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[54]	Title:	PYRIMIDINE-2,4-DIAMINE DERIVATIVES FOR TREATMENT OF CANCER		
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[57]	Abstract:	A compound of formula (I), or a pharmaceutically-acceptable salt thereof. The compound is useful in the treatment of cancer or other diseases that may benefit from inhibition of MTH1.		

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

Field of the Invention

The invention relates to novel compounds, compositions and methods for 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

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

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, 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 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 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cancer cell survival, premature senescence and DNA strand breaks (Rai et al, PNAS, 106(1)2009:169-174), Helleday et al unpublished data).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-/- 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 shrinked the tumour (Helleday et al, unpublished data).

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.

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.

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.

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

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.

International patent application WO 2006/078886 describes 2,4-diaminopyrimidines 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 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-hydroxyphenethyl. Several scientific publications describe the use of one of the compounds (*N*4-(1,3-benzodioxol-5-ylmethyl)-6-(3-methoxyphenyl)-2,4-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 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, 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-alkylaminogroup 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 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.

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*-alkyl-amino)-6-arylpyrimidines.

Summary of the invention

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 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 achieved by inhibition of MTH1

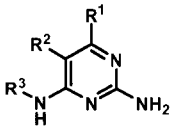
Brief description of the drawings

Figure 1. Effect on cell survival following MTH1 siRNA depletion in various human 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)

Detailed description of the Invention

There is provided a compound of formula I,

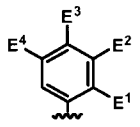


(I)

for use in the treatment of cancer

wherein:

R^1 represents heteroaryl connected to the pyrimidine of formula I via a carbon atom of the heteroaryl ring, which heteroaryl ring 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



;

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;

E^3 and E^4 each idependently 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;

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

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 -C_{1-9}alkyl optionally substituted by one or more Z^4;

each 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, -$N(R^n)S(O)_2R^o$, -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 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, -$N(R^n)S(O)_2R^o$, -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;

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^{py}, -$OC(O)R^q$, -$OS(O)_2R^r$, -$S(O)_mR^s$, -$S(O)_2N(R^t)R^u$, 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;

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 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 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;

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;

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;

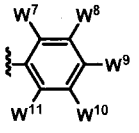
each Y^3 independently represents halogen, $-R^{a1}$, -CN, $-C(O)R^{b1}$, $-C(O)N(R^{c1})R^{d1}$, $-C(O)OR^{e1}$, $-N(R^{f1})R^{g1}$, $-N(R^{h1})C(O)R^{i1}$, $-N(R^{j1})C(O)OR^{k1}$, $-N(R^{l1})C(O)N(R^{m1})R^{n1}$, $-N(R^{o1})S(O)_2R^{p1}$, $-OR^{q1}$, $-OC(O)R^{r1}$, $-OS(O)_2R^{s1}$, $-S(O)_mR^{t1}$, $-S(O)_2N(R^{u1})R^{v1}$, 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;

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

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;

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, $-C(O)R^{b2}$, $-C(O)N(R^{c2})R^{d2}$, $-C(O)OR^{e2}$, $-N(R^{f2})R^{g2}$, $-N(R^{h2})C(O)R^{i2}$, $-N(R^{j2})C(O)OR^{k2}$, $-N(R^{l2})C(O)N(R^{m2})R^{n2}$, $-N(R^{o2})S(O)_2R^{p2}$, $-OR^{q2}$, $-OC(O)R^{r2}$, $-OS(O)_2R^{s2}$, $-S(O)_mR^{t2}$, $-S(O)_2N(R^{u2})R^{v2}$, 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, or =O;

each Z^2 and Z^3 independently represents halogen, $-R^{a2}$, -CN, $-C(O)R^{b2}$, $-C(O)N(R^{c2})R^{d2}$, $-C(O)OR^{e2}$, $-N(R^{f2})R^{g2}$, $-N(R^{h2})C(O)R^{i2}$, $-N(R^{j2})C(O)OR^{k2}$, $-N(R^{l2})C(O)N(R^{m2})R^{n2}$, $-N(R^{o2})S(O)_2R^{p2}$, $-OR^{q2}$, $-OC(O)R^{r2}$, $-OS(O)_2R^{s2}$, $-S(O)_mR^{t2}$, $-S(O)_2N(R^{u2})R^{v2}$, 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 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 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 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;

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;

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, $-C(O)R^{b3}$, $-C(O)N(R^{c3})R^{d3}$, $-C(O)OR^{e3}$, $-N(R^{f3})R^{g3}$, $-N(R^{h3})C(O)R^{i3}$, $-N(R^{j3})C(O)OR^{k3}$, $-N(R^{l3})C(O)N(R^{m3})R^{n3}$, $-N(R^{o3})S(O)_2R^{p3}$, $-OR^{q3}$, $-OC(O)R^{r3}$, $-OS(O)_2R^{s3}$, $-S(O)_mR^{t3}$, $-S(O)_2N(R^{u3})R^{v3}$, 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;

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

W^9 represents hydrogen, halogen, $-R^{a3}$, -CN, $-C(O)R^{b3}$, $-C(O)N(R^{c3})R^{d3}$, $-C(O)OR^{e3}$, $-N(R^{f3})R^{g3}$, $-N(R^{h3})C(O)R^{i3}$, $-N(R^{j3})C(O)OR^{k3}$, $-N(R^{l3})C(O)N(R^{m3})R^{n3}$, $-N(R^{o3})S(O)_2R^{p3}$, $-OR^{q3x}$, $-OC(O)R^{r3}$, $-OS(O)_2R^{s3}$, $-S(O)_mR^{t3}$, $-S(O)_2N(R^{u3})R^{v3}$, 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;

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 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 substituted by one or more G^3;

R^{q3x} represents C_{2-6} alkyl optionally substituted by one or more G^3;

each G^1 and G^2 independently represents halogen, $-R^{a4}$, -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;

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;

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

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;

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

or a pharmaceutically acceptable salt thereof;

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 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.

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.

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.

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 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, 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, imidazolinyl, morpholinyl, 7-oxabicyclo[2.2.1]heptanyl, 6-oxabicyclo[3.2.1]-octanyl, oxetanyl, oxiranyl, piperazinyl, 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).

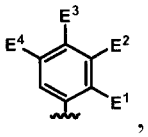
The term "aryl", when used herein, includes C_{6-14} (e.g. C_{6-10}) aromatic groups. Such groups may be monocyclic or bicyclic and, when bicyclic, be either wholly or partly aromatic. C_{6-10} aryl groups that may be mentioned include phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, indanyl, and the like (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.

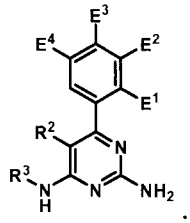
For the avoidance of doubt, in cases in which the identity of two or more substituents in a compound of the invention may be the same, the actual identities of the respective substituents are not in any way interdependent.

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

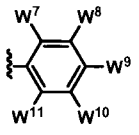


,

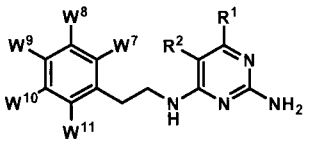
it is connected to the rest of formula I by the bond interrupted by the wiggly line, and formula I can thus be represented by



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



then, if e.g. R^3 is C_2alkyl, 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 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.

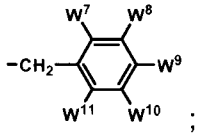
Particular compounds of formula I that may be mentioned include those in which:
R^2 represents hydrogen or -C_{1-12}alkyl optionally substituted by one or more Z^1; and
R^3 represents -C_{1-12}alkyl optionally substituted by one or more Z^1 or heterocycloalkyl optionally substituted by one or more Z^2.

For example, compounds of formula I that may be mentioned include those in which R^2 represents methyl, or preferably, hydrogen and R^3 represents:

(a) -C_{1-12}alkyl (for example -C_{1-6}alkyl) optionally substituted by two, or preferably, one Z^1 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

(d) 

;

(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, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl or morpholinyl 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 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.

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-aromaticring 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.

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.

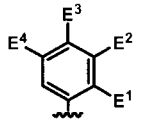
Particular compounds of formula I that may be mentioned include those in which R^1 represents heteroaryl.

Preferred compounds of formula I where R^1 represents heteroaryl that may be 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 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, 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 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.

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

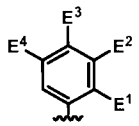
E^1 represents hydrogen, or more preferably -F, -Cl, $-CH_3$, $-CF_3$, CN or $-OCH_3$; or E^1, E^3 and E^4 represent hydrogen and

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-methylphenyl), , $-N(H)C(O)CH_3$, $-N(H)C(O)CH{=}CH_2$, $-N(H)C(O)CH{=}CHCH_2NMe_2$, $-N(H)C(O)CH{=}CHPh$, $-N(H)C(O)C{\equiv}CH$, -N(H)C(O)(2-hydroxyphenyl), -N(H)C(O)(6-hydroxypyrid-2-yl), -N(H)C(O)(5-chloro-2-hydroxyphenyl), $-N(H)C(O)CH_2CH_2C(O)$(1-pyrrolidinyl), $-N(H)C(O)CH_2(OH)$, -N(H)C(O)CH(OH)Ph, $-N(H)C(O)C(O)CH_3$, -N(H)C(O)C(O)Ph, $-N(H)S(O)_2CH{=}CH_2$, or $-OCH_3$; or

E^1, E^2 and E^4 represent hydrogen and

E^3 represent -F, -Cl, $-CH_3$, $-CF_3$, $-C(CH_3)_3$, $-CH{=}CH_2$, $-CH{=}CHC(O)OH$, $-CH{=}CHC(O)OCH_3$, $-CH_2NH_2$, , -CN, $-CH_2N(H)C(O)CH{=}CH_2$, $-CH_2OH$, -C(O)H, $C(O)CH_3$, $-C(O)CF_3$, $-C(O)N(H)CH_3$, $-C(O)N(H)CH_2$(2-furanyl), -C(O)(4-morpholinyl), -C(O)OH, $-C(O)OCH_3$, $-N(H)C(O)CH_3$, $-N(H)C(O)CH{=}CH_2$, $-N(H)S(O)_2CH_3$, $-OCH(CH_3)_2$, $-OCH_3$, $-OCF_3$, $-S(O)_2CH_3$, or $-S(O)_2$(4-morpholinyl).

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



where:

E^3 and E^4 represent hydrogen; and

E^1 represents -F and E^2 represent -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, $-CH_3$, $-CF_3$, -CN or $-N(H)C(O)CH{=}CH_2$; 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

E^1 represents $-CH_3$ and E^3 represents -Cl or $-OCH_2$phenyl; 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 represent -F, -Cl, $-CH_3$, $-CF_3$ or $-OCH_3$; or

E^1 represents $-CH_3$ and E^4 represent -F, -Cl, $-CH_3$, $-CF_3$, -CN, $-N(H)C(O)CH=CH_2$ or $-S(O)_2$(4-morpholinyl); 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

E^1 and E^4 represent hydrogen; and

E^2 represents -F and E^3 represents -F, -Cl, -OH or $-OCH_3$; or

E^2 represents -Cl and E^3 represents -F or -C(O)(4-morpholinyl); or

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

E^1 represents $-OCH_3$ and E^3 represents -OH; or

E^1 represents-CH_2OCH_3 and E^3 represents (piperidin-4-yl)methoxy or ((1-*tert*butoxycarbonyl)piperidin-4-yl)methoxy; or

E^1 and E^3 represent hydrogen; and

E^2 and E^4 represent -F; or

E^2 and E^4 represent $-CF_3$; 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 $-OCH_3$; 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

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

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

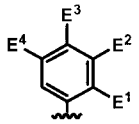
E^1 represents hydrogen; and

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 $-CH_3$.

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



where:

E^1, E^3 and E^4 represent hydrogen and

E^2 represents $-CH=CHC(O)OCH_3$, $-CH_2NH_2$, $-CH_2N(H)C(O)CH=CH_2$, $-CH_2OH$, $-N(H)C(O)CH=CH_2$, $-N(H)C(O)CH=CHCH_2NMe_2$, -N(H)C(O)CH=CHPh, $-N(H)C(O)C\equiv CH$, $-N(H)C(O)CH_2(OH)$, -N(H)C(O)CH(OH)Ph, $-N(H)C(O)C(O)CH_3$, $-N(H)C(O)C(O)Ph$ or $-N(H)S(O)_2CH=CH_2$; or

E^1, E^2 and E^4 represent hydrogen and

E^3 represents $-CH=CH_2$, $-CH=CHC(O)OH$, $-CH=CHC(O)OCH_3$, $-CH_2NH_2$, $-CH_2N(H)C(O)CH=CH_2$, $-CH_2OH$, -C(O)H, $-C(O)CH_3$, $-C(O)CF_3$, $-N(H)C(O)CH=CH_2$; or

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

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, $-CH_3$ or -CN; or

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

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

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

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

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

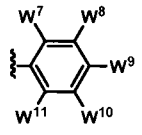
E^2 and E^4 represent $-CH_3$ and E^3 represents -OH; or

E^3 represents hydrogen; and

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

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, $-C(O)R^{b2}$, $-C(O)N(R^{c2})R^{d2}$, $-C(O)OR^{e2}$, $-N(R^{f2})R^{g2}$, $-N(R^{h2})C(O)R^{i2}$, $-N(R^{j2})C(O)OR^{k2}$, $-N(R^{l2})C(O)N(R^{m2})R^{n2}$, $-N(R^{o2})S(O)_2R^{p2}$, $-OR^{q2}$, $-S(O)_mR^{t2}$, $-S(O)_2N(R^{u2})R^{v2}$, heterocycloalkyl optionally substituted by one or more substituents selected from W^5, aryl 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, $-R^{a2}$, $-C(O)N(R^{c2})R^{d2}$, $-N(R^{f2})R^{g2}$, $-N(R^{h2})C(O)R^{i2}$, $-N(R^{j2})C(O)OR^{k2}$, $-N(R^{l2})C(O)N(R^{m2})R^{n2}$, $-N(R^{o2})S(O)_2R^{p2}$, $-OR^{q2}$, $-S(O)_mR^{t2}$, $-S(O)_2N(R^{u2})R^{v2}$, 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.

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, $-R^{a2}$, $-C(O)N(R^{c2})R^{d2}$, $-N(R^{f2})R^{g2}$, $-N(R^{h2})C(O)R^{i2}$, $-N(R^{j2})C(O)OR^{k2}$, $-N(R^{l2})C(O)N(R^{m2})R^{n2}$, $-N(R^{o2})S(O)_2R^{p2}$, $-OR^{q2}$, $-S(O)_mR^{t2}$, $-S(O)_2N(R^{u2})R^{v2}$, 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; and/or

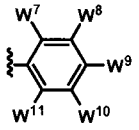
(b) Z^4 is not present or is selected from -F, $-C(O)N(R^{c2})R^{d2}$, $-N(R^{f2})R^{g2}$, $-N(R^{h2})C(O)R^{i2}$, $-N(R^{j2})C(O)OR^{k2}$, $-N(R^{l2})C(O)N(R^{m2})R^{n2}$, $-N(R^{o2})S(O)_2R^{p2}$, $-OR^{q2}$, $-S(O)_mR^{t2}$, $-S(O)_2N(R^{u2})R^{v2}$, heterocycloalkyl optionally substituted by one 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.

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-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)$_2$Me, -OMe, -OCF$_3$ and -OEt.

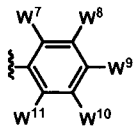
Preferred compounds of formula I where Z^1 represents heterocycloalkyl that may be mentioned are those where Z^1 represents dihydropyridinyl, imidazolinyl, morpholinyl, oxanyl, piperazinyl, piperidinyl, pyrrolidinyl and quinuclidinyl, wherein the heterocycloalkyl is optionally substituted by one or more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

Preferred compounds of formula I where Z^1 represents



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)$_2$$R^{p3}$, -O$R^{q3x}$, -OC(O)$R^{r3}$, -OS(O)$_2$$R^{s3}$, -S(O)$_m$$R^{t3}$, -S(O)$_2$N($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)$_2$$R^{p3}$, -O$R^{q3x}$, -OC(O)$R^{r3}$, -OS(O)$_2$$R^{s3}$, -S(O)$_m$$R^{t3}$, -S(O)$_2$N($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 $-S(O)_2CH_3$; or

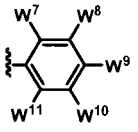
(b) W^7, W^9, W^{10} and W^{11} represents hydrogen and W^8 represents -F, -Br, -CN, $-N(H)C(O)CH_3$, $-OCH_3$ or $-S(O)_2CH_3$; or

(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 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 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.

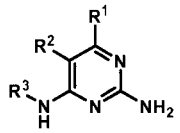
Preferred compounds of formula I where Z^1 represents heteroaryl that may be mentioned are those where Z^1 represents benzimidazolyl, benzodioxinyl, benzoxazolyl, furanyl, imidazolyl, imidazopyridinyl, indolyl, isoquinolinyl, oxadiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridyl, pyrrolopyridinyl, quinolinyl,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

triazolyl, wherein the heteroaryl is optionally substituted 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-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, 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, $-CH_3$, cyclopropyl, $-CF_3$, -CN, $-NH_2$, $-N(CH_3)_2$, $-SO_2CH_3$, $-SO_2NH_2$ and $-SO)_2N(CH_3)_2$.

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



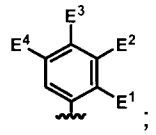
(I)

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, $-C_{1-6}$alkyl optionally substituted by one or more Y^2 and heterocycloalkyl optionally substituted by one or more Y^3; or

aryl represented by



;

E^1, E^2, E^3 and E^4 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, but where at least one of E^1, E^2, E^3 and E^4 is other than hydrogen;

R^2 represents hydrogen, halogen or -C_{1-12}alkyl optionally substituted by one or more Z^1;

R^3 represents -C_{1-12}alkyl substituted by one or more Z^1 or heterocycloalkyl optionally substituted by one or more Z^2; or

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;

each 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)$_2R^o$, -OR^p, -OC(O)R^q, -OS(O)$_2R^r$, -S(O)$_mR^s$, -S(O)$_2$N(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;

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 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^i 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 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 and R^r independently represent -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;

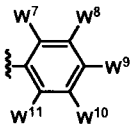
each Y^3 independently represents halogen, $-R^{a1}$, -CN, $-C(O)R^{b1}$, $-C(O)N(R^{c1})R^{d1}$, $-C(O)OR^{e1}$, $-N(R^{f1})R^{g1}$, $-N(R^{h1})C(O)R^{i1}$, $-N(R^{j1})C(O)OR^{k1}$, $-N(R^{l1})C(O)N(R^{m1})R^{n1}$, $-N(R^{o1})S(O)_2R^{p1}$, $-OR^{q1}$, $-OC(O)R^{r1}$, $-OS(O)_2R^{s1}$, $-S(O)_mR^{t1}$, $-S(O)_2N(R^{u1})R^{v1}$, 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;

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

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 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 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, $-C(O)R^{b2}$, $-C(O)N(R^{c2})R^{d2}$, $-C(O)OR^{e2}$, $-N(R^{f2})R^{g2}$, $-N(R^{h2})C(O)R^{i2}$, $-N(R^{j2})C(O)OR^{k2}$, $-N(R^{l2})C(O)N(R^{m2})R^{n2}$, $-N(R^{o2})S(O)_2R^{p2}$, $-OR^{q2}$, $-OC(O)R^{r2}$, $-OS(O)_2R^{s2}$, $-S(O)_mR^{t2}$, $-S(O)_2N(R^{u2})R^{v2}$, 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, $-C(O)R^{b2}$, $-C(O)N(R^{c2})R^{d2}$, $-C(O)OR^{e2}$, $-N(R^{f2})R^{g2}$, $-N(R^{h2})C(O)R^{i2}$, $-N(R^{j2})C(O)OR^{k2}$, $-N(R^{l2})C(O)N(R^{m2})R^{n2}$, $-N(R^{o2})S(O)_2R^{p2}$, $-OR^{q2}$, $-OC(O)R^{r2}$, $-OS(O)_2R^{s2}$, $-S(O)_mR^{t2}$, $-S(O)_2N(R^{u2})R^{v2}$, 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 substituents selected from W^6;

each Z^4 independently represents halogen, -CN, $-C(O)R^{b2}$, $-C(O)N(R^{c2})R^{d2}$, $-C(O)OR^{e2}$, $-N(R^{f2})R^{g2}$, $-N(R^{h2})C(O)R^{i2}$, $-N(R^{j2})C(O)OR^{k2}$, $-N(R^{l2})C(O)N(R^{m2})R^{n2}$, $-N(R^{o2})S(O)_2R^{p2}$, $-OR^{q2}$, $-OC(O)R^{r2}$, $-OS(O)_2R^{s2}$, $-S(O)_mR^{t2}$, $-S(O)_2N(R^{u2})R^{v2}$, 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 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 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;

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 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 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, -$C(O)R^{b3}$, -$C(O)N(R^{c3})R^{d3}$, -$C(O)OR^{e3}$, -$N(R^{f3})R^{g3}$, -$N(R^{h3})C(O)R^{i3}$, -$N(R^{j3})C(O)OR^{k3}$, -$N(R^{l3})C(O)N(R^{m3})R^{n3}$, -$N(R^{o3})S(O)_2R^{p3}$, -$OR^{q3}$, -$OC(O)R^{r3}$, -$OS(O)_2R^{s3}$, -$S(O)_mR^{t3}$, -$S(O)_2N(R^{u3})R^{v3}$, 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;

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

each W^8 and W^{10} 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 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;

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;

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 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 represent C_{1-6} alkyl optionally substituted by one or more G^3;

R^{q3x} represents C_{2-6} alkyl optionally substituted by one or more G^3;

each G^1 and G^2 independently represents halogen, $-R^{a4}$, -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;

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;

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

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;

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]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;

or a pharmaceutically acceptable salt thereof;

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 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.

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.

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.

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 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, 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, imidazolinyl, 7-oxabicyclo[2.2.1]heptanyl, 6-oxabicyclo[3.2.1]-octanyl, oxetanyl, oxiranyl, piperazinyl, 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).

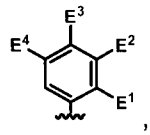
The term "aryl", when used herein, includes C_{6-14} (e.g. C_{6-10}) aromatic groups. Such groups may be monocyclic or bicyclic and, when bicyclic, be either wholly or partly aromatic. C_{6-10} aryl groups that may be mentioned include phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, indanyl, and the like (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.

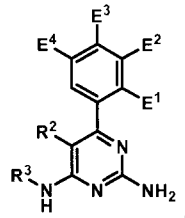
Heteroatoms that may be mentioned include phosphorus, silicon, boron and, preferably, oxygen, nitrogen and sulfur.

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.

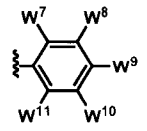
For the avoidance of doubt, when R^1 is defined as



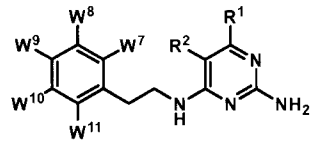
it is connected to the rest of formula I by the bond interrupted by the wiggly line, and formula I can thus be represented by



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_2alkyl, 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 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).

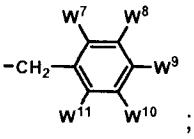
The skilled person will appreciate that compounds of the invention that are the subject of this invention include those that are stable. That is, compounds of the invention include those that are sufficiently robust to survive isolation from e.g. a reaction mixture to a useful degree of purity.

Particular compounds of formula I that may be mentioned include those in which:
R^2 represents hydrogen or -C_{1-12}alkyl optionally substituted by one or more Z^1; and
R^3 represents -C_{1-12}alkyl substituted by one or more Z^1 or heterocycloalkyl optionally substituted by one or more Z^2.

For example, compounds of formula I that may be mentioned include those in which R^2 represents methyl, or preferably, hydrogen and R^3 represents:

(a) -C_{1-12}alkyl (for example -C_{1-6}alkyl) substituted by two, or preferably, one Z^1 or;

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

(c) 

;

(d) -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

(e) -C_{3-6}alkyl or a heterocycloalkyl selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclopropylethyl, cyclobutylethyl, cyclopropylpropyl, oxetanyl, tetrahydrofuryl, tetrahydropyranyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl or morpholinyl wherein the C_{3-6}alkyl is 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 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.

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

(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.

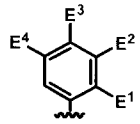
Particular compounds of formula I that may be mentioned include those in which R^1 represents heteroaryl.

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

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.

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.

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



where:

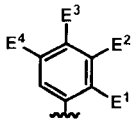
E^2, E^3 and E^4 represent hydrogen and

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-morpholinyl).

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



where:

E^3 and E^4 represent hydrogen; and

E^1 represents -F and E^2 represent -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 represent -F, -Cl, $-CH_3$, $-CF_3$ or $-OCH_3$; or

E^1 represents $-CH_3$ and E^4 represent -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

E^1 and E^4 represent hydrogen; and

E^2 represents -F and E^3 represents -F, -Cl, -OH or $-OCH_3$; or

E^2 represents -Cl and E^3 represents -F; or

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

E^1 represents $-OCH_3$ and E^3 represents -OH; or

E^1 and E^3 represent hydrogen; and

E^2 and E^4 represent -F; or

E^2 and E^4 represent $-CF_3$; 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 $-OCH_3$; 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

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

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

E^1 represents hydrogen; and

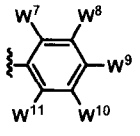
E^2 and E^4 represent $-CH_3$ and E^3 represents -OH; or

E^3 represents hydrogen; and

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

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

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

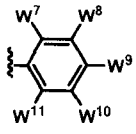
(b) Z^2 is not present or is selected from -F, $-R^{a2}$, $-C(O)N(R^{c2})R^{d2}$, $-N(R^{f2})R^{g2}$, $-N(R^{h2})C(O)R^{i2}$, $-N(R^{j2})C(O)OR^{k2}$, $-N(R^{l2})C(O)N(R^{m2})R^{n2}$, $-N(R^{o2})S(O)_2R^{p2}$, $-OR^{q2}$, $-S(O)_mR^{t2}$, $-S(O)_2N(R^{u2})R^{v2}$, heterocycloalkyl optionally substituted 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.

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, $-R^{a2}$, $-C(O)N(R^{c2})R^{d2}$, $-N(R^{f2})R^{g2}$, $-N(R^{h2})C(O)R^{i2}$, $-N(R^{j2})C(O)OR^{k2}$, $-N(R^{l2})C(O)N(R^{m2})R^{n2}$, $-N(R^{o2})S(O)_2R^{p2}$, $-OR^{q2}$, $-S(O)_mR^{t2}$, $-S(O)_2N(R^{u2})R^{v2}$, 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; and/or

(b) Z^4 is not present or is selected from -F, $-C(O)N(R^{c2})R^{d2}$, $-N(R^{f2})R^{g2}$, $-N(R^{h2})C(O)R^{i2}$, $-N(R^{j2})C(O)OR^{k2}$, $-N(R^{l2})C(O)N(R^{m2})R^{n2}$, $-N(R^{o2})S(O)_2R^{p2}$, $-OR^{q2}$, $-S(O)_mR^{t2}$, $-S(O)_2N(R^{u2})R^{v2}$, 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.

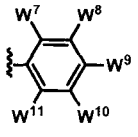
More particularly preferred compounds of formula I that may be mentioned include those in which Z^1 represents -F, -CN, $-C(O)N(R^{c2})R^{d2}$, $-N(R^{f2})R^{g2}$, $-N(R^{h2})C(O)R^{i2}$, $-N(R^{l2})C(O)N(R^{m2})R^{n2}$, $-N(R^{o2})S(O)_2R^{p2}$, $-OR^{q2}$, $-S(O)_mR^{t2}$, $-S(O)_2N(R^{u2})R^{v2}$, heterocycloalkyl optionally substituted by one or more substituents selected from W^5, 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.

Other more particularly preferred compounds of formula I that may be mentioned include those in which Z^1 represents $-C(O)N(R^{c2})R^{d2}$, $-N(R^{f2})R^{g2}$, $-N(R^{h2})C(O)R^{i2}$, $-N(R^{l2})C(O)N(R^{m2})R^{n2}$, $-N(R^{o2})S(O)_2R^{p2}$, $-OR^{q2}$, $-S(O)_mR^{t2}$, $-S(O)_2N(R^{u2})R^{v2}$ or aryl represented by



.

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^{t2} 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.

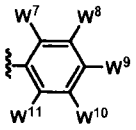
Preferred compounds of formula I that may be mentioned are those where where Z^1 represents $-OR^{q2}$ and R^{q2} represents aryl optionally substituted by one or more substituents selected from W^6, or heteroaryl optionally substituted by one or more substituents selected from W^6.

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.

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.

Preferred compounds of formula I where Z^1 represents heterocycloalkyl that may be mentioned are those where Z^1 represents dihydropyridinyl, imidazolinyl, 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:

(a) each W^8 and W^{10} are independently selected from -F, -Cl, $-CH_3$, $-CN$, $-CF_3$, or more preferably hydrogen and W^9 is selected from $-R^{a3}$, -CN, $-C(O)R^{b3}$, $-C(O)N(R^{c3})R^{d3}$, $-C(O)OR^{e3}$, $-N(R^{f3})R^{g3}$, $-N(R^{h3})C(O)R^{i3}$, $-N(R^{j3})C(O)OR^{k3}$, $-N(R^{l3})C(O)N(R^{m3})R^{n3}$, $-N(R^{o3})S(O)_2R^{p3}$, $-OR^{q3x}$, $-OC(O)R^{r3}$, $-OS(O)_2R^{s3}$, $-S(O)_mR^{t3}$, $-S(O)_2N(R^{u3})R^{v3}$, 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; and

(b) each W^9 and W^{10} are independently selected from -F, -Cl, $-CH_3$, $-CN$, $-CF_3$, or more preferably hydrogen and W^8 is selected from $-R^{a3}$, -CN, $-C(O)R^{b3}$, $-C(O)N(R^{c3})R^{d3}$, $-C(O)OR^{e3}$, $-N(R^{f3})R^{g3}$, $-N(R^{h3})C(O)R^{i3}$, $-N(R^{j3})C(O)OR^{k3}$, $-N(R^{l3})C(O)N(R^{m3})R^{n3}$, $-N(R^{o3})S(O)_2R^{p3}$, $-OR^{q3x}$, $-OC(O)R^{r3}$, $-OS(O)_2R^{s3}$, $-S(O)_mR^{t3}$, $-S(O)_2N(R^{u3})R^{v3}$, 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 W^8 and W^{10} represents 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; or

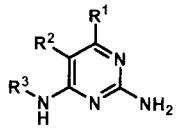
W^9 and W^{10} represents hydrogen and W^8 represents -F, -Cl, -CN, $-CH_3$, $-NMe_2$, $-S(O)_2NH_2$ or $-S(O)_2NMe_2$.

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 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-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, 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, $-CH_3$, cyclopropyl, $-CF_3$, -CN, $-NH_2$, $-N(CH_3)_2$, $-SO_2CH_3$, $-SO_2NH_2$ and $-SO)_2N(CH_3)_2$.

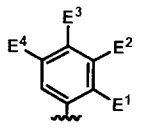
In yet another embodiment of the invention there is provided a compound of formula I,



(I)

wherein:

R^1 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 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



;

E^1 represents 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;

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;

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

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 -C_{1-9}alkyl optionally substituted by one or more Z^4;

each 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, -$N(R^n)S(O)_2R^o$, -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 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, -$N(R^n)S(O)_2R^o$, -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;

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 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 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 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;

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;

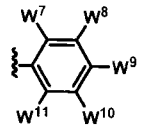
each R^{a1}, R^{b1}, R^{c1}, R^{d1}, R^{e1}, R^{f1}, R^{h1}, R^{i1}, R^{j1}, R^{l1}, R^{m1}, R^{n1}, R^{o1}, R^{q1}, R^{r1}, R^{t1}, R^{u1} and R^{v1} independently represents hydrogen, C_{1-6} alkyl optionally substituted by one or more

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

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;

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, -$C(O)R^{b2}$, -$C(O)N(R^{c2})R^{d2}$, -$C(O)OR^{e2}$, -$N(R^{f2})R^{g2}$, -$N(R^{h2})C(O)R^{i2}$, -$N(R^{j2})C(O)OR^{k2}$, -$N(R^{l2})C(O)N(R^{m2})R^{n2}$, -$N(R^{o2})S(O)_2R^{p2}$, -$OR^{q2}$, -$OC(O)R^{r2}$, -$OS(O)_2R^{s2}$, -$S(O)_mR^{t2}$, -$S(O)_2N(R^{u2})R^{v2}$, 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, or =O;

each Z^2 and Z^3 independently represents halogen, -R^{a2}, -CN, -$C(O)R^{b2}$, -$C(O)N(R^{c2})R^{d2}$, -$C(O)OR^{e2}$, -$N(R^{f2})R^{g2}$, -$N(R^{h2})C(O)R^{i2}$, -$N(R^{j2})C(O)OR^{k2}$, -$N(R^{l2})C(O)N(R^{m2})R^{n2}$, -$N(R^{o2})S(O)_2R^{p2}$, -$OR^{q2}$, -$OC(O)R^{r2}$, -$OS(O)_2R^{s2}$, -$S(O)_mR^{t2}$, -$S(O)_2N(R^{u2})R^{v2}$, 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 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^{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 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 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;

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;

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, $-C(O)R^{b3}$, $-C(O)N(R^{c3})R^{d3}$, $-C(O)OR^{e3}$, $-N(R^{f3})R^{g3}$, $-N(R^{h3})C(O)R^{i3}$, $-N(R^{j3})C(O)OR^{k3}$,

$-N(R^{l3})C(O)N(R^{m3})R^{n3}$, $-N(R^{o3})S(O)_2R^{p3}$, $-OR^{q3}$, $-OC(O)R^{r3}$, $-OS(O)_2R^{s3}$, $-S(O)_mR^{t3}$, $-S(O)_2N(R^{u3})R^{v3}$, 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;

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 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

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 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;

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

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

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;

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

or a pharmaceutically acceptable salt thereof;

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 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.

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.

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.

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 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, 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, imidazolinyl, morpholinyl, 7-oxabicyclo[2.2.1]heptanyl, 6-oxabicyclo[3.2.1]-octanyl, oxetanyl, oxiranyl, piperazinyl, 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).

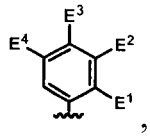
The term "aryl", when used herein, includes C_{6-14} (e.g. C_{6-10}) aromatic groups. Such groups may be monocyclic or bicyclic and, when bicyclic, be either wholly or partly aromatic. C_{6-10} aryl groups that may be mentioned include phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, indanyl, and the like (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.

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



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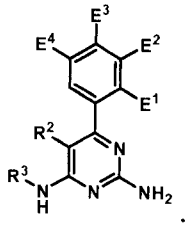
it is connected to the rest of formula I by the bond interrupted by the wiggly line, and formula I can thus be represented by



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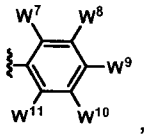
Likewise, when R^3 is -$C_{1\text{-}12}$ alkyl substituted by Z^1, and Z^1 is represented by



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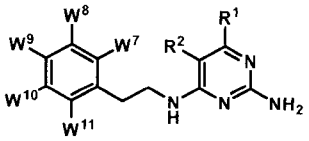
then, if e.g. R^3 is C_2alkyl, then formula I can be represented by



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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.

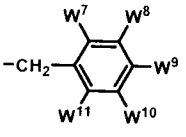
Particular compounds of formula I that may be mentioned include those in which:
R^2 represents hydrogen or -C_{1-12}alkyl optionally substituted by one or more Z^1; and
R^3 represents -C_{1-12}alkyl optionally substituted by one or more Z^1 or heterocycloalkyl optionally substituted by one or more Z^2.

For example, compounds of formula I that may be mentioned include those in which R^2 represents methyl, or preferably, hydrogen and R^3 represents:

(a) -C_{1-12}alkyl (for example -C_{1-6}alkyl) optionally substituted by two, or preferably, one Z^1 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

(d) 

;

(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, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl or morpholinyl 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 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.

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-aromaticring is:

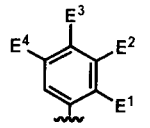
(a) unsubstituted; or

(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.

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 E^1 represents 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 (preferably at least one of E^2 and E^4) represents Y^{1b} or -C_{1-6}alkyl optionally substituted by one or more Y^2.

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

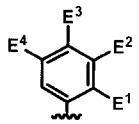
Preferred compounds of formula I where R^1 represents heteroaryl that may be mentioned are those where R^1 represents benzofuranyl, benzothiophenyl, dihydrobenzofuranyl, indazolyl, indolyl, isoquinolinyl, isoxazolyl, pyridinyl, pyrrolyl and quinolinyl.

Particularly preferred compounds of formula I where R^1 represents heteroaryl that 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, 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 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 $-CF_3$.

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



where:

E^3 and E^4 represent hydrogen; and

E^1 represents -F and E^2 represent -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, $-CH_3$, $-CF_3$, -CN or $-N(H)C(O)CH=CH_2$; 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

E^1 represents $-CH_3$ and E^3 represents -Cl or $-OCH_2$phenyl; 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 represent -F, -Cl, $-CH_3$, $-CF_3$ or $-OCH_3$; or

E^1 represents $-CH_3$ and E^4 represent -F, -Cl, $-CH_3$, $-CF_3$, -CN, $-N(H)C(O)CH=CH_2$ or $-S(O)_2$(4-morpholinyl); 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

E^1 and E^4 represent hydrogen; and
E^2 represents -F and E^3 represents -F, -Cl, -OH or $-OCH_3$; or
E^2 represents -Cl and E^3 represents -F or -C(O)(4-morpholinyl); or
E^2 represents $-CH_3$ and E^3 represents -F or $-OCH_3$; or
E^1 represents $-OCH_3$ and E^3 represents -OH; or
E^1 represents-$-CH_2OCH_3$ and E^3 represents (piperidin-4-yl)methoxy or
((1-*tert*butoxycarbonyl)piperidin-4-yl)methoxy; or

E^1 and E^3 represent hydrogen; and
E^2 and E^4 represent -F; or
E^2 and E^4 represent $-CF_3$; 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 $-OCH_3$; 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

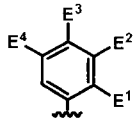
E^2 represents hydrogen; and
E^1, E^3 and E^4 represent -F; or
E^3 and E^4 represent -Cl and E^1 represents $-CH_3$; or
E^1 and E^4 represent -Cl and E^1 represents $-OCH_3$; or
E^1 and E^4 represent $-CH_3$ and E^3 represents -F, $-CH_3$ or $-OCH_3$; or
E^1 represents -F, E^3 represents $-CH_3$ and E^4 represents -Cl; or
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

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 $-CH_3$.

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



where:

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

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, $-CH_3$ or -CN; or

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

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

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

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

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

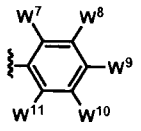
E^2 and E^4 represent $-CH_3$ and E^3 represents -OH; or

E^3 represents hydrogen; and

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

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, $-C(O)R^{b2}$, $-C(O)N(R^{c2})R^{d2}$, $-C(O)OR^{e2}$, $-N(R^{f2})R^{g2}$, $-N(R^{h2})C(O)R^{i2}$, $-N(R^{j2})C(O)OR^{k2}$, $-N(R^{l2})C(O)N(R^{m2})R^{n2}$, $-N(R^{o2})S(O)_2R^{p2}$, $-OR^{q2}$, $-S(O)_mR^{t2}$, $-S(O)_2N(R^{u2})R^{v2}$, heterocycloalkyl optionally substituted by one or more substituents selected from W^5, aryl 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, $-R^{a2}$, $-C(O)N(R^{c2})R^{d2}$, $-N(R^{f2})R^{g2}$, $-N(R^{h2})C(O)R^{i2}$, $-N(R^{j2})C(O)OR^{k2}$, $-N(R^{l2})C(O)N(R^{m2})R^{n2}$, $-N(R^{o2})S(O)_2R^{p2}$, $-OR^{q2}$, $-S(O)_mR^{t2}$, $-S(O)_2N(R^{u2})R^{v2}$, 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.

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, $-R^{a2}$, $-C(O)N(R^{c2})R^{d2}$, $-N(R^{f2})R^{g2}$, $-N(R^{h2})C(O)R^{i2}$, $-N(R^{j2})C(O)OR^{k2}$, $-N(R^{l2})C(O)N(R^{m2})R^{n2}$, $-N(R^{o2})S(O)_2R^{p2}$, $-OR^{q2}$, $-S(O)_mR^{t2}$, $-S(O)_2N(R^{u2})R^{v2}$, heterocycloalkyl optionally substituted by one or more substituents selected from W^5, aryl optionally substituted by one or more substituents

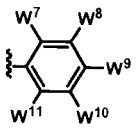
selected from W^6, or heteroaryl optionally substituted by one or more substituents selected from W^6; and/or

(b) Z^4 is not present or is selected from -F, $-C(O)N(R^{c2})R^{d2}$, $-N(R^{f2})R^{g2}$, $-N(R^{h2})C(O)R^{i2}$, $-N(R^{j2})C(O)OR^{k2}$, $-N(R^{l2})C(O)N(R^{m2})R^{n2}$, $-N(R^{o2})S(O)_2R^{p2}$, $-OR^{q2}$, $-S(O)_mR^{t2}$, $-S(O)_2N(R^{u2})R^{v2}$, 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.

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-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.

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.

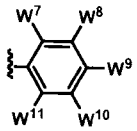
Preferred compounds of formula I where Z^1 represents



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 $-S(O)_2CH_3$; or

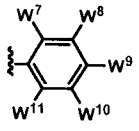
(b) W^7, W^9, W^{10} and W^{11} represents hydrogen and W^8 represents -F, -Br, -CN, $-N(H)C(O)CH_3$, $-OCH_3$ or $-S(O)_2CH_3$; or

(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 $-CH_3$.

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 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 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)O$C(CH_3)_3$, -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.

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 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-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, 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, -CH_3, cyclopropyl, -CF_3, -CN, -NH_2, -$N(CH_3)_2$, -SO_2CH_3, -SO_2NH_2 and -$SO)_2N(CH_3)_2$.

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 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.

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 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 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 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 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".

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.

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.

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, 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, 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, osteochronfroma (osteocartilaginous 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.

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.

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.

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.

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

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.

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.

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 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.

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 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 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.

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 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.

"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).

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

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 in the treatment of cancer,

wherein each of components (A) and (B) is formulated in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier.

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).

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

(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 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,

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 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 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:

(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.

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 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.

aq	aqueous
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
EtOAc	ethyl acetate
EtOH	ethanol
MeOH	methanol
MeCN	acetonitrile
Pd-C	palladium on carbon
sat.	saturated
TFA	trifluoroacetic acid
THF	tetrahydrofuran
min.	minutes
h.	hours
Hunigs base	*N,N*-diisopropylethylamine
DCM	dichloromethane
n-BuOH	butan-1-ol
iPrOH	propan-2-ol
NEt_3	trethylamine
Boc	*tert*-butoxycabonyl
HATU	(1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo-[4,5-b]pyridinium 3-oxid hexafluorophosphate
NMP	*N*-methylpyrrolidine
LCMS	liquid-chromatography electrospray mass spectroscopy
NMR	nuclear magnetic resonance
NCS	N-chlorosuccinimide
$Pd(PPh_3)_4$	tetrakis(triphenylphosphine)palladium (0)
$B(OMe)_3$	trimethylborate
n-BuLi	n-butyl lithium
MeI	iodomethane
NaOMe	sodium methoxide

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

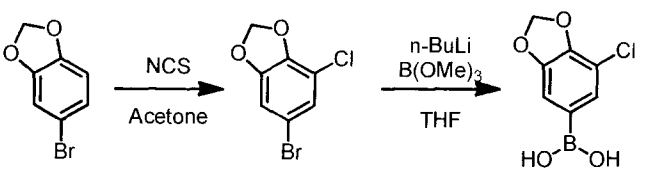
Starting materials and chemical reagents specified in the syntheses described below are commercially available, e.g. from Sigma-Aldrich, Fine Chemicals Combi-Blocks and other vendors.

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 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 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

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



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

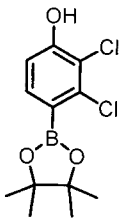
To a solution of 5-bromo-2H-1,3-benzodioxole (60 µL, 0.50 mmol, 1 eq.) in acetonitrile (1 mL) was added 1-chloropyrrolidine-2,5-dione (73 mg, 0.55 mmol, 1.1 eq.). The reaction was stirred overnight at room temperature. After completion of the reaction, the reaction mixture was concentrated and purified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

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 °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 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 % → 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).

Intermediate 2

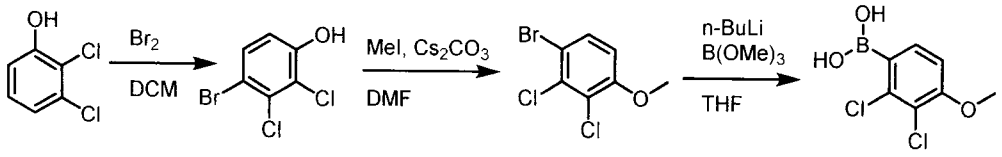
2,3-dichloro-4-(tetramethyl-1,3,2-dioxaborolan-2-yl)phenol.



To a solution of 4-bromo-2,3-dichlorophenol (250 mg, 1.03 mmol, 1 eq.) in THF (10 mL) was added, at -78 °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 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 % → 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).

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 µL, 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 $Na_2S_2O_3$, the organic layer was washed with brine, dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (Pentane/EtOAc 100 % → 25:1) to afford the desired product as a white solid (685 mg, 46 %). LCMS $[M+H]^+$ 239; ^1H NMR (400 MHz, DMSO-d_6) 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.

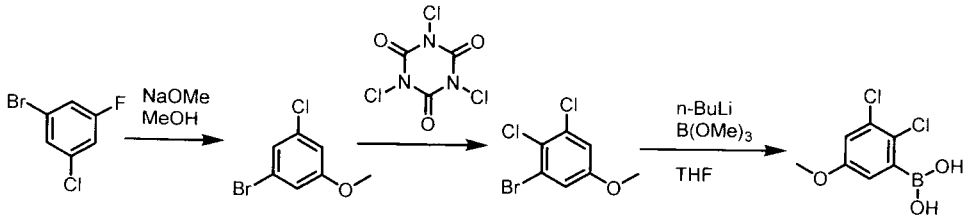
To a solution of 4-bromo-2,3-dichlorophenol (200 mg, 0.83 mmol, 1 eq.) in DMF (3 mL) was added Cs_2CO_3 (538 mg, 1.65 mmol, 2 eq.) followed by iodomethane (208 µL, 3.3 mmol, 4 eq.). The reaction mixture was stirred at 70 °C for 3 h. The reaction was stopped by addition of H_2O, extracted with DCM, dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (Pentane/EtOAc 100 % → 20:1) to afford the desired product as a white solid (190 mg, 89 %). LCMS $[M+H]^+$ 256; ^1H NMR (400 MHz, $CDCl_3$) 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 µL, 0.59 mmol, 1.5 eq.). The reaction mixture was stirred at this temperature for 30 min, before addition of $B(OMe)_3$ (218 µL, 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 $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by column chromatography (Pentane/EtOAc 100 % → 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

(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 H_2O, brine, dried over $MgSO_4$ and concentrated. The product was obtained as a white solid (747 mg, 71 %). LCMS $[M+H]^+$ 220; ^1H NMR (400 MHz, CD_3Cl) 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).

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

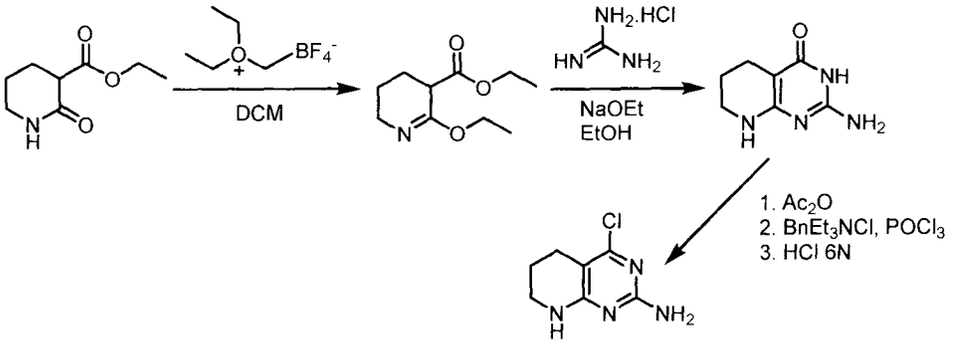
To a solution of 1-bromo-3-chloro-5-methoxybenzene (300 mg, 1.35 mmol, 1 eq.) in DMF (5 mL) was added trichloro-1,3,5-triazinane-2,4,6-trione (115 mg, 0.49 mmol, 0.36 eq.) and the reaction was stirred at 50 °C for 3 h. The reaction mixture was concentrated and the crude product was purified by column 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, CD_3Cl) δ_H 7.09 (1H, d, J = 3.0 Hz), 6.97 (1H, d, J = 3.0 Hz), 3.77 (3H, s).

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 µL, 0.51 mmol, 1.5 eq.). The reaction mixture was stirred at this temperature for 30 min, before addition of $B(OMe)_3$ (191 µL, 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 dried over $MgSO_4$ and evaporated under reduced pressure to afford the desired product as a white solid (75 mg, 100%). LCMS $[M+H]^+$ 221.

Intermediate 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 %). ^{1}H 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). ^{1}H 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).

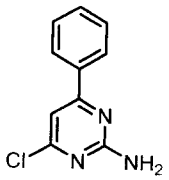
Step 3: 4-chloro-5H,6H,7H,8H-pyrido[2,3-d]pyrimidin-2-amine.

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 $POCl_3$ (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 $NaHCO_3$, brine and dried over Na_2SO_4. 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, $CDCl_3$) 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).

Intermediate 6

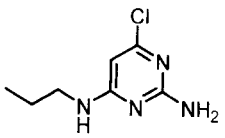
4-chloro-6-phenylpyrimidin-2-amine.



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.), K_2CO_3 (5.06 g, 36.6 mmol, 2 eq.) and $Pd(PPh_3)_4$ (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, $CDCl_3$) δ_H 8.27 – 8.20 (2H, m), 8.16 – 8.05 (3H, m), 7.19 (2H, s), 6.76 (1H, s).

Intermediate 7

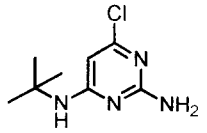
6-chloro-4-N-propylpyrimidine-2,4-diamine.



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

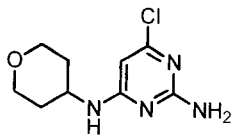
4-N-tert-butyl-6-chloropyrimidine-2,4-diamine.



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

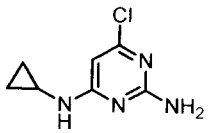
6-chloro-4-N-(oxan-4-yl)pyrimidine-2,4-diamine.



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

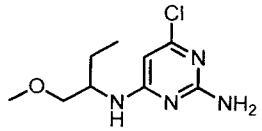
6-chloro-4-N-cyclopropylpyrimidine-2,4-diamine.



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 µL, 1.1 mmol, 1.1 eq.) and Hünig's base (260 µL, 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 H_2O, brine, dried over $MgSO_4$ and concentrated to afford the desired product as an off-white solid (152 mg, 82 %). LCMS $[M+H]^+$ 185; ^1H NMR (400 MHz, DMSO-d_6) 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).

Intermediate 11

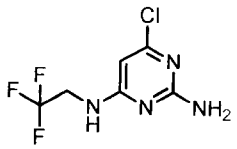
6-chloro-4-N-(1-methoxybutan-2-yl)pyrimidine-2,4-diamine.



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 µL, 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 H_2O, brine, dried over $MgSO_4$ and concentrated to afford the desired product as an off-white solid (592 mg, 84 %). LCMS $[M+H]^+$ 231.

Intermediate 12

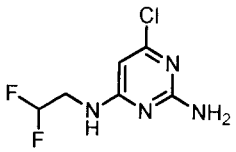
6-chloro-4-N-(2,2,2-trifluoroethyl)pyrimidine-2,4-diamine.



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 NEt_3 (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 H_2O, brine, dried over $MgSO_4$ and concentrated to afford the desired product as a yellow solid (59 mg, 26 %). LCMS $[M+H]^+$ 227.

Intermediate 13

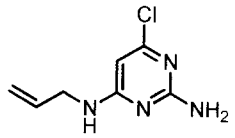
6-chloro-4-N-(2,2-difluoroethyl)pyrimidine-2,4-diamine.



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 H_2O, brine, dried over $MgSO_4$ and concentrated to afford the desired product as a yellow solid (80 mg, 38 %). LCMS $[M+H]^+$ 209.

Intermediate 14

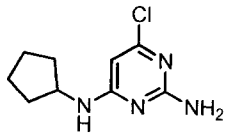
6-chloro-4-N-(prop-2-en-1-yl)pyrimidine-2,4-diamine.



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 H_2O, brine, dried over $MgSO_4$ and concentrated to afford the desired product as a yellow solid (471 mg, 84 %). LCMS $[M+H]^+$ 185.

Intermediate 15

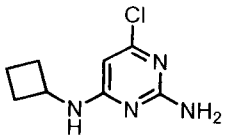
6-chloro-4-N-cyclopentylpyrimidine-2,4-diamine.



To a solution of 4,6-dichloropyrimidin-2-amine (500 mg, 3.04 mmol, 1 eq.) in n-BuOH (10 mL) were added cyclopentanamine (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 H_2O, brine, dried over $MgSO_4$ and concentrated to afford the desired product as a brown foam (620 mg, quantitative). LCMS $[M+H]^+$ 213.

Intermediate 16

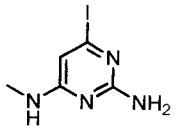
6-chloro-4-N-cyclobutylpyrimidine-2,4-diamine.



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 µL, 1.52 mmol, 1 eq.) and Hünig´s base (292 µL, 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 H_2O, brine, dried over $MgSO_4$ and concentrated to afford the desired product as a white solid (248 mg, 80 %). LCMS $[M+H]^+$ 199.

Intermediate 17

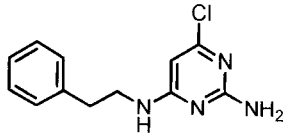
6-iodo-4-N-methylpyrimidine-2,4-diamine.



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 $NaHCO_3$, brine, dried over $MgSO_4$ 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, $CDCl_3$) δ_H 6.27 (1H, s), 2.80 (3H, s).

Intermediate 18

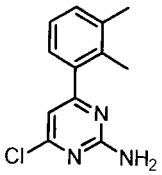
6-chloro-4-N-(2-phenylethyl)pyrimidine-2,4-diamine.



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 µL, 0.60 mmol, 1.1 eq.) and Hünig´s base (100 µg, 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 EtOAc and washed with H_2O, brine, dried over $MgSO_4$ 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.

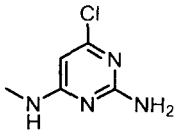


A mixture of 2-amino-4,6-dichloropyrimidine (0.82 g, 5.0 mmol, 1 eq.), 2,3-dimethylphenylboronic acid (0.75 g, 5.0 mmol, 1 eq.), K_2CO_3 (1.38 g, 10.0 mmol, 2 eq.) and palladium tetrakis(triphenylphosphine)palladium (0) (0.12 g, 0.10 mmol, 0.1 eq.) in 1,4-dioxane (20 mL) and water (5 mL) was heated in a sealed 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, CD_3OD) 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).

Intermediate 20

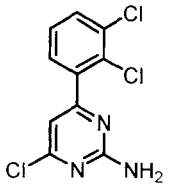
4-chloro-6-(2,3-dichlorophenyl)pyrimidin-2-amine.



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 the desired product as a buff solid (2.90 g, 91%). LCMS $[M+H]^+$ 159.

Intermediate 21

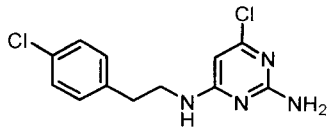
6-chloro-4-N-methylpyrimidine-2,4-diamine.



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

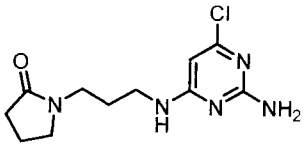
6-Chloro-4-N-[2-(4-chlorophenyl)ethyl]pyrimidine-2,4-diamine.



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 MgSO4, filtered and concentrated to give the desired product as a buff solid (0.61 g, 71%). LCMS $[M+H]^+$ 283.

Intermediate 23

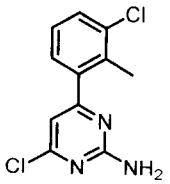
1-{3-[(2-amino-6-chloropyrimidin-4-yl)amino]propyl}pyrrolidin-2-one.



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.

Intermediate 24

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

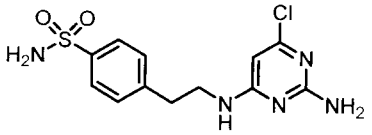


A stirred mixture of 2-amino-4,6-dichloropyrimidine (0.50 g, 3.1 mmol), 3-chloro-2-methylphenylboronic acid (0.57 g, 3.4 mmol), Na_2CO_3 (1.0 g, 9.8 mmol), palladium tetrakis(triphenylphosphine)palladium (0) (88 mg, 0.076 mmol), dioxane (22 mL) and water (8 mL) were heated in a sealed tube at 90°C for 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 $MgSO_4$ 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-d_6) δ_H ppm 7.52 - 7.56 (1 H, dd, J_1 = 6.5 Hz, J_2 = 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).

Intermediate 25

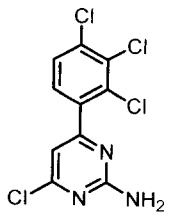
4-{2-[(2-amino-6-chloropyrimidin-4-yl)amino]ethyl}benzene-1-sulfonamide.



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 $NaHCO_3$ (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, CD_3OD) 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

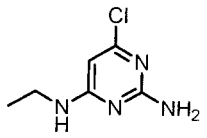
4-chloro-6-(2,3,4-trichlorophenyl)pyrimidin-2-amine.



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

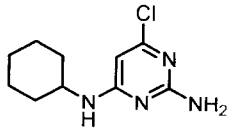
6-chloro-4-N-ethylpyrimidine-2,4-diamine



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 H_2O. The aqueous layer was extracted twice with EtOAc and once with $CHCl_3$/^{i}PrOH (3:1). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated to afford the desired product as a white solid. LCMS $[M+H]^+$ 173; ^1H NMR (400 MHz, $CDCl_3$) 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

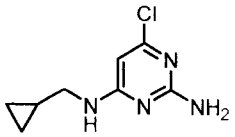
6-chloro-4-N-cyclohexylpyrimidine-2,4-diamine.



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 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 H_2O. The aqueous layer was extracted twice with EtOAc and once with $CHCl_3$/^{i}PrOH (3:1). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated to afford the desired product as a white solid. LCMS $[M+H]^+$ 227; ^1H NMR (400 MHz, $CDCl_3$) 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).

Intermediate 29

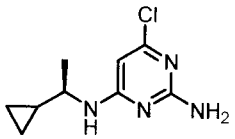
6-chloro-4-N-(cyclopropylmethyl)pyrimidine-2,4-diamine.



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 overnight at 95 °C. The solvent was removed in vacuo. The crude product was taken up in EtOAc and H_2O. The aqueous layer was extracted twice with EtOAc and once with $CHCl_3$/^{i}PrOH (3:1). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated to afford the desired product as a white solid. LCMS $[M+H]^+$ 199; ^1H NMR (400 MHz, $CDCl_3$) 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

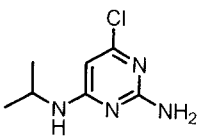
6-chloro-4-N-[(1R)-1-cyclopropylethyl]pyrimidine-2,4-diamine.



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 µL, 6.09 mmol, 1 eq.) and Hünig's base (292 µL, 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 H_2O. The aqueous layer was extracted twice with EtOAc and once with $CHCl_3$/^{i}PrOH (3:1). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated to afford the desired product as a colourless oil (321 mg, 99%). LCMS $[M+H]^+$ 213; ^1H NMR (400 MHz, $CDCl_3$) 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.

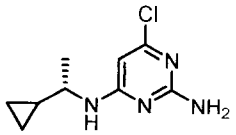


To a solution of 4,6-dichloropyrimidin-2-amine (500 mg, 3.05 mmol, 1 eq.) in n-BuOH (9

mL) were added propan-2-amine (262 µL, 6.09 mmol, 1 eq.) and Hünig´s base (584 µL, 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 H_2O. The aqueous layer was extracted twice with EtOAc and once with $CHCl_3$/^{i}PrOH (3:1). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated to afford the desired product as a white solid (569 mg, 99%). LCMS $[M+H]^+$ 187; ^1H NMR (400 MHz, $CDCl_3$) 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).

Intermediate 32

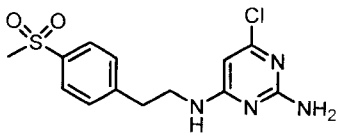
6-chloro-4-N-[(1S)-1-cyclopropylethyl]pyrimidine-2,4-diamine.



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 µL, 6.09 mmol, 1 eq.) and Hünig´s base (292 µL, 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 H_2O. The aqueous layer was extracted twice with EtOAc and once with $CHCl_3$/^{i}PrOH (3:1). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated to afford the desired product as a colourless oil (296 mg, 91%). LCMS $[M+H]^+$ 213; ^1H NMR (400 MHz, $CDCl_3$) 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).

Intermediate 33

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

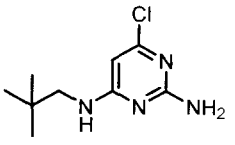


A mixture of 4,6-dichloropyrimidin-2-amine (500 mg, 3.0 mmol), 2-(4-methylsulfonylphenyl)ethanamine (600 mg, 3.0 mmol) and Hünig's base (0.63 mL, 3.6 mmol) in 2-propanol (10 mL) was heated at reflux for 15 h. The reaction mixture was poured into $NaHCO_3$ (aq) and extracted three times with DCM. The combined organic layers were dried and concentrated. The crude mixture was purified by column

chromatography which afforded the title compound. LCMS [M+H]+ 327; ^{1}H 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

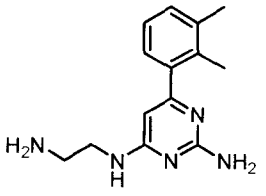
6-chloro-4-N-(2,2-dimethylpropyl)pyrimidine-2,4-diamine.



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 µL, 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 H_2O. The aqueous layer was extracted twice with EtOAc and once with $CHCl_3$/^{i}PrOH (3:1). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated to afford the desired product as a white solid. LCMS $[M+H]^+$ 215; ^{1}H NMR (400 MHz, $CDCl_3$) 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).

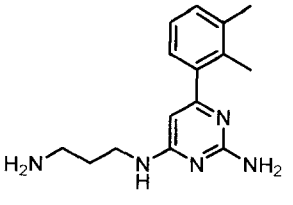
Step 2: tert-Butyl N-[2-[(2-amino-6-chloro-pyrimidin-4-yl)amino]ethyl]carbamate (850 mg, 2.95 mmol), (2,3-dimethylphenyl)boronic acid (532 mg, 3,55 mmol), palladium

tetrakis(triphenylphosphine)palladium (0) (34 mg, 0.030 mmol), and K_2CO_3 (1020 mg, 7.39 mmol) were suspended in 1,4-dioxane (10 ml) and H_2O (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% NH_4OH] in DCM) afforded 4-N-(2-aminoethyl)-6-(2,3-dimethylphenyl)pyrimidine-2,4-diamine (500 mg, 1.94 mmol). LCMS $[M+H]^+$ 258.

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).

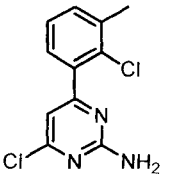
Step 2: tert-Butyl N-[3-[(2-amino-6-chloro-pyrimidin-4-yl)amino]propyl]carbamate (790 mg, 2.6 mmol), (2,3-dimethylphenyl)boronic acid (470 mg, 3.1 mmol), palladium tetrakis(triphenylphosphine)palladium (0) (60 mg, 0.050 mmol), and K_2CO_3 (720 mg 5.2 mmol) were suspended in 1,4-dioxane (6.0 ml) and H_2O (1.5 ml). The resulting mixture was heated at 90 °C for 16 h and then poured into H_2O 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).

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% NH_4OH] 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

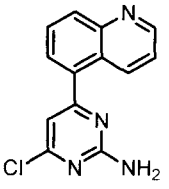
4-chloro-6-(2-chloro-3-methylphenyl)pyrimidin-2-amine.



To a suspension of 4,6-dichloropyrimidin-2-amine (250 mg, 1.52 mmol, 1 eq) in dioxane/H_2O (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 $Pd(PPh_3)_4$ (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, $CDCl_3$) 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).

Intermediate 38

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

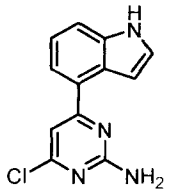


To a suspension of 4,6-dichloropyrimidin-2-amine (150 mg, 0.91 mmol, 1 eq) in dioxane/H_2O (5 mL, 4:1) was added (quinolin-5-yl)boronic acid (158 mg, 0.91 mmol, 1 eq) followed by potassium carbonate (253 mg, 1.83 mmol, 2 eq) and $Pd(PPh_3)_4$ (26 mg, 0.020 mmol, 0.025 eq). The resulting mixture was stirred 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%). LCMS $[M+H]^+$ 257; ^1H NMR (400 MHz, $CDCl_3$) 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

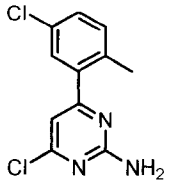
4-chloro-6-(1H-indol-4-yl)pyrimidin-2-amine.



To a suspension of 4,6-dichloropyrimidin-2-amine (150 mg, 0.91 mmol, 1 eq) in dioxane/H_2O (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 $Pd(PPh_3)_4$ (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, $CDCl_3$) 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), 7.18 (1H, s), 7.00 – 6.99 (1H, m), 5.90 (2H, br s).

Intermediate 40

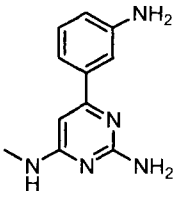
4-chloro-6-(5-chloro-2-methylphenyl)pyrimidin-2-amine.



To a suspension of 4,6-dichloropyrimidin-2-amine (150 mg, 0.91 mmol, 1 eq) in dioxane/H_2O (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 $Pd(PPh_3)_4$ (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 an off-white solid (98 mg, 42%). LCMS $[M+H]^+$ 254; ^1H NMR (400 MHz, $CDCl_3$) 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

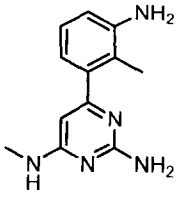
6-(3-aminophenyl)-4-N-methylpyrimidine-2,4-diamine.



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 magnesium sulfate, concentrated and purified by flash chromatography (0→15 % MeOH in DCM) to give the title compound. LCMS $[M+H]^+$ 216.

Intermediate 42

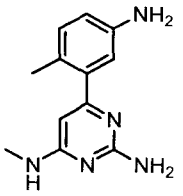
6-(3-amino-2-methylphenyl)-4-N-methylpyrimidine-2,4-diamine.



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 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; ^{1}H NMR (400 MHz, DMSO-d_6) 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).

Intermediate 43

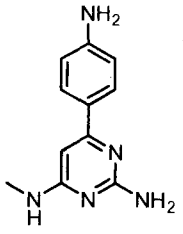
6-(5-amino-2-methylphenyl)-4-N-methylpyrimidine-2,4-diamine.



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.

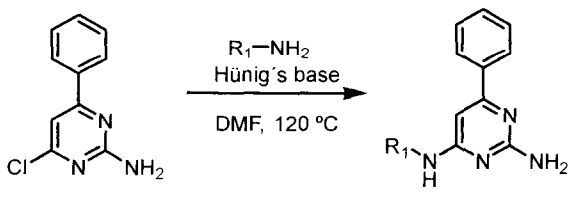
Intermediate 44

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



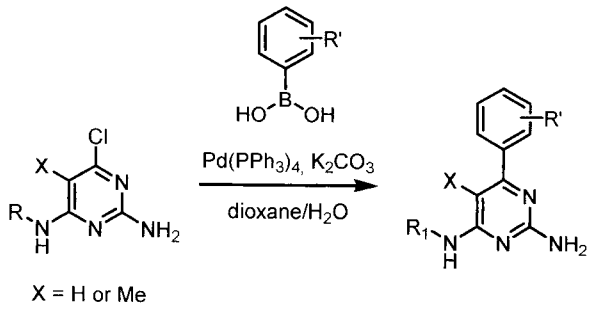
Tetrakis(triphenylphosphine)palladium (0) (5 mol%) was added to a stirred mixture of 6-chloro-4-N-methylpyrimidine-2,4-diamine (1.0 mmol), 4-(tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.3 eq.), sodium carbonate (3.2 eq.), 1,4-dioxane (4 mL) and water (1 mL) in a tube. The tube was sealed and the reaction 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

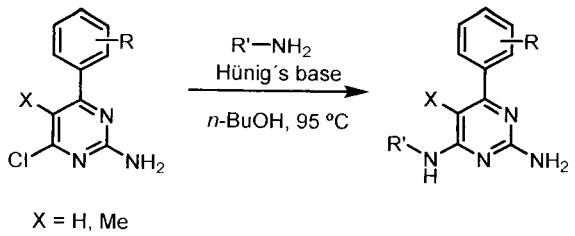


General Procedure 1: To a mixture of 4-chloro-6-phenylpyrimidin-2-amine (1 equiv.) is added Hünig's base (3.4 equiv.) and an appropriate amine (1.6 equiv.) in DMF (500 µL).

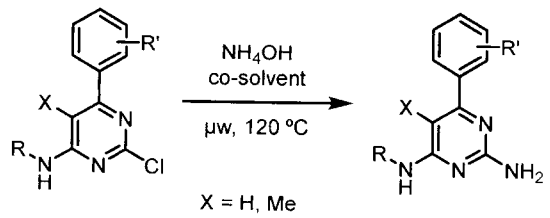
The mixture is heated at 120 °C overnight. The crude mixture is purified by preparative HPLC to afford the desired product.



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 $Pd(PPh_3)_4$ (0.1 equiv.). 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.

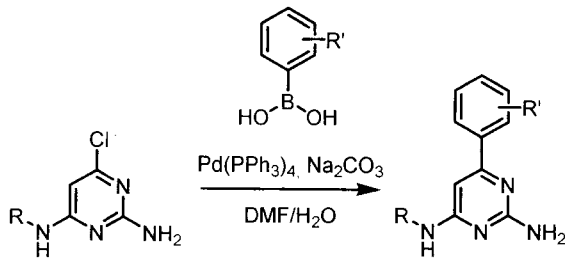


General Procedure 3: To a mixture of a suitable chloropyrimidine derivative (1 equiv.) is added Hünig´s base (3.4 equiv.) and an appropriate amine (1.6 equiv.) in *n*-BuOH (500 µL). The mixture is heated at 95 °C overnight. The crude mixture was purified by preparative HPLC to afford the desired product.

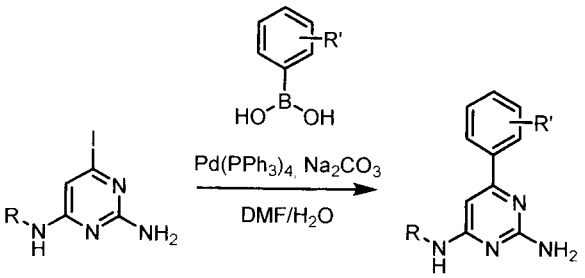


General Procedure 4: A solution of an appropriate chloropyrimidine derivative (1 equiv.) in ammonium hydroxide (25% aq.) is heated in the microwave at 120 °C until completion of the reaction as monitored by LCMS. The solvent is then evaporated and the product

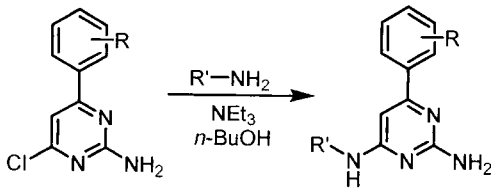
is dried under vacuum. Further purification by preparative HPLC is performed when required.



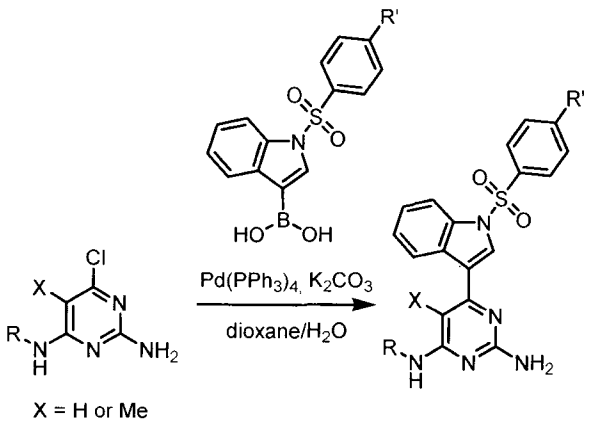
General Procedure 5: To a mixture of a suitable chloropyrimidine derivative (1 equiv.) in DMF/water (9:1) is added the appropriate boronic acid (or boronic ester) derivative (1.1 equiv.), Na_2CO_3 (2 equiv.) and $Pd(PPh_3)_4$ (0.1 equiv.). The mixture is heated at 120 °C overnight or in the microwave 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.), Na_2CO_3 (2 equiv.) and $Pd(PPh_3)_4$ (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.

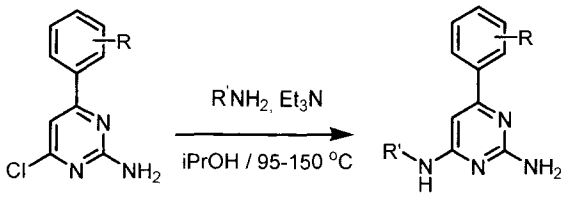


General procedure 7: A mixture of a suitable 6-aryl-4-chloropyrimidin-2-amine (1 equiv.), a suitable amine (1.5 equiv.) and triethylamine (2 equiv.) in *n*-butanol (1.5 mL) is heated in a sealed tube at 95°C overnight. Concentrated and purified by preparative HPLC to give the desired product.

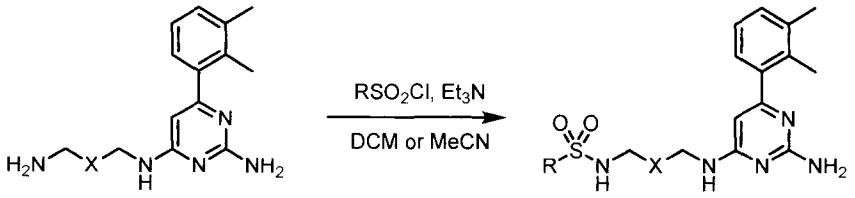


X = H or Me

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 product.

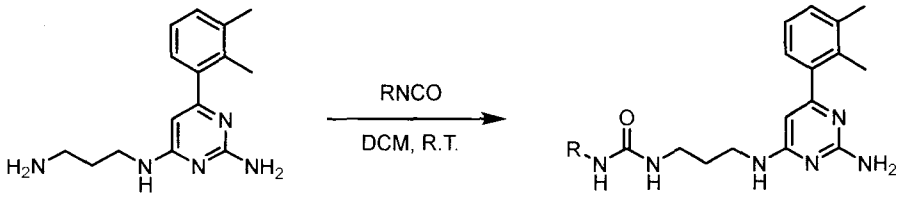


General procedure 9: A mixture of a suitable amine (1 equiv.), and a suitable chloropyrimidine derivative (1.2 equiv.) and triethylamine (1.5 equiv.) in 2-propanol (1.0 mL) is heated in a sealed tube at 95 °C overnight or at 150 °C for 15 min in a microwave reactor. The reaction mixture is then concentrated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

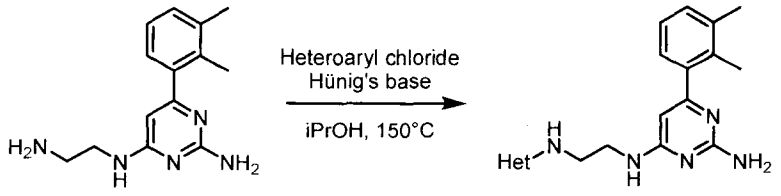


X = CH2, CH2CH2, $CH(CH_3)_2$ or a bond

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 Hünig´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 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.

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).

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 – 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-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-methanesulfonylphenyl)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).

Example 6

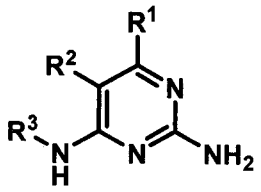
4-N-(cyclopropylmethyl)-6-phenylpyrimidine-2,4-diamine.

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), 1.15 – 0.95 (1H, m), 0.51 (1H, d, J = 5.8 Hz), 0.27 (1H, d, J = 5.8 Hz).

Example 7

Claims

1. A compound of formula I,



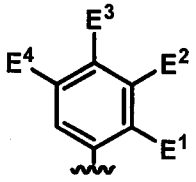
(I)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 represents:

heteroaryl selected from 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, where the heteroaryl is connected to the pyrimidine of formula I via a carbon atom of the heteroaryl ring, where the heteroaryl 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



; where

E^3 and E^4 each indepedently represent hydrogen, and E^1 represents -F and E^2 represent -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;

R^2 represents hydrogen;

R^3 represents $-C_{2-6}$alkyl substituted by one Z^1

each Y^1 independently represents halogen, -CN, $-C(O)R^a$, $-C(O)N(R^b)R^c$, $-C(O)OR^d$, $-N(R^e)R^f$, $-N(R^g)C(O)R^h$, $-N(R^i)C(O)OR^j$, $-N(R^k)C(O)N(R^l)R^m$, -

morpholinyl, 4-methylpiperazin-1-yl, 4-methylpiperidin-1-ylmethyl or 1,2,3-thiadiazol-4-yl

10. A compound as claimed in Claim 1, selected from:

4-N-[2-(4-chlorophenyl)ethyl]-6-(2,3-dichlorophenyl)pyrimidine-2,4-diamine;

4-(2-{[2-amino-6-(2,3-dichlorophenyl)pyrimidin-4-yl]amino}ethyl)benzene-1-sulfonamide;

4-(2-{[2-amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-yl]amino}ethyl)benzene-1-sulfonamide;

4-(2-{[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}ethyl)benzene-1-sulfonamide;

6-(2,3-dimethylphenyl)-4-N-[2-(4-methanesulfonylphenyl)ethyl]pyrimidine-2,4-diamine;

4-(2-{[2-amino-6-(3-chloro-2-methylphenyl)pyrimidin-4-yl]amino}ethyl)-N,N-dimethylbenzene-1-sulfonamide;

4-(2-{[2-amino-6-(2,3-dichlorophenyl)pyrimidin-4-yl]amino}ethyl)-N,N-dimethylbenzene-1-sulfonamide;

4-(2-{[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}ethyl)-N,N-dimethylbenzene-1-sulfonamide;

6-[(2-{[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}ethyl)amino]pyridine-3-sulfonamide;

6-(2,3-dichlorophenyl)-4-N-[2-(4-methanesulfonylphenyl)ethyl]pyrimidine-2,4-diamine; and

4-[(2-{[2-amino-6-(2,3-dimethylphenyl)pyrimidin-4-yl]amino}ethyl)amino]benzene-1-sulfonamide,

or a pharmaceutically acceptable salt thereof.

11. A compound as claimed in Claim 1, selected from:

6-(2,3-dimethylphenyl)-4-N-(2-phenylethyl)pyrimidine-2,4-diamine;

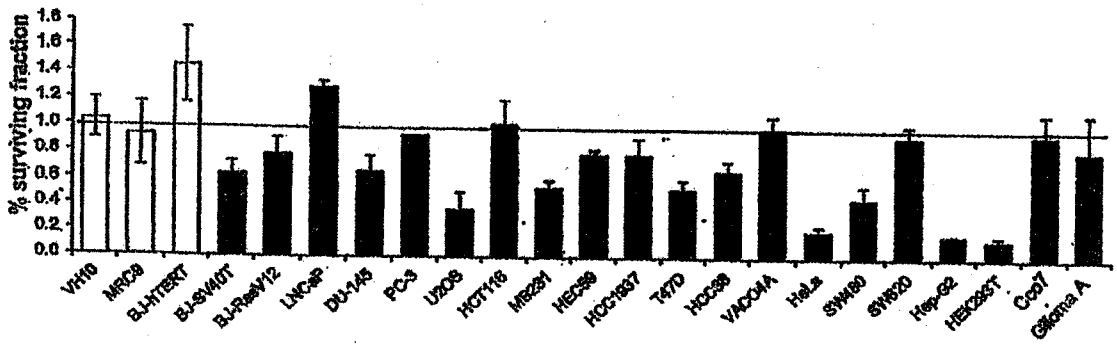


FIGURE 1

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