CHEMICAL COMPOUNDS

The invention relates to chemical compounds, or pharmaceutically acceptable salts thereof, which possess B-Raf inhibitory activity and are accordingly useful for their anti-cancer activity and thus in methods of treatment of the human or animal body. The invention also relates to processes for the manufacture of said chemical compounds, to pharmaceutical compositions containing them and to their use in the manufacture of medicaments of use in the production of an anti-cancer effect in a warm-blooded animal such as man.

The classical Ras, Raf, MAP protein kinase/extracellular signal –regulated kinase kinase (MEK), extracellular signal –regulated kinase (ERK) pathway plays a central role in the regulation of a variety of cellular functions dependent upon cellular context, including cellular proliferation, differentiation, survival, immortalization and angiogenesis (reviewed in Peyssonnaux and Eychene, Biology of the Cell, 2001, 93,3-62). In this pathway, Raf family members are recruited to the plasma membrane upon binding to guanosine triphosphate (GTP) loaded Ras resulting in the phosphorylation and activation of Raf proteins. Activated Rafs then phosphorylate and activate MEKs, which in turn phosphorylate and activate ERKs. Upon activation, ERKs translocate from the cytoplasm to the nucleus resulting in the phosphorylation and regulation of activity of transcription factors such as Elk-1 and Myc.

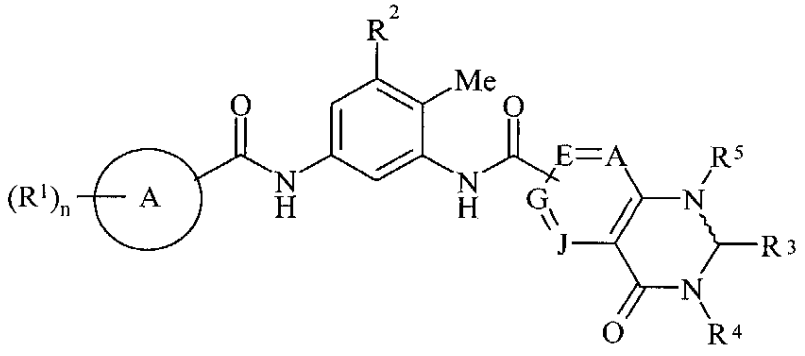
The Ras/Raf/MEK/ERK pathway has been reported to contribute to the tumorigenic phenotype by inducing immortalisation, growth factor-independent growth, insensitivity to growth-inhibitory signals, ability to invade and metastasis, stimulating angiogenesis and inhibition of apoptosis (reviewed in Kolch et al., Exp.Rev. Mol. Med., 2002, 25 April, http://www.expertreviews.org/02004386h.htm). In fact, ERK phosphorylation is enhanced in approximately 30% of all human tumours (Hoshino et al., Oncogene, 1999, 18, 813-822). This may be a result of overexpression and/or mutation of key members of the pathway.

Three Raf serine/threonine protein kinase isoforms have been reported Raf-1 /c-Raf, B-Raf and A-Raf (reviewed in Mercer and Pritchard, Biochim. Biophys. Acta, 2003, 1653, 25-40), the genes for which are thought to have arisen from gene duplication. All three Raf genes are expressed in most tissues with high-level expression of B-Raf in neuronal tissue and A-Raf in urogenital tissue. The highly homologous Raf family members have overlapping but distinct biochemical activities and biological functions (Hagemann and Rapp, Expt. Cell Res. 1999, 253, 34-46). Expression of all three Raf genes is required for normal murine

development however both c-Raf and B-Raf are required to complete gestation. B-Raf -/- mice die at E12.5 due to vascular haemorrhaging caused by increased apoptosis of endothelial cells (Wojnowski et al., Nature Genet., 1997, 16, 293-297). B-Raf is reportedly the major isoform involved in cell proliferation and the primary target of oncogenic Ras. Activating somatic missense mutations have been identified exclusively for B-Raf, occurring with a frequency of 66% in malignant cutaneous melanomas (Davies et al., Nature, 2002, 417, 949-954) and also present in a wide range of human cancers, including but not limited to papillary thyroid tumours (Cohen et al., J. Natl. Cancer Inst., 2003, 95, 625-627), cholangiocarcinomas (Tannapfel et al., Gut, 2003, 52, 706-712), colon and ovarian cancers (Davies et al., Nature, 2002, 417, 949-954). The most frequent mutation in B-Raf (80%) is a glutamic acid for valine substitution at position 600. These mutations increase the basal kinase activity of B-Raf and are thought to uncouple Raf/MEK/ERK signalling from upstream proliferation drives including Ras and growth factor receptor activation resulting in constitutive activation of ERK. Mutated B-Raf proteins are transforming in NIH3T3 cells (Davies et al., Nature, 2002, 417, 949-954) and melanocytes (Wellbrock et al., Cancer Res., 2004, 64, 2338-2342) and have also been shown to be essential for melanoma cell viability and transformation (Hingorani et al., Cancer Res., 2003, 63, 5198-5202). As a key driver of the Raf/MEK/ERK signalling cascade, B-Raf represents a likely point of intervention in tumours dependent on this pathway.

AstraZeneca application WO 00/07991 discloses certain benzene-1,3-aminocarbonyl compounds which are inhibitors of the production of cytokines such as TNF, in particular of TNFα, and various interleukins, in particular IL-1. The present inventors have surprisingly found that certain benzene-1,3-aminocarbonyl compounds are potent B-Raf inhibitors and are accordingly expected to be useful in the treatment of neoplastic disease.

Accordingly, the present invention provides a compound of formula **(I)**:



(I)

wherein:

Ring A is carbocyclyl or heterocyclyl; wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^6;

R^1 is a substituent on carbon and is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, carbocyclyl-R^7- or heterocyclyl-R^8-; wherein R^1 may be optionally substituted on carbon by one or more R^9; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{10};

n is selected from 0-4; wherein the values of R^1 may be the same or different;

R^2 is selected from hydrogen, halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, carbocyclyl-R^{11}- or heterocyclyl-R^{12}-; wherein R^2 may be optionally substituted on carbon by one or more R^{13}; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{14};

one of **A**, **E**, **G** and **J** is C which is attached to the -C(O)NH- of formula **(I)**; the other three are independently selected from CR^{15} or N;

R^3 and **R^{15}** are independently selected from hydrogen, halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, carbocyclyl-R^{16}- or heterocyclyl-R^{17}-; wherein R^3 and R^{15} independently of each other may be optionally substituted on carbon by one or more R^{18}; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{19};

$\mathbf{R^4}$ and $\mathbf{R^5}$ are independently selected from hydrogen, C_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl, C_{1-6}alkoxycarbonyl, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl and *N,N*-(C_{1-6}alkyl)carbamoyl; wherein R^4 and R^5 independently of each other may be optionally substituted on carbon by one or more R^{20};

the bond " ~ "between the -NR^5- and -CR^3- of formula **(I)** is either (i) a single bond wherein R^5 is as defined above, or (ii) a double bond wherein R^5 is absent;

$\mathbf{R^9}$, $\mathbf{R^{13}}$, $\mathbf{R^{18}}$ and $\mathbf{R^{20}}$ are independently selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, N-(C_{1-6}alkyl)amino, N,N-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, N-(C_{1-6}alkyl)carbamoyl, N,N-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, N-(C_{1-6}alkyl)sulphamoyl, N,N-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, carbocyclyl-R^{21}- or heterocyclyl-R^{22}-; wherein R^9, R^{13}, R^{18} and R^{20} independently of each other may be optionally substituted on carbon by one or more R^{23}; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{24};

$\mathbf{R^7}$, $\mathbf{R^8}$, $\mathbf{R^{11}}$, $\mathbf{R^{12}}$, $\mathbf{R^{16}}$, $\mathbf{R^{17}}$, $\mathbf{R^{21}}$ and $\mathbf{R^{22}}$ are independently selected from a direct bond, -O-, -N(R^{25})-, -C(O)-, -N(R^{26})C(O)-, -C(O)N(R^{27})-, -S(O)$_s$-, -SO_2N(R^{28})- or -N(R^{29})SO_2-; wherein $\mathbf{R^{25}}$, $\mathbf{R^{26}}$, $\mathbf{R^{27}}$, $\mathbf{R^{28}}$ and $\mathbf{R^{29}}$ is hydrogen or C_{1-6}alkyl and **s** is 0-2;

$\mathbf{R^6}$, $\mathbf{R^{10}}$, $\mathbf{R^{14}}$, $\mathbf{R^{19}}$ and $\mathbf{R^{24}}$ are independently selected from C_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl, C_{1-6}alkoxycarbonyl, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl;

$\mathbf{R^{23}}$ is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl;

or a pharmaceutically acceptable salt thereof;

with the proviso that said compound is not *N*-(5-{[3-(dimethylamino)benzoyl]amino}-2-methylphenyl)-4-oxo-3,4-dihydroquinazoline-6-carboxamide.

In this specification the term "alkyl" includes both straight and branched chain alkyl groups. References to individual alkyl groups such as "propyl" are specific for the straight chain version only and references to individual branched chain alkyl groups such as 'isopropyl' are specific for the branched chain version only. For example, "C_{1-6}alkyl" includes C_{1-4}alkyl, C_{1-3}alkyl, propyl, isopropyl and *t*-butyl. A similar convention applies to other radicals, for example "phenylC_{1-6}alkyl" includes phenylC_{1-4}alkyl, benzyl, 1-phenylethyl and 2-phenylethyl. The term "halo" refers to fluoro, chloro, bromo and iodo.

Where optional substituents are chosen from "one or more" groups it is to be understood that this definition includes all substituents being chosen from one of the specified groups or the substituents being chosen from two or more of the specified groups.

A "heterocyclyl" is a saturated, partially saturated or unsaturated, mono or bicyclic ring containing 4-12 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked, wherein a -CH_2- group can optionally be replaced by a -C(O)-, and a ring sulphur atom may be optionally oxidised to form the S-oxides. Examples and suitable values of the term "heterocyclyl" are morpholino, piperidyl, pyridyl, pyranyl, pyrrolyl, pyrazolyl, isothiazolyl, indolyl, quinolyl, thienyl, 1,3-benzodioxolyl, thiadiazolyl, piperazinyl, thiazolidinyl, pyrrolidinyl, thiomorpholino, pyrrolinyl, homopiperazinyl, 3,5-dioxapiperidinyl, tetrahydropyranyl, imidazolyl, pyrimidyl, pyrazinyl, pyridazinyl, isoxazolyl, *N*-methylpyrrolyl, 4-pyridone, 1-isoquinolone, 2-pyrrolidone, 4-thiazolidone, pyridine-*N*-oxide and quinoline-*N*-oxide. A particular example of the term "heterocyclyl" is pyrazolyl. In one aspect of the invention a "heterocyclyl" is a saturated, partially saturated or unsaturated, monocyclic ring containing 5 or 6 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, it may, unless otherwise specified, be carbon or nitrogen linked, a -CH_2- group can optionally be replaced by a -C(O)-and a ring sulphur atom may be optionally oxidised to form the S-oxides.

A "carbocyclyl" is a saturated, partially saturated or unsaturated, mono or bicyclic carbon ring that contains 3-12 atoms; wherein a -CH_2- group can optionally be replaced by a -C(O)-. Particularly "carbocyclyl" is a monocyclic ring containing 5 or 6 atoms or a bicyclic ring containing 9 or 10 atoms. Suitable values for "carbocyclyl" include cyclopropyl, cyclobutyl, 1-oxocyclopentyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, phenyl, naphthyl, tetralinyl, indanyl or 1-oxoindanyl. A particular example of "carbocyclyl" is phenyl.

An example of "C_{1-6}alkanoyloxy" is acetoxy. Examples of "C_{1-6}alkoxycarbonyl" include methoxycarbonyl, ethoxycarbonyl, *n*- and *t*-butoxycarbonyl. Examples of

"C_{1-6}alkoxy" include methoxy, ethoxy and propoxy. Examples of "C_{1-6}alkanoylamino" include formamido, acetamido and propionylamino. Examples of "C_{1-6}alkyl$S(O)_a$ wherein a is 0 to 2" include methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl and ethylsulphonyl. Examples of "C_{1-6}alkanoyl" include propionyl and acetyl. Examples of "*N*-(C_{1-6}alkyl)amino" include methylamino and ethylamino. Examples of "*N,N*-(C_{1-6}alkyl)$_2$amino" include di-*N*-methylamino, di-(*N*-ethyl)amino and *N*-ethyl-*N*-methylamino. Examples of "C_{2-6}alkenyl" are vinyl, allyl and 1-propenyl. Examples of "C_{2-6}alkynyl" are ethynyl, 1-propynyl and 2-propynyl. Examples of "*N*-(C_{1-6}alkyl)sulphamoyl" are *N*-(methyl)sulphamoyl and *N*-(ethyl)sulphamoyl. Examples of "*N*-(C_{1-6}alkyl)$_2$sulphamoyl" are *N,N*-(dimethyl)sulphamoyl and *N*-(methyl)-*N*-(ethyl)sulphamoyl. Examples of "*N*-(C_{1-6}alkyl)carbamoyl" are *N*-(C_{1-4}alkyl)carbamoyl, methylaminocarbonyl and ethylaminocarbonyl. Examples of "*N,N*-(C_{1-6}alkyl)$_2$carbamoyl" are *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, dimethylaminocarbonyl and methylethylaminocarbonyl. Examples of "C_{1-6}alkylsulphonyl" are mesyl, ethylsulphonyl and isopropylsulphonyl. Examples of "C_{1-6}alkylsulphonylamino" are mesylamino, ethylsulphonylamino and isopropylsulphonylamino.

A suitable pharmaceutically acceptable salt of a compound of the invention is, for example, an acid-addition salt of a compound of the invention which is sufficiently basic, for example, an acid-addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, sulphuric, phosphoric, trifluoroacetic, citric or maleic acid. In addition a suitable pharmaceutically acceptable salt of a compound of the invention which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a physiologically-acceptable cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

Some compounds of the formula **(I)** may have chiral centres and/or geometric isomeric centres (E- and Z- isomers), and it is to be understood that the invention encompasses all such optical, diastereoisomers and geometric isomers that possess B-Raf inhibitory activity. The invention further relates to any and all tautomeric forms of the compounds of the formula **(I)** that possess B-Raf inhibitory activity.

It is also to be understood that certain compounds of the formula **(I)** can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be

understood that the invention encompasses all such solvated forms which possess B-Raf inhibitory activity.

Particular values of variable groups are as follows. Such values may be used where appropriate with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

Ring A is carbocyclyl.

Ring A is heterocyclyl; wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^6.

Ring A is phenyl, thienyl, pyridyl or thiazolyl.

Ring A is phenyl.

R^1 is a substituent on carbon and is selected from halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy or C_{1-6}alkoxycarbonyl; wherein R^1 may be optionally substituted on carbon by one or more R^9; wherein

R^9 is selected from halo, cyano, N,N-(C_{1-6}alkyl)$_2$amino or heterocyclyl-R^{22}-; and

R^{22} is selected from a direct bond.

R^1 is a substituent on carbon and is selected from halo, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl or C_{1-6}alkyl; wherein R^1 may be optionally substituted on carbon by one or more R^9; wherein

R^9 is selected from halo or cyano.

R^1 is a substituent on carbon and is selected from halo or C_{1-6}alkyl; wherein R^1 may be optionally substituted on carbon by one or more R^9; wherein

R^9 is selected from halo or cyano.

R^1 is a substituent on carbon and is selected from chloro, hydroxy, methyl, isopropyl, methoxy, ethoxy or methoxycarbonyl; wherein R^1 may be optionally substituted on carbon by one or more R^9; wherein

R^9 is selected from fluoro, cyano, dimethylamino or pyrrolidinyl.

R^1 is a substituent on carbon and is selected from chloro, methyl, *N,N*-dimethylsulphamoyl or isopropyl; wherein R^1 may be optionally substituted on carbon by one or more R^9; wherein

R^9 is selected from fluoro or cyano.

R^1 is a substituent on carbon and is selected from chloro, methyl or isopropyl; wherein R^1 may be optionally substituted on carbon by one or more R^9; wherein

R^9 is selected from fluoro or cyano.

R^1 is a substituent on carbon and is selected from 1-methyl-1-cyanoethyl, trifluoromethyl, chloro, methoxycarbonyl, 2-dimethylaminoethoxy, methoxy, hydroxy and 2-pyrrolidin-1-ylethoxy.

R^1 is a substituent on carbon and is selected from chloro, trifluoromethyl, *N,N*-dimethylsulphamoyl or 1-methyl-1-cyanoethyl.

R^1 is a substituent on carbon and is selected from chloro, trifluoromethyl or 1-methyl-1-cyanoethyl.

n is selected from 0-2; wherein the values of R^1 may be the same or different.

n is selected from 1-2; wherein the values of R^1 may be the same or different.

n is 1.

n is 2; wherein the values of R^1 may be the same or different.

R^2 is selected from hydrogen.

one of A, E, G and J is C which is attached to the -C(O)NH- of formula **(I)**; the other three are all CR^{16} or two are CR^{16} and one is N.

one of A, E, G and J is C which is attached to the -C(O)NH- of formula **(I)**; the other three are CR^{15}; wherein R^{15} is hydrogen.

G is C which is attached to the -C(O)NH- of formula **(I)**; A, E and J are CR^{15}; wherein R^{15} is hydrogen.

G is C which is attached to the -C(O)NH- of formula **(I)**.

E is C which is attached to the -C(O)NH- of formula **(I)**.

A and J are CR^{15} wherein R^{15} is hydrogen.

R^{15} is hydrogen.

E is CR^{15}.

E is N.

G is CR^{15}.

R^3 is hydrogen or C_{1-6}alkyl.

R^3 is hydrogen or methyl.

R^3 is hydrogen.

R^4 is selected from hydrogen or C_{1-6}alkyl; wherein R^4 may be optionally substituted on carbon by one or more R^{20}; wherein

R^{20} is selected from hydroxy, carbocyclyl-R^{21}- or heterocyclyl-R^{22}-; wherein R^{20} may be optionally substituted on carbon by one or more R^{23};

R^{21} and R^{22} are a direct bond;

R^{23} is methyl.

R^4 is hydrogen or C_{1-6}alkyl.

R^4 is selected from hydrogen, methyl, ethyl or propyl; wherein R^4 may be optionally substituted on carbon by one or more R^{20}; wherein

R^{20} is selected from hydroxy, cyclopropyl, 1,3-dioxolanyl or morpholino; wherein R^{20} may be optionally substituted on carbon by one or more R^{23};

R^{23} is methyl.

R^4 is hydrogen, methyl, ethyl, 3-morpholinopropyl, cyclopropylmethyl, 2,2-dimethyl-1,3-dioxolan-4-ylmethyl, 2,3-dihydroxypropyl or 2-hydroxyethyl.

R^4 is hydrogen or methyl.

R^5 is hydrogen.

the bond " ~ "between the -NR^5- and -CR^3- of formula **(I)** is a single bond.

the bond " ~ "between the -NR^5- and -CR^3- of formula **(I)** is a single bond and R^5 is hydrogen.

the bond " ~ "between the -NR^5- and -CR^3- of formula **(I)** is a double bond wherein R^5 is absent.

Therefore in a further aspect of the invention there is provided a compound of formula **(I)** wherein:

Ring A is carbocyclyl;

R^1 is a substituent on carbon and is selected from halo, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl or C_{1-6}alkyl; wherein R^1 may be optionally substituted on carbon by one or more R^9;

n is selected from 1-2; wherein the values of R^1 may be the same or different;

R^2 is selected from hydrogen;

one of A, E, G and J is C which is attached to the -C(O)NH- of formula **(I)**; the other three are CR^{15};

R^3 is hydrogen;

R^4 is hydrogen or C_{1-6}alkyl;

R^5 is hydrogen;

the bond " ~ "between the -NR^5- and -CR^3- of formula **(I)** is either (i) a single bond wherein R^5 is as defined above, or (ii) a double bond wherein R^5 is absent;

R^9 is selected from halo or cyano;

R^{15} is hydrogen;

or a pharmaceutically acceptable salt thereof.

Therefore in a further aspect of the invention there is provided a compound of formula **(I)** wherein:

Ring A is carbocyclyl;

R^1 is a substituent on carbon and is selected from halo or C_{1-6}alkyl; wherein R^1 may be optionally substituted on carbon by one or more R^9;

n is selected from 1-2; wherein the values of R^1 may be the same or different;

R^2 is selected from hydrogen;

one of A, E, G and J is C which is attached to the -C(O)NH- of formula **(I)**; the other three are CR^{15};

R^3 is hydrogen;

R^4 is hydrogen or C_{1-6}alkyl;

R^5 is hydrogen;

the bond " ~ "between the -NR^5- and -CR^3- of formula **(I)** is either (i) a single bond wherein R^5 is as defined above, or (ii) a double bond wherein R^5 is absent;

R^9 is selected from halo or cyano;

R^{15} is hydrogen;

or a pharmaceutically acceptable salt thereof.

Therefore in a further aspect of the invention there is provided a compound of formula **(I)** wherein:

Ring A is phenyl;

R^1 is a substituent on carbon and is selected from chloro, trifluoromethyl, *N,N*-dimethylsulphamoyl or 1-methyl-1-cyanoethyl;

n is selected from 1-2; wherein the values of R^1 may be the same or different;

R^2 is selected from hydrogen;

G is C which is attached to the -C(O)NH- of formula **(I)**; A, E and J are CR^{15}; wherein R^{15} is hydrogen;

R^3 is hydrogen;

R^4 is hydrogen or methyl;

R^5 is hydrogen;

the bond " ~ "between the -NR^5- and -CR^3- of formula **(I)** is either (i) a single bond wherein R^5 is as defined above, or (ii) a double bond wherein R^5 is absent;

or a pharmaceutically acceptable salt thereof.

Therefore in a further aspect of the invention there is provided a compound of formula **(I)** wherein:

Ring A is phenyl;

R^1 is a substituent on carbon and is selected from chloro, trifluoromethyl or 1-methyl-1-cyanoethyl;

n is selected from 1-2; wherein the values of R^1 may be the same or different;

R^2 is selected from hydrogen;

G is C which is attached to the -C(O)NH- of formula **(I)**; A, E and J are CR^{15}; wherein R^{15} is hydrogen;

R^3 is hydrogen;

R^4 is hydrogen or methyl;

R^5 is hydrogen;

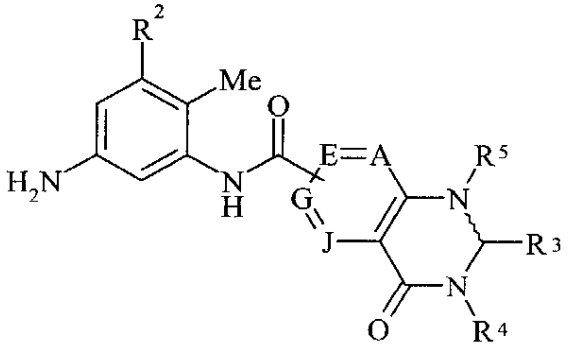
the bond " ~ "between the $-NR^5-$ and $-CR^3-$ of formula **(I)** is either (i) a single bond wherein R^5 is as defined above, or (ii) a double bond wherein R^5 is absent;

or a pharmaceutically acceptable salt thereof.

In another aspect of the invention, preferred compounds of the invention are any one of the Examples or a pharmaceutically acceptable salt thereof.

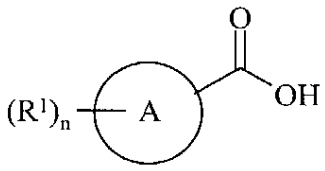
Another aspect of the present invention provides a process for preparing a compound of formula **(I)** or a pharmaceutically acceptable salt thereof which process (wherein variable are, unless otherwise specified, as defined in formula **(I)**) comprises of:

Process a) reacting an amine of the formula **(II)**



(II)

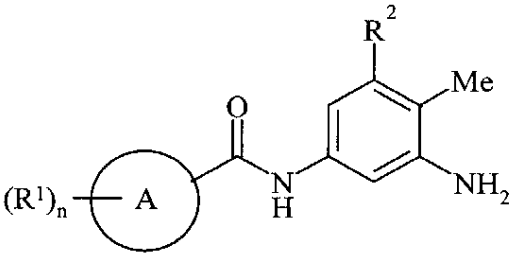
with an acid of formula **(III)**:



(III)

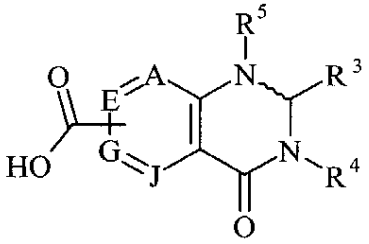
or an activated acid derivative thereof;

Process b) reacting an amine of formula **(IV)**:



(IV)

with an acid of formula **(V)**:



(V)

or an activated acid derivative thereof;

Process c) for compounds of formula **(I)** wherein R^4 is not hydrogen; reacting a compound of formula **(I)** wherein R^4 is hydrogen with a compound of formula **(VI)**:

$$R^4\text{-}L$$

(VI)

wherein L is a displaceable group and R^4 is not hydrogen;

and thereafter if necessary:

i) converting a compound of the formula **(I)** into another compound of the formula **(I)**;

ii) removing any protecting groups;

iii) forming a pharmaceutically acceptable salt.

L is a displaceable group, suitable values for L are for example, a halo for example a chloro or bromo.

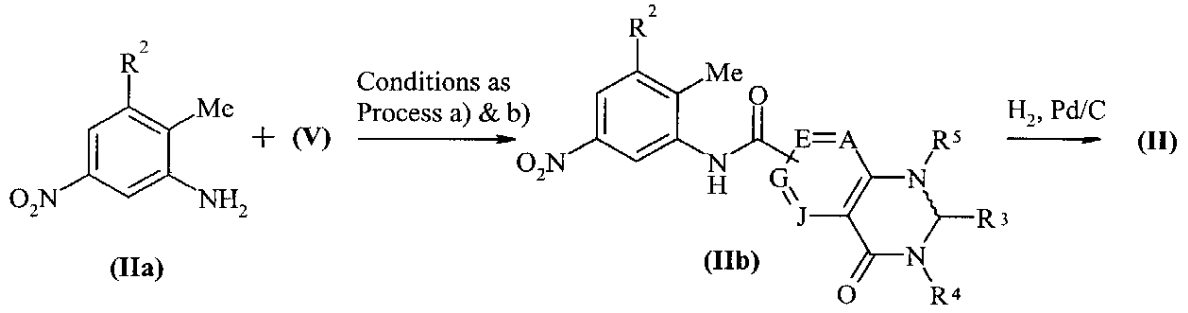
Specific reaction conditions for the above reactions are as follows.

Process a) and *Process b)* Amines of formula **(II)** and acids of formula **(III)** and amines of

formula **(IV)** and acids of formula **(V)** may be coupled together in the presence of a suitable coupling reagent. Standard peptide coupling reagents known in the art can be employed as suitable coupling reagents, or for example carbonyldiimidazole and dicyclohexyl-carbodiimide, optionally in the presence of a catalyst such as dimethylaminopyridine or 4-pyrrolidinopyridine, optionally in the presence of a base for example triethylamine, pyridine, or 2,6-di-*alkyl*-pyridines such as 2,6-lutidine or 2,6-di-*tert*-butylpyridine. Suitable solvents include dimethylacetamide, dichloromethane, benzene, tetrahydrofuran and dimethylformamide. The coupling reaction may conveniently be performed at a temperature in the range of –40 to 40°C.

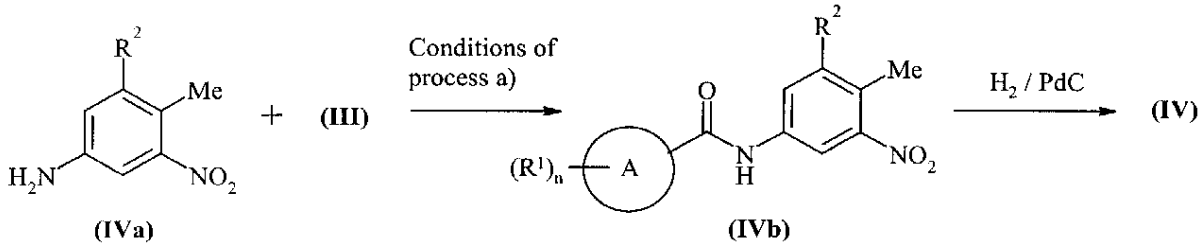
Suitable activated acid derivatives include acid halides, for example acid chlorides, and active esters, for example pentafluorophenyl esters. The reaction of these types of compounds with amines is well known in the art, for example they may be reacted in the presence of a base, such as those described above, and in a suitable solvent, such as those described above. The reaction may conveniently be performed at a temperature in the range of -40 to 40°C.

Amines of formula **(II)** may be prepared according to *Scheme 1*:



Scheme 1

Amines of formula **(IV)** may be prepared according to *Scheme 2*:



Scheme 2

Compounds of formula **(IIa)**, **(III)**, **(IVa)** and **(V)** are commercially available compounds, or they are known in the literature or they may be prepared by standard processes known in the art.

Process c) Compounds of formula **(I)** and **(VI)** can be reacted together in solvents such as DMF or CH_3CN in the presence of a base such as K_2CO_3 or Cs_2CO_3. The reaction usually requires thermal conditions in the range of 50 °C to 100 °C.

Compounds of formula **(VI)** are commercially available compounds, or they are known in the literature or they may be prepared by standard processes known in the art.

It will be appreciated that certain of the various ring substituents in the compounds of the present invention may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or immediately following the processes mentioned above, and as such are included in the process aspect of the invention. Such reactions and modifications include, for example, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents and oxidation of substituents. The reagents and reaction conditions for such procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of a nitro group using concentrated nitric acid, the introduction of an acyl group using, for example, an acyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; the introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; and the introduction of a halogeno group. Particular examples of modifications include the reduction of a nitro group to an amino group by for example, catalytic hydrogenation with a nickel catalyst or treatment with iron in the presence of hydrochloric acid with heating; oxidation of alkylthio to alkylsulphinyl or alkylsulphonyl.

It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in the compounds. The instances where protection is necessary or desirable and suitable methods for protection are known to those skilled in the art. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Green, Protective Groups in Organic Synthesis, John Wiley and Sons, 1991). Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting

group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *t*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

As stated hereinbefore the compounds defined in the present invention possesses anti-cancer activity which is believed to arise from the B-Raf inhibitory activity of the compound. These properties may be assessed, for example, using the procedure set out below:-

B-Raf in vitro ELISA assay

Activity of human recombinant, purified wild type His-B-Raf protein kinase was determined in vitro using an enzyme-linked immunosorbent assay (ELISA) assay format,

which measures phosphorylation of the B-Raf substrate, human recombinant, purified His-derived (detagged) MEK1. The reaction utilized 2.5 nM B-Raf, 0.15 μM MEK1 and 10 μM adenosine triphosphate (ATP) in 40 mM N-(2-hydroxyethyl)piperazine-N'-(2-ethanesulfonic acid hemisodium salt (HEPES), 5 mM 1,4-dithio-DL-threitol (DTT), 10 mM $MgCl_2$, 1 mM ethylenediaminetetraacetic acid (EDTA) and 0.2 M NaCl (1x HEPES buffer), with or without compound at various concentrations, in a total reaction volume of 25 μl in 384 well plates. B-Raf and compound were preincubated in 1x HEPES buffer for 1 hour at 25 °C. Reactions were initiated with addition of MEK1 and ATP in 1x HEPES buffer and incubated at 25 °C for 50 minutes and reactions stopped by addition of 10 μl 175 mM EDTA (final concentration 50 mM) in 1 x HEPES buffer. 5 μl of the assay mix was then diluted 1:20 into 50 mM EDTA in 1 x HEPES buffer, transferred to 384 well black high protein binding plates and incubated overnight at 4 °C. Plates were washed in tris buffered saline containing 0.1% Tween20 (TBST), blocked with 50 μl Superblock (Pierce) for 1 hour at 25 °C, washed in TBST, incubated with 50 μl rabbit polyclonal anti-phospho-MEK antibody (Cell Signaling) diluted 1:1000 in TBS for 2 hours at 25 °C , washed with TBST, incubated with 50 μl goat anti-rabbit horseradish peroxidase -linked antibody (Cell Signaling) diluted 1:2000 in TBS for 1 hour at 25 °C and washed with TBST. 50 μl of fluorogenic peroxidase substrate (Quantablu - Pierce) was added and following incubation for 45-60 minutes, 50 μl QuantabluSTOP (Pierce) was added. Blue fluorescent product was detected at excitation 325 nm and emission 420 nm using a TECAN Ultra plate reader. Data was graphed and IC_{50}s calculated using Excel Fit (Microsoft).

When tested in the above *in vitro* assay, the compounds of the present invention exhibited activity less than 30 μM. For example the following results were obtained:

Example No	**IC_{50} (μM)**
6	0.003
1	0.001

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula **(I)**, or a pharmaceutically acceptable salt thereof, as defined hereinbefore, in association with a pharmaceutically-acceptable diluent or carrier.

The composition may be in a form suitable for oral administration, for example as a tablet or capsule, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) as a sterile solution, suspension or emulsion, for topical

administration as an ointment or cream or for rectal administration as a suppository.

In general the above compositions may be prepared in a conventional manner using conventional excipients.

The compound of formula **(I)** will normally be administered to a warm-blooded animal at a unit dose within the range 1-1000 mg/kg, and this normally provides a therapeutically-effective dose. Preferably a daily dose in the range of 10-100 mg/kg is employed. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient.

According to a further aspect of the present invention there is provided a compound of the formula **(I)**, or a pharmaceutically acceptable salt thereof, as defined hereinbefore for use in a method of treatment of the human or animal body by therapy.

We have found that the compounds defined in the present invention, or a pharmaceutically acceptable salt thereof, are effective anti-cancer agents which property is believed to arise from their B-Raf inhibitory properties. Accordingly the compounds of the present invention are expected to be useful in the treatment of diseases or medical conditions mediated alone or in part by B-Raf , i.e. the compounds may be used to produce a B-Raf inhibitory effect in a warm-blooded animal in need of such treatment.

Thus the compounds of the present invention provide a method for treating cancer characterised by inhibition of B-Raf, i.e. the compounds may be used to produce an anti-cancer effect mediated alone or in part by the inhibition of B-Raf.

Such a compound of the invention is expected to possess a wide range of anti-cancer properties as activating mutations in B-Raf have been observed in many human cancers, including but not limited to, melanoma, papillary thyroid tumors, cholangiocarcinomas, colon, ovarian and lung cancers. Thus it is expected that a compound of the invention will possess anti-cancer activity against these cancers. It is in addition expected that a compound of the present invention will possess activity against a range of leukaemias, lymphoid malignancies and solid tumours such as carcinomas and sarcomas in tissues such as the liver, kidney, bladder, prostate, breast and pancreas. In particular such compounds of the invention are expected to slow advantageously the growth of primary and recurrent solid tumours of, for example, the skin, colon, thyroid, lungs and ovaries. More particularly such compounds of the invention, or a pharmaceutically acceptable salt thereof, are expected to inhibit the growth of

those primary and recurrent solid tumours which are associated with B-Raf, especially those tumours which are significantly dependent on B-Raf for their growth and spread, including for example, certain tumours of the skin, colon, thyroid, lungs and ovaries. Particularly the compounds of the present invention are useful in the treatment of melanomas.

Thus according to this aspect of the invention there is provided a compound of the formula **(I)**, or a pharmaceutically acceptable salt thereof, as defined hereinbefore for use as a medicament.

According to a further aspect of the invention there is provided the use of a compound of the formula **(I)**, or a pharmaceutically acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the production of a B-Raf inhibitory effect in a warm-blooded animal such as man.

According to this aspect of the invention there is provided the use of a compound of the formula **(I)**, or a pharmaceutically acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the production of an anti-cancer effect in a warm-blooded animal such as man.

According to a further feature of the invention, there is provided the use of a compound of the formula **(I)**, or a pharmaceutically acceptable salt thereof, as defined herein before in the manufacture of a medicament for use in the treatment of melanoma, papillary thyroid tumours, cholangiocarcinomas, colon cancer, ovarian cancer, lung cancer, leukaemias, lymphoid malignancies, carcinomas and sarcomas in the liver, kidney, bladder, prostate, breast and pancreas, and primary and recurrent solid tumours of the skin, colon, thyroid, lungs and ovaries.

According to a further feature of this aspect of the invention there is provided a method for producing a B-Raf inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, as defined above.

According to a further feature of this aspect of the invention there is provided a method for producing an anti-cancer effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, as defined above.

According to an additional feature of this aspect of the invention there is provided a method of treating melanoma, papillary thyroid tumours, cholangiocarcinomas, colon cancer, ovarian cancer, lung cancer, leukaemias, lymphoid malignancies, carcinomas and sarcomas in

the liver, kidney, bladder, prostate, breast and pancreas, and primary and recurrent solid tumours of the skin, colon, thyroid, lungs and ovaries, in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula **(I)** or a pharmaceutically acceptable salt thereof as defined herein before.

In a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula **(I)**, or a pharmaceutically acceptable salt thereof, as defined herein before in association with a pharmaceutically-acceptable diluent or carrier for use in the production of a B-Raf inhibitory effect in a warm-blooded animal such as man.

In a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula **(I)**, or a pharmaceutically acceptable salt thereof, as defined herein before in association with a pharmaceutically-acceptable diluent or carrier for use in the production of an anti-cancer effect in a warm-blooded animal such as man.

In a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula **(I)**, or a pharmaceutically acceptable salt thereof, as defined herein before in association with a pharmaceutically-acceptable diluent or carrier for use in the treatment of melanoma, papillary thyroid tumours, cholangiocarcinomas, colon cancer, ovarian cancer, lung cancer, leukaemias, lymphoid malignancies, carcinomas and sarcomas in the liver, kidney, bladder, prostate, breast and pancreas, and primary and recurrent solid tumours of the skin, colon, thyroid, lungs and ovaries in a warm-blooded animal such as man.

According to a further aspect of the invention there is provided the use of *N*-(5-{[3-(dimethylamino)benzoyl]amino}-2-methylphenyl)-4-oxo-3,4-dihydroquinazoline-6-carboxamide, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the production of a B-Raf inhibitory effect in a warm-blooded animal such as man.

According to this aspect of the invention there is provided the use of *N*-(5-{[3-(dimethylamino)benzoyl]amino}-2-methylphenyl)-4-oxo-3,4-dihydroquinazoline-6-carboxamide, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the production of an anti-cancer effect in a warm-blooded animal such as man.

According to a further feature of the invention, there is provided the use of *N*-(5-{[3-(dimethylamino)benzoyl]amino}-2-methylphenyl)-4-oxo-3,4-dihydroquinazoline-6-

carboxamide, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of melanoma, papillary thyroid tumours, cholangiocarcinomas, colon cancer, ovarian cancer, lung cancer, leukaemias, lymphoid malignancies, carcinomas and sarcomas in the liver, kidney, bladder, prostate, breast and pancreas, and primary and recurrent solid tumours of the skin, colon, thyroid, lungs and ovaries.

According to a further feature of this aspect of the invention there is provided a method for producing a B-Raf inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of *N*-(5-{[3-(dimethylamino)benzoyl]amino}-2-methylphenyl)-4-oxo-3,4-dihydroquinazoline-6-carboxamide, or a pharmaceutically acceptable salt thereof.

According to a further feature of this aspect of the invention there is provided a method for producing an anti-cancer effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of *N*-(5-{[3-(dimethylamino)benzoyl]amino}-2-methylphenyl)-4-oxo-3,4-dihydroquinazoline-6-carboxamide, or a pharmaceutically acceptable salt thereof.

According to an additional feature of this aspect of the invention there is provided a method of treating melanoma, papillary thyroid tumours, cholangiocarcinomas, colon cancer, ovarian cancer, lung cancer, leukaemias, lymphoid malignancies, carcinomas and sarcomas in the liver, kidney, bladder, prostate, breast and pancreas, and primary and recurrent solid tumours of the skin, colon, thyroid, lungs and ovaries, in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of *N*-(5-{[3-(dimethylamino)benzoyl]amino}-2-methylphenyl)-4-oxo-3,4-dihydroquinazoline-6-carboxamide or a pharmaceutically acceptable salt thereof.

In a further aspect of the invention there is provided a pharmaceutical composition which comprises *N*-(5-{[3-(dimethylamino)benzoyl]amino}-2-methylphenyl)-4-oxo-3,4-dihydroquinazoline-6-carboxamide, or a pharmaceutically acceptable salt thereof, as defined herein before in association with a pharmaceutically-acceptable diluent or carrier for use in the production of a B-Raf inhibitory effect in a warm-blooded animal such as man.

In a further aspect of the invention there is provided a pharmaceutical composition which comprises *N*-(5-{[3-(dimethylamino)benzoyl]amino}-2-methylphenyl)-4-oxo-3,4-dihydroquinazoline-6-carboxamide, or a pharmaceutically acceptable salt thereof, as defined

herein before in association with a pharmaceutically-acceptable diluent or carrier for use in the production of an anti-cancer effect in a warm-blooded animal such as man.

In a further aspect of the invention there is provided a pharmaceutical composition which comprises *N*-(5-{[3-(dimethylamino)benzoyl]amino}-2-methylphenyl)-4-oxo-3,4-dihydroquinazoline-6-carboxamide, or a pharmaceutically acceptable salt thereof, as defined herein before in association with a pharmaceutically-acceptable diluent or carrier for use in the treatment of melanoma, papillary thyroid tumours, cholangiocarcinomas, colon cancer, ovarian cancer, lung cancer, leukaemias, lymphoid malignancies, carcinomas and sarcomas in the liver, kidney, bladder, prostate, breast and pancreas, and primary and recurrent solid tumours of the skin, colon, thyroid, lungs and ovaries in a warm-blooded animal such as man.

The B-Raf inhibitory treatment defined hereinbefore may be applied as a sole therapy or may involve, in addition to the compound of the invention, conventional surgery or radiotherapy or chemotherapy. Such chemotherapy may include one or more of the following categories of anti-tumour agents :-

(i) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as alkylating agents (for example cis-platin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan and nitrosoureas); antimetabolites (for example antifolates such as fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside and hydroxyurea; antitumour antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol and taxotere); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan and camptothecin);

(ii) cytostatic agents such as antioestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene and iodoxyfene), oestrogen receptor down regulators (for example fulvestrant), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprorelin and buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrozole, vorazole and exemestane) and inhibitors of 5α-reductase such as finasteride;

(iii) Agents which inhibit cancer cell invasion (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function);

(iv) inhibitors of growth factor function, for example such inhibitors include growth factor antibodies, growth factor receptor antibodies (for example the anti-erbb2 antibody trastuzumab [Herceptin™] and the anti-erbb1 antibody cetuximab [C225]) , farnesyl transferase inhibitors, MEK inhibitors, tyrosine kinase inhibitors and serine/threonine kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors such as N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, AZD1839), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) and 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (CI 1033)), for example inhibitors of the platelet-derived growth factor family and for example inhibitors of the hepatocyte growth factor family;

(v) antiangiogenic agents such as those which inhibit the effects of vascular endothelial growth factor, (for example the anti-vascular endothelial cell growth factor antibody bevacizumab [Avastin™], compounds such as those disclosed in International Patent Applications WO 97/22596, WO 97/30035, WO 97/32856 and WO 98/13354) and compounds that work by other mechanisms (for example linomide, inhibitors of integrin $\alpha v\beta 3$ function and angiostatin);

(vi) vascular damaging agents such as Combretastatin A4 and compounds disclosed in International Patent Applications WO 99/02166, WO00/40529, WO 00/41669, WO01/92224, WO02/04434 and WO02/08213;

(vii) antisense therapies, for example those which are directed to the targets listed above, such as ISIS 2503, an anti-ras antisense;

(viii) gene therapy approaches, including for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy;

(ix) immunotherapy approaches, including for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies;

(x) cell cycle inhibitors including for example CDK inhibitiors (eg flavopiridol) and other inhibitors of cell cycle checkpoints (eg checkpoint kinase); inhibitors of aurora kinase and other kinases involved in mitosis and cytokinesis regulation (eg mitotic kinesins); and histone deacetylase inhibitors; and

(xi) endothelin antagonists, including endothelin A antagonists, endothelin B antagonists and endothelin A and B antagonists; for example ZD4054 and ZD1611 (WO 96 40681), atrasentan and YM598.

Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment. Such combination products employ the compounds of this invention within the dosage range described hereinbefore and the other pharmaceutically-active agent within its approved dosage range.

In addition to their use in therapeutic medicine, the compounds of formula **(I)** and their pharmaceutically acceptable salts are also useful as pharmacological tools in the development and standardisation of in vitro and *in vivo* test systems for the evaluation of the effects of inhibitors of B-Raf in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

In the above other pharmaceutical composition, process, method, use and medicament manufacture features, the alternative and preferred embodiments of the compounds of the invention described herein also apply.

Examples

The invention will now be illustrated by the following non limiting examples in which, unless stated otherwise:

(i) temperatures are given in degrees Celsius (°C); operations were carried out at room or ambient temperature, that is, at a temperature in the range of 18-25°C;

(ii) organic solutions were dried over anhydrous sodium sulphate; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 Pascals; 4.5-30mmHg) with a bath temperature of up to 60 °C;

(iii) in general, the course of reactions was followed by TLC and reaction times are given for illustration only;

(iv) final products had satisfactory proton nuclear magnetic resonance (NMR) spectra and/or mass spectral data;

(v) yields are given for illustration only and are not necessarily those which can be obtained by diligent process development; preparations were repeated if more material was required;

(vii) when given, NMR data is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 400 MHz using perdeuterio dimethyl sulphoxide (DMSO-d_6) as solvent unless otherwise indicated;

(vii) chemical symbols have their usual meanings; SI units and symbols are used;

(viii) solvent ratios are given in volume:volume (v/v) terms; and

(ix) mass spectra were run with an electron energy of 70 electron volts in the chemical ionization (CI) mode using a direct exposure probe; where indicated ionization was effected by electron impact (EI), fast atom bombardment (FAB) or electrospray (ESP); values for m/z are given; generally, only ions which indicate the parent mass are reported; and unless otherwise stated, the mass ion quoted is $(MH)^+$;

(x) where a synthesis is described as being analogous to that described in a previous example the amounts used are the millimolar ratio equivalents to those used in the previous example;

(xi) the following abbreviations have been used:

HATU	*O*-(7-Azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate
THF	tetrahydrofuran;
DMF	*N,N*-dimethylformamide;
EtOAc	ethyl acetate;
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
HOBt	hydroxybenzotriazole
DCM	dichloromethane; and
DMSO	dimethylsulphoxide;

(xii) "ISCO" refers to normal phase flash column chromatography using 12g and 40g pre-packed silica gel cartridges used according to the manufacturers instruction obtained from ISCO, Inc, 4700 superior street Lincoln, NE, USA.; and

(xiii) "Gilson HPLC" refers to a YMC-AQC18 reverse phase HPLC Column with dimension 20mm/100 and 50mm/250 in water/acetonitrile with 0.1% TFA as mobile phase, obtained from Waters Corporation 34, Maple street, Milford MA,USA.

(xiv) Parr Hydrogenator or Parr shaker type hydrogenators are systems for treating chemicals with hydrogen in the presence of a catalyst at pressures up to 5 atmospheres (60 psig) and temperatures to 80 °C.

Example 1

N-(5-{[3-(1-Cyano-1-methylethyl)benzoyl]amino}-2-methylphenyl)-4-oxo-3,4-dihydroquinazoline-6-carboxamide

A solution of *N*-(5-amino-2-methylphenyl)-4-oxo-3,4-dihydroquinazoline-6-carboxamide (Method 11) (120 mg, 0.408 mmol), 3-(1-cyano-1-methylethyl)benzoic acid (Method 3) (77 mg, 0.408 mmol) and diisopropylethylamine (213 μL, 1.22 mmol, 3.0 equiv) in 2 ml of DMF was treated with HATU (186 mg, 0.490 mmol, 1.2 equiv). The reaction was stirred at 50 °C for 12 hours. The reaction was quenched with H_2O and extracted with EtOAc. The organics were dried with NaCl (sat) and then Na_2SO_4 (s) and removed under reduced pressure. The resulting solid was purified by a Gilson HPLC to give 16 mg of a white solid (8%). NMR (400 MHz): 10.32 (s, 1H), 10.25 (s, 1H), 8.79 (d, 1H), 8.36 (dd, 1H), 8.22 (s, 1H), 8.04 (s, 1H), 7.93 (d, 1H), 7.79 (m, 2H), 7.74 (d, 1H), 7.60 (m, 2H), 7.26 (d, 1H), 2.23 (s, 3H), 1.74 (s, 6H); *m/z* 466.

Examples 2-4

The following compounds were prepared by the procedure of Example 1, using the indicated starting materials.

Ex	Compound	NMR	m/z	SM
2	N-(2-Methyl-5-{[3-(trifluoromethyl)benzoyl]amino}phenyl)-4-oxo-3,4-dihydroquinazoline-6-carboxamide	10.49 (s, 1H), 10.26 (s, 1H), 8.79 (d, 1H), 8.36 (dd, 1H), 8.30 (s, 1H), 8.26 (d, 1H), 8.01 (d, 1H), 7.96 (d, 1H), 7.84 (s, 1H), 7.79 (d, 1H), 7.61 (d, 1H), 7.27 (d, 1H), 2.23 (s, 3H)	467	Method 11 and 3-(trifluoromethyl)-benzoyl chloride
3	N-(5-{[4-Chloro-3-(trifluoromethyl)benzoyl]amino}-2-methylphenyl)-4-oxo-3,4-dihydroquinazoline-6-carboxamide	10.53 (s, 1H), 10.25 (s, 1H), 8.79 (d, 1H), 8.39 (s, 1H), 8.35 (dd, 1H), 8.26 (d, 1H), 8.20 (s, 1H), 7.92 (d, 1H), 7.82 (s, 1H), 7.79 (d, 1H), 7.60 (d, 1H), 7.27 (d, 1H), 2.23 (s, 3H)	501	Method 11 and Method 9

Ex	Compound	NMR	m/z	SM
4	N-(2-Methyl-5-{[3-(trifluoromethyl)benzoyl] amino}phenyl)-4-oxo-1,2,3,4-tetrahydroquinazoline-6-carboxamide	10.45 (s, 1H), 9.76 (s, 1H), 8.35 (s, 1H), 8.29 (s, 1H), 8.26 (d, 1H), 7.99 (s, 1H), 7.96 (d, 1H), 7.88 (d, 1H), 7.77 (m, 2H), 7.58 (d, 1H), 7.24 (d, 1H), 7.17 (s, 1H), 6.80 (d, 1H), 2.19 (s, 3H)	469	Method 13 and 3-(trifluoromethyl)-benzoyl chloride
5	*N*-[5-({3-[(Dimethylamino)sulfonyl] benzoyl}amino)-2-methylphenyl]-3-methyl-4-oxo-3,4-dihydroquinazoline-6-carboxamide	10.54 (s, 1H), 10.27 (s, 1H), 8.82 (s, 1H), 8.48 (s, 1H), 8.36 (d, 1H), 8.30 (m, 2H), 7.95 (d, 1H), 7.81 (m, 3H), 7.62 (d, 1H), 7.28 (d, 1H), 3.53 (s, 3H), 2.65 (s, 6H), 2.23 (s, 3H)	520	Method 12 and Method 6

Example 6

N-(5-{[3-(1-Cyano-1-methylethyl)benzoyl]amino}-2-methylphenyl)-3-methyl-4-oxo-3,4-dihydroquinazoline-6-carboxamide

A stirred mixture of *N*-(3-amino-4-methylphenyl)-3-(1-cyano-1-methylethyl)benzamide (Method 5) (102 mg, 0.348 mmol), 3-methyl-4-oxo-3,4-dihydroquinazoline-6-carboxylic acid (Method 6) (84 mg, 0.348 mmol) and diisopropylethylamine (182 μL, 1.04 mmol, 3.0 equiv) in 2 ml of DMF was treated with HATU (159 mg, 0.417 mmol, 1.2 equiv). The reaction was stirred at 50 °C for 12 hours. The reaction was quenched with H_2O and extracted with EtOAc. The organics were dried with NaCl (sat) and then Na_2SO_4 (s) and removed under reduced pressure. The resulting solid was purified by column chromatography utilizing an ISCO system (EtOAc and MeOH 9:1) to give 128 mg of light yellow solid (77%). NMR (400 MHz): 10.34 (s, 1H), 10.28 (s, 1H), 8.82 (d, 1H), 8.53 (s, 1H), 8.37 (dd, 1H), 8.04 (s, 1H), 7.94 (d, 1H), 7.80 (m, 2H), 7.73 (d, 1H), 7.59 (m, 2H), 7.26 (d, 1H), 3.53 (s, 3H), 2.22 (s, 3H), 1.74 (s, 6H); *m/z* 480.

Preparation of Starting Materials

Method 1

3-Cyanomethyl-benzoic acid methyl ester

A suspension of methyl-3-(bromomethyl)benzoate (13.5 g, 58.9 mmol) and sodium cyanide (4.33 g, 88.4 mmol) in DMF (25 ml) and water (1 ml) was stirred at 75 °C for 5 hours. The reaction mixture was quenched with water (50 ml) and extracted with EtOAc (100 ml × 3). The combined organics were dried with Na_2SO_4(s) and concentrated under reduced pressure. The resulting residue was purified by column chromatography utilizing an ISCO system (hexane-EtOAc) to give7.2 g (70%) of colourless oil. NMR (400 MHz): 7.90 (s, 1H), 7.86 (d, 1H), 7.60 (d, 1H), 7.50 (m, 1H), 4.10 (s, 2H), 3.80 (s, 3H); *m/z* 175.

Method 2

3-(1-Cyano-1-methylethyl)benzoic acid methyl ester

A solution of 3-cyanomethyl-benzoic acid methyl ester (Method 1; 7.2 g, 41.1 mmol) in anhydrous DMSO (80 ml) was treated with sodium hydride (60%, 4.9 g, 123.3 mmol, 3 eq). Methyl iodide was then added dropwise at 0°C. The reaction mixture was stirred at 25 °C for 12 hours. The reaction mixture was then quenched with water (200 ml) and extracted with EtOAc. The combined organics were dried with Na_2SO_4(s) and concentrated under reduced pressure. The crude product was purified by column chromatography utilizing an ISCO system (hexane-EtOAc) to give 5.5 g (66%) of a colourless oil. NMR (400 MHz): 8.05 (s, 1H), 7.90 (d, 1H), 7.75 (d, 1H), 7.55 (m, 1H), 3.80 (s, 3H), 1.62 (s, 6H); *m/z* 203.

Method 3

3-(1-Cyano-1-methylethyl)benzoic acid

A solution of 3-(1-cyano-1-methylethyl)benzoic acid methyl ester (Method 2; 5.5 g, 27.1 mmol) in 100 ml of THF/MeOH/H_2O (3:1:1) was treated with lithium hydroxide (1.95 g) in 20 ml water. The mixture was stirred at 25 °C for 12 hours. The volatile solvent was removed under reduced pressure and the resulting solution was diluted with water, then acidified with 10% HCl to pH = 1-3. The resulting white solid (4.83 g, 94%) was filtered, washed with water, and dried. NMR (400 MHz): 13.00 (s, 1H), 7.95 (s, 1H), 7.80 (d, 1H), 7.65 (d, 1H), 7.45 (m, 1H), 1.60 (s, 6H); *m/z* 189.

Method 4

3-(1-Cyano-1-methylethyl)-*N*-(4-methyl-3-nitro-phenyl)benzamide

A mixture of 4-methyl-3-nitroaniline (2.74 g, 18 mmol), 3-(1-cyano-1-methylethyl) benzoic acid (Method 3; 3.4 g, 18 mmol), EDCI (6.9 g, 36 mmol), HOBt (2.43 g, 18 mmol) and diisopropyl ethyl amine (3.48 g, 27 mmol) in DMF (30 ml) was stirred at 25 °C for 12 hours. The reaction mixture was diluted with DCM and then washed with water. The organic phase was dried with NaCl(sat) and then Na_2SO_4(s). The solvent was removed by reduced pressure and the resulting product was purified by column chromatography utilizing an ISCO system (hexane-EtOAc) to give 4.4 g (53%). NMR (400 MHz): 10.50 (s, 1H), 8.40 (s, 1H), 7.40-7.95 (m, 6H), 3.20 (s, 3H), 1.65 (s, 6H); *m/z* 323.

Method 5

N-(3-Amino-4-methylphenyl)-3-(1-cyano-1-methylethyl)benzamide

A suspension of 3-(1-cyano-1-methylethyl)-*N*-(4-methyl-3-nitro-phenyl)benzamide (Method 4; 4 g, 13.9 mmol) and 5% Pd on carbon in hydrazine hydrate (100 ml) and ethanol (100 ml) was heated to reflux for 3 hours, then stirred at 80 °C for 12 hours. The palladium/carbon was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography using an ISCO system (hexane-EtOAc) to give 3.7 g (91%) of an orange gum. NMR (400 MHz): 9.95 (s, 1H), 8.00 (s, 1H), 7.90 (d, 1H), 7.70 (d, 1H), 7.55 (m, 1H), 7.05 (s, 1H), 6.80-6.87 (m, 2H), 4.85 (s, 2H), 2.05 (s, 3H), 1.85 (s, 6H); *m/z* 293.

Method 6

3-Methyl-4-oxo-3,4-dihydroquinazoline-6-carboxylic acid

4-Aminoisophthalic acid (1.00 g, 5.52 mmol) was reacted with N-methylformamide (15 ml) at 180 °C for 4 hours. The reaction was quenched with H_2O and extracted with EtOAc. The aqueous layer was acidified with 10% HCl and the resulting precipitate was collected by vacuum filtration to give 504 mg (45%) of a yellow-white solid; *m/z* 205.

Method 7

The following compound was prepared by the procedure of Method 6, using the appropriate amino-benzoic acid (commercially available unless otherwise indicated) and the appropriate formamide as starting materials.

Meth	Compound	m/z	SM
7	4-Oxo-3,4-dihydroquinazoline-6-carboxylic acid	191	4-Aminoisophthalic acid

Method 8

4-Oxo-3,4-dihydroquinazoline-6-carbonyl chloride

A solution of 4-oxo-3,4-dihydroquinazoline-6-carboxylic acid (Method 7) (500 mg, 2.63 mmol), oxalyl chloride (0.343 ml, 3.94 mmol, 1.5 equiv) and catalytic DMF (50 ml) in DCM (8 ml) was stirred at 25 °C for 12 hours. The solvents were removed under reduced pressure. The resulting product was utilized without further purification; *m/z* 209.

Method 9

4-Chloro-3-(trifluoromethyl)benzoyl chloride

A solution of 4-chloro-3-(trifluoromethyl)benzoic acid (1.02 g, 4.54 mmol), oxalyl chloride (0.59 ml, 6.81 mmol, 1.5 equiv) and catalytic DMF (50 ml) in DCM (10 ml) was stirred at 25 °C for 12 hours. The solvents were removed under reduced pressure. The resulting product was utilized without further purification; *m/z* 244.

Method 10

N-(2-Methyl-5-nitrophenyl)-4-oxo-3,4-dihydroquinazoline-6-carboxamide

A solution of 4-methyl-3-nitro-phenylamine (365 mg, 2.40 mmol) in DMF (6 ml) was treated with 4-oxo-3,4-dihydroquinazoline-6-carbonyl chloride (Method 8) (500 mg, 2.40 mmol). The mixture was stirred at 25 °C for 12 hours. The reaction was then quenched with 10% NaOH(aq). The resulting solid was collected by vacuum filtration to give 638 g (82%) of a light yellow solid; *m/z* 325.

Method 11

N-(5-Amino-2-methylphenyl)-4-oxo-3,4-dihydroquinazoline-6-carboxamide

A suspension of *N*-(2-methyl-5-nitrophenyl)-4-oxo-3,4-dihydroquinazoline-6-carboxamide (Method 10) (638 mg, 1.97 mmol) and 30% Pd on carbon (100 mg) (100 ml) in MeOH (20 ml) was placed on a Parr hydrogenator at 50 psi for 8 hours. The palladium/carbon was removed by filtration and the filtrate was concentrated under reduced pressure to give 485 mg (84%); *m/z* 295.

Method 12

The following compound was prepared by the procedure of Method 11, using the appropriate starting material.

Meth	Compound	m/z	SM
12	*N*-(3-Amino-4-methylphenyl)-3-[(dimethylamino)sulfonyl] benzamide	334	Method 15

Method 13

N-(5-Amino-2-methylphenyl)-4-oxo-1,2,3,4-tetrahydroquinazoline-6-carboxamide

A suspension of *N*-(5-amino-2-methylphenyl)-4-oxo-3,4-dihydroquinazoline-6-carboxamide (Method 11) (240 mg, 13.9 mmol) and 30% Pd on carbon (50 mg) (20 ml) in MeOH (20 ml) was placed on a Parr hydrogenator at 60 psi for 8 hours. The palladium/carbon was removed by filtration and the filtrate was concentrated under reduced pressure to give 100 mg (46%); *m/z* 296.

Method 14

3-[(Dimethylamino)sulfonyl]benzoic acid

A solution of 3-(chlorosulfonyl)benzoic acid (2.60 g, 12 mmol) in DCM (20 ml) was treated with dimethylamine (2.0 M in THF, 20 ml, 40 mmol, 3.3 equiv). After 30 min, the reaction was quenched with 10% HCl and extracted with EtOAc. The organics were washed with $NaCl_{(sat)}$ and then dried with $Na_2SO_{4(s)}$. The organics were then removed under reduced pressure to give 1.80 g, 65%; *m/z* 229.

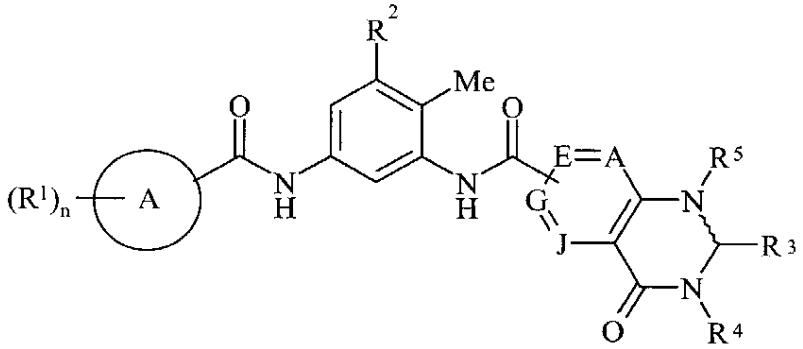
Method 15

3-[(Dimethylamino)sulfonyl]-*N*-(4-methyl-3-nitrophenyl)benzamide

A solution of 3-[(dimethylamino)sulfonyl]benzoic acid (Method 14) (1.00 g, 4.36mmol), 4-methyl-3-nitroaniline (664 mg, 4.36 mmol) and diisopropylethylamine (2.3 ml, 13.08 mmol, 3.0 equiv) in 10 ml of DMF was treated with HATU (2.00 g, 5.23 mmol, 1.2 equiv). The reaction was stirred at 50 °C for 12 hours. The reaction was quenched with H_2O and extracted with EtOAc. A precipitate resulted during this process, thus the solid was collected by vacuum filtration to give 1.14 g, 72% of the desired product; *m/z* 365.

Claims

1. A compound of formula **(I)**:



(I)

wherein:

Ring A is carbocyclyl or heterocyclyl; wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^6;

R^1 is a substituent on carbon and is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, carbocyclyl-R^7- or heterocyclyl-R^8-; wherein R^1 may be optionally substituted on carbon by one or more R^9; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{10};

n is selected from 0-4; wherein the values of R^1 may be the same or different;

R^2 is selected from hydrogen, halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, carbocyclyl-R^{11}- or heterocyclyl-R^{12}-; wherein R^2 may be optionally substituted on carbon by one or more R^{13}; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{14};

one of **A**, **E**, **G** and **J** is C which is attached to the -C(O)NH- of formula **(I)**; the other three are independently selected from CR^{15} or N;

$\mathbf{R^3}$ and $\mathbf{R^{15}}$ are independently selected from hydrogen, halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, carbocyclyl-R^{16}- or heterocyclyl-R^{17}-; wherein R^3 and R^{15} independently of each other may be optionally substituted on carbon by one or more R^{18}; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{19};

$\mathbf{R^4}$ and $\mathbf{R^5}$ are independently selected from hydrogen, C_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl, C_{1-6}alkoxycarbonyl, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl and *N,N*-(C_{1-6}alkyl)carbamoyl; wherein R^4 and R^5 independently of each other may be optionally substituted on carbon by one or more R^{20};

the bond " ~ "between the -NR^5- and -CR^3- of formula **(I)** is either (i) a single bond wherein R^5 is as defined above, or (ii) a double bond wherein R^5 is absent;

$\mathbf{R^9}$, $\mathbf{R^{13}}$, $\mathbf{R^{18}}$ and $\mathbf{R^{20}}$ are independently selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, N-(C_{1-6}alkyl)amino, N,N-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, N-(C_{1-6}alkyl)carbamoyl, N,N-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, N-(C_{1-6}alkyl)sulphamoyl, N,N-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, carbocyclyl-R^{21}- or heterocyclyl-R^{22}-; wherein R^9, R^{13}, R^{18} and R^{20} independently of each other may be optionally substituted on carbon by one or more R^{23}; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{24};

$\mathbf{R^7}$, $\mathbf{R^8}$, $\mathbf{R^{11}}$, $\mathbf{R^{12}}$, $\mathbf{R^{16}}$, $\mathbf{R^{17}}$, $\mathbf{R^{21}}$ and $\mathbf{R^{22}}$ are independently selected from a direct bond, -O-, -N(R^{25})-, -C(O)-, -N(R^{26})C(O)-, -C(O)N(R^{27})-, -S(O)$_s$-, -SO_2N(R^{28})- or -N(R^{29})SO_2-; wherein $\mathbf{R^{25}}$, $\mathbf{R^{26}}$, $\mathbf{R^{27}}$, $\mathbf{R^{28}}$ and $\mathbf{R^{29}}$ is hydrogen or C_{1-6}alkyl and **s** is 0-2;

$\mathbf{R^6}$, $\mathbf{R^{10}}$, $\mathbf{R^{14}}$, $\mathbf{R^{19}}$ and $\mathbf{R^{24}}$ are independently selected from C_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl, C_{1-6}alkoxycarbonyl, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl;

R^{23} is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl;

or a pharmaceutically acceptable salt thereof;

with the proviso that said compound is not *N*-(5-{[3-(dimethylamino)benzoyl]amino}-2-methylphenyl)-4-oxo-3,4-dihydroquinazoline-6-carboxamide.

2. A compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, as claimed in claim 1 wherein Ring A is phenyl.

3. A compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, as claimed in either claim 1 or claim 2 wherein R^1 is a substituent on carbon and is selected from halo, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl or C_{1-6}alkyl; wherein R^1 may be optionally substituted on carbon by one or more R^9; wherein R^9 is selected from halo or cyano.

4. A compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-3 wherein n is selected from 0-2; wherein the values of R^1 may be the same or different.

5. A compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-4 wherein R^2 is selected from hydrogen.

6. A compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-5 wherein G is C which is attached to the -C(O)NH- of formula **(I)**; A, E and J are CR^{15}; wherein R^{15} is hydrogen.

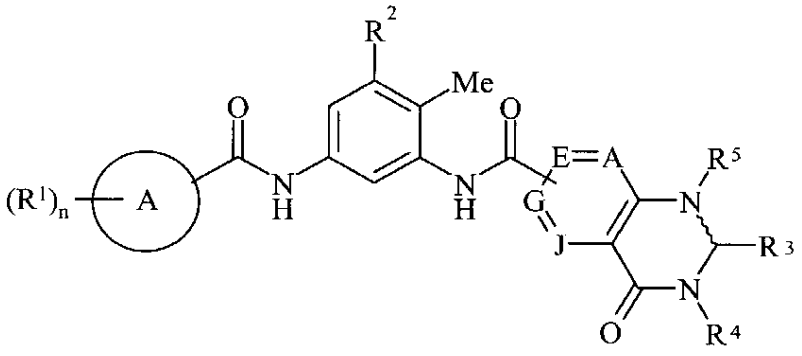
7. A compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-6 wherein R^3 is hydrogen.

8. A compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-7 wherein R^4 is hydrogen or C_{1-6}alkyl.

9. A compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-8 wherein the bond " ~ "between the $-NR^5-$ and $-CR^3-$ of formula **(I)** is a single bond and R^5 is hydrogen.

10. A compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-9 wherein the bond " ~ "between the $-NR^5-$ and $-CR^3-$ of formula **(I)** is a double bond wherein R^5 is absent.

11. A compound of formula **(I)**:



(I)

wherein:

Ring A is phenyl;

R^1 is a substituent on carbon and is selected from chloro, trifluoromethyl, *N,N*-dimethylsulphamoyl or 1-methyl-1-cyanoethyl;

n is selected from 1-2; wherein the values of R^1 may be the same or different;

R^2 is selected from hydrogen;

G is C which is attached to the -C(O)NH- of formula **(I)**; A, E and J are CR^{15}; wherein R^{15} is hydrogen;

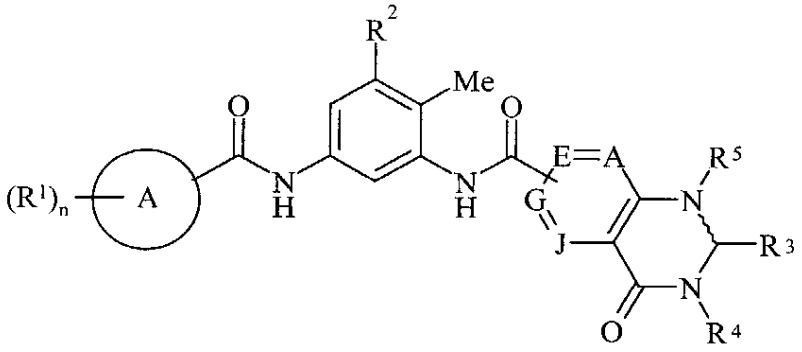
R^3 is hydrogen;

R^4 is hydrogen or methyl;

R^5 is hydrogen;

the bond " ~ "between the -NR^5- and -CR^3- of formula **(I)** is either (i) a single bond wherein R^5 is as defined above, or (ii) a double bond wherein R^5 is absent;
or a pharmaceutically acceptable salt thereof.

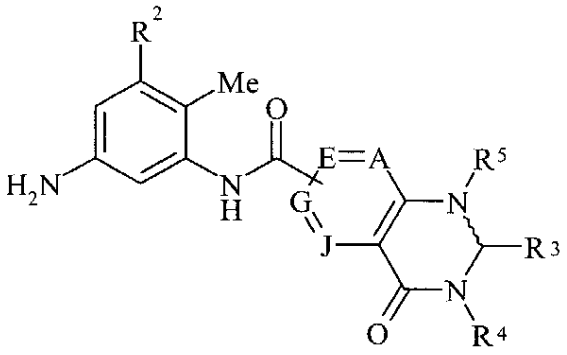
12. A compound of formula **(I)**:



(I)

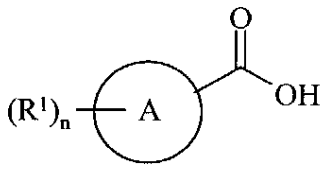
selected from:
N-(5-{[3-(1-cyano-1-methylethyl)benzoyl]amino}-2-methylphenyl)-4-oxo-3,4-dihydroquinazoline-6-carboxamide;
N-(2-methyl-5-{[3-(trifluoromethyl)benzoyl] amino}phenyl)-4-oxo-3,4-dihydroquinazoline-6-carboxamide;
N-(5-{[4-chloro-3-(trifluoromethyl)benzoyl] amino}-2-methylphenyl)-4-oxo-3,4-dihydroquinazoline-6-carboxamide;
N-(2-methyl-5-{[3-(trifluoromethyl)benzoyl] amino}phenyl)-4-oxo-1,2,3,4-tetrahydroquinazoline-6-carboxamide;
N-[5-({3-[(dimethylamino) sulfonyl]benzoyl}amino)-2-methylphenyl]-3-methyl-4-oxo-3,4-dihydroquinazoline-6-carboxamide;
N-(5-{[3-(1-cyano-1-methylethyl)benzoyl]amino}-2-methylphenyl)-3-methyl-4-oxo-3,4-dihydroquinazoline-6-carboxamide;
or a pharmaceutically acceptable salt thereof.

13. A process for preparing a compound of formula **(I)** or a pharmaceutically acceptable salt thereof, as claimed in claim 1, which process, wherein variable are, unless otherwise specified, as defined in claim 1, comprises of:
Process a) reacting an amine of the formula **(II)**



(II)

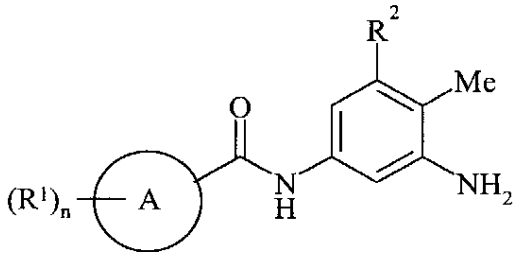
with an acid of formula **(III)**:



(III)

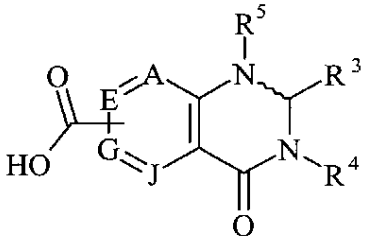
or an activated acid derivative thereof;

Process b) reacting an amine of formula **(IV)**:



(IV)

with an acid of formula **(V)**:



(V)

or an activated acid derivative thereof;

Process c) for compounds of formula **(I)** wherein R^4 is not hydrogen; reacting a compound of formula **(I)** wherein R^4 is hydrogen with a compound of formula **(VI)**:

R^4-L

(VI)

wherein L is a displaceable group and R^4 is not hydrogen;

and thereafter if necessary:

i) converting a compound of the formula **(I)** into another compound of the formula **(I)**;

ii) removing any protecting groups;

iii) forming a pharmaceutically acceptable salt.

14. A pharmaceutical composition which comprises a compound of the formula **(I)**, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-12, in association with a pharmaceutically-acceptable diluent or carrier.

15. A compound of the formula **(I)**, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-12, for use as a medicament.

16. The use of a compound of the formula **(I)**, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-12, in the manufacture of a medicament for use in the production of a B-Raf inhibitory effect in a warm-blooded animal such as man.

17. The use of a compound of the formula **(I)**, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-12, in the manufacture of a medicament for use in the production of an anti-cancer effect in a warm-blooded animal such as man.

18. The use of a compound of the formula **(I)**, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-12, in the manufacture of a medicament for use in the treatment of melanoma, papillary thyroid tumours, cholangiocarcinomas, colon cancer, ovarian cancer, lung cancer, leukaemias, lymphoid malignancies, carcinomas and sarcomas in the liver, kidney, bladder, prostate, breast and pancreas, and primary and recurrent solid tumours of the skin, colon, thyroid, lungs and ovaries.

19. A pharmaceutical composition which comprises a compound of the formula **(I)**, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-12, in association

with a pharmaceutically-acceptable diluent or carrier for use in the production of a B-Raf inhibitory effect in a warm-blooded animal such as man.

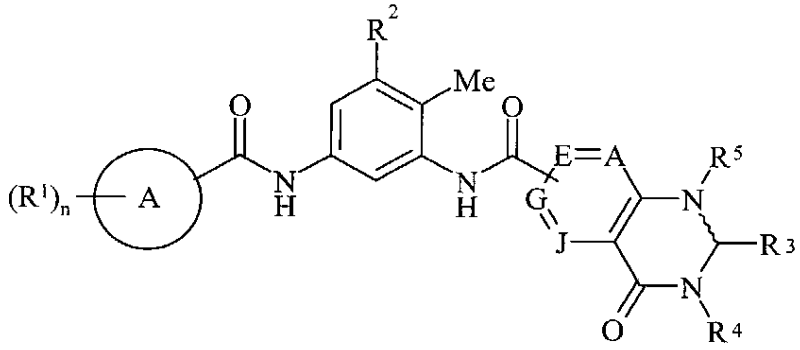
20. A pharmaceutical composition which comprises a compound of the formula **(I)**, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-12, in association with a pharmaceutically-acceptable diluent or carrier for use in the production of an anti-cancer effect in a warm-blooded animal such as man.

21. A pharmaceutical composition which comprises a compound of the formula **(I)**, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-12, in association with a pharmaceutically-acceptable diluent or carrier for use in the treatment of melanoma, papillary thyroid tumours, cholangiocarcinomas, colon cancer, ovarian cancer, lung cancer, leukaemias, lymphoid malignancies, carcinomas and sarcomas in the liver, kidney, bladder, prostate, breast and pancreas, and primary and recurrent solid tumours of the skin, colon, thyroid, lungs and ovaries in a warm-blooded animal such as man.

A B S T R A C T

Title: Chemical Compounds

The invention relates to chemical compounds of the formula **(I)**:



(I)

or pharmaceutically acceptable salts thereof, which possess B-Raf inhibitory activity and are accordingly useful for their anti-cancer activity and thus in methods of treatment of the human or animal body. The invention also relates to processes for the manufacture of said chemical compounds, to pharmaceutical compositions containing them and to their use in the manufacture of medicaments of use in the production of an anti-cancer effect in a warm-blooded animal such as man.