text{CHCH}_2\text{NMe}_2$, $-\text{N}(\text{H})\text{C}(\text{O})\text{CH}=\text{CHPh}$, $-\text{N}(\text{H})\text{C}(\text{O})\text{C}\equiv\text{CH}$, $-\text{N}(\text{H})\text{C}(\text{O})\text{CH}_2(\text{OH})$, $-\text{N}(\text{H})\text{C}(\text{O})\text{CH}(\text{OH})\text{Ph}$, $-\text{N}(\text{H})\text{C}(\text{O})\text{C}(\text{O})\text{CH}_3$, $-\text{N}(\text{H})\text{C}(\text{O})\text{C}(\text{O})\text{Ph}$ or $-\text{N}(\text{H})\text{S}(\text{O})_2\text{CH}=\text{CH}_2$; or
- 5 E^1 , E^2 and E^4 represent hydrogen and E^3 represents $-\text{CH}=\text{CH}_2$, $-\text{CH}=\text{CHC}(\text{O})\text{OH}$, $-\text{CH}=\text{CHC}(\text{O})\text{OCH}_3$, $-\text{CH}_2\text{NH}_2$, $-\text{CH}_2\text{N}(\text{H})\text{C}(\text{O})\text{CH}=\text{CH}_2$, $-\text{CH}_2\text{OH}$, $-\text{C}(\text{O})\text{H}$, $-\text{C}(\text{O})\text{CH}_3$, $-\text{C}(\text{O})\text{CF}_3$, $-\text{N}(\text{H})\text{C}(\text{O})\text{CH}=\text{CH}_2$; or E^3 and E^4 represent hydrogen; and
- 10 E^1 represents $-\text{F}$ and E^2 represents $-\text{F}$, $-\text{Cl}$, or $-\text{CF}_3$; or E^1 represents $-\text{Cl}$ and E^2 represents $-\text{Cl}$, $-\text{CH}_3$ or $-\text{CF}_3$; or E^1 represents $-\text{CH}_3$ and E^2 represents $-\text{Cl}$, $-\text{CH}_3$, $-\text{CN}$ or $-\text{N}(\text{H})\text{C}(\text{O})\text{CH}=\text{CH}_2$; or E^2 and E^4 represent hydrogen; and E^1 and E^3 represent $-\text{F}$; or
- 15 E^1 represents $-\text{Cl}$ and E^3 represents $-\text{F}$ or $-\text{Cl}$; or E^1 represents $-\text{CH}_3$ and E^3 represents $-\text{Cl}$; or E^2 and E^3 represent hydrogen; and E^1 represents $-\text{F}$ and E^4 represents $-\text{Cl}$, $-\text{CH}_3$ or $-\text{CN}$; or E^1 represents $-\text{Cl}$ and E^4 represents $-\text{F}$, $-\text{Cl}$, $-\text{CH}_3$ or $-\text{CF}_3$; or
- 20 E^1 represents $-\text{CH}_3$ and E^4 represent, $-\text{Cl}$, $-\text{CH}_3$, $-\text{CF}_3$, $-\text{CN}$ or $-\text{N}(\text{H})\text{C}(\text{O})\text{CH}=\text{CH}$; or E^1 represents $-\text{CF}_3$ and E^4 represents $-\text{F}$ or $-\text{CF}_3$; or E^1 represents $-\text{CN}$ and E^4 represents $-\text{Cl}$; or E^4 represents hydrogen; and
- 25 E^1 , E^2 and E^3 represent $-\text{F}$; or E^1 and E^2 represent $-\text{CH}_3$ and E^3 represents $-\text{F}_3$; or E^2 and E^3 represent $-\text{Cl}$ and E^1 represents $-\text{CH}_3$; or E^2 represents hydrogen; and E^1 , E^3 and E^4 represent $-\text{F}$; or
- 30 E^3 and E^4 represent $-\text{Cl}$ and E^1 represents $-\text{CH}_3$; or E^1 and E^4 represent $-\text{CH}_3$ and E^3 represents $-\text{F}$ or $-\text{CH}_3$; or E^1 represents $-\text{F}$, E^3 represents $-\text{CH}_3$ and E^4 represents $-\text{Cl}$; or E^1 represents $-\text{Cl}$, E^3 represents $-\text{F}$ and E^4 represents $-\text{CH}_3$; or E^1 represents $-\text{Cl}$, E^3 represents $-\text{CH}_3$ and E^4 represents $-\text{F}$; or
- 35 E^1 and E^4 represent $-\text{CH}_3$ and E^3 represents $-\text{F}$; or

E¹ represents -CH₃, E³ represents -CF₃ and E⁴ represents -Cl; or

E¹ represents hydrogen; and

E² and E⁴ represent -CH₃ and E³ represents -OH; or

E³ represents hydrogen; and

5 E¹ and E² represent -Cl and E⁴ represents -CH₃.

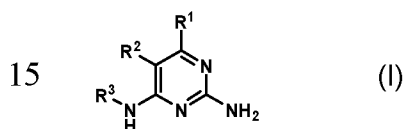
13. A compound for use as claimed in any one of Claims 1 to 9 wherein:

R¹ represents heteroaryl.

10 14. A compound for use as claimed in Claim 13 wherein:

R¹ represents benzofuranyl, benzothiophenyl, dihydrobenzofuranyl, indolyl, isoquinolinyl, pyridinyl or quinolinyl.

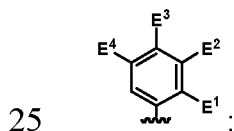
15. A compound of formula I,



or a pharmaceutically acceptable salt thereof, wherein:

R¹ represents:

indanyl, naphthyl, tetrahydronaphthyl or heteroaryl, the latter connected to the
 20 pyrimidine of formula I via a carbon atom of the heteroaryl ring, which indanyl, naphthyl, tetrahydronaphthyl and heteroaryl rings are optionally substituted by one or more substituents selected from Y¹, -C₁₋₆alkyl optionally substituted by one or more Y² and heterocycloalkyl optionally substituted by one or more Y³; or aryl represented by



E¹, E², E³ and E⁴ represents hydrogen, Y¹, -C₁₋₆alkyl optionally substituted by one or more Y² or heterocycloalkyl optionally substituted by one or more Y³, but where at least one of E¹, E², E³ and E⁴ is other than hydrogen;

30

R² represents hydrogen, halogen or -C₁₋₁₂alkyl optionally substituted by one or more Z¹;

R³ represents -C₁₋₁₂alkyl substituted by one or more Z¹ or heterocycloalkyl
 5 optionally substituted by one or more Z²; or

R² and R³ are linked together to form, along with the atoms to which they are attached, a 5- to 8-membered non-aromatic ring, wherein the link formed by R² and R³ is optionally substituted by one or more substituents selected from Z³ or
 10 -C₁₋₉alkyl optionally substituted by one or more Z⁴;

each Y¹ independently represents halogen, -CN, -C(O)R^a, -C(O)N(R^b)R^c,
 -C(O)OR^d, -N(R^e)R^f, -N(R^g)C(O)R^h, -N(Rⁱ)C(O)OR^j, -N(R^k)C(O)N(R^l)R^m, -NO₂,
 -N(Rⁿ)S(O)₂R^o,
 15 -OR^p, -OC(O)R^q, -OS(O)₂R^r, -S(O)_mR^s, -S(O)₂N(R^t)R^u, heterocycloalkyl optionally substituted by one or more substituents selected from W², aryl optionally substituted by one or more substituents selected from W³, or heteroaryl optionally substituted by one or more substituents selected from W³;

20 each R^a, R^b, R^c, R^d, R^e, R^g, R^h, Rⁱ, R^k, R^l, R^m, Rⁿ, R^p, R^q, R^s, R^t and R^u independently represents hydrogen, -C₁₋₆ alkyl optionally substituted by one or more substituents selected from W¹, heterocycloalkyl optionally substituted by one or more substituents selected from W², aryl optionally substituted by one or more substituents selected from W³, or heteroaryl optionally substituted by one or
 25 more substituents selected from W³; or

any two R^b and R^c, R^e and R^f, Rⁱ and R^m and/or R^t and R^u are linked together to form, along with the nitrogen atom to which they are attached, a 3- to 8-membered monocyclic or bicyclic ring, which ring optionally contains one or two
 30 heteroatoms and which ring optionally is substituted by one or more substituents selected from W², C₁₋₃alkyl optionally substituted by one or more substituents selected from W¹, and =O;

each R^f, R^j, R^o and R^r independently represent -C₁₋₆ alkyl optionally substituted by
 35 one or more substituents selected from W¹, heterocycloalkyl optionally substituted

by one or more substituents selected from W^2 , aryl optionally substituted by one or more substituents selected from W^3 or heteroaryl optionally substituted by one or more substituents selected from W^3 ;

- 5 each Y^2 independently represents halogen, $-CN$, $-C(O)R^{b1}$, $-C(O)N(R^{c1})R^{d1}$, $-C(O)OR^{e1}$, $-N(R^{f1})R^{g1}$, $-N(R^{h1})C(O)R^{i1}$, $-N(R^{j1})C(O)OR^{k1}$, $-N(R^{l1})C(O)N(R^{m1})R^{n1}$, $-N(R^{o1})S(O)_2R^{p1}$, $-OR^{q1}$, $-OC(O)R^{r1}$, $-OS(O)_2R^{s1}$, $-S(O)_mR^{t1}$, $-S(O)_2N(R^{u1})R^{v1}$, heterocycloalkyl optionally substituted by one or more substituents selected from W^1 , aryl optionally substituted by one or more substituents selected from W^2 ,
 10 heteroaryl optionally substituted by one or more substituents selected from W^2 ;

- each Y^3 independently represents halogen, $-R^{a1}$, $-CN$, $-C(O)R^{b1}$, $-C(O)N(R^{c1})R^{d1}$, $-C(O)OR^{e1}$, $-N(R^{f1})R^{g1}$, $-N(R^{h1})C(O)R^{i1}$, $-N(R^{j1})C(O)OR^{k1}$, $-N(R^{l1})C(O)N(R^{m1})R^{n1}$, $-N(R^{o1})S(O)_2R^{p1}$, $-OR^{q1}$, $-OC(O)R^{r1}$, $-OS(O)_2R^{s1}$, $-S(O)_mR^{t1}$, $-S(O)_2N(R^{u1})R^{v1}$,
 15 heterocycloalkyl optionally substituted by one or more substituents selected from W^1 , aryl optionally substituted by one or more substituents selected from W^2 , heteroaryl optionally substituted by one or more substituents selected from W^2 , or $=O$;

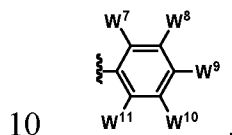
- 20 each R^{a1} , R^{b1} , R^{c1} , R^{d1} , R^{e1} , R^{f1} , R^{h1} , R^{i1} , R^{j1} , R^{l1} , R^{m1} , R^{n1} , R^{o1} , R^{q1} , R^{r1} , R^{t1} , R^{u1} and R^{v1} independently represents hydrogen, C_{1-6} alkyl optionally substituted by one or more substituents selected from W^1 , heterocycloalkyl optionally substituted by one or more substituents selected from W^2 , aryl optionally substituted by one or more substituents selected from W^3 , or heteroaryl optionally substituted by one or more substituents selected from W^3 ; or
 25

- any two R^{c1} and R^{d1} , R^{f1} and R^{g1} , R^{m1} and R^{n1} and/or R^{u1} and R^{v1} are linked together to form, along with the nitrogen atom to which they are attached, a 3- to 8-membered monocyclic or bicyclic ring, which ring optionally contains one or two
 30 heteroatoms and which ring optionally is substituted by one or more substituents selected from W^2 , C_{1-3} alkyl optionally substituted by one or more substituents selected from W^1 , and $=O$;

- each R^{g1} , R^{k1} , R^{p1} and R^{s1} independently represent $-C_{1-6}$ alkyl optionally
 35 substituted by one or more substituents selected from W^1 , heterocycloalkyl

optionally substituted by one or more substituents selected from W^2 , aryl
optionally substituted by one or more substituents selected from W^3 , or heteroaryl
optionally substituted by one or more substituents selected from W^3 ;

- 5 each Z^1 independently represents halogen, $-CN$, $-C(O)R^{b2}$, $-C(O)N(R^{c2})R^{d2}$,
 $-C(O)OR^{e2}$, $-N(R^{f2})R^{g2}$, $-N(R^{h2})C(O)R^{i2}$, $-N(R^{j2})C(O)OR^{k2}$, $-N(R^{l2})C(O)N(R^{m2})R^{n2}$,
 $-N(R^{o2})S(O)_2R^{p2}$, $-OR^{q2}$, $-OC(O)R^{r2}$, $-OS(O)_2R^{s2}$, $-S(O)_mR^{t2}$, $-S(O)_2N(R^{u2})R^{v2}$,
heterocycloalkyl optionally substituted by one or more substituents selected from
 W^5 , aryl represented by



heteroaryl having 1 to 3 nitrogen atoms, one oxygen atom and/or one sulfur atom
and optionally substituted by one or more substituents selected from W^6 ;

- each Z^2 and Z^3 independently represents halogen, $-R^{a2}$, $-CN$, $-C(O)R^{b2}$,
15 $-C(O)N(R^{c2})R^{d2}$, $-C(O)OR^{e2}$, $-N(R^{f2})R^{g2}$, $-N(R^{h2})C(O)R^{i2}$, $-N(R^{j2})C(O)OR^{k2}$,
 $-N(R^{l2})C(O)N(R^{m2})R^{n2}$, $-N(R^{o2})S(O)_2R^{p2}$, $-OR^{q2}$, $-OC(O)R^{r2}$, $-OS(O)_2R^{s2}$, $-S(O)_mR^{t2}$,
 $-S(O)_2N(R^{u2})R^{v2}$, heterocycloalkyl optionally substituted by one or more
substituents selected from W^5 , aryl optionally substituted by one or more
substituents selected from W^6 , or heteroaryl optionally substituted by one or more
20 substituents selected from W^6 ;

- each Z^4 independently represents halogen, $-CN$, $-C(O)R^{b2}$, $-C(O)N(R^{c2})R^{d2}$,
 $-C(O)OR^{e2}$, $-N(R^{f2})R^{g2}$, $-N(R^{h2})C(O)R^{i2}$, $-N(R^{j2})C(O)OR^{k2}$, $-N(R^{l2})C(O)N(R^{m2})R^{n2}$,
 $-N(R^{o2})S(O)_2R^{p2}$, $-OR^{q2}$, $-OC(O)R^{r2}$, $-OS(O)_2R^{s2}$, $-S(O)_mR^{t2}$, $-S(O)_2N(R^{u2})R^{v2}$,
25 heterocycloalkyl optionally substituted by one or more substituents selected from
 W^5 , aryl optionally substituted by one or more substituents selected from W^6 ,
heteroaryl optionally substituted by one or more substituents selected from W^6 , or
 $=O$;

- 30 each R^{a2} , R^{b2} , R^{c2} , R^{d2} , R^{e2} , R^{f2} , R^{h2} , R^{i2} , R^{j2} , R^{l2} , R^{m2} , R^{n2} , R^{o2} , R^{r2} , R^{t2} , R^{u2} and
 R^{v2} independently represents hydrogen or C_{1-6} alkyl optionally substituted by one
or more substituents selected from W^4 , heterocycloalkyl optionally substituted by
one or more substituents selected from W^5 , aryl optionally substituted by one or

more substituents selected from W^6 , or heteroaryl optionally substituted by one or more substituents selected from W^6 ; or

any two R^{c2} and R^{d2} , R^{f2} and R^{g2} , R^{m2} and R^{n2} and/or R^{u2} and R^{v2} are linked
 5 together to form, along with the nitrogen atom to which they are attached, a 3- to 8-membered monocyclic or bicyclic ring, which ring optionally contains one or two heteroatoms and which ring optionally is substituted by one or more substituents selected from W^5 , C_{1-3} alkyl optionally substituted by one or more substituents selected from W^4 , and =O;

10

each R^{g2} , R^{k2} , R^{p2} , R^{q2} and R^{s2} independently represent $-C_{1-6}$ alkyl optionally substituted by one or more substituents selected from W^4 , heterocycloalkyl optionally substituted by one or more substituents selected from W^5 , aryl optionally substituted by one or more substituents selected from W^6 , or heteroaryl
 15 optionally substituted by one or more substituents selected from W^6 ;

each W^1 and W^4 independently represents halogen, -CN, $-N(R^{f3})R^{g3}$, $-N(R^{h3})C(O)R^{i3}$, $-N(R^{j3})C(O)OR^{k3}$, $-N(R^{l3})C(O)N(R^{m3})R^{n3}$, $-N(R^{o3})S(O)_2R^{p3}$, $-OR^{q3}$, $-OC(O)R^{r3}$, $-OS(O)_2R^{s3}$, $-S(O)_mR^{t3}$, $-S(O)_2N(R^{u3})R^{v3}$, heterocycloalkyl optionally
 20 substituted by one or more substituents selected from G^1 , aryl optionally substituted by one or more substituents selected from G^2 , heteroaryl optionally substituted by one or more substituents selected from G^2 , or =O;

each W^2 , W^3 , W^5 and W^6 independently represents halogen, $-R^{a3}$, -CN, $-C(O)R^{b3}$,
 25 $-C(O)N(R^{c3})R^{d3}$, $-C(O)OR^{e3}$, $-N(R^{f3})R^{g3}$, $-N(R^{h3})C(O)R^{i3}$, $-N(R^{j3})C(O)OR^{k3}$, $-N(R^{l3})C(O)N(R^{m3})R^{n3}$, $-N(R^{o3})S(O)_2R^{p3}$, $-OR^{q3}$, $-OC(O)R^{r3}$, $-OS(O)_2R^{s3}$, $-S(O)_mR^{t3}$, $-S(O)_2N(R^{u3})R^{v3}$, heterocycloalkyl optionally substituted by one or more substituents selected from G^1 , aryl optionally substituted by one or more substituents selected from G^2 , heteroaryl (optionally substituted by one or more
 30 substituents selected from G^2 , or =O;

W^7 and W^{11} represents hydrogen;

each W^8 and W^{10} independently represents hydrogen, halogen, $-R^{a3}$, -CN, -
 35 $C(O)R^{b3}$,

- C(O)N(R^{c3})R^{d3}, -C(O)OR^{e3}, -N(R^{f3})R^{g3}, -N(R^{h3})C(O)Rⁱ³, -N(R^{j3})C(O)OR^{k3},
 -N(R^{l3})C(O)N(R^{m3})Rⁿ³, -N(R^{o3})S(O)₂R^{p3}, -OR^{q3}, -OC(O)R^{r3}, -OS(O)₂R^{s3}, -S(O)_mR^{t3},
 -S(O)₂N(R^{u3})R^{v3}, heterocycloalkyl optionally substituted by one or more
 substituents selected from G¹, aryl optionally substituted by one or more
 5 substituents selected from G², or heteroaryl optionally substituted by one or more
 substituents selected from G²;

- W⁹ represents halogen, -R^{a3}, -CN, -C(O)R^{b3}, -C(O)N(R^{c3})R^{d3}, -C(O)OR^{e3}, -
 N(R^{f3})R^{g3},
 10 -N(R^{h3})C(O)Rⁱ³, -N(R^{j3})C(O)OR^{k3}, -N(R^{l3})C(O)N(R^{m3})Rⁿ³, -N(R^{o3})S(O)₂R^{p3}, -OR^{q3x},
 -OC(O)R^{r3}, -OS(O)₂R^{s3}, -S(O)_mR^{t3}, -S(O)₂N(R^{u3})R^{v3}, heterocycloalkyl optionally
 substituted by one or more substituents selected from G¹, aryl optionally
 substituted by one or more substituents selected from G², or heteroaryl optionally
 substituted by one or more substituents selected from G²;

- 15 each R^{a3}, R^{b3}, R^{c3}, R^{d3}, R^{e3}, R^{f3}, R^{h3}, Rⁱ³, R^{j3}, R^{l3}, R^{m3}, Rⁿ³, R^{o3}, R^{q3}, R^{r3}, R^{t3}, R^{u3}
 and R^{v3} independently represents hydrogen or -C₁₋₆ alkyl optionally substituted by
 one or more G³; or
- 20 any two R^{c3} and R^{d3}, R^{f3} and R^{g3}, R^{m3} and Rⁿ³ and/or R^{u3} and R^{v3} are linked
 together to form, along with the nitrogen atom to which they are attached, a 4- to
 6-membered ring, which ring optionally contains one heteroatom and which ring
 optionally is substituted by one or more G²;
- 25 each R^{g3}, R^{k3}, R^{p3}, R^{q3} and R^{s3} independently represent C₁₋₆ alkyl optionally
 substituted by one or more G³;

R^{q3x} represents C₂₋₆ alkyl optionally substituted by one or more G³;

- 30 each G¹ and G² independently represents halogen, -R^{a4}, -CN, -C(O)R^{b4},
 -C(O)N(R^{c4})R^{d4}, -C(O)OR^{e4}, -N(R^{f4})R^{g4}, -N(R^{h4})C(O)Rⁱ⁴, -N(R^{j4})C(O)OR^{k4},
 -N(R^{l4})C(O)N(R^{m4})Rⁿ⁴, -N(R^{o4})S(O)₂R^{p4}, -OR^{q4}, -OC(O)R^{r4}, -OS(O)₂R^{s4}, -S(O)_mR^{t4},
 -S(O)₂N(R^{u4})R^{v4}, or =O;

G^3 represents halogen, $-CN$, $-C(O)R^{b4}$, $-C(O)N(R^{c4})R^{d4}$, $-C(O)OR^{e4}$, $-N(R^{f4})R^{g4}$, $-N(R^{h4})C(O)R^{i4}$, $-N(R^{j4})C(O)OR^{k4}$, $-N(R^{l4})C(O)N(R^{m4})R^{n4}$, $-N(R^{o4})S(O)_2R^{p4}$, $-OR^{q4}$, $-OC(O)R^{r4}$, $-OS(O)_2R^{s4}$, $-S(O)_mR^{t4}$, $-S(O)_2N(R^{u4})R^{v4}$, or $=O$;

- 5 each R^{a4} , R^{b4} , R^{c4} , R^{d4} , R^{e4} , R^{f4} , R^{h4} , R^{i4} , R^{j4} , R^{l4} , R^{m4} , R^{n4} , R^{o4} , R^{q4} , R^{r4} , R^{t4} , R^{u4} and R^{v4} independently represents hydrogen or $-C_{1-6}$ alkyl optionally substituted by one or more $-F$; or

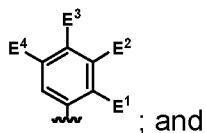
- 10 any two R^{c4} and R^{d4} , R^{f4} and R^{g4} , R^{m4} and R^{n4} and/or R^{u4} and R^{v4} are linked together to form, along with the nitrogen atom to which they are attached, a 3- to 6-membered ring, which ring optionally substituted by one or more $-F$, $-CH_3$, $-CH_2CH_3$, $-CHF_2$, $-CF_3$, $-CH_2CF_3$, or $=O$;

- 15 each R^{g4} , R^{k4} , R^{p4} and R^{s4} independently represent C_{1-6} alkyl optionally substituted by one or more $-F$;

each m independently represents 0, 1 or 2;

- 20 provided that the compound is not
 6-(3-pyridinyl)- N^4 -[[4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]methyl]-2,4-pyrimidinediamine,
 6-(3-pyridinyl)- N^4 -[[5-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]-2-pyridinyl]methyl]-2,4-pyrimidinediamine,
 6-(3-pyridinyl)- N^4 -[[5-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]-2-pyrimidinyl]-
 25 methyl]-2,4-pyrimidinediamine,
 N^4 -[2-(diethylamino)ethyl]-6-(3,4,5-trimethoxyphenyl)-2,4-pyrimidinediamine,
 N^4 -[3-(4-morpholinyl)propyl]-6-(3,4,5-trimethoxyphenyl)-2,4-pyrimidinediamine, or
 N^4 -[2-(4-morpholinyl)ethyl]-6-(3,4,5-trimethoxyphenyl)-2,4-pyrimidinediamine.

- 30 16. A compound as claimed in Claim 15 wherein:
 R^1 represents heteroaryl connected to the pyrimidine of formula I via a carbon atom of the heteroaryl ring, which heteroaryl is optionally substituted by one or more substituents selected from Y^1 , or $-C_{1-6}$ alkyl optionally substituted by one or more Y^2 ; or
 35 aryl represented by



R^2 represents hydrogen or methyl; and

R^3 represents $-C_{1-6}$ alkyl substituted by Z^1 or heterocycloalkyl optionally substituted by one or more Z^2 .

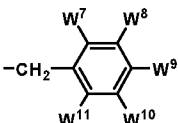
5

17. A compound as claimed in Claim 16 wherein:

R^2 represents hydrogen and R^3 represents $-C_{2-6}$ alkyl substituted by Z^1 .

18. A compound as claimed in Claim 16 wherein:

10

R^2 represents hydrogen and R^3 represents .

19. A compound as claimed in Claim 16 wherein:

R^2 represents hydrogen and Z^1 represents heteroaryl having 1 to 3 nitrogen atoms, one oxygen atom and/or one sulfur atom and which heteroaryl is optionally substituted by one or more substituents selected from W^3 .

15

20. A compound as claimed in Claim 16 wherein:

R^2 represents hydrogen and R^3 represents $-C_{3-6}$ alkyl or a heterocycloalkyl selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclopropylethyl, cyclobutylethyl, cyclopropylpropyl, oxetanyl, tetrahydrofuryl, tetrahydropyranyl, azetidiny, pyrrolidiny, piperidiny, piperaziny or morpholiny wherein the C_{3-6} alkyl is substituted by one or two Z^1 and the heterocycloalkyl is optionally substituted by one or two Z^2 .

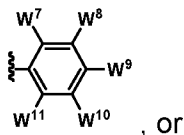
25

21. A compound as claimed in any one of Claims 16, 17, 18 and 20 wherein:

Z^1 represents halogen, $-CN$, $-C(O)R^{b2}$, $-C(O)N(R^{c2})R^{d2}$, $-C(O)OR^{e2}$, $-N(R^{f2})R^{g2}$, $-N(R^{h2})C(O)R^{i2}$, $-N(R^{l2})C(O)N(R^{m2})R^{n2}$, $-N(R^{o2})S(O)_2R^{p2}$, $-OR^{q2}$, $-S(O)_mR^{l2}$, $-S(O)_2N(R^{u2})R^{v2}$, heterocycloalkyl optionally substituted by one or more

substituents selected from W^5 , aryl represented by

30

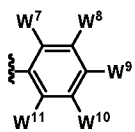


, or

heteroaryl having 1 to 3 nitrogen atoms, one oxygen atom and/or one sulfur atom and optionally substituted by one or more substituents selected from W^6 .

- 5 22. A compound as claimed in Claim 21 wherein:

Z^1 represents -F, -CN, -C(O)N(R^{c2})R^{d2}, -N(R^{f2})R^{g2}, -N(R^{h2})C(O)Rⁱ², -N(R^{l2})C(O)N(R^{m2})Rⁿ², -N(R^{o2})S(O)₂R^{p2}, -OR^{q2}, -S(O)_mR^{l2}, -S(O)₂N(R^{u2})R^{v2}, heterocycloalkyl optionally substituted by one or more substituents selected from W^5 , aryl represented by

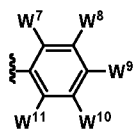


10 , or

heteroaryl having 1 to 3 nitrogen atoms, one oxygen atom and/or one sulfur atom and optionally substituted by one or more substituents selected from W^6 .

23. A compound as claimed in Claim 22 wherein:

- 15 Z^1 represents -C(O)N(R^{c2})R^{d2}, -N(R^{f2})R^{g2}, -N(R^{h2})C(O)Rⁱ², -N(R^{l2})C(O)N(R^{m2})Rⁿ², -N(R^{o2})S(O)₂R^{p2}, -OR^{q2}, -S(O)_mR^{l2}, -S(O)₂N(R^{u2})R^{v2} or aryl represented by



; and

R^{c2}, R^{f2}, R^{h2}, R^{l2}, R^{m2}, R^{o2}, and R^{u2} represents hydrogen; and

R^{d2}, R^{g2}, Rⁱ², Rⁿ², R^{p2}, R^{q2}, R^{l2} and R^{v2} represents aryl optionally substituted by one or more substituents selected from W^6 , or heteroaryl optionally substituted by one or more substituents selected from W^6 .

- 20

24. A compound as claimed in Claim 15, wherein:

R² and R³ are linked together to form, along with the atoms to which they are attached, a 5- to 6-membered non-aromatic ring, wherein the link formed by R² and R³ is optionally substituted by one or more substituents selected from Z^3 and/or -C₁₋₉alkyl optionally substituted by one or more Z^4 .

- 25

25. A compound as claimed in Claim 24, wherein:

- Z^3 is not present or is selected from -F, $-R^{a2}$, $-C(O)N(R^{c2})R^{d2}$, $-N(R^{f2})R^{g2}$, $-N(R^{h2})C(O)R^{i2}$, $-N(R^{j2})C(O)OR^{k2}$, $-N(R^{l2})C(O)N(R^{m2})R^{n2}$, $-N(R^{o2})S(O)_2R^{p2}$, $-OR^{q2}$, $-S(O)_mR^{l2}$, $-S(O)_2N(R^{u2})R^{v2}$, heterocycloalkyl optionally substituted by one or more substituents selected from W^5 , aryl optionally substituted by one or more substituents selected from W^6 , or heteroaryl optionally substituted by one or more substituents selected from W^6 ; and/or
- Z^4 is not present or is selected from -F, $-C(O)N(R^{c2})R^{d2}$, $-N(R^{f2})R^{g2}$, $-N(R^{h2})C(O)R^{i2}$, $-N(R^{j2})C(O)OR^{k2}$, $-N(R^{l2})C(O)N(R^{m2})R^{n2}$, $-N(R^{o2})S(O)_2R^{p2}$, $-OR^{q2}$, $-S(O)_mR^{l2}$, $-S(O)_2N(R^{u2})R^{v2}$, heterocycloalkyl optionally substituted by one or more substituents selected from W^5 , aryl optionally substituted by one or more substituents selected from W^6 , or heteroaryl optionally substituted by one or more substituents selected from W^6 .

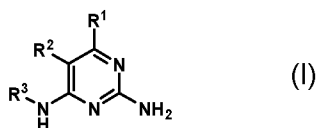
26. A compound as claimed in any one of Claims 15 to 25 wherein:
- E^2 , E^3 and E^4 represent hydrogen and
- E^1 represents -F, -Cl, $-CH_3$, $-CF_3$, CN or $-OCH_3$; or
- E^1 , E^3 and E^4 represent hydrogen and E^2 represents -F, -Cl, $-CH_3$, $-CF_3$, -CN; or
- E^1 , E^2 and E^4 represent hydrogen and E^3 represents -F, -Cl, $-CH_3$, $-CF_3$, $-C(CH_3)_3$, $-CH=CH_2$, $-OCF_3$, $-S(O)_2CH_3$, or $-S(O)_2(4\text{-morpholinyl})$; or
- E^3 and E^4 represent hydrogen; and
- E^1 represents -F and E^2 represents -F, -Cl, $-CH_3$ or $-CF_3$; or
- E^1 represents -Cl and E^2 represents -F, -Cl, $-CH_3$ or $-CF_3$; or
- E^1 represents $-CH_3$ and E^2 represents -F, -Cl, $-CH_3$, $-CF_3$ or -CN; or
- E^2 and E^4 represent hydrogen; and
- E^1 represents -Cl and E^3 represents -F or -Cl; or
- E^1 represents $-CH_3$ and E^3 represents -Cl; or
- E^1 represents $-OCH_3$ and E^3 represents -F; or
- E^2 and E^3 represent hydrogen; and
- E^1 represents -F and E^4 represents -Cl, $-CH_3$ or -CN; or
- E^1 represents -Cl and E^4 represents -F, -Cl, $-CH_3$, $-CF_3$ or $-OCH_3$; or
- E^1 represents $-CH_3$ and E^4 represents -F, -Cl, $-CH_3$, $-CF_3$ or -CN; or
- E^1 represents $-CF_3$ and E^4 represents -F or $-CF_3$; or
- E^1 represents -CN and E^4 represents -Cl; or
- E^1 represents $-OCH_3$ and E^4 represents -F, -Cl, Br, $-CH_3$, $-CH(CH_3)_2$, $-C(CH_3)_3$, -CN or $-OCH_3$; or

- E¹ and E⁴ represent hydrogen; and
E² represents -F and E³ represents -F, -Cl, -OH or -OCH₃; or
E² represents -Cl and E³ represents -F; or
E² represents -CH₃ and E³ represents -F or -OCH₃; or
5 E¹ represents -OCH₃ and E³ represents -OH; or
E¹ and E³ represent hydrogen; and
E² and E⁴ represent -F; or
E² and E⁴ represent -CF₃; or
E⁴ represents hydrogen; and
10 E¹, E² and E³ represent -F; or
E¹ and E² represent -Cl and E³ represents -Cl, -OH or -OCH₃; or
E¹ and E² represent -CH₃ and E³ represents -F or -OCH₃; or
E² and E³ represent -Cl and E¹ represents -CH₃; or
E² represents hydrogen; and
15 E¹, E³ and E⁴ represent -F; or
E³ and E⁴ represent -Cl and E¹ represents -CH₃; or
E¹ and E⁴ represent -Cl and E¹ represents -OCH₃; or
E¹ and E⁴ represent -CH₃ and E³ represents -F, -CH₃ or -OCH₃; or
E¹ represents -F, E³ represents -CH₃ and E⁴ represents -Cl; or
20 E¹ represents -Cl, E³ represents -F and E⁴ represents -CH₃; or
E¹ represents -Cl, E³ represents -CH₃ and E⁴ represents -F; or
E¹ and E⁴ represent -CH₃ and E³ represents -F; or
E¹ represents -CH₃, E⁴ represents -Cl and E³ represents -CF₃ or -OCH₃; or
E¹ represents hydrogen; and
25 E² and E⁴ represent -CH₃ and E³ represents -OH; or
E³ represents hydrogen; and
E¹ and E² represent -Cl and E⁴ represents -CH₃.

27. A compound as claimed in any one of Claims 16 to 25 wherein:
30 R¹ represents heteroaryl.

28. A compound as claimed in Claim 27 wherein:
R¹ represents benzofuranyl, benzothiophenyl, dihydrobenzofuranyl, indolyl,
isoquinoliny, pyridinyl and quinoliny.
35

29. A compound of formula I,



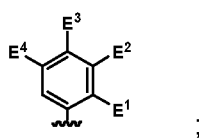
or a pharmaceutically acceptable salt thereof,

wherein:

5

R¹ represents heteroaryl connected to the pyrimidine of formula I via a carbon atom of the heteroaryl ring, which heteroaryl ring is substituted by one or more substituents selected from Y¹, -C₁₋₆alkyl optionally substituted by one or more Y² and heterocycloalkyl optionally substituted by one or more Y³; or aryl represented by

10



E¹ represents Y^{1a} or -C₁₋₆alkyl optionally substituted by one or more Y²; and at least one of E², E³ and E⁴ represents Y^{1b} or -C₁₋₆alkyl optionally substituted by one or more Y²;

15

R² represents hydrogen, halogen, -CN, -C₁₋₁₂alkyl optionally substituted by one or more Z¹, or heterocycloalkyl optionally substituted by one or more Z²;

R³ represents -C₁₋₁₂alkyl optionally substituted by one or more Z¹ or

20 heterocycloalkyl optionally substituted by one or more Z²; or

R² and R³ are linked together to form, along with the atoms to which they are attached, a 5- to 8-membered non-aromatic ring, wherein the link formed by R² and R³ is optionally substituted by one or more substituents selected from Z³ and

25 -C₁₋₉alkyl optionally substituted by one or more Z⁴;

each Y¹ independently represents halogen, -CN, -C(O)R^a, -C(O)N(R^b)R^c, -C(O)OR^d, -N(R^e)R^f, -N(R^g)C(O)R^h, -N(Rⁱ)C(O)OR^j, -N(R^k)C(O)N(R^l)R^m, -NO₂, -N(Rⁿ)S(O)₂R^o, -OR^p, -OC(O)R^q, -OS(O)₂R^r, -S(O)_mR^s, -S(O)₂N(R^t)R^u,

30 heterocycloalkyl optionally substituted by one or more substituents selected from W², aryl optionally substituted by one or more substituents selected from W³ or

heteroaryl optionally substituted by one or more substituents selected from W^3 ;

Y^{1a} represents halogen, $-CN$, $-C(O)R^a$, $-C(O)N(R^b)R^c$, $-C(O)OR^d$, $-N(R^e)R^f$,
 $-N(R^g)C(O)R^h$, $-N(R^i)C(O)OR^j$, $-N(R^k)C(O)N(R^l)R^m$, $-NO_2$, $-N(R^n)S(O)_2R^o$,
 5 $-OR^{px}$, $-OC(O)R^q$, $-OS(O)_2R^r$, $-S(O)_mR^s$, $-S(O)_2N(R^t)R^u$, heterocycloalkyl optionally
 substituted by one or more substituents selected from W^2 , aryl optionally
 substituted by one or more substituents selected from W^3 or heteroaryl optionally
 substituted by one or more substituents selected from W^3 ;

10 Y^{1b} represents halogen, $-CN$, $-C(O)R^a$, $-C(O)N(R^b)R^c$, $-C(O)OR^d$, $-N(R^e)R^f$,
 $-N(R^g)C(O)R^h$, $-N(R^i)C(O)OR^j$, $-N(R^k)C(O)N(R^l)R^m$, $-NO_2$, $-N(R^n)S(O)_2R^o$,
 $-OR^p$, $-OC(O)R^q$, $-OS(O)_2R^r$, $-S(O)_mR^s$, $-S(O)_2N(R^t)R^u$, heterocycloalkyl optionally
 substituted by one or more substituents selected from W^2 , aryl optionally
 substituted by one or more substituents selected from W^3 or heteroaryl optionally
 15 substituted by one or more substituents selected from W^3 ;

each R^a , R^b , R^c , R^d , R^e , R^g , R^h , R^i , R^k , R^l , R^m , R^n , R^p , R^q , R^s , R^t and R^u
 independently represents hydrogen, $-C_{1-6}$ alkyl optionally substituted by one or
 more substituents selected from W^1 , heterocycloalkyl optionally substituted by
 20 one or more substituents selected from W^2 , aryl optionally substituted by one or
 more substituents selected from W^3 , or heteroaryl optionally substituted by one or
 more substituents selected from W^3 ; or

any two R^b and R^c , R^e and R^f , R^l and R^m and/or R^t and R^u are linked together to
 25 form, along with the nitrogen atom to which they are attached, a 3- to 8-
 membered monocyclic or bicyclic ring, which ring optionally contains one or two
 further heteroatoms and which ring optionally is substituted by one or more
 substituents selected from W^2 , C_{1-3} alkyl optionally substituted by one or more
 substituents selected from W^1 , and $=O$;

30 each R^f , R^j , R^o , R^r and R^{px} independently represents C_{1-6} alkyl optionally
 substituted by one or more substituents selected from W^1 , heterocycloalkyl
 optionally substituted by one or more substituents selected from W^2 , aryl
 optionally substituted by one or more substituents selected from W^3 or heteroaryl
 35 optionally substituted by one or more substituents selected from W^3 ;

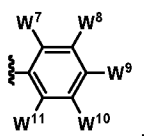
- each Y^2 independently represents halogen, $-CN$, $-C(O)R^{b1}$, $-C(O)N(R^{c1})R^{d1}$, $-C(O)OR^{e1}$, $-N(R^{f1})R^{g1}$, $-N(R^{h1})C(O)R^{i1}$, $-N(R^{j1})C(O)OR^{k1}$, $-N(R^{l1})C(O)N(R^{m1})R^{n1}$, $-N(R^{o1})S(O)_2R^{p1}$, $-OR^{q1}$, $-OC(O)R^{r1}$, $-OS(O)_2R^{s1}$, $-S(O)_mR^{t1}$, $-S(O)_2N(R^{u1})R^{v1}$,
 5 heterocycloalkyl optionally substituted by one or more substituents selected from W^1 , aryl optionally substituted by one or more substituents selected from W^2 , heteroaryl optionally substituted by one or more substituents selected from W^2 , or $=O$;
- 10 each Y^3 independently represents halogen, $-R^{a1}$, $-CN$, $-C(O)R^{b1}$, $-C(O)N(R^{c1})R^{d1}$, $-C(O)OR^{e1}$, $-N(R^{f1})R^{g1}$, $-N(R^{h1})C(O)R^{i1}$, $-N(R^{j1})C(O)OR^{k1}$, $-N(R^{l1})C(O)N(R^{m1})R^{n1}$, $-N(R^{o1})S(O)_2R^{p1}$, $-OR^{q1}$, $-OC(O)R^{r1}$, $-OS(O)_2R^{s1}$, $-S(O)_mR^{t1}$, $-S(O)_2N(R^{u1})R^{v1}$, heterocycloalkyl optionally substituted by one or more substituents selected from W^1 , aryl optionally substituted by one or more substituents selected from W^2 ,
 15 heteroaryl optionally substituted by one or more substituents selected from W^2 , or $=O$;

- each R^{a1} , R^{b1} , R^{c1} , R^{d1} , R^{e1} , R^{f1} , R^{h1} , R^{i1} , R^{j1} , R^{l1} , R^{m1} , R^{n1} , R^{o1} , R^{q1} , R^{r1} , R^{t1} , R^{u1} and R^{v1} independently represents hydrogen, C_{1-6} alkyl optionally substituted by
 20 one or more substituents selected from W^1 , heterocycloalkyl optionally substituted by one or more substituents selected from W^2 , aryl optionally substituted by one or more substituents selected from W^3 , or heteroaryl optionally substituted by one or more substituents selected from W^3 ; or
- 25 any two R^{c1} and R^{d1} , R^{f1} and R^{g1} , R^{m1} and R^{n1} and/or R^{u1} and R^{v1} are linked together to form, along with the nitrogen atom to which they are attached, a 3- to 8-membered monocyclic or bicyclic ring, which ring optionally contains one or two heteroatoms and which ring optionally is substituted by one or more substituents selected from W^2 , C_{1-3} alkyl optionally substituted by one or more substituents
 30 selected from W^1 , and $=O$;

each R^{g1} , R^{k1} , R^{p1} and R^{s1} independently represents $-C_{1-6}$ alkyl optionally substituted by one or more substituents selected from W^1 , heterocycloalkyl optionally substituted by one or more substituents selected from W^2 , aryl

optionally substituted by one or more substituents selected from W^3 , or heteroaryl optionally substituted by one or more substituents selected from W^3 ;

- each Z^1 independently represents halogen, -CN, $-C(O)R^{b2}$, $-C(O)N(R^{c2})R^{d2}$,
 5 $-C(O)OR^{e2}$, $-N(R^{f2})R^{g2}$, $-N(R^{h2})C(O)R^{i2}$, $-N(R^{j2})C(O)OR^{k2}$, $-N(R^{l2})C(O)N(R^{m2})R^{n2}$,
 $-N(R^{o2})S(O)_2R^{p2}$, $-OR^{q2}$, $-OC(O)R^{r2}$, $-OS(O)_2R^{s2}$, $-S(O)_mR^{t2}$, $-S(O)_2N(R^{u2})R^{v2}$,
 heterocycloalkyl optionally substituted by one or more substituents selected from W^5 , aryl represented by



- 10 heteroaryl having 1 to 3 nitrogen atoms, one oxygen atom and/or one sulfur atom and optionally substituted by one or more substituents selected from W^6 , or =O;

- each Z^2 and Z^3 independently represents halogen, $-R^{a2}$, -CN, $-C(O)R^{b2}$,
 $-C(O)N(R^{c2})R^{d2}$, $-C(O)OR^{e2}$, $-N(R^{f2})R^{g2}$, $-N(R^{h2})C(O)R^{i2}$, $-N(R^{j2})C(O)OR^{k2}$,
 15 $-N(R^{l2})C(O)N(R^{m2})R^{n2}$, $-N(R^{o2})S(O)_2R^{p2}$, $-OR^{q2}$, $-OC(O)R^{r2}$, $-OS(O)_2R^{s2}$, $-S(O)_mR^{t2}$,
 $-S(O)_2N(R^{u2})R^{v2}$, heterocycloalkyl optionally substituted by one or more
 substituents selected from W^5 , aryl optionally substituted by one or more
 substituents selected from W^6 , or heteroaryl optionally substituted by one or more
 substituents selected from W^6 ;

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- each Z^4 independently represents halogen, -CN, $-C(O)R^{b2}$, $-C(O)N(R^{c2})R^{d2}$,
 $-C(O)OR^{e2}$, $-N(R^{f2})R^{g2}$, $-N(R^{h2})C(O)R^{i2}$, $-N(R^{j2})C(O)OR^{k2}$, $-N(R^{l2})C(O)N(R^{m2})R^{n2}$,
 $-N(R^{o2})S(O)_2R^{p2}$, $-OR^{q2}$, $-OC(O)R^{r2}$, $-OS(O)_2R^{s2}$, $-S(O)_mR^{t2}$, $-S(O)_2N(R^{u2})R^{v2}$,
 heterocycloalkyl optionally substituted by one or more substituents selected from
 25 W^5 , aryl optionally substituted by one or more substituents selected from W^6 ,
 heteroaryl optionally substituted by one or more substituents selected from W^6 , or
 =O;

- each R^{a2} , R^{b2} , R^{c2} , R^{d2} , R^{e2} , R^{f2} , R^{h2} , R^{i2} , R^{j2} , R^{l2} , R^{m2} , R^{n2} , R^{o2} , R^{q2} , R^{r2} , R^{t2} , R^{u2}
 30 and R^{v2} independently represents hydrogen, C_{1-6} alkyl optionally substituted by
 one or more substituents selected from W^4 , heterocycloalkyl optionally substituted
 by one or more substituents selected from W^5 , aryl optionally substituted by one

or more substituents selected from W^6 , or heteroaryl optionally substituted by one or more substituents selected from W^6 ; or

any two R^{c2} and R^{d2} , R^{f2} and R^{g2} , R^{m2} and R^{n2} and/or R^{u2} and R^{v2} are linked
 5 together to form, along with the nitrogen atom to which they are attached, a 3- to 8-membered monocyclic or bicyclic ring, which ring optionally contains one or two heteroatoms and which ring optionally is substituted by one or more substituents selected from W^5 , C_{1-3} alkyl optionally substituted by one or more substituents selected from W^4 , and =O;

10

each R^{g2} , R^{k2} , R^{p2} and R^{s2} independently represents C_{1-6} alkyl optionally substituted by one or more substituents selected from W^4 , heterocycloalkyl optionally substituted by one or more substituents selected from W^5 , aryl optionally substituted by one or more substituents selected from W^6 , or heteroaryl
 15 optionally substituted by one or more substituents selected from W^6 ;

20

each W^1 and W^4 independently represents halogen, -CN, $-N(R^{f3})R^{g3}$, $-N(R^{h3})C(O)R^{i3}$, $-N(R^{j3})C(O)OR^{k3}$, $-N(R^{l3})C(O)N(R^{m3})R^{n3}$, $-N(R^{o3})S(O)_2R^{p3}$, $-OR^{q3}$, $-OC(O)R^{r3}$, $-OS(O)_2R^{s3}$, $-S(O)_mR^{t3}$, $-S(O)_2N(R^{u3})R^{v3}$, heterocycloalkyl optionally substituted by one or more substituents selected from G^1 , aryl optionally substituted by one or more substituents selected from G^2 , heteroaryl optionally substituted by one or more substituents selected from G^2 , or =O;

25

each W^2 , W^3 , W^5 and W^6 independently represents halogen, $-R^{a3}$, -CN, $-C(O)R^{b3}$, $-C(O)N(R^{c3})R^{d3}$, $-C(O)OR^{e3}$, $-N(R^{f3})R^{g3}$, $-N(R^{h3})C(O)R^{i3}$, $-N(R^{j3})C(O)OR^{k3}$, $-N(R^{l3})C(O)N(R^{m3})R^{n3}$, $-N(R^{o3})S(O)_2R^{p3}$, $-OR^{q3}$, $-OC(O)R^{r3}$, $-OS(O)_2R^{s3}$, $-S(O)_mR^{t3}$, $-S(O)_2N(R^{u3})R^{v3}$, heterocycloalkyl optionally substituted by one or more substituents selected from G^1 , aryl optionally substituted by one or more substituents selected from G^2 , heteroaryl (optionally substituted by one or more substituents selected from G^2 , or =O;

30

each W^7 , W^8 , W^9 , W^{10} and W^{11} independently represents hydrogen, halogen, $-R^{a3}$, -CN, $-C(O)R^{b3}$, $-C(O)N(R^{c3})R^{d3}$, $-C(O)OR^{e3}$, $-N(R^{f3})R^{g3}$, $-N(R^{h3})C(O)R^{i3}$, $-N(R^{j3})C(O)OR^{k3}$, $-N(R^{l3})C(O)N(R^{m3})R^{n3}$, $-N(R^{o3})S(O)_2R^{p3}$, $-OR^{q3}$, $-OC(O)R^{r3}$, $-OS(O)_2R^{s3}$, $-S(O)_mR^{t3}$, $-S(O)_2N(R^{u3})R^{v3}$, heterocycloalkyl optionally substituted by

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one or more substituents selected from G^1 , aryl optionally substituted by one or more substituents selected from G^2 , or heteroaryl optionally substituted by one or more substituents selected from G^2 ;

- 5 each R^{a3} , R^{b3} , R^{c3} , R^{d3} , R^{e3} , R^{f3} , R^{h3} , R^{i3} , R^{j3} , R^{l3} , R^{m3} , R^{n3} , R^{o3} , R^{q3} , R^{r3} , R^{t3} , R^{u3} and R^{v3} independently represents hydrogen or C_{1-6} alkyl optionally substituted by one or more G^3 ; or

- any two R^{c3} and R^{d3} , R^{f3} and R^{g3} , R^{m3} and R^{n3} and/or R^{u3} and R^{v3} are linked
10 together to form, along with the nitrogen atom to which they are attached, a 4- to 6-membered ring, which ring optionally contains one heteroatom and which ring optionally is substituted by one or more G^2 ;

- each R^{g3} , R^{k3} , R^{p3} , R^{q3} and R^{s3} independently represents C_{1-6} alkyl optionally
15 substituted by one or more G^3 ;

- each G^1 and G^2 independently represents halogen, $-R^{a4}$, $-CN$, $-C(O)R^{b4}$,
 $-C(O)N(R^{c4})R^{d4}$, $-C(O)OR^{e4}$, $-N(R^{f4})R^{g4}$, $-N(R^{h4})C(O)R^{i4}$, $-N(R^{j4})C(O)OR^{k4}$,
 $-N(R^{l4})C(O)N(R^{m4})R^{n4}$, $-N(R^{o4})S(O)_2R^{p4}$, $-OR^{q4}$, $-OC(O)R^{r4}$, $-OS(O)_2R^{s4}$, $-S(O)_mR^{t4}$,
20 $-S(O)_2N(R^{u4})R^{v4}$, or $=O$;

- G^3 represents halogen, $-CN$, $-C(O)R^{b4}$, $-C(O)N(R^{c4})R^{d4}$, $-C(O)OR^{e4}$, $-N(R^{f4})R^{g4}$,
 $-N(R^{h4})C(O)R^{i4}$, $-N(R^{j4})C(O)OR^{k4}$, $-N(R^{l4})C(O)N(R^{m4})R^{n4}$, $-N(R^{o4})S(O)_2R^{p4}$, $-OR^{q4}$,
 $-OC(O)R^{r4}$, $-OS(O)_2R^{s4}$, $-S(O)_mR^{t4}$, $-S(O)_2N(R^{u4})R^{v4}$, or $=O$;
25

each R^{a4} , R^{b4} , R^{c4} , R^{d4} , R^{e4} , R^{f4} , R^{h4} , R^{i4} , R^{j4} , R^{l4} , R^{m4} , R^{n4} , R^{o4} , R^{q4} , R^{r4} , R^{t4} , R^{u4} and R^{v4} independently represents hydrogen or C_{1-6} alkyl optionally substituted by one or more $-F$; or

- 30 any two R^{c4} and R^{d4} , R^{f4} and R^{g4} , R^{m4} and R^{n4} and/or R^{u4} and R^{v4} are linked together to form, along with the nitrogen atom to which they are attached, a 3- to 6-membered ring, which ring optionally substituted by one or more $-F$, $-CH_3$, $-CH_2CH_3$, $-CHF_2$, $-CF_3$, $-CH_2CF_3$, or $=O$;

each R^{g4} , R^{k4} , R^{p4} and R^{s4} independently represent C_{1-6} alkyl optionally substituted by one or more -F;

each m independently represents 0, 1 or 2;

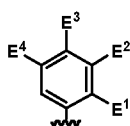
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provided that the compound is not

*N*⁴-cyclopropyl-6-(4-methoxy-2-methylphenyl)-2,4-pyrimidinediamine.

30. A compound as claimed in Claim 29, wherein:

10 R^1 is represented by



and;

E^3 and E^4 represent hydrogen; and

E^1 represents -F and E^2 represent -F, -Cl, -CH₃ or -CF₃; or

E^1 represents -Cl and E^2 represents -F, -Cl, -CH₃ or -CF₃; or

15 E^1 represents -CH₃ and E^2 represents -F, -Cl, -CH₃, -CF₃, -CN or -N(H)C(O)CH=CH₂; or

E^2 and E^4 represent hydrogen; and

E^1 represents -F and E^3 represents -F or phenyl; or

E^1 represents -Cl and E^3 represents -F or -Cl; or

20 E^1 represents -CH₃ and E^3 represents -Cl or -OCH₂phenyl; or

E^1 represents -OCH₃ and E^3 represents -F; or

E^2 and E^3 represent hydrogen; and

E^1 represents -F and E^4 represents -Cl, -CH₃ or -CN; or

E^1 represents -Cl and E^4 represent -F, -Cl, -CH₃, -CF₃ or -OCH₃; or

25 E^1 represents -CH₃ and E^4 represent -F, -Cl, -CH₃, -CF₃, -CN,

-N(H)C(O)CH=CH₂ or -S(O)₂(4-morpholinyl); or

E^1 represents -CF₃ and E^4 represents -F or -CF₃; or

E^1 represents -CN and E^4 represents -Cl; or

E^1 represents -OCH₃ and E^4 represents -F, -Cl, Br, -CH₃, -CH(CH₃)₂, -C(CH₃)₃,

30 -CN or -OCH₃; or

E^1 and E^4 represent hydrogen; and

E^2 represents -F and E^3 represents -F, -Cl, -OH or -OCH₃; or

E^2 represents -Cl and E^3 represents -F or -C(O)(4-morpholinyl); or

- E² represents -CH₃ and E³ represents -F or -OCH₃; or
E¹ represents -OCH₃ and E³ represents -OH; or
E¹ represents -CH₂OCH₃ and E³ represents (piperidin-4-yl)methoxy or
((1-*tert*butoxycarbonyl)piperidin-4-yl)methoxy; or
- 5 E¹ and E³ represent hydrogen; and
E² and E⁴ represent -F; or
E² and E⁴ represent -CF₃; or
E⁴ represents hydrogen; and
E¹, E² and E³ represent -F; or
- 10 E¹ and E² represent -Cl and E³ represents -Cl, -OH or -OCH₃; or
E¹ and E² represent -CH₃ and E³ represents -F or -OCH₃; or
E² and E³ represent -Cl and E¹ represents -CH₃; or
E² represents hydrogen; and
E¹, E³ and E⁴ represent -F; or
- 15 E³ and E⁴ represent -Cl and E¹ represents -CH₃; or
E¹ and E⁴ represent -Cl and E¹ represents -OCH₃; or
E¹ and E⁴ represent -CH₃ and E³ represents -F, -CH₃ or -OCH₃; or
E¹ represents -F, E³ represents -CH₃ and E⁴ represents -Cl; or
E¹ represents -Cl, E³ represents -F and E⁴ represents -CH₃; or
- 20 E¹ represents -Cl, E³ represents -CH₃ and E⁴ represents -F; or
E¹ and E⁴ represent -CH₃ and E³ represents -F; or
E¹ represents -CH₃, E⁴ represents -Cl and E³ represents -CF₃ or -OCH₃; or
E¹ represents hydrogen; and
E² and E⁴ represent -CH₃ and E³ represents -OH; or
- 25 E³ represents hydrogen; and
E¹ and E² represent -Cl and E⁴ represents -CH₃.
31. A compound as claimed in Claim 30, wherein:
E³ and E⁴ represent hydrogen; and
- 30 E¹ represents -F and E² represents -F, -Cl, or -CF₃; or
E¹ represents -Cl and E² represents -Cl, -CH₃ or -CF₃; or
E¹ represents -CH₃ and E² represents -Cl, -CH₃, -CN or -N(H)C(O)CH=CH₂; or
E² and E⁴ represent hydrogen; and
E¹ and E³ represent -F; or
- 35 E¹ represents -Cl and E³ represents -F or -Cl; or

- E^1 represents $-CH_3$ and E^3 represents $-Cl$; or
 E^2 and E^3 represent hydrogen; and
 E^1 represents $-F$ and E^4 represents $-Cl$, $-CH_3$ or $-CN$; or
 E^1 represents $-Cl$ and E^4 represents $-F$, $-Cl$, $-CH_3$ or $-CF_3$; or
 5 E^1 represents $-CH_3$ and E^4 represent, $-Cl$, $-CH_3$, $-CF_3$, $-CN$ or $-N(H)C(O)CH=CH$; or
 E^1 represents $-CF_3$ and E^4 represents $-F$ or $-CF_3$; or
 E^1 represents $-CN$ and E^4 represents $-Cl$; or
 E^4 represents hydrogen; and
 10 E^1 , E^2 and E^3 represent $-F$; or
 E^1 and E^2 represent $-CH_3$ and E^3 represents $-F_3$; or
 E^2 and E^3 represent $-Cl$ and E^1 represents $-CH_3$; or
 E^2 represents hydrogen; and
 E^1 , E^3 and E^4 represent $-F$; or
 15 E^3 and E^4 represent $-Cl$ and E^1 represents $-CH_3$; or
 E^1 and E^4 represent $-CH_3$ and E^3 represents $-F$ or $-CH_3$; or
 E^1 represents $-F$, E^3 represents $-CH_3$ and E^4 represents $-Cl$; or
 E^1 represents $-Cl$, E^3 represents $-F$ and E^4 represents $-CH_3$; or
 E^1 represents $-Cl$, E^3 represents $-CH_3$ and E^4 represents $-F$; or
 20 E^1 and E^4 represent $-CH_3$ and E^3 represents $-F$; or
 E^1 represents $-CH_3$, E^3 represents $-CF_3$ and E^4 represents $-Cl$; or
 E^1 represents hydrogen; and
 E^2 and E^4 represent $-CH_3$ and E^3 represents $-OH$; or
 E^3 represents hydrogen; and
 25 E^1 and E^2 represent $-Cl$ and E^4 represents $-CH_3$.

32. A compound as claimed in any one of Claims 29 to 31, wherein:
 R^2 represents hydrogen, halogen, $-CN$ or $-C_{1-6}$ alkyl optionally substituted by one
 or more Z^1 .

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33. A compound as claimed in Claim 32, wherein:
 R^2 represents hydrogen or methyl.

34. A compound as claimed in any one of Claims 29 to 33, wherein:
 35 R^3 represents $-C_{1-6}$ alkyl optionally substituted by Z^1 .

35. A compound as claimed in any one of Claims 29 to 33, wherein:

R^3 represents $-C_{2-6}$ alkyl optionally substituted by Z^1 or heterocycloalkyl optionally substituted by Z^2 .

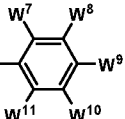
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36. A compound as claimed in any one of Claims 29 to 33, wherein:

R^3 represents $-C_{1-2}$ alkyl optionally substituted with one or more -F.

37. A compound as claimed in any one of Claims 29 to 33, wherein:

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R^3 represents $-\text{CH}_2-$  .

38. A compound as claimed in any one of Claims 29 to 33, wherein:

R^3 represents $-C_{1-6}$ alkyl substituted by heteroaryl having 1 to 3 nitrogen atoms, one oxygen atom and/or one sulfur atom and which heteroaryl is optionally

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substituted by one or more substituents selected from W^3

39. A compound as claimed in any one of Claims 29 to 33, wherein:

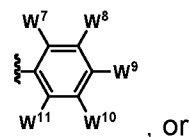
R^3 represents $-C_{3-6}$ alkyl or a heterocycloalkyl selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclopropylethyl, cyclobutylethyl, cyclopropylpropyl, oxetanyl, tetrahydrofuryl, tetrahydropyranyl, azetidiny, pyrrolidinyl, piperidinyl, piperazinyl or morpholinyl wherein the C_{3-6} alkyl is optionally substituted by Z^1 and the heterocycloalkyl is optionally substituted by Z^2 .

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40. A compound as claimed in any one of Claims 34, 35, 38 and 39 wherein:

Z^1 represents -F, -CN, $-\text{C}(\text{O})\text{R}^{b2}$, $-\text{C}(\text{O})\text{N}(\text{R}^{c2})\text{R}^{d2}$, $-\text{C}(\text{O})\text{OR}^{e2}$, $-\text{N}(\text{R}^{f2})\text{R}^{g2}$, $-\text{N}(\text{R}^{h2})\text{C}(\text{O})\text{R}^{i2}$, $-\text{N}(\text{R}^{j2})\text{C}(\text{O})\text{OR}^{k2}$, $-\text{N}(\text{R}^{l2})\text{C}(\text{O})\text{N}(\text{R}^{m2})\text{R}^{n2}$, $-\text{N}(\text{R}^{o2})\text{S}(\text{O})_2\text{R}^{p2}$, $-\text{OR}^{q2}$, $-\text{S}(\text{O})_m\text{R}^{l2}$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{u2})\text{R}^{v2}$, heterocycloalkyl optionally substituted by one or more substituents selected from W^5 , aryl represented by

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heteroaryl having 1 to 3 nitrogen atoms, one oxygen atom and/or one sulfur atom and optionally substituted by one or more substituents selected from W⁶.

41. A compound as claimed in Claim 40 wherein:

- 5 Z¹ represents -F, -CN, -C(O)NH₂, -C(O)N(R^{c2})R^{d2}, -C(O)-(4-morpholinyl), -C(O)OEt, -N(H)C(O)Me, -N(H)C(O)Rⁱ², -N(H)C(O)CH₂NMe₂, -N(H)C(O)OCMe₃, -N(H)C(O)OCH₂Ph, -N(Me)C(O)OCMe₃, -N(H)C(O)N(H)Me, -N(H)C(O)N(H)CHMe₂, -N(H)S(O)₂Me, -OMe, -OCF₃, -OEt, or heterocycloalkyl selected from dihydropyridinyl, imidazoliny, morpholinyl, oxanyl, piperazinyl, 10 piperidinyl, pyrrolidinyl and quinuclidinyl, wherein the heterocycloalkyl is optionally substituted by one or more substituents selected from W⁵.

42. A compound as claimed in Claim 40 wherein:

- each W⁷, W¹⁰ and W¹¹ independently represents hydrogen, halogen, -R^{a3} or -CN; 15 and one of W⁸ and W⁹ represents hydrogen, halogen, -R^{a3} or -CN and the other represents halogen, -R^{a3}, -CN, -C(O)R^{b3}, -C(O)N(R^{c3})R^{d3}, -C(O)OR^{e3}, -N(R^{f3})R^{g3}, -N(R^{h3})C(O)Rⁱ³, -N(R^{j3})C(O)OR^{k3}, -N(R^{l3})C(O)N(R^{m3})Rⁿ³, -N(R^{o3})S(O)₂R^{p3}, -OR^{q3x}, -OC(O)R^{r3}, -OS(O)₂R^{s3}, -S(O)_mR^{t3}, -S(O)₂N(R^{u3})R^{v3}, heterocycloalkyl optionally substituted by one or more substituents selected from G¹, aryl optionally 20 substituted by one or more substituents selected from G², or heteroaryl optionally substituted by one or more substituents selected from G².

43. A compound as claimed in any one of Claims 29 to 31, wherein:

- R² and R³ are linked together to form, along with the atoms to which they are 25 attached, a 5- to 6-membered non-aromatic ring, wherein the link formed by R² and R³ is optionally substituted by one or more substituents selected from Z³ or -C₁₋₉alkyl optionally substituted by one or more Z⁴.

44. A compound as claimed in Claim 43, wherein:

- 30 Z³ is not present or is selected from -F, -R^{a2}, -C(O)N(R^{c2})R^{d2}, -N(R^{f2})R^{g2}, -N(R^{h2})C(O)Rⁱ², -N(R^{j2})C(O)OR^{k2}, -N(R^{l2})C(O)N(R^{m2})Rⁿ², -N(R^{o2})S(O)₂R^{p2}, -OR^{q2}, -S(O)_mR^{t2}, -S(O)₂N(R^{u2})R^{v2}, heterocycloalkyl optionally substituted by one or more substituents selected from W⁵, aryl optionally substituted by one or more substituents selected from W⁶, or heteroaryl optionally substituted by one or more 35 substituents selected from W⁶; and/or

- (b) Z^4 is not present or is selected from $-F$, $-C(O)N(R^{c2})R^{d2}$, $-N(R^{f2})R^{g2}$, $-N(R^{h2})C(O)R^{i2}$, $-N(R^{j2})C(O)OR^{k2}$, $-N(R^{l2})C(O)N(R^{m2})R^{n2}$, $-N(R^{o2})S(O)_2R^{p2}$, $-OR^{q2}$, $-S(O)_mR^{l2}$, $-S(O)_2N(R^{u2})R^{v2}$, heterocycloalkyl optionally substituted by one or more substituents selected from W^5 , aryl optionally substituted by one or more substituents selected from W^6 , or heteroaryl optionally substituted by one or more substituents selected from W^6 .

45. A pharmaceutical formulation comprising a compound as claimed in any one of Claims 15 to 44, or a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

46. A pharmaceutical formulation as claimed in Claim 45, for use in the treatment of cancer.

47. A compound as claimed in any one of the claims 15 to 44, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer.

48. A compound for use as claimed in any one of Claims 1 to 14, or a formulation for use as claimed in Claim 46, or a compound for use as claimed in Claim 47, wherein the disease is selected from Soft Tissue Cancers: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung cancers/diseases: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal cancers/diseases: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma); Genitourinary tract cancers/diseases: kidney (adenocarcinoma, Wilm's tumor [nephroblastoma], lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis

(seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver cancers/diseases: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Bone cancers/diseases: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochondroma (osteochondrogenous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system cancers/diseases: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma [pinealoma], glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological cancers/diseases: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma [serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma], granulosa-thecal cell tumors, Sertoli- Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma); Hematologic cancers/diseases: blood and bone marrow (myeloid leukemia [acute and chronic], acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma [malignant lymphoma]; Skin cancers/diseases: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids; Adrenal glands cancers/diseases, neuroblastoma, neurofibromatosis and head and neck cancers.

49. A compound or formulation for use as claimed in Claim 48, wherein the cancer is selected from the group consisting of breast cancers, prostate cancers, lung cancers, oesophageal cancers, colon cancers, brain cancers, skin cancers, ovarian cancers, testicular cancers, neurofibromatosis and leukemias.

50. A compound as claimed in any one of the Claims 15 to 44, or a pharmaceutically acceptable salt thereof, for use as a pharmaceutical.

- 5 51. A combination product comprising:
(A) a compound as claimed in any one of Claims 15 to 44, or a pharmaceutically acceptable salt thereof; and
(B) one or more other therapeutic agent(s) that is/are useful in the treatment of a disease as defined in Claim 48 or 49,
10 wherein each one of components (A) and (B) is formulated in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier.

52. A combination product as claimed in Claim 51, wherein component (B) is selected from the group consisting of anti-microtubule agents, platinum
15 coordination complexes, alkylating agents, antibiotic agents, topoisomerase II inhibitors, antimetabolites, topoisomerase I inhibitors, hormones and hormonal analogues, signal transduction pathway inhibitors; kinase inhibitors; angiogenesis inhibitors; immunotherapeutic agents; pro-apoptotic agents; and cell cycle
signaling inhibitors.

- 20 53. A method of treatment of a disease as defined in Claim 48 or 49, which method comprises administration of a therapeutically effective amount of a compound for use as claimed in any one of the Claims 1 to 14 or a compound as claimed in any one of Claims 15 to 44, or a pharmaceutically acceptable salt
25 thereof, to a patient in need of such treatment.

54. A compound for use as claimed in any one of Claims 1 to 14 or Claim 47, wherein the treatment further comprises radiation therapy.

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