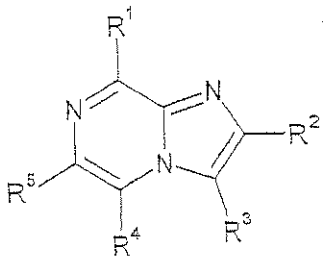
International patent applications WO 2004/072080 and WO 2004/072081 both disclose various imidazopyrazines, which may be useful as modulators of HSP90 complex or as modulators of a certain protein kinase. International patent application WO 02/060492 also discloses various imidazopyrazines, which may be useful as inhibitors of a certain protein kinase (JAK kinases). However, all of these documents predominantly relate to imidazopyrazines that are unsubstituted at the 2-, 3- and 5-position.

International patent application WO 2004/022562 discloses various imidazopyrazines that may be useful as modulators of kinase activity. However, this document predominantly relates to imidazopyrazines that are substituted at the 8-position with an amino group containing an aromatic ring and/or imidazopyrazines that are unsubstituted at the 2-, 3-, and 4-position.

International patent application WO 02/062800 discloses various compounds for use as antagonists on a corticotropin-releasing-factor receptor. International patent application WO 88/04298 also discloses ceratin compounds for use as medicaments. However, these documents do not predominantly relate to imidazopyrazines substituted at the 6-position with an aromatic group and/or relate to those imidazopyrazines unsubstituted at the 2-, 3-, and 4-position.

Summary

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



I

wherein:

R^1 represents:

(a) $-N(R^{1a})R^{1b}$,

in which R^{1a} and R^{1b} are linked together to form, together with the nitrogen atom to which they are necessarily attached, a 5- to 7-membered ring optionally containing a further one or two heteroatoms, optionally containing one or two double bonds, and which ring is optionally substituted by one or more substituents selected from =O and B^1;

(b) a heterocycloalkyl group (attached to the requisite imidazopyrazine *via* a carbon atom), optionally substituted by one or more substituents selected from =O and B^2;

(c) a monocyclic heteroaryl group optionally substituted by one or more substituents selected from B^3;

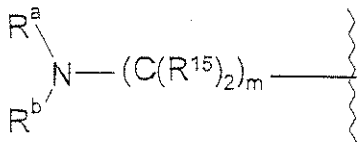
R^2 and R^3 independently represent:

(i) hydrogen;

(ii) Q^1;

(iii) C_{1-12} alkyl optionally substituted by one or more substituents selected from =O, =S, $=N(R^{10a})$ and Q^2; or

R^2 or R^3 may represent a fragment of formula IA,



IA

m represents 0, 1, 2, 3, 4, 5 or 6;

each R^{15} represents hydrogen, halo or C_{1-6} alkyl optionally substituted by one or more substituents selected from E^1; or

the two R^{15} groups may linked together to form (along with the requisite carbon atom to which those R^{15} groups are necessarily attached) a 3- to 6-membered (spiro-cyclic) ring, which ring optionally contains one or more double bonds, and optionally contains a further heteroatom selected from nitrogen, sulfur and oxygen, and which ring is optionally substituted by one or more substituents selected from E^2;

R^a and R^b are linked together, along with the requisite nitrogen atom to which they are necessarily attached, to form a first 3- to 7-membered cyclic group, optionally containing one further heteroatom selected from nitrogen, sulfur and oxygen, and which ring:

(a) is fused to a second ring that is either a 3- to 7-membered saturated heterocycloalkyl group containing one to four heteroatoms selected from oxygen, sulfur and nitrogen, a 3- to 12-membered saturated carbocyclic ring, or an unsaturated 5- to 12-membered carbocyclic or heterocyclic ring;

(b) comprises a linker group $-(C(R^x)_2)_p-$ and/or $-(C(R^x)_2)_r-O-(C(R^x)_2)_s-$ (wherein p is 1 or 2; r is 0 or 1; s is 0 or 1; and each R^x independently represents hydrogen or C_{1-6} alkyl), linking together any two non-adjacent atoms of the first 3- to 7-membered ring (i.e. forming a bridged structure); or

(c) comprises a second ring that is either a 3- to 12-membered saturated carbocyclic ring or a 3- to 7-membered saturated heterocycloalkyl group containing one to four heteroatoms selected from oxygen and nitrogen, and which second ring is linked together with the first ring *via* a single carbon atom common to both rings (i.e. forming a spiro-cycle),

all of which cyclic groups, defined by the linkage of R^a and R^b, are optionally substituted by one or more substituents selected from =O and E^3;

R^4 represents hydrogen or a substituent selected from halo, -CN, $-OR^{10b}$, $-N(R^{10b})R^{11b}$, $-C(O)N(R^{10b})R^{11b}$, $-C(O)R^{10b}$, C_{1-6} alkyl and heterocycloalkyl, which latter two groups are optionally substituted by one or more substituents selected from E^4 and =O;

but wherein at least one of R^2, R^3 and R^4 represents a substituent other than hydrogen;

R^5 represents aryl or heteroaryl (both of which are optionally substituted by one or more substituents selected from E^5);

each Q^1 and Q^2 independently represents, on each occasion when used herein: halo, -CN, $-NO_2$, $-N(R^{10a})R^{11a}$, $-OR^{10a}$, $-C(=Y)-R^{10a}$, $-C(=Y)-OR^{10a}$, $-C(=Y)N(R^{10a})R^{11a}$, $-OC(=Y)-R^{10a}$, $-OC(=Y)-OR^{10a}$, $-OC(=Y)N(R^{10a})R^{11a}$, $-OS(O)_2OR^{10a}$, $-OP(=Y)(OR^{10a})(OR^{11a})$, $-OP(OR^{10a})(OR^{11a})$, $-N(R^{12a})C(=Y)R^{11a}$, $-N(R^{12a})C(=Y)OR^{11a}$, $-N(R^{12a})C(=Y)N(R^{10a})R^{11a}$, $-NR^{12a}S(O)_2R^{10a}$, $-NR^{12a}S(O)_2N(R^{10a})R^{11a}$, $-S(O)_2N(R^{10a})R^{11a}$, $-SC(=Y)R^{10a}$, $-S(O)_2R^{10a}$, $-SR^{10a}$, $-S(O)R^{10a}$, C_{1-12} alkyl, heterocycloalkyl (which latter two groups are optionally substituted by one or more substituents selected from =O, =S, $=N(R^{10a})$ and E^6), aryl or heteroaryl (which latter two groups are optionally substituted by one or more substituents selected from E^7);

each B^1, B^2 and B^3 independently represent halo, $-NO_2$, -CN, $-N(R^{10a})R^{11a}$, $-OR^{10a}$, $-C(=Y)-R^{10a}$, $-C(=Y)-OR^{10a}$, $-C(=Y)N(R^{10a})R^{11a}$, $-N(R^{12a})C(=Y)R^{11a}$, $-N(R^{12a})C(=Y)OR^{11a}$, $-N(R^{12a})C(=Y)N(R^{10a})R^{11a}$, $-NR^{12a}S(O)_2R^{10a}$, $-NR^{12a}S(O)_2N(R^{10a})R^{11a}$, $-S(O)_2N(R^{10a})R^{11a}$, $-SC(=Y)R^{10a}$, $-SC(=Y)OR^{10a}$, $-S(O)_2R^{10a}$, C_{1-12} alkyl, heterocycloalkyl (which latter two groups are optionally substituted by one or more substituents selected from =O and E^6), aryl or heteroaryl (which latter two groups are optionally substituted by one or more substituents selected from E^9);

or, any two B^1 substituents, when attached to the same carbon atom (thereby forming a spiro-cycle), may be linked together to form, a 3- to 12- membered ring, optionally containing one or more heteroatoms, which ring optionally contains one or more double bonds, and which ring is itself optionally substituted by one or more substituents selected from halo, =O and C_{1-3} alkyl optionally substituted by one or more fluoro atoms;

each R^{10a}, R^{11a}, R^{12a}, R^{10b} and R^{11b} independently represent, on each occasion when used herein, hydrogen, C_{1-12} alkyl, heterocycloalkyl (which latter two groups are optionally substituted by one or more substituents selected from =O, =S, =N(R^{20}) and E^{10}), aryl or heteroaryl (which latter two groups are optionally substituted by one or more substituents selected from E^{11}); or

any relevant pair of R^{10a}, R^{11a} and R^{12a} and/or any pair of R^{10b} and R^{11b} may be linked together to form a 3- to 20-membered ring, optionally containing one or more heteroatoms, optionally containing one or more unsaturations, and which ring is optionally substituted by one or more substituents selected from =O, =S, =N(R^{20}) and E^{12};

each E^1, E^2, E^3, E^4, E^5, E^6, E^7, E^8, E^9, E^{10}, E^{11} and E^{12} independently represents, on each occasion when used herein:

(i) Q^4;

(ii) C_{1-12} alkyl optionally substituted by one or more substituents selected from =O and Q^5; or

any two E^1, E^2, E^3, E^4, E^5, E^6, E^7, E^8, E^9, E^{10}, E^{11} or E^{12} groups may be linked together to form a 3- to 12-membered ring, optionally containing one or more unsaturations, and which ring is optionally substituted by one or more substituents selected from =O and J^1;

each Q^4 and Q^5 independently represent, on each occasion when used herein:

halo, -CN, -NO_2, -N(R^{20})R^{21}, -OR^{20}, -C(=Y)-R^{20}, -C(=Y)-OR^{20}, -C(=Y)N(R^{20})R^{21}, -OC(=Y)-R^{20}, -OC(=Y)-OR^{20}, -OC(=Y)N(R^{20})R^{21}, -$OS(O)_2OR^{20}$, -OP(=Y)(OR^{20})(OR^{21}), -OP(OR^{20})(OR^{21}), -N(R^{22})C(=Y)R^{21}, -N(R^{22})C(=Y)OR^{21}, -N(R^{22})C(=Y)N(R^{20})R^{21}, -N$R^{22}S(O)_2R^{20}$, -N$R^{22}S(O)_2N(R^{20})R^{21}$, -$S(O)_2N(R^{20})R^{21}$,

$-SC(=Y)R^{20}$, $-S(O)_2R^{20}$, $-SR^{20}$, $-S(O)R^{20}$, C_{1-6} alkyl, heterocycloalkyl (which latter two groups are optionally substituted by one or more substituents selected from =O and J^2), aryl or heteroaryl (which latter two groups are optionally substituted by one or more substituents selected from J^3);

each Y independently represents, on each occasion when used herein, =O, =S, $=NR^{23}$ or =N-CN;

each R^{20}, R^{21}, R^{22} and R^{23} independently represent, on each occasion when used herein, hydrogen, C_{1-6} alkyl, heterocycloalkyl (which latter two groups are optionally substituted by one or more substituents selected from J^4 and =O), aryl or heteroaryl (which latter two groups are optionally substituted by one or more substituents selected from J^5); or

any relevant pair of R^{20}, R^{21} and R^{22}, may be linked together to form a 3- to 20-membered ring, optionally containing one or more heteroatoms, optionally containing one or more unsaturations, and which ring is optionally substituted by one or more substituents selected from J^6 and =O;

each J^1, J^2, J^3, J^4, J^5 and J^6 independently represents, on each occasion when used herein:

(i) Q^7;

(ii) C_{1-6} alkyl or heterocycloalkyl, both of which are optionally substituted by one or more substituents selected from =O and Q^8;

each Q^7 and Q^8 independently represents, on each occasion when used herein: -CN, halo, $-N(R^{50})R^{51}$, $-OR^{50}$, $-C(=Y^a)-R^{50}$, $-C(=Y^a)-OR^{50}$, $-C(=Y^a)N(R^{50})R^{51}$, $-N(R^{52})C(=Y^a)R^{51}$, $-NR^{52}S(O)_2R^{50}$, $-S(O)_2R^{50}$, $-SR^{50}$, $-S(O)R^{50}$ or C_{1-6} alkyl optionally substituted by one or more fluoro atoms;

each Y^a independently represents, on each occasion when used herein, =O, =S, $=NR^{53}$ or =N-CN;

each R^{50}, R^{51}, R^{52} and R^{53} independently represents, on each occasion when used herein, hydrogen or C_{1-6} alkyl optionally substituted by one or more substituents selected from fluoro, $-OR^{60}$ and $-N(R^{61})R^{62}$; or
any relevant pair of R^{50}, R^{51} and R^{52} may be linked together to form, a 3- to 8-membered ring, optionally containing one or more heteroatoms, optionally containing one or more unsaturations, and which ring is optionally substituted by one or more substituents selected from =O and C_{1-3} alkyl;

R^{60}, R^{61} and R^{62} independently represent hydrogen or C_{1-6} alkyl optionally substituted by one or more fluoro atoms;

or a pharmaceutically acceptable ester, amide, solvate or salt thereof.

In a second aspect, there is provided a compound of formula I as defined above, or a pharmaceutically acceptable ester, amide, solvate or salt thereof, for use as a pharmaceutical.

In a third aspect, there is provided a pharmaceutical formulation including a compound of formula I, as defined above, or a pharmaceutically acceptable ester, amide, solvate or salt thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

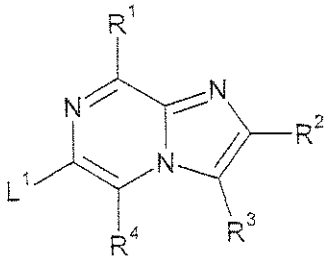
In a fourth aspect, there is provided a compound, as defined above, or a pharmaceutically acceptable ester, amide, solvate or salt thereof, for use in the treatment of a disease in which inhibition of a PI3-K and/or mTOR is desired and/or required, wherein the disease is selected from the group consisting of cancer, a cardiovascular disease, a viral infection, inflammation, an obstructive airways disease, an allergic disease, an inflammatory disease, immunosuppression, benign prostate hyperplasia, familial adenomatosis, polyposis, neuro-fibromatosis, psoriasis, a bone disorder, atherosclerosis, vascular smooth cell proliferation associated with atherosclerosis, pulmonary fibrosis, arthritis glomerulonephritis and post-surgical stenosis, restenosis, stroke, diabetes, hepatomegaly, Alzheimer's disease, cystic fibrosis, an immunodeficiency disorder, a destructive bone disorder, an infectious disease, thrombin-induced platelet aggregation, chronic myelogenous leukaemia or liver disease.

In a fifth aspect, there is provided the use of a compound of formula I, as defined above, or a pharmaceutically acceptable ester, amide, solvate or salt thereof, for the manufacture of a medicament for the treatment of a disease in which inhibition of a PI3-K and/or mTOR is desired and/or required, wherein the disease is selected from the group consisting of cancer, a cardiovascular disease, a viral infection, inflammation, an obstructive airway disease, an allergic disease, an inflammatory disease, immunosuppression, benign prostate hyperplasia, familial adenomatosis, polyposis, neuro-fibromatosis, psoriasis, a bone disorder, atherosclerosis, vascular smooth cell proliferation associated with atherosclerosis, pulmonary fibrosis, arthritis glomerulonephritis and post-surgical stenosis, restenosis, stroke, diabetes, hepatomegaly, Alzheimer's disease, cystic fibrosis, an immunodeficiency disorder, a destructive bone disorder,

an infectious disease, thrombin-induced platelet aggregation, chronic myelogenous leukaemia or liver disease.

In a sixth aspect, there is provided a combination product comprising: (A) a compound of formula I as defined above, or a pharmaceutically-acceptable ester, amide, solvate or salt thereof; and (B) another therapeutic agent that is useful in the treatment of cancer and/or a proliferative disease, wherein each of components (A) and (B) is formulated in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier.

In a seventh aspect, there is provided a process for the preparation of a compound of formula I as defined above, which process comprises: (i) reaction of a compound of formula I, which comprises reaction of a compound of formula IB,



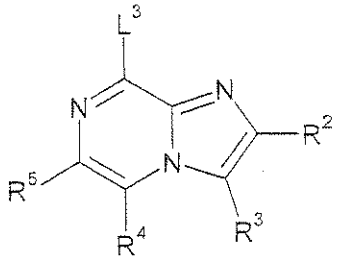
IB

wherein L^1 represents a suitable leaving group, and R^1, R^2, R^3, and R^4 are as defined above, with a compound of formula IC,

$$R^5\text{-}L^2 \qquad \text{IC}$$

wherein L^2 represents a suitable group, and R^5 is as defined above;

(ii) reaction of a compound of formula ID,

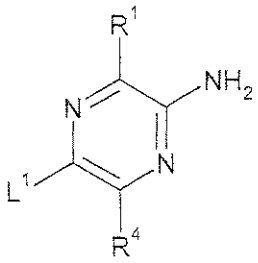


ID

wherein L^3 represents a suitable leaving group, and R^2, R^3, R^4 and R^5 are as defined above, with a compound of formula IE,

R^1-L^4 IE

wherein L^4 represents a suitable leaving group, and R^1 is as defined above; (iii) reaction of a compound of formula IF,



IF

wherein R^1 and R^4 are as defined above, and L^1 is as defined above, with a compound of formula IG,

R^2-C(O)-C(R^3)(H)-L^5 IG

wherein L^5 represents a suitable leaving group, and R^2 and R^3 are as defined above, followed by reaction with a compound of formula IC as defined above;

(iv) reaction of a compound of formula IF as defined above but in which L^1 is replaced with a R^5 group (and R^5 is as defined above), with a compound of formula IH,

R^3-C(H)(L^{6a})-C(H)(L^{6b})-R^3 IH

wherein L^{6a} and L^{6b} independently represent a suitable leaving group, and each R^3 is as defined above;

(v) for compounds of formula I in which R^3 or R^4 represents bromo, iodo or chloro, reaction of a corresponding compound of formula I, in which R^3 or R^4 (as appropriate) represents hydrogen, with a reagent that is a source of halide ions;

(vi) for compounds of formula I in which R^3 or R^4 represents a substituent other that hydrogen, or halo (e.g. bromo, iodo or chloro), reaction of a corresponding compound of formula I, in which R^3 or R^4 (as appropriate) represents bromo, chloro or iodo, with a compound of formula IJ,

$R^{3/4}$-L^7 IJ

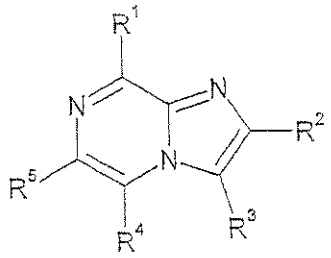
wherein $R^{3/4}$ represents R^3 or R^4 (as appropriate), and L^7 represents a suitable leaving group.

In an eighth aspect, there is provided a process for the preparation of a pharmaceutical formulation as defined above, which process comprises bringing into association a compound of formula I, as defined above, or a pharmaceutically acceptable ester, amide, solvate or salt thereof with a pharmaceutically-acceptable adjuvant, diluent or carrier.

In a ninth aspect, there is provided a process for the preparation of a combination product as defined above, which process comprises bringing into association a compound of formula I, as defined above, or a pharmaceutically acceptable ester, amide, solvate or salt thereof with the other therapeutic agent that is useful in the treatment of cancer and/or a proliferative disease, and at least one pharmaceutically-acceptable adjuvant, diluent or carrier.

Disclosure of the Invention

According to the invention, there is provided a compound of formula I,



I

wherein:

R^1 represents:

(a) $-N(R^{1a})R^{1b}$,