

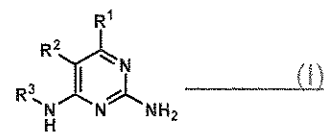
Int., Ed. (2013), Vol. 52. The compounds are organometallic and are not 2-amino-4-(*N*-alkylamino)-6-arylpyrimidines.

Summary of the invention

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

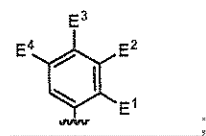
15 The present ~~disclosure~~invention aims at providing new treatments for cancer that can be achieved by inhibition of MTH1.

In an aspect, there is provided the use of a compound of formula I,



20 or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancer,
wherein:

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



- E¹ represents hydrogen, Y^{1a}, -C₁₋₆alkyl optionally substituted by one or more Y² or heterocycloalkyl optionally substituted by one or more Y³.
- E² represents hydrogen, Y^{1b}, -C₁₋₆alkyl optionally substituted by one or more Y² or heterocycloalkyl optionally substituted by one or more Y³.
- 5 E³ and E⁴ each independently represents hydrogen, Y¹, -C₁₋₆alkyl optionally substituted by one or more Y² or heterocycloalkyl optionally substituted by one or more Y³.
- R² represents hydrogen, halogen, -CN, -C₁₋₁₂alkyl optionally substituted by one or more Z¹, or heterocycloalkyl optionally substituted by one or more Z².
- 10 R³ represents -C₁₋₁₂alkyl optionally substituted by one or more Z¹ or heterocycloalkyl optionally substituted by one or more Z²; or
- 15 R² and R³ are linked together to form, along with the atoms to which they are attached, a 5- to 8-membered non-aromatic ring, wherein the link formed by R² and R³ is optionally substituted by one or more substituents selected from Z³ and -C₁₋₉alkyl optionally substituted by one or more Z⁴.
- 20 each Y¹ independently represents halogen, -CN, -C(O)R^a, -C(O)N(R^b)R^c, -C(O)OR^d, -N(R^e)R^f, -N(R^g)C(O)R^h, -N(Rⁱ)C(O)OR^j, -N(R^k)C(O)N(R^l)R^m, -NO₂, -N(Rⁿ)S(O)₂R^o, -OR^p, -OC(O)R^q, -OS(O)₂R^r, -S(O)_mR^s, -S(O)₂N(R^t)R^u, heterocycloalkyl optionally substituted by one or more substituents selected from W², aryl optionally substituted by one or more substituents selected from W³ or
- 25 heteroaryl optionally substituted by one or more substituents selected from W³.
- Y^{1a} represents halogen, -CN, -C(O)R^a, -C(O)N(R^b)R^c, -C(O)OR^d, -N(R^e)R^f, -N(R^g)C(O)R^h, -N(Rⁱ)C(O)OR^j, -N(R^k)C(O)N(R^l)R^m, -NO₂, -N(Rⁿ)S(O)₂R^o, -OR^{px}, -OC(O)R^q, -OS(O)₂R^r, -S(O)_mR^s, -S(O)₂N(R^t)R^u, heterocycloalkyl optionally
- 30 substituted by one or more substituents selected from W², aryl optionally substituted by one or more substituents selected from W³ or heteroaryl optionally substituted by one or more substituents selected from W³.
- Y^{1b} represents halogen, -CN, -C(O)R^a, -C(O)N(R^b)R^c, -C(O)OR^d, -N(R^e)R^f, -N(R^g)C(O)R^h, -N(Rⁱ)C(O)OR^j, -N(R^k)C(O)N(R^l)R^m, -NO₂, -N(Rⁿ)S(O)₂R^o,
- 35

-OR^{py}, -OC(O)R^a, -OS(O)₂R^r, -S(O)_mR^s, -S(O)₂N(R¹)R^u, heterocycloalkyl optionally substituted by one or more substituents selected from W², aryl optionally substituted by one or more substituents selected from W³ or heteroaryl optionally substituted by one or more substituents selected from W³;

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

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

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

R^{py} represents hydrogen, -C₂₋₆ alkyl optionally substituted by one or more substituents selected from W¹, heterocycloalkyl optionally substituted by one or more substituents selected from W², aryl optionally substituted by one or more substituents selected from W³, or heteroaryl optionally substituted by one or more substituents selected from W³;

each Y² 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)Rⁱ¹, -N(R^{j1})C(O)OR^{k1}, -N(R^{l1})C(O)N(R^{m1})Rⁿ¹, -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

W¹, aryl optionally substituted by one or more substituents selected from W², heteroaryl optionally substituted by one or more substituents selected from W², or =O;

5 each Y³ 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)Rⁱ¹, -N(R^{j1})C(O)OR^{k1}, -N(R^{l1})C(O)N(R^{m1})Rⁿ¹, -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 W¹, aryl optionally substituted by one or more substituents selected from W²,

10 heteroaryl optionally substituted by one or more substituents selected from W², or =O;

each R^{a1}, R^{b1}, R^{c1}, R^{d1}, R^{e1}, R^{f1}, R^{h1}, Rⁱ¹, R^{j1}, R^{l1}, R^{m1}, Rⁿ¹, R^{o1}, R^{q1}, R^{r1}, R^{t1}, R^{u1} and R^{v1} independently represents hydrogen, C₁₋₆ alkyl optionally substituted by one or more substituents selected from W¹, heterocycloalkyl optionally substituted by one or more substituents selected from W², aryl optionally substituted by one or more substituents selected from W³, or heteroaryl optionally substituted by one or more substituents selected from W³; or

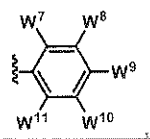
20 any two R^{c1} and R^{d1}, R^{f1} and R^{g1}, R^{m1} and Rⁿ¹ and/or R^{u1} and R^{v1} are linked together to form, along with the nitrogen atom to which they are attached, a 3- to 8-membered monocyclic or bicyclic ring, which ring optionally contains one or two heteroatoms and which ring optionally is substituted by one or more substituents selected from W², C₁₋₃alkyl optionally substituted by one or more substituents selected from W¹, and =O;

25 each R^{g1}, R^{k1}, R^{p1} and R^{s1} independently represents -C₁₋₆ alkyl optionally substituted by one or more substituents selected from W¹, heterocycloalkyl optionally substituted by one or more substituents selected from W², aryl optionally substituted by one or more substituents selected from W³, or heteroaryl optionally substituted by one or more substituents selected from W³;

30 each Z¹ 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)Rⁱ², -N(R^{j2})C(O)OR^{k2}, -N(R^{l2})C(O)N(R^{m2})Rⁿ², -N(R^{o2})S(O)₂R^{p2}, -OR^{q2}, -OC(O)R^{r2}, -OS(O)₂R^{s2}, -S(O)_mR^{t2}, -S(O)₂N(R^{u2})R^{v2},

35 -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, $-R^{a2}$, $-\text{CN}$, $-\text{C}(\text{O})\text{R}^{b2}$, $-\text{C}(\text{O})\text{N}(\text{R}^{c2})\text{R}^{d2}$, $-\text{C}(\text{O})\text{OR}^{e2}$, $-\text{N}(\text{R}^{f2})\text{R}^{g2}$, $-\text{N}(\text{R}^{h2})\text{C}(\text{O})\text{R}^{i2}$, $-\text{N}(\text{R}^{j2})\text{C}(\text{O})\text{OR}^{k2}$, $-\text{N}(\text{R}^{l2})\text{C}(\text{O})\text{N}(\text{R}^{m2})\text{R}^{n2}$, $-\text{N}(\text{R}^{o2})\text{S}(\text{O})_2\text{R}^{p2}$, $-\text{OR}^{q2}$, $-\text{OC}(\text{O})\text{R}^{r2}$, $-\text{OS}(\text{O})_2\text{R}^{s2}$, $-\text{S}(\text{O})_m\text{R}^{l2}$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{u2})\text{R}^{v2}$, heterocycloalkyl optionally substituted by one or more substituents selected from W^5 , aryl optionally substituted by one or more substituents selected from W^6 , or heteroaryl optionally substituted by one or more substituents selected from W^6 ;

each Z^4 independently represents halogen, $-\text{CN}$, $-\text{C}(\text{O})\text{R}^{b2}$, $-\text{C}(\text{O})\text{N}(\text{R}^{c2})\text{R}^{d2}$, $-\text{C}(\text{O})\text{OR}^{e2}$, $-\text{N}(\text{R}^{f2})\text{R}^{g2}$, $-\text{N}(\text{R}^{h2})\text{C}(\text{O})\text{R}^{i2}$, $-\text{N}(\text{R}^{j2})\text{C}(\text{O})\text{OR}^{k2}$, $-\text{N}(\text{R}^{l2})\text{C}(\text{O})\text{N}(\text{R}^{m2})\text{R}^{n2}$, $-\text{N}(\text{R}^{o2})\text{S}(\text{O})_2\text{R}^{p2}$, $-\text{OR}^{q2}$, $-\text{OC}(\text{O})\text{R}^{r2}$, $-\text{OS}(\text{O})_2\text{R}^{s2}$, $-\text{S}(\text{O})_m\text{R}^{l2}$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{u2})\text{R}^{v2}$, heterocycloalkyl optionally substituted by one or more substituents selected from 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^{s2} , 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^{q2} , 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, $-CN$, $-N(R^{f3})R^{g3}$, $-N(R^{h3})C(O)R^{i3}$, $-N(R^{i3})C(O)OR^{k3}$, $-N(R^{i3})C(O)N(R^{m3})R^{n3}$, $-N(R^{o3})S(O)_2R^{p3}$, $-OR^{q3}$, $-OC(O)R^{r3}$, $-OS(O)_2R^{s3}$, $-S(O)_mR^{t3}$, $-S(O)_2N(R^{u3})R^{v3}$, 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, $-R^{a3}$, $-CN$, $-C(O)R^{b3}$, $-C(O)N(R^{c3})R^{d3}$, $-C(O)OR^{e3}$, $-N(R^{f3})R^{g3}$, $-N(R^{h3})C(O)R^{i3}$, $-N(R^{i3})C(O)OR^{k3}$, $-N(R^{i3})C(O)N(R^{m3})R^{n3}$, $-N(R^{o3})S(O)_2R^{p3}$, $-OR^{q3}$, $-OC(O)R^{r3}$, $-OS(O)_2R^{s3}$, $-S(O)_mR^{t3}$, $-S(O)_2N(R^{u3})R^{v3}$, 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, $-R^{a3}$, $-CN$, $-C(O)R^{b3}$, $-C(O)N(R^{c3})R^{d3}$, $-C(O)OR^{e3}$, $-N(R^{f3})R^{g3}$, $-N(R^{h3})C(O)R^{i3}$, $-N(R^{i3})C(O)OR^{k3}$, $-N(R^{i3})C(O)N(R^{m3})R^{n3}$, $-N(R^{o3})S(O)_2R^{p3}$, $-OR^{q3}$, $-OC(O)R^{r3}$, $-OS(O)_2R^{s3}$, $-S(O)_mR^{t3}$, $-S(O)_2N(R^{u3})R^{v3}$, 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, $-R^{a3}$, $-CN$, $-C(O)R^{b3}$, $-C(O)N(R^{c3})R^{d3}$, $-C(O)OR^{e3}$, $-N(R^{f3})R^{g3}$, $-N(R^{h3})C(O)R^{i3}$, $-N(R^{i3})C(O)OR^{k3}$, $-N(R^{i3})C(O)N(R^{m3})R^{n3}$, $-N(R^{o3})S(O)_2R^{p3}$, $-OR^{q3}$, $-OC(O)R^{r3}$, $-OS(O)_2R^{s3}$, $-S(O)_mR^{t3}$, $-S(O)_2N(R^{u3})R^{v3}$,

- 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 ;
- 5 each R^{a3} , R^{b3} , R^{c3} , R^{d3} , R^{e3} , R^{f3} , R^{h3} , R^{i3} , R^{j3} , R^{l3} , R^{m3} , R^{n3} , R^{o3} , R^{q3} , R^{r3} , R^{t3} , R^{u3} and R^{v3} independently represents hydrogen or C_{1-6} alkyl optionally substituted by one or more G^3 ; or
- 10 any two R^{c3} and R^{d3} , R^{f3} and R^{g3} , R^{m3} and R^{h3} 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 ;
- 15 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 ;
- 20 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 $=O$;
- 25 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 $=O$;
- 30 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
- 35 any two R^{c4} and R^{d4} , R^{f4} and R^{g4} , R^{m4} and R^{h4} 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 the compound is not

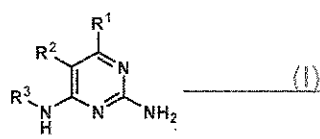
6-(3-pyridinyl)- N^4 -[[4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]methyl]-2,4-pyrimidinediamine,

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

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

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

In another aspect, there is provided a compound of formula I,

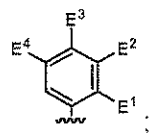


or a pharmaceutically acceptable salt thereof, wherein:

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;

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

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

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

each Y¹ independently represents halogen, -CN, -C(O)R^a, -C(O)N(R^b)R^c, -C(O)OR^d, -N(R^e)R^f, -N(R^g)C(O)R^h, -N(Rⁱ)C(O)OR^j, -N(R^k)C(O)N(R^l)R^m, -NO₂, -N(Rⁿ)S(O)₂R^o,

-OR^p, -OC(O)R^q, -OS(O)₂R^r, -S(O)_mR^s, -S(O)₂N(R^t)R^u, heterocycloalkyl optionally substituted by one or more substituents selected from W², aryl optionally substituted by one or more substituents selected from W³, or heteroaryl optionally substituted by one or more substituents selected from W³;

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

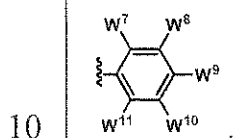
any two R^b and R^c, R^e and R^f, Rⁱ and R^m and/or R^l and R^u are linked together to form, along with the nitrogen atom to which they are attached, a 3- to 8-membered monocyclic or bicyclic ring, which ring optionally contains one or two heteroatoms and which ring optionally is substituted by one or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

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

- by one or more substituents selected from W^2 , aryl optionally substituted by one or more substituents selected from W^3 or heteroaryl optionally substituted by one or more substituents selected from W^3 ;
- 5 each Y^2 independently represents halogen, $-\text{CN}$, $-\text{C}(\text{O})\text{R}^{b1}$, $-\text{C}(\text{O})\text{N}(\text{R}^{c1})\text{R}^{d1}$, $-\text{C}(\text{O})\text{OR}^{e1}$, $-\text{N}(\text{R}^{f1})\text{R}^{g1}$, $-\text{N}(\text{R}^{h1})\text{C}(\text{O})\text{R}^{i1}$, $-\text{N}(\text{R}^{i1})\text{C}(\text{O})\text{OR}^{k1}$, $-\text{N}(\text{R}^{l1})\text{C}(\text{O})\text{N}(\text{R}^{m1})\text{R}^{n1}$, $-\text{N}(\text{R}^{o1})\text{S}(\text{O})_2\text{R}^{p1}$, $-\text{OR}^{q1}$, $-\text{OC}(\text{O})\text{R}^{r1}$, $-\text{OS}(\text{O})_2\text{R}^{s1}$, $-\text{S}(\text{O})_m\text{R}^{t1}$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{u1})\text{R}^{v1}$, heterocycloalkyl optionally substituted by one or more substituents selected from W^1 , aryl optionally substituted by one or more substituents selected from W^2 , heteroaryl optionally substituted by one or more substituents selected from W^2 ;
- 10 each Y^3 independently represents halogen, $-\text{R}^{a1}$, $-\text{CN}$, $-\text{C}(\text{O})\text{R}^{b1}$, $-\text{C}(\text{O})\text{N}(\text{R}^{c1})\text{R}^{d1}$, $-\text{C}(\text{O})\text{OR}^{e1}$, $-\text{N}(\text{R}^{f1})\text{R}^{g1}$, $-\text{N}(\text{R}^{h1})\text{C}(\text{O})\text{R}^{i1}$, $-\text{N}(\text{R}^{i1})\text{C}(\text{O})\text{OR}^{k1}$, $-\text{N}(\text{R}^{l1})\text{C}(\text{O})\text{N}(\text{R}^{m1})\text{R}^{n1}$, $-\text{N}(\text{R}^{o1})\text{S}(\text{O})_2\text{R}^{p1}$, $-\text{OR}^{q1}$, $-\text{OC}(\text{O})\text{R}^{r1}$, $-\text{OS}(\text{O})_2\text{R}^{s1}$, $-\text{S}(\text{O})_m\text{R}^{t1}$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{u1})\text{R}^{v1}$, 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 $=\text{O}$;
- 15 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
- 20 any two R^{c1} and R^{d1} , R^{h1} 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 $=\text{O}$;
- 25 each R^{g1} , R^{k1} , R^{p1} and R^{s1} independently represent $-\text{C}_{1-6}$ 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 ;

- 5 each Z^1 independently represents halogen, $-\text{CN}$, $-\text{C}(\text{O})\text{R}^{b2}$, $-\text{C}(\text{O})\text{N}(\text{R}^{c2})\text{R}^{d2}$,
 $-\text{C}(\text{O})\text{OR}^{e2}$, $-\text{N}(\text{R}^{f2})\text{R}^{g2}$, $-\text{N}(\text{R}^{h2})\text{C}(\text{O})\text{R}^{i2}$, $-\text{N}(\text{R}^{j2})\text{C}(\text{O})\text{OR}^{k2}$, $-\text{N}(\text{R}^{l2})\text{C}(\text{O})\text{N}(\text{R}^{m2})\text{R}^{n2}$,
 $-\text{N}(\text{R}^{o2})\text{S}(\text{O})_2\text{R}^{p2}$, $-\text{OR}^{q2}$, $-\text{OC}(\text{O})\text{R}^{r2}$, $-\text{OS}(\text{O})_2\text{R}^{s2}$, $-\text{S}(\text{O})_m\text{R}^{l2}$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{u2})\text{R}^{v2}$,
heterocycloalkyl optionally substituted by one or more substituents selected from
 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 ;

- 15 each Z^2 and Z^3 independently represents halogen, $-\text{R}^{a2}$, $-\text{CN}$, $-\text{C}(\text{O})\text{R}^{b2}$,
 $-\text{C}(\text{O})\text{N}(\text{R}^{c2})\text{R}^{d2}$, $-\text{C}(\text{O})\text{OR}^{e2}$, $-\text{N}(\text{R}^{f2})\text{R}^{g2}$, $-\text{N}(\text{R}^{h2})\text{C}(\text{O})\text{R}^{i2}$, $-\text{N}(\text{R}^{j2})\text{C}(\text{O})\text{OR}^{k2}$,
 $-\text{N}(\text{R}^{l2})\text{C}(\text{O})\text{N}(\text{R}^{m2})\text{R}^{n2}$, $-\text{N}(\text{R}^{o2})\text{S}(\text{O})_2\text{R}^{p2}$, $-\text{OR}^{q2}$, $-\text{OC}(\text{O})\text{R}^{r2}$, $-\text{OS}(\text{O})_2\text{R}^{s2}$, $-\text{S}(\text{O})_m\text{R}^{l2}$,
 $-\text{S}(\text{O})_2\text{N}(\text{R}^{u2})\text{R}^{v2}$, heterocycloalkyl optionally substituted by one or more
substituents selected from W^5 , aryl optionally substituted by one or more
substituents selected from W^6 , or heteroaryl optionally substituted by one or more
20 substituents selected from W^6 ;

- 25 each Z^4 independently represents halogen, $-\text{CN}$, $-\text{C}(\text{O})\text{R}^{b2}$, $-\text{C}(\text{O})\text{N}(\text{R}^{c2})\text{R}^{d2}$,
 $-\text{C}(\text{O})\text{OR}^{e2}$, $-\text{N}(\text{R}^{f2})\text{R}^{g2}$, $-\text{N}(\text{R}^{h2})\text{C}(\text{O})\text{R}^{i2}$, $-\text{N}(\text{R}^{j2})\text{C}(\text{O})\text{OR}^{k2}$, $-\text{N}(\text{R}^{l2})\text{C}(\text{O})\text{N}(\text{R}^{m2})\text{R}^{n2}$,
 $-\text{N}(\text{R}^{o2})\text{S}(\text{O})_2\text{R}^{p2}$, $-\text{OR}^{q2}$, $-\text{OC}(\text{O})\text{R}^{r2}$, $-\text{OS}(\text{O})_2\text{R}^{s2}$, $-\text{S}(\text{O})_m\text{R}^{l2}$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{u2})\text{R}^{v2}$,
heterocycloalkyl optionally substituted by one or more substituents selected from
 W^5 , aryl optionally substituted by one or more substituents selected from W^6 ,
heteroaryl optionally substituted by one or more substituents selected from W^6 , or
 $=\text{O}$;

- 30 each R^{a2} , R^{b2} , R^{c2} , R^{d2} , R^{e2} , R^{f2} , R^{g2} , 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^{q2} , 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, $-CN$, $-N(R^{i3})R^{q3}$, $-N(R^{h3})C(O)R^{i3}$, $-N(R^{i3})C(O)OR^{k3}$, $-N(R^{i3})C(O)N(R^{m3})R^{n3}$, $-N(R^{o3})S(O)_2R^{p3}$, $-OR^{q3}$, $-OC(O)R^{r3}$, $-OS(O)_2R^{s3}$, $-S(O)_mR^{i3}$, $-S(O)_2N(R^{u3})R^{v3}$, 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, $-R^{a3}$, $-CN$, $-C(O)R^{b3}$, $-C(O)N(R^{c3})R^{d3}$, $-C(O)OR^{e3}$, $-N(R^{f3})R^{g3}$, $-N(R^{h3})C(O)R^{i3}$, $-N(R^{i3})C(O)OR^{k3}$, $-N(R^{i3})C(O)N(R^{m3})R^{n3}$, $-N(R^{o3})S(O)_2R^{p3}$, $-OR^{q3}$, $-OC(O)R^{r3}$, $-OS(O)_2R^{s3}$, $-S(O)_mR^{i3}$, $-S(O)_2N(R^{u3})R^{v3}$, 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, $-R^{a3}$, $-CN$, $-C(O)R^{b3}$,

- $\text{-C(O)N(R}^{c3}\text{)R}^{d3}$, -C(O)OR^{e3} , $\text{-N(R}^{f3}\text{)R}^{g3}$, $\text{-N(R}^{h3}\text{)C(O)R}^{i3}$, $\text{-N(R}^{j3}\text{)C(O)OR}^{k3}$,
 $\text{-N(R}^{l3}\text{)C(O)N(R}^{m3}\text{)R}^{n3}$, $\text{-N(R}^{o3}\text{)S(O)}_2\text{R}^{p3}$, -OR^{q3} , -OC(O)R^{r3} , $\text{-OS(O)}_2\text{R}^{s3}$, $\text{-S(O)}_m\text{R}^{t3}$,
 $\text{-S(O)}_2\text{N(R}^{u3}\text{)R}^{v3}$, heterocycloalkyl optionally substituted by one or more
substituents selected from G^1 , aryl optionally substituted by one or more
5 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} , $\text{-C(O)N(R}^{c3}\text{)R}^{d3}$, -C(O)OR^{e3} , $\text{-N(R}^{f3}\text{)R}^{g3}$,
10 $\text{-N(R}^{h3}\text{)C(O)R}^{i3}$, $\text{-N(R}^{j3}\text{)C(O)OR}^{k3}$, $\text{-N(R}^{l3}\text{)C(O)N(R}^{m3}\text{)R}^{n3}$, $\text{-N(R}^{o3}\text{)S(O)}_2\text{R}^{p3}$, -OR^{q3x} ,
 -OC(O)R^{r3} , $\text{-OS(O)}_2\text{R}^{s3}$, $\text{-S(O)}_m\text{R}^{t3}$, $\text{-S(O)}_2\text{N(R}^{u3}\text{)R}^{v3}$, heterocycloalkyl optionally
substituted by one or more substituents selected from G^1 , aryl optionally
substituted by one or more substituents selected from G^2 , or heteroaryl optionally
substituted by one or more substituents selected from G^2 ;
- 15 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
- 20 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 ;
- 25 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 ;
- 30 each G^1 and G^2 independently represents halogen, -R^{a4} , -CN , -C(O)R^{b4} ,
 $\text{-C(O)N(R}^{c4}\text{)R}^{d4}$, -C(O)OR^{e4} , $\text{-N(R}^{f4}\text{)R}^{g4}$, $\text{-N(R}^{h4}\text{)C(O)R}^{i4}$, $\text{-N(R}^{j4}\text{)C(O)OR}^{k4}$,
 $\text{-N(R}^{l4}\text{)C(O)N(R}^{m4}\text{)R}^{n4}$, $\text{-N(R}^{o4}\text{)S(O)}_2\text{R}^{p4}$, -OR^{q4} , -OC(O)R^{r4} , $\text{-OS(O)}_2\text{R}^{s4}$, $\text{-S(O)}_m\text{R}^{t4}$,
 $\text{-S(O)}_2\text{N(R}^{u4}\text{)R}^{v4}$, or $=\text{O}$;

G^3 represents halogen, $-\text{CN}$, $-\text{C}(\text{O})\text{R}^{b4}$, $-\text{C}(\text{O})\text{N}(\text{R}^{c4})\text{R}^{d4}$, $-\text{C}(\text{O})\text{OR}^{e4}$, $-\text{N}(\text{R}^{f4})\text{R}^{g4}$, $-\text{N}(\text{R}^{h4})\text{C}(\text{O})\text{R}^{i4}$, $-\text{N}(\text{R}^{j4})\text{C}(\text{O})\text{OR}^{k4}$, $-\text{N}(\text{R}^{l4})\text{C}(\text{O})\text{N}(\text{R}^{m4})\text{R}^{n4}$, $-\text{N}(\text{R}^{o4})\text{S}(\text{O})_2\text{R}^{p4}$, $-\text{OR}^{q4}$, $-\text{OC}(\text{O})\text{R}^{r4}$, $-\text{OS}(\text{O})_2\text{R}^{s4}$, $-\text{S}(\text{O})_m\text{R}^{t4}$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{u4})\text{R}^{v4}$, or $=\text{O}$;

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

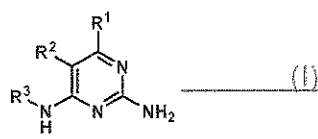
10 any two R^{c4} and R^{d4} , R^{f4} and R^{g4} , R^{m4} and R^{n4} and/or R^{u4} and R^{v4} are linked together to form, along with the nitrogen atom to which they are attached, a 3- to 6-membered ring, which ring optionally substituted by one or more $-\text{F}$, $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CHF}_2$, $-\text{CF}_3$, $-\text{CH}_2\text{CF}_3$, or $=\text{O}$;

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

each m independently represents 0, 1 or 2;

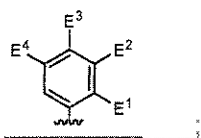
20 provided that the compound is not
 6-(3-pyridinyl)- N^4 -[4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]methyl]-2,4-pyrimidinediamine,
 6-(3-pyridinyl)- N^4 -[5-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]-2-pyridinyl]methyl]-2,4-pyrimidinediamine,
 6-(3-pyridinyl)- N^4 -[5-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]-2-pyrimidinyl]-methyl]-2,4-pyrimidinediamine,
 25 N^4 -[2-(diethylamino)ethyl]-6-(3,4,5-trimethoxyphenyl)-2,4-pyrimidinediamine,
 N^4 -[3-(4-morpholinyl)propyl]-6-(3,4,5-trimethoxyphenyl)-2,4-pyrimidinediamine, or
 N^4 -[2-(4-morpholinyl)ethyl]-6-(3,4,5-trimethoxyphenyl)-2,4-pyrimidinediamine.

30 In yet another aspect, there is provided a compound of formula I,



or a pharmaceutically acceptable salt thereof,
 wherein:

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



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

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

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

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

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

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

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

- substituted by one or more substituents selected from W^3 ;
- Y^{1b} represents halogen, $-\text{CN}$, $-\text{C}(\text{O})\text{R}^a$, $-\text{C}(\text{O})\text{N}(\text{R}^b)\text{R}^c$, $-\text{C}(\text{O})\text{OR}^d$, $-\text{N}(\text{R}^e)\text{R}^f$,
 $-\text{N}(\text{R}^g)\text{C}(\text{O})\text{R}^h$, $-\text{N}(\text{R}^i)\text{C}(\text{O})\text{OR}^j$, $-\text{N}(\text{R}^k)\text{C}(\text{O})\text{N}(\text{R}^l)\text{R}^m$, $-\text{NO}_2$, $-\text{N}(\text{R}^n)\text{S}(\text{O})_2\text{R}^o$,
5 $-\text{OR}^p$, $-\text{OC}(\text{O})\text{R}^q$, $-\text{OS}(\text{O})_2\text{R}^r$, $-\text{S}(\text{O})_m\text{R}^s$, $-\text{S}(\text{O})_2\text{N}(\text{R}^t)\text{R}^u$, heterocycloalkyl optionally
substituted by one or more substituents selected from W^2 , aryl optionally
substituted by one or more substituents selected from W^3 or heteroaryl optionally
substituted by one or more substituents selected from W^3 ;
- 10 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
15 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^l and R^u are linked together to
form, along with the nitrogen atom to which they are attached, a 3- to 8-
membered monocyclic or bicyclic ring, which ring optionally contains one or two
20 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 $=\text{O}$;
- each R^f , R^l , R^o , R^r and R^{px} independently represents C_{1-6} alkyl optionally
25 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, $-\text{CN}$, $-\text{C}(\text{O})\text{R}^{b1}$, $-\text{C}(\text{O})\text{N}(\text{R}^{c1})\text{R}^{d1}$,
 $-\text{C}(\text{O})\text{OR}^{e1}$, $-\text{N}(\text{R}^{f1})\text{R}^{g1}$, $-\text{N}(\text{R}^{h1})\text{C}(\text{O})\text{R}^{i1}$, $-\text{N}(\text{R}^{j1})\text{C}(\text{O})\text{OR}^{k1}$, $-\text{N}(\text{R}^{l1})\text{C}(\text{O})\text{N}(\text{R}^{m1})\text{R}^{n1}$,
 $-\text{N}(\text{R}^{o1})\text{S}(\text{O})_2\text{R}^{p1}$, $-\text{OR}^{q1}$, $-\text{OC}(\text{O})\text{R}^{r1}$, $-\text{OS}(\text{O})_2\text{R}^{s1}$, $-\text{S}(\text{O})_m\text{R}^{t1}$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{u1})\text{R}^{v1}$,
heterocycloalkyl optionally substituted by one or more substituents selected from
 W^1 , aryl optionally substituted by one or more substituents selected from W^2 ,
35 heteroaryl optionally substituted by one or more substituents selected from W^2 , or

=O;

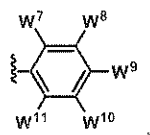
each Y^3 independently represents halogen, $-R^{a1}$, $-CN$, $-C(O)R^{b1}$, $-C(O)N(R^{c1})R^{d1}$,
5 $-C(O)OR^{e1}$, $-N(R^{f1})R^{g1}$, $-N(R^{h1})C(O)R^{i1}$, $-N(R^{j1})C(O)OR^{k1}$, $-N(R^{l1})C(O)N(R^{m1})R^{n1}$,
 $-N(R^{o1})S(O)_2R^{p1}$, $-OR^{q1}$, $-OC(O)R^{r1}$, $-OS(O)_2R^{s1}$, $-S(O)_mR^{t1}$, $-S(O)_2N(R^{u1})R^{v1}$,
heterocycloalkyl optionally substituted by one or more substituents selected from W^1 , aryl optionally substituted by one or more substituents selected from W^2 ,
heteroaryl optionally substituted by one or more substituents selected from W^2 , or
10 =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
15 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
20 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, $-CN$, $-C(O)R^{b2}$, $-C(O)N(R^{c2})R^{d2}$,
30 $-C(O)OR^{e2}$, $-N(R^{f2})R^{g2}$, $-N(R^{h2})C(O)R^{i2}$, $-N(R^{j2})C(O)OR^{k2}$, $-N(R^{l2})C(O)N(R^{m2})R^{n2}$,
 $-N(R^{o2})S(O)_2R^{p2}$, $-OR^{q2}$, $-OC(O)R^{r2}$, $-OS(O)_2R^{s2}$, $-S(O)_mR^{t2}$, $-S(O)_2N(R^{u2})R^{v2}$,
heterocycloalkyl optionally substituted by one or more substituents selected from
35 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 $=O$;

5 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 ;

15 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 $=O$;

20 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

30 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, $-\text{CN}$, $-\text{N}(\text{R}^{f3})\text{R}^{g3}$, $-\text{N}(\text{R}^{h3})\text{C}(\text{O})\text{R}^{i3}$, $-\text{N}(\text{R}^{j3})\text{C}(\text{O})\text{OR}^{k3}$, $-\text{N}(\text{R}^{l3})\text{C}(\text{O})\text{N}(\text{R}^{m3})\text{R}^{n3}$, $-\text{N}(\text{R}^{o3})\text{S}(\text{O})_2\text{R}^{p3}$, $-\text{OR}^{q3}$, $-\text{OC}(\text{O})\text{R}^{r3}$, $-\text{OS}(\text{O})_2\text{R}^{s3}$, $-\text{S}(\text{O})_m\text{R}^{t3}$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{u3})\text{R}^{v3}$, heterocycloalkyl optionally substituted by one or more substituents selected from G^1 , aryl optionally substituted by one or more substituents selected from G^2 , heteroaryl optionally substituted by one or more substituents selected from G^2 , or $=\text{O}$;
- each W^2 , W^3 , W^5 and W^6 independently represents halogen, $-\text{R}^{a3}$, $-\text{CN}$, $-\text{C}(\text{O})\text{R}^{b3}$, $-\text{C}(\text{O})\text{N}(\text{R}^{c3})\text{R}^{d3}$, $-\text{C}(\text{O})\text{OR}^{e3}$, $-\text{N}(\text{R}^{f3})\text{R}^{g3}$, $-\text{N}(\text{R}^{h3})\text{C}(\text{O})\text{R}^{i3}$, $-\text{N}(\text{R}^{j3})\text{C}(\text{O})\text{OR}^{k3}$, $-\text{N}(\text{R}^{l3})\text{C}(\text{O})\text{N}(\text{R}^{m3})\text{R}^{n3}$, $-\text{N}(\text{R}^{o3})\text{S}(\text{O})_2\text{R}^{p3}$, $-\text{OR}^{q3}$, $-\text{OC}(\text{O})\text{R}^{r3}$, $-\text{OS}(\text{O})_2\text{R}^{s3}$, $-\text{S}(\text{O})_m\text{R}^{t3}$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{u3})\text{R}^{v3}$, heterocycloalkyl optionally substituted by one or more substituents selected from G^1 , aryl optionally substituted by one or more substituents selected from G^2 , heteroaryl (optionally substituted by one or more substituents selected from G^2 , or $=\text{O}$;
- each W^7 , W^8 , W^9 , W^{10} and W^{11} independently represents hydrogen, halogen, $-\text{R}^{a3}$, $-\text{CN}$, $-\text{C}(\text{O})\text{R}^{b3}$, $-\text{C}(\text{O})\text{N}(\text{R}^{c3})\text{R}^{d3}$, $-\text{C}(\text{O})\text{OR}^{e3}$, $-\text{N}(\text{R}^{f3})\text{R}^{g3}$, $-\text{N}(\text{R}^{h3})\text{C}(\text{O})\text{R}^{i3}$, $-\text{N}(\text{R}^{j3})\text{C}(\text{O})\text{OR}^{k3}$, $-\text{N}(\text{R}^{l3})\text{C}(\text{O})\text{N}(\text{R}^{m3})\text{R}^{n3}$, $-\text{N}(\text{R}^{o3})\text{S}(\text{O})_2\text{R}^{p3}$, $-\text{OR}^{q3}$, $-\text{OC}(\text{O})\text{R}^{r3}$, $-\text{OS}(\text{O})_2\text{R}^{s3}$, $-\text{S}(\text{O})_m\text{R}^{t3}$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{u3})\text{R}^{v3}$, heterocycloalkyl optionally substituted by one or more substituents selected from G^1 , aryl optionally substituted by one or more substituents selected from G^2 , or heteroaryl optionally substituted by one or 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 G²;

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

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

G³ represents halogen, -CN, -C(O)R^{b4}, -C(O)N(R^{c4})R^{d4}, -C(O)OR^{e4}, -N(R^{f4})R^{g4}, -N(R^{h4})C(O)Rⁱ⁴, -N(R^{j4})C(O)OR^{k4}, -N(R^{l4})C(O)N(R^{m4})Rⁿ⁴, -N(R^{o4})S(O)₂R^{p4}, -OR^{q4}, -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}, Rⁱ⁴, R^{j4}, R^{l4}, R^{m4}, Rⁿ⁴, R^{o4}, R^{q4}, R^{r4}, R^{t4}, R^{u4} and R^{v4} independently represents hydrogen or C₁₋₆ alkyl optionally substituted by one or more -F; or

any two R^{c4} and R^{d4}, R^{f4} and R^{g4}, R^{m4} and Rⁿ⁴ 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, -CH₃, -CH₂CH₃, -CHF₂, -CF₃, -CH₂CF₃, or =O;

each R^{g4}, R^{k4}, R^{p4} and R^{s4} independently represent C₁₋₆ alkyl optionally substituted by one or more -F;

each m independently represents 0, 1 or 2;

provided that the compound is not
N¹-cyclopropyl-6-(4-methoxy-2-methylphenyl)-2,4-pyrimidinediamine.

In another aspect, there is provided a pharmaceutical formulation comprising a compound as defined above, or a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

In another aspect, there is provided the use of a pharmaceutical formulation as defined above, in the manufacture of a medicament for treating cancer.

In another aspect, there is provided the use of a compound as defined above, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating cancer.

In another aspect, there is provided a compound as defined above or a pharmaceutically acceptable salt thereof, for use as a pharmaceutical.

In yet another aspect, there is provided a combination product comprising:
(A) a compound as defined above, or a pharmaceutically acceptable salt thereof;
and
(B) one or more other therapeutic agent(s) that is/are useful in the treatment of a disease,
wherein each one of components (A) and (B) is formulated in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier.

In another aspect, there is provided a therapeutically effective amount of a compound as defined above, or a pharmaceutically acceptable salt thereof, for use in therapy.

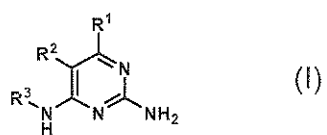
Brief description of the drawings

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,

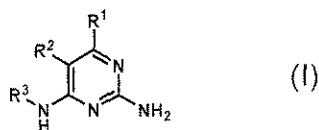


for use in the treatment of cancer
wherein:

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Claims

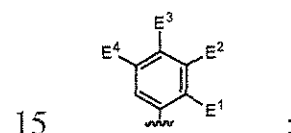
1. Use of aA compound of formula I,



5

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of cancer,
wherein:

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



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

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

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

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

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

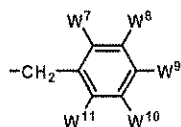
30 R² and R³ are linked together to form, along with the atoms to which they are attached, a 5- to 8-membered non-aromatic ring, wherein the link formed by R² and R³ is optionally substituted by one or more substituents selected from Z³ and

2. ~~A compound for~~The use as claimed in Claim 1, wherein:
 R^2 represents hydrogen, halogen, -CN or -C₁₋₁₂alkyl optionally substituted by one or more Z¹; and
 R^3 represents -C₁₋₁₂alkyl optionally substituted by one or more Z¹ or
 5 heterocycloalkyl optionally substituted by one or more Z².

3. ~~A compound for~~The use as claimed in Claim 2, wherein:
 R^2 represents hydrogen, -CN or -C₁₋₃alkyl optionally substituted by one or more -F; and
 10 R^3 represents -C₂₋₆alkyl optionally substituted by one or more Z¹ or heterocycloalkyl optionally substituted by one or more Z².

4. ~~A compound for~~The use as claimed in Claim 3, wherein:
 R^2 represents hydrogen; and
 15 R^3 represents a -C₃₋₆alkyl or a heterocycloalkyl selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclopropylethyl, cyclobutylethyl, cyclopropylpropyl, oxetanyl, tetrahydrofuryl, tetrahydropyranyl, azetidiny, pyrrolidiny, piperidiny, piperaziny or morpholinyl wherein the C₃₋₆alkyl is optionally substituted by one or more Z¹
 20 and the heterocycloalkyl is optionally substituted by one or more Z².

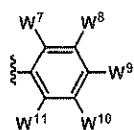
5. ~~A compound for~~The use as claimed in Claim 2, wherein:
 R^2 represents hydrogen and R^3 represents



25 or heteroaryl (having 1 to 3 nitrogen atoms, one oxygen atom and/or one sulfur atom and optionally substituted by one or more substituents selected from W³).

6. ~~A compound for~~The use as claimed in any one of Claims 1 to 5 wherein:
 Z¹ represents -F, -CN, -C(O)R^{b2}, -C(O)N(R^{c2})R^{d2}, -C(O)OR^{e2}, -N(R^{f2})R^{g2},
 30 -N(R^{h2})C(O)Rⁱ², -N(R^{j2})C(O)OR^{k2}, -N(R^{l2})C(O)N(R^{m2})Rⁿ², -N(R^{o2})S(O)₂R^{p2}, -OR^{q2},
 -S(O)_mR^{l2}, -S(O)₂N(R^{u2})R^{v2}, heterocycloalkyl selected from dihydropyridiny, morpholinyl, piperaziny, piperidiny and pyrrolidiny which heterocycloalkyl is

optionally substituted by one or more substituents selected from W^5 , aryl represented by



heteroaryl selected from benzimidazolyl, benzodioxinyl, benzoxazolyl, furanyl,

- 5 imidazolyl, imidazopyridinyl, indolyl, isoquinolinyl, oxadiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridyl, pyrrolopyridinyl, quinolinyl, thiazolyl, thiophenyl and triazolyl, which heteroaryl is optionally substituted by one or more substituents selected from W^6 ;

- 10 Z^2 represents $-F$, $-R^{a2}$, $-C(O)N(R^{c2})R^{d2}$, $-N(R^{f2})R^{g2}$, $-N(R^{h2})C(O)R^{i2}$, $-N(R^{j2})C(O)OR^{k2}$, $-N(R^{l2})C(O)N(R^{m2})R^{n2}$, $-N(R^{o2})S(O)_2R^{p2}$, $-OR^{q2}$, $-S(O)_mR^{l2}$, $-S(O)_2N(R^{u2})R^{v2}$, heterocycloalkyl optionally substituted by one or more substituents selected from W^5 , aryl optionally substituted by one or more substituents selected from W^6 , or heteroaryl optionally substituted by one or more substituents selected from W^6 ;

each 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

- 20 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 .

25

7. ~~A compound for~~The use as claimed in Claim 2, wherein:

R^2 represents hydrogen; and

R^3 represents $-C_{1-2}$ alkyl optionally substituted with one or more $-F$.

- 30 8. ~~A compound for~~The use as claimed in Claim 1, wherein:

R^2 and R^3 are linked together to form, along with the atoms to which they are attached, a 5- to 6-membered non-aromatic ring, wherein the link formed by R^2

and R³ is optionally substituted by one or more substituents selected from Z³ and/or -C₁₋₉alkyl optionally substituted by one or more Z⁴.

9. ~~A compound for~~The use as claimed in Claim 8, wherein:
- 5 Z³ is not present or is selected from -F, -R^{a2}, -C(O)N(R^{c2})R^{d2}, -N(R^{f2})R^{g2}, -N(R^{h2})C(O)Rⁱ², -N(R^{j2})C(O)OR^{k2}, -N(R^{l2})C(O)N(R^{m2})Rⁿ², -N(R^{o2})S(O)₂R^{p2}, -OR^{q2}, -S(O)_mRⁱ², -S(O)₂N(R^{u2})R^{v2}, heterocycloalkyl optionally substituted by one or more substituents selected from W⁵, aryl optionally substituted by one or more substituents selected from W⁶, or heteroaryl optionally substituted by one or more substituents selected from W⁶; and/or
- 10 Z⁴ is not present or is selected from -F, -C(O)N(R^{c2})R^{d2}, -N(R^{f2})R^{g2}, -N(R^{h2})C(O)Rⁱ², -N(R^{j2})C(O)OR^{k2}, -N(R^{l2})C(O)N(R^{m2})Rⁿ², -N(R^{o2})S(O)₂R^{p2}, -OR^{q2}, -S(O)_mRⁱ², -S(O)₂N(R^{u2})R^{v2}, heterocycloalkyl optionally substituted by one or more substituents selected from W⁵, aryl optionally substituted by one or more substituents selected from W⁶, or heteroaryl optionally substituted by one or more substituents selected from W⁶.
- 15 substituents selected from W⁶.

10. ~~A compound for~~The use as claimed in any one of Claims 1 to 9 wherein:
- E¹ is Y^{1a} or -C₁₋₆alkyl optionally substituted by one or more Y² and at least one of
- 20 E², E³ and E⁴ represents Y^{1b}, -C₁₋₆alkyl optionally substituted by one or more Y².

11. ~~A compound for~~The use as claimed in any one of Claims 1 to 10 wherein:
- Y¹ independently represents halogen, -CN, -C(O)R^a, -C(O)N(R^b)R^c, -C(O)OR^d, -N(R^e)R^f, -N(R^g)C(O)R^h, -N(Rⁱ)C(O)OR^j, -N(R^k)C(O)N(R^l)R^m, -NO₂, -N(Rⁿ)S(O)₂R^o, -OC(O)R^q, -OS(O)₂R^r, -S(O)_mR^s or -S(O)₂N(R^t)R^u;
- 25 Y^{1a} represents halogen, -CN, -C(O)R^a, -C(O)N(R^b)R^c, -C(O)OR^d, -N(R^e)R^f, -N(R^g)C(O)R^h, -N(Rⁱ)C(O)OR^j, -N(R^k)C(O)N(R^l)R^m, -NO₂, -N(Rⁿ)S(O)₂R^o, -OC(O)R^q, -OS(O)₂R^r, -S(O)_mR^s or -S(O)₂N(R^t)R^u; and
- Y^{1b} represents halogen, -CN, -C(O)R^a, -C(O)N(R^b)R^c, -C(O)OR^d, -N(R^e)R^f, -N(R^g)C(O)R^h, -N(Rⁱ)C(O)OR^j, -N(R^k)C(O)N(R^l)R^m, -NO₂, -N(Rⁿ)S(O)₂R^o, -OC(O)R^q, -OS(O)₂R^r, -S(O)_mR^s or -S(O)₂N(R^t)R^u.
- 30

12. ~~A compound for~~The use as claimed in Claim 11 wherein:
- 35 E¹, E³ and E⁴ represent hydrogen and

E¹ represents -CH₃, E³ represents -CF₃ and E⁴ represents -Cl; or

E¹ represents hydrogen; and

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

E³ represents hydrogen; and

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

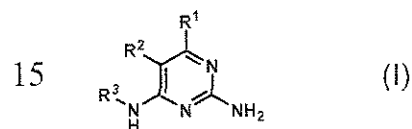
13. ~~A compound for~~The use as claimed in any one of Claims 1 to 9 wherein:

R¹ represents heteroaryl.

10 14. ~~A compound for~~The use as claimed in Claim 13 wherein:

R¹ represents benzofuranyl, benzothiophenyl, dihydrobenzofuranyl, indolyl, isoquinolinyl, pyridinyl or quinolinyl.

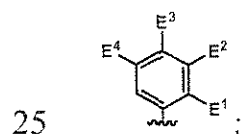
15. A compound of formula I,



or a pharmaceutically acceptable salt thereof, wherein:

R¹ represents:

indanyl, naphthyl, tetrahydronaphthyl or heteroaryl, the latter connected to the
20 pyrimidine of formula I via a carbon atom of the heteroaryl ring, which indanyl,
naphthyl, tetrahydronaphthyl and heteroaryl rings are optionally substituted by
one or more substituents selected from Y¹, -C₁₋₆alkyl optionally substituted by one
or more Y² and heterocycloalkyl optionally substituted by one or more Y³; or
aryl represented by



E¹, E², E³ and E⁴ represents hydrogen, Y¹, -C₁₋₆alkyl optionally substituted by one
or more Y² or heterocycloalkyl optionally substituted by one or more Y³, but where
at least one of E¹, E², E³ and E⁴ is other than hydrogen;

(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 .

45. A pharmaceutical formulation comprising a compound as claimed in any one of Claims 15 to 44, or a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

46. Use of aA pharmaceutical formulation as claimed in Claim 45, in the manufacture of a medicament for use in the treatment of cancer.

47. Use of aA compound as claimed in any one of the claims 15 to 44, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of cancer.

48. Use of Aa compound for use as claimed in any one of Claims 1 to 14, or use of a formulation for use as claimed in Claim 46, or use of a compound for use as claimed in Claim 47, wherein the disease is selected from Soft Tissue Cancers: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung cancers/diseases: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal cancers/diseases: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma); Genitourinary tract cancers/diseases: kidney (adenocarcinoma, Wilm's tumor [nephroblastoma], lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis

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

49. Use of aA compound or formulation ~~for use as~~ claimed in Claim 48, wherein the cancer is selected from the group consisting of breast cancers, prostate cancers, lung cancers, oesophageal cancers, colon cancers, brain cancers, skin cancers, ovarian cancers, testicular cancers, neurofibromatosis and leukemias.

50. A compound as claimed in any one of the Claims 15 to 44, or a pharmaceutically acceptable salt thereof, for use as a pharmaceutical.

51. A combination product comprising:

- 5 (A) a compound as claimed in any one of Claims 15 to 44, or a pharmaceutically acceptable salt thereof; and
(B) one or more other therapeutic agent(s) that is/are useful in the treatment of a disease as defined in Claim 48 or 49,
wherein each one of components (A) and (B) is formulated in admixture with a
10 pharmaceutically-acceptable adjuvant, diluent or carrier.

52. A combination product as claimed in Claim 51, wherein component (B) is selected from the group consisting of anti-microtubule agents, platinum coordination complexes, alkylating agents, antibiotic agents, topoisomerase II
15 inhibitors, antimetabolites, topoisomerase I inhibitors, hormones and hormonal analogues, signal transduction pathway inhibitors; kinase inhibitors; angiogenesis inhibitors; immunotherapeutic agents; pro-apoptotic agents; and cell cycle signaling inhibitors.

20 ~~53. A method of treatment of a disease as defined in Claim 48 or 49, which method comprises administration of a therapeutically effective amount of a compound for use as claimed in any one of the Claims 1 to 14 or a compound as claimed in any one of Claims 15 to 44, or a pharmaceutically acceptable salt thereof, for use in therapy to a patient in need of such treatment.~~

25 ~~54. Use of aA compound for use as claimed in any one of Claims 1 to 14 or Claim 47, wherein the treatment further comprises radiation therapy.~~