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(54) Title: QUINOLINE DERIVATIVES AS P13 KINASE INHIBITORS

(57) Abstract: A series of quinoline derivatives, substituted at the 2-position by a heteroaryl group attached via an alkylene chain optionally linked to a heteroatom, and at the 3-position by a carbocyclic or heterocylic ring, being selective inhibitors of PD kinase enzymes, are accordingly of benefit in medicine, for example in the treatment of inflammatory, autoimmune, cardiovascular, neurodegenerative, metabolic, oncological, nociceptive or ophthalmic conditions.

QUINOLINE DERIVATIVES AS P13 KINASE INHIBITORS

The present invention relates to a class of substituted quinoline derivatives, and to their use in therapy. These compounds are selective inhibitors of phosphoinositide 3-kinase (PI3K) enzymes, and are accordingly of benefit as pharmaceutical agents, especially in the treatment of adverse inflammatory, autoimmune, cardiovascular, neurodegenerative, metabolic, oncological, nociceptive and ophthalmic conditions.

The PI3K pathway is implicated in a variety of physiological and pathological functions that are believed to be operative in a range of human diseases. Thus, PI3Ks provide a critical signal for cell proliferation, cell survival, membrane trafficking, glucose transport, neurite outgrowth, membrane ruffling, superoxide production, actin reorganization and chemotaxis (cf. S. Ward *et al.*, *Chemistry & Biology*, 2003, **10**, 207-213; and S.G. Ward & P. Finan, *Current Opinion in Pharmacology*, 2003, **3**, 426-434); and are known to be involved in the pathology of cancer, and metabolic, inflammatory and cardiovascular diseases (cf. M.P. Wymann *et al.*, *Trends in Pharmacol. Sci.*, 2003, **24**, 366-376). Aberrant upregulation of the PI3K pathway is implicated in a wide variety of human cancers (cf. S. Brader & S.A. Eccles, *Tumori*, 2004, **90**, 2-8).

The compounds in accordance with the present invention, being potent and selective PI3K inhibitors, are therefore beneficial in the treatment and/or prevention of various human ailments. These include autoimmune and inflammatory disorders such as rheumatoid arthritis, multiple sclerosis, asthma, inflammatory bowel disease, psoriasis and transplant rejection; cardiovascular disorders including thrombosis, cardiac hypertrophy, hypertension, and irregular contractility of the heart (e.g. during heart failure); neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, Huntington's disease, stroke, amyotrophic lateral sclerosis, spinal cord injury, head trauma and seizures; metabolic disorders such as obesity and type 2 diabetes; oncological conditions including leukaemia, glioblastoma, lymphoma, melanoma, and human cancers of the liver, bone, skin, brain, pancreas, lung, breast, stomach, colon, rectum, prostate, ovary and cervix; pain and nociceptive disorders; and ophthalmic disorders including age-related macular degeneration (ARMD).

In addition, the compounds in accordance with the present invention may be beneficial as pharmacological standards for use in the development of new biological tests and in the search for new pharmacological agents. Thus, the compounds of this invention

may be useful as radioligands in assays for detecting compounds capable of binding to human PI3K enzymes.

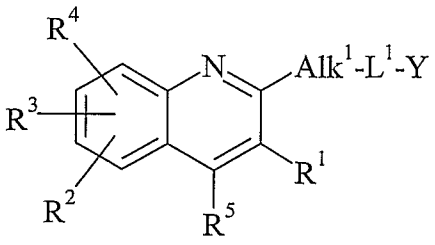
WO 2008/118454, WO 2008/118455 and WO 2008/118468 describe various series of quinoline and quinoxaline derivatives that are structurally related to each other and are stated to be useful to inhibit the biological activity of human PI3Kδ and to be of use in treating PI3K-mediated conditions or disorders.

Copending international patent application PCT/GB2008/004171, published on 2 July 2009 as WO 2009/081105 (claiming priority from United Kingdom patent applications 0725030.1 and 0815177.1), describes a class of quinoline and quinoxaline derivatives as selective inhibitors of PI3K enzymes that are of benefit in the treatment of adverse inflammatory, autoimmune, cardiovascular, neurodegenerative, metabolic, oncological, nociceptive and ophthalmic conditions.

None of the prior art available to date, however, discloses or suggests the precise structural class of substituted quinoline derivatives as provided by the present invention.

The compounds of the present invention are potent and selective PI3K inhibitors having a binding affinity (IC_{50}) for the human PI3Kα and/or PI3Kβ and/or PI3Kγ and/or PI3Kδ isoform of 50 μM or less, generally of 20 μM or less, usually of 5 μM or less, typically of 1 μM or less, suitably of 500 nM or less, ideally of 100 nM or less, and preferably of 20 nM or less (the skilled person will appreciate that a *lower* IC_{50} figure denotes a *more active* compound). The compounds of the invention may possess at least a 10-fold selective affinity, typically at least a 20-fold selective affinity, suitably at least a 50-fold selective affinity, and ideally at least a 100-fold selective affinity, for the human PI3Kα and/or PI3Kβ and/or PI3Kγ and/or PI3Kδ isoform relative to other human kinases.

The present invention provides a compound of formula (I) or an *N*-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof:



(I)

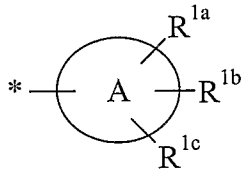
wherein

Alk^1 represents an optionally substituted straight or branched C_{1-3} alkylene chain;

L^1 represents oxygen, sulfur, NR^6 or a covalent bond;

Y represents an optionally substituted mono- or bicyclic heteroaryl group containing at least one nitrogen atom;

R^1 represents a group of formula (a):



(a)

in which the asterisk (*) represents the point of attachment of the ring A to the remainder of the molecule;

A represents a saturated, partially saturated or unsaturated 4-, 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 heteroatoms selected from N, O and S, but containing no more than one O or S atom;

R^{1a}, R^{1b} and R^{1c} independently represent hydrogen, halogen, cyano, nitro, oxo, C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, C_{3-7} heterocycloalkyl (optionally substituted by C_{1-6} alkyl), heteroaryl, trifluoromethyl, hydroxy, C_{1-6} alkoxy, difluoromethoxy, trifluoromethoxy, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, C_{2-6} alkylcarbonylamino, C_{2-6} alkoxycarbonylamino, C_{1-6} alkylsulfonylamino, formyl, C_{2-6} alkylcarbonyl, carboxy, C_{2-6} alkoxycarbonyl, aminocarbonyl, C_{1-6} alkylaminocarbonyl, di(C_{1-6})alkylaminocarbonyl, aminosulfonyl, C_{1-6} alkylaminosulfonyl or di(C_{1-6})alkylaminosulfonyl;

R^2, R^3, R^4 and R^5 independently represent hydrogen, halogen, cyano, nitro, C_{1-6} alkyl, trifluoromethyl, aryl(C_{1-6})alkyl, hydroxy, C_{1-6} alkoxy, difluoromethoxy, trifluoromethoxy, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, C_{2-6} alkylcarbonylamino, C_{2-6} alkoxycarbonylamino, C_{1-6} alkylsulfonylamino, formyl, C_{2-6} alkylcarbonyl, carboxy, C_{2-6} alkoxycarbonyl, aminocarbonyl, C_{1-6} alkylaminocarbonyl, di(C_{1-6})alkylaminocarbonyl, aminosulfonyl, C_{1-6} alkylaminosulfonyl or di(C_{1-6})alkylaminosulfonyl; and

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

Where any of the groups in the compounds of formula (I) above is stated to be optionally substituted, this group may be unsubstituted, or substituted by one or more

substituents. Typically, such groups will be unsubstituted, or substituted by one or two substituents.

For use in medicine, the salts of the compounds of formula (I) will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds of the invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound of the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, methanesulphonic acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, citric acid, tartaric acid or phosphoric acid. Furthermore, where the compounds of the invention carry an acidic moiety, e.g. carboxy, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g. sodium or potassium salts; alkaline earth metal salts, e.g. calcium or magnesium salts; and salts formed with suitable organic ligands, e.g. quaternary ammonium salts.

The present invention includes within its scope solvates of the compounds of formula (I) above. Such solvates may be formed with common organic solvents, e.g. hydrocarbon solvents such as benzene or toluene; chlorinated solvents such as chloroform or dichloromethane; alcoholic solvents such as methanol, ethanol or isopropanol; ethereal solvents such as diethyl ether or tetrahydrofuran; or ester solvents such as ethyl acetate. Alternatively, the solvates of the compounds of formula (I) may be formed with water, in which case they will be hydrates.

Suitable alkyl groups which may be present on the compounds of the invention include straight-chained and branched C_{1-6} alkyl groups, for example C_{1-4} alkyl groups. Typical examples include methyl and ethyl groups, and straight-chained or branched propyl, butyl and pentyl groups. Particular alkyl groups include methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl, 2,2-dimethylpropyl and 3-methylbutyl. Derived expressions such as "C_{1-6} alkoxy", "C_{1-6} alkylthio", "C_{1-6} alkylsulphonyl" and "C_{1-6} alkylamino" are to be construed accordingly.

The expression "C_{1-3} alkylene chain" refers to a divalent straight or branched alkylene chain containing 1 to 3 carbon atoms. Typical examples include methylene, ethylene, methylmethylene, ethylmethylene and dimethylmethylene.

Specific C_{3-7} cycloalkyl groups are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

Suitable aryl groups include phenyl and naphthyl, preferably phenyl.

Suitable aryl(C_{1-6})alkyl groups include benzyl, phenylethyl, phenylpropyl and naphthylmethyl.

Suitable heterocycloalkyl groups, which may comprise benzo-fused analogues thereof, include azetidinyl, tetrahydrofuranyl, dihydrobenzofuranyl, pyrrolidinyl, indolinyl, thiazolidinyl, imidazolidinyl, tetrahydropyranyl, chromanyl, piperidinyl, 1,2,3,4-tetrahydroquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, piperazinyl, 1,2,3,4-tetrahydro-quinoxalinyl, homopiperazinyl, morpholinyl, benzoxazinyl and thiomorpholinyl.

Suitable heteroaryl groups include furyl, benzofuryl, dibenzofuryl, thienyl, benzothienyl, dibenzothienyl, pyrrolyl, indolyl, pyrrolo[2,3-*b*]pyridinyl, pyrrolo[3,2-*c*]pyridinyl, pyrazolyl, pyrazolo[1,5-*a*]pyridinyl, indazolyl, oxazolyl, benzoxazolyl, isoxazolyl, thiazolyl, benzothiazolyl, isothiazolyl, imidazolyl, benzimidazolyl, imidazo[1,2-*a*]pyridinyl, imidazo[4,5-*b*]pyridinyl, imidazo[1,2-*a*]pyrimidinyl, imidazo[1,2-*a*]pyrazinyl, oxadiazolyl, thiadiazolyl, triazolyl, benzotriazolyl, tetrazolyl, pyridinyl, quinolinyl, isoquinolinyl, pyridazinyl, cinnolinyl, pyrimidinyl, pyrazinyl, quinoxalinyl and chromenyl groups.

The term "halogen" as used herein is intended to include fluorine, chlorine, bromine and iodine atoms, typically fluorine, chlorine or bromine.

Where the compounds of formula (I) have one or more asymmetric centres, they may accordingly exist as enantiomers. Where the compounds of the invention possess two or more asymmetric centres, they may additionally exist as diastereomers. The invention is to be understood to extend to all such enantiomers and diastereomers, and to mixtures thereof in any proportion, including racemates. Formula (I) and the formulae depicted hereinafter are intended to represent all individual stereoisomers and all possible mixtures thereof, unless stated or shown otherwise. In addition, compounds of formula (I) may exist as tautomers, for example keto ($CH_2C{=}O$)↔enol (CH=CHOH) tautomers or amide (NHC=O)↔hydroxyimine (N=COH) tautomers. Formula (I) and the formulae depicted hereinafter are intended to represent all individual tautomers and all possible mixtures thereof, unless stated or shown otherwise.

It is to be understood that each individual atom present in formula (I), or in the formulae depicted hereinafter, may in fact be present in the form of any of its naturally occurring isotopes, with the most abundant isotope(s) being preferred. Thus, by way of example, each individual hydrogen atom present in formula (I), or in the formulae depicted

hereinafter, may be present as a ^{1}H, ^{2}H (deuterium) or ^{3}H (tritium) atom, preferably ^{1}H. Similarly, by way of example, each individual carbon atom present in formula (I), or in the formulae depicted hereinafter, may be present as a ^{12}C, ^{13}C or ^{14}C atom, preferably ^{12}C.

Examples of suitable substituents on the alkylene chain represented by Alk^1 include trifluoromethyl, aryl, oxo, hydroxy, C_{1-6} alkoxy, C_{2-6} alkoxycarbonyl(C_{1-6})alkoxy, aminocarbonyl(C_{1-6})alkoxy, trifluoromethoxy, aminocarbonyl, C_{1-6} alkylaminocarbonyl and di(C_{1-6})alkylaminocarbonyl.

Examples of particular substituents on the alkylene chain represented by Alk^1 include trifluoromethyl, phenyl, oxo, hydroxy, ethoxy, ethoxycarbonylmethoxy, aminocarbonylmethoxy, trifluoromethoxy, aminocarbonyl, methylaminocarbonyl and dimethylaminocarbonyl.

Typical values of Alk^1 include methylene ($-CH_2-$), (methyl)methylene, ethylene ($-CH_2CH_2-$), (ethyl)methylene, (dimethyl)methylene, (methyl)ethylene and (dimethyl)ethylene, any of which chains may be optionally substituted by one or more substituents. Suitably, such chains are unsubstituted, monosubstituted or disubstituted. Preferably, such chains are unsubstituted or monosubstituted. In one embodiment, such chains are unsubstituted. In another embodiment, such chains are monosubstituted.

Suitable values of Alk^1 include $-CH_2-$ (methylene), $-CH(CH_3)-$ (methylmethylene) and $-CH(CH_2CH_3)-$ (ethylmethylene).

Alk^1 typically represents methylene.

Suitably, L^1 represents oxygen or sulfur.

In one embodiment, L^1 represents oxygen. In another embodiment, L^1 represents sulfur. In a further embodiment, L^1 represents NR^6. In a still further embodiment, L^1 represents a covalent bond.

The expression "mono- or bicyclic heteroaryl group containing at least one nitrogen atom" in relation to the group Y refers in particular to a mono- or bicyclic aromatic ring system containing one, two, three or four heteroatoms selected from oxygen, sulfur and nitrogen atoms, with at least one of the heteroatoms being nitrogen. The ring Y may be linked to the group L^1 through any available carbon or nitrogen atom. Suitable examples include pyrrolyl, pyridinyl, indolyl, quinolinyl, isoquinolinyl, imidazolyl, pyrazolyl, triazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, indazolyl, benzimidazolyl, furopyridinyl, thienopyridinyl, benzoxazolyl, benzothiazolyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, imidazopyridinyl, pyrazolopyridinyl, purinyl,

pyrazolopyrimidinyl, pyrrolopyrimidinyl, triazolopyrimidinyl, pyridopyrimidinyl, pyridopyrazinyl, pyridopyridazinyl, naphthyridinyl and pteridinyl.

Suitable values of Y include pyrimidinyl and purinyl, either of which groups may be optionally substituted by one or more substituents.

Alternative values of Y include pyrrolyl, indolyl, quinolinyl, isoquinolinyl, imidazolyl, pyrazolyl, triazolyl, pyridazinyl, pyrazinyl, triazinyl, indazolyl, benzimidazolyl, furopyridinyl, thienopyridinyl, benzoxazolyl, benzothiazolyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, triazolopyrimidinyl, pyridopyrimidin-4-yl, pyridopyrazinyl, pyridopyridazinyl, naphthyridinyl and pteridinyl, any of which groups may be optionally substituted by one or more substituents.

Particular values of Y include pyrimidinyl, triazinyl and purinyl, any of which groups may be optionally substituted by one or more substituents. In one embodiment, Y represents optionally substituted pyrimidinyl. In another embodiment, Y represents optionally substituted triazinyl. In a further embodiment, Y represents optionally substituted purinyl.

Examples of optional substituents which may be present on the group Y include one, two or three substituents independently selected from halogen, cyano, nitro, oxo, C_{1-6} alkyl, trifluoromethyl, hydroxy, C_{1-6} alkoxy, difluoromethoxy, trifluoromethoxy, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, arylamino, C_{2-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, formyl, C_{2-6} alkylcarbonyl, C_{3-6} cycloalkylcarbonyl, C_{3-6} heterocycloalkylcarbonyl, carboxy, C_{2-6} alkoxycarbonyl, aminocarbonyl, C_{1-6} alkylaminocarbonyl, di(C_{1-6})alkylaminocarbonyl, aminosulfonyl, C_{1-6} alkylaminosulfonyl and di(C_{1-6})alkylaminosulfonyl.

Typical examples of optional substituents on the group Y include C_{1-6} alkyl and amino.

Examples of particular substituents on the group Y include fluoro, chloro, bromo, cyano, nitro, oxo, methyl, isopropyl, trifluoromethyl, hydroxy, methoxy, difluoromethoxy, trifluoromethoxy, methylthio, methylsulfinyl, methylsulfonyl, amino, methylamino, *tert*-butylamino, dimethylamino, phenylamino, acetylamino, methoxycarbonylamino, methylsulfonylamino, formyl, acetyl, cyclopropylcarbonyl, azetidinylcarbonyl, *N*-methylazetidinylcarbonyl, pyrrolidinylcarbonyl, *N*-methylpyrrolidinylcarbonyl, piperidinylcarbonyl, *N*-methylpiperidinylcarbonyl, piperazinylcarbonyl, *N*-methylpiperazinylcarbonyl, morpholinylcarbonyl, carboxy, methoxycarbonyl,

aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, aminosulfonyl, methylaminosulfonyl and dimethylaminosulfonyl.

Typical examples of particular substituents on the group Y include methyl and amino.

Typical values of Y include aminopyrimidinyl (especially 2-aminopyrimidin-4-yl), (amino)(methyl)pyrimidinyl (especially 2-amino-4-methylpyrimidin-6-yl), (amino)-(methyl)triazinyl (especially 2-amino-4-methyltriazin-6-yl) and purinyl (especially purin-6-yl).

Suitable values for the group -Alk^1-L^1-Y include 2-aminopyrimidin-4-yloxy-methyl, 2-amino-4-methylpyrimidin-6-yloxymethyl, 2-amino-4-methyltriazin-6-yl-oxymethyl and purin-6-ylthiomethyl.

In one embodiment, A is a four-membered monocyclic ring. In another embodiment, A is a five-membered monocyclic ring. In a further embodiment, A is a six-membered monocyclic ring. In an additional embodiment, A is a seven-membered monocyclic ring.

In one embodiment, ring A is fully saturated. In another embodiment, ring A is partially saturated. In a further embodiment, ring A is unsaturated.

In one embodiment, ring A contains no heteroatoms (i.e. it is a carbocyclic ring). In another embodiment, ring A contains one heteroatom selected from N, O and S. In a further embodiment, ring A contains two heteroatoms selected from N, O and S, of which not more than one is O or S. In a still further embodiment, ring A contains three heteroatoms selected from N, O and S, of which not more than one is O or S. In a yet further embodiment, ring A contains four heteroatoms selected from N, O and S, of which not more than one is O or S.

Suitably, ring A represents phenyl.

Typical values of R^{1a}, R^{1b} and/or R^{1c} include hydrogen, halogen, C_{1-6} alkyl, trifluoromethyl, C_{1-6} alkoxy, trifluoromethoxy, C_{2-6} alkylcarbonylamino and aryl.

Suitably, R^{1a}, R^{1b} and R^{1c} independently represent hydrogen, fluoro, chloro, bromo, cyano, nitro, oxo, methyl, ethyl, isopropyl, cyclopropyl, azetidinyl, *N*-methylazetidinyl, tetrahydrofuranyl, pyrrolidinyl, *N*-methylpyrrolidinyl, imidazolidinyl, *N*-methylimidazolidinyl, tetrahydropyranyl, piperidinyl, *N*-methylpiperidinyl, piperazinyl, *N*-methylpiperazinyl, morpholinyl, thiomorpholinyl, phenyl, pyrrolyl, furyl, thienyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, oxadiazolyl,

thiadiazolyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, tetrazolyl, triazinyl, trifluoromethyl, hydroxy, methoxy, difluoromethoxy, trifluoromethoxy, methylthio, methylsulfinyl, methylsulfonyl, amino, methylamino, dimethylamino, acetylamino, methoxycarbonylamino, methylsulfonylamino, formyl, acetyl, carboxy, methoxycarbonyl, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, aminosulfonyl, methylaminosulfonyl or dimethylaminosulfonyl.

Typically, R^{1a} represents hydrogen, halogen, C_{1-6} alkyl, trifluoromethyl, C_{1-6} alkoxy, trifluoromethoxy, C_{2-6} alkylcarbonylamino or aryl.

Suitably, R^{1a} represents hydrogen.

Typically, R^{1b} represents hydrogen, halogen or C_{1-6} alkyl.

Suitably, R^{1b} represents hydrogen.

Typically, R^{1c} represents hydrogen.

In a particular embodiment, R^{1b} and R^{1c} both represent hydrogen.

Typical values of R^2, R^3, R^4 and/or R^5 include hydrogen, halogen, C_{1-6} alkyl, aryl(C_{1-6})alkyl and C_{1-6} alkoxy.

Suitably, R^2, R^3, R^4 and R^5 independently represent hydrogen, fluoro, chloro, bromo, cyano, nitro, methyl, ethyl, trifluoromethyl, benzyl, hydroxy, methoxy, difluoromethoxy, trifluoromethoxy, methylthio, methylsulfinyl, methylsulfonyl, amino, methylamino, dimethylamino, acetylamino, methoxycarbonylamino, methylsulfonylamino, formyl, acetyl, carboxy, methoxycarbonyl, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, aminosulfonyl, methylaminosulfonyl or dimethylaminosulfonyl.

Typically, R^2 represents hydrogen, halogen, C_{1-6} alkyl, aryl(C_{1-6})alkyl or C_{1-6} alkoxy.

Suitably, R^2 represents hydrogen or C_{1-6} alkyl, typically methyl.

In one embodiment, R^2 represents hydrogen. In another embodiment, R^2 represents halogen, particularly fluoro or chloro. In one aspect of that embodiment, R^2 represents fluoro. In another aspect of that embodiment, R^2 represents chloro. In a further embodiment, R^2 represents C_{1-6} alkyl, particularly methyl or ethyl. In one aspect of that embodiment, R^2 represents methyl. In another aspect of that embodiment, R^2 represents ethyl. In a still further embodiment, R^2 represents aryl(C_{1-6})alkyl, especially benzyl. In an additional embodiment, R^2 represents C_{1-6} alkoxy, especially methoxy.

Typically, R^3 represents hydrogen or halogen.

In one embodiment, R^3 represents hydrogen. In another embodiment, R^3 represents halogen, particularly fluoro or chloro. In one aspect of that embodiment, R^3 represents fluoro. In another aspect of that embodiment, R^3 represents chloro.

Typically, R^4 represents hydrogen.

In a particular embodiment, R^3 and R^4 both represent hydrogen.

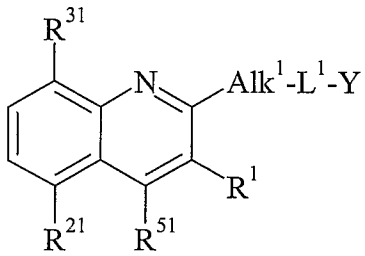
Typically, R^5 represents hydrogen or C_{1-6} alkyl, especially methyl.

In one embodiment, R^5 represents hydrogen. In another embodiment, R^5 represents C_{1-6} alkyl, particularly methyl.

In one embodiment, R^6 represents hydrogen. In another embodiment, R^6 represents C_{1-6} alkyl, especially methyl.

Suitable values of the group R^6 include hydrogen and methyl.

One sub-class of compounds according to the invention is represented by the compounds of formula (IIA) and *N*-oxides thereof, and pharmaceutically acceptable salts and solvates thereof:



(IIA)

wherein

R^{21} represents hydrogen, halogen, C_{1-6} alkyl, aryl(C_{1-6})alkyl or C_{1-6} alkoxy;

R^{31} represents hydrogen or halogen;

R^{51} represents hydrogen or C_{1-6} alkyl; and

Alk^1, L^1, Y and R^1 are as defined above.

In one embodiment, R^{21} represents hydrogen. In another embodiment, R^{21} represents halogen, particularly fluoro or chloro. In one aspect of that embodiment, R^{21} represents fluoro. In another aspect of that embodiment, R^{21} represents chloro. In a further embodiment, R^{21} represents C_{1-6} alkyl, particularly methyl or ethyl. In one aspect of that embodiment, R^{21} represents methyl. In another aspect of that embodiment, R^{21}

represents ethyl. In a still further embodiment, R^{21} represents aryl(C_{1-6})alkyl, especially benzyl. In an additional embodiment, R^{21} represents C_{1-6} alkoxy, especially methoxy.

In one embodiment, R^{31} represents hydrogen. In another embodiment, R^{31} represents halogen, particularly fluoro or chloro. In one aspect of that embodiment, R^{31} represents fluoro. In another aspect of that embodiment, R^{31} represents chloro.

In one embodiment, R^{51} represents hydrogen. In another embodiment, R^{51} represents C_{1-6} alkyl, particularly methyl.

Specific novel compounds in accordance with the present invention include each of the compounds whose preparation is described in the accompanying Examples, and pharmaceutically acceptable salts and solvates thereof.

The present invention also provides a pharmaceutical composition which comprises a compound in accordance with the invention as described above, or a pharmaceutically acceptable salt or solvate thereof, in association with one or more pharmaceutically acceptable carriers.

Pharmaceutical compositions according to the invention may take a form suitable for oral, buccal, parenteral, nasal, topical, ophthalmic or rectal administration, or a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets, lozenges or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methyl cellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogenphosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents, emulsifying agents, non-aqueous vehicles or preservatives. The preparations may also contain buffer salts, flavouring agents, colouring agents or sweetening agents, as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds of formula (I) may be formulated for parenteral administration by injection, e.g. by bolus injection or infusion. Formulations for injection may be presented in unit dosage form, e.g. in glass ampoules or multi-dose containers, e.g. glass vials. The compositions for injection may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising, preserving and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

In addition to the formulations described above, the compounds of formula (I) may also be formulated as a depot preparation. Such long-acting formulations may be administered by implantation or by intramuscular injection.

For nasal administration or administration by inhalation, the compounds according to the present invention may be conveniently delivered in the form of an aerosol spray presentation for pressurised packs or a nebuliser, with the use of a suitable propellant, e.g. dichlorodifluoromethane, fluorotrichloromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas or mixture of gases.

The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack or dispensing device may be accompanied by instructions for administration.

For topical administration the compounds of use in the present invention may be conveniently formulated in a suitable ointment containing the active component suspended or dissolved in one or more pharmaceutically acceptable carriers. Particular carriers include, for example, mineral oil, liquid petroleum, propylene glycol, polyoxyethylene, polyoxypropylene, emulsifying wax and water. Alternatively, the compounds of use in the present invention may be formulated in a suitable lotion containing the active component suspended or dissolved in one or more pharmaceutically acceptable carriers. Particular carriers include, for example, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, benzyl alcohol, 2-octyldodecanol and water.

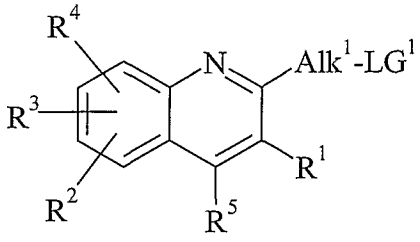
For ophthalmic administration the compounds of use in the present invention may be conveniently formulated as micronized suspensions in isotonic, pH-adjusted sterile saline, either with or without a preservative such as a bactericidal or fungicidal agent, for

example phenylmercuric nitrate, benzylalkonium chloride or chlorhexidine acetate. Alternatively, for ophthalmic administration compounds may be formulated in an ointment such as petrolatum.

For rectal administration the compounds of use in the present invention may be conveniently formulated as suppositories. These can be prepared by mixing the active component with a suitable non-irritating excipient which is solid at room temperature but liquid at rectal temperature and so will melt in the rectum to release the active component. Such materials include, for example, cocoa butter, beeswax and polyethylene glycols.

The quantity of a compound of use in the invention required for the prophylaxis or treatment of a particular condition will vary depending on the compound chosen and the condition of the patient to be treated. In general, however, daily dosages may range from around 10 ng/kg to 1000 mg/kg, typically from 100 ng/kg to 100 mg/kg, e.g. around 0.01 mg/kg to 40 mg/kg body weight, for oral or buccal administration, from around 10 ng/kg to 50 mg/kg body weight for parenteral administration, and from around 0.05 mg to around 1000 mg, e.g. from around 0.5 mg to around 1000 mg, for nasal administration or administration by inhalation or insufflation.

The compounds of formula (I) above may be prepared by a process which comprises reacting a compound of formula (III) with a compound of formula (IV):



(III)

$H\text{-}L^1\text{-}Y$

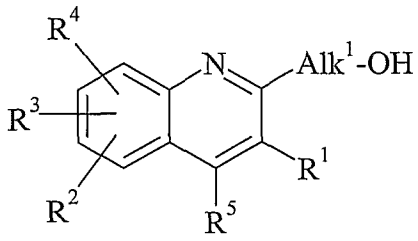
(IV)

wherein Alk^1, L^1, Y, R^1, R^2, R^3, R^4 and R^5 are as defined above, and LG^1 represents a suitable leaving group.

The leaving group LG^1 is typically a halogen atom, e.g. bromo.

The reaction is conveniently effected at ambient or elevated temperature in a suitable solvent, e.g. *N,N*-dimethylformamide or acetonitrile. The reaction may be performed in the presence of a suitable base, e.g. an inorganic base such as potassium carbonate, cesium carbonate, sodium hydride or aqueous sodium hydroxide.

The intermediates of formula (III) above wherein LG^1 is bromo may be prepared from a compound of formula (V):



(V)

wherein Alk^1, R^1, R^2, R^3, R^4 and R^5 are as defined above; by bromination.

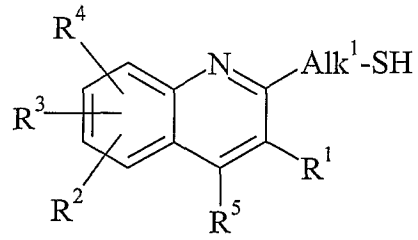
The reaction is conveniently effected by stirring compound (V) with an appropriate brominating agent, e.g. phosphorus tribromide, in a suitable solvent, e.g. a halogenated hydrocarbon such as dichloromethane.

In another procedure, the compounds of formula (I) wherein L^1 represents oxygen may be prepared by a process which comprises reacting a compound of formula (V) as defined above with a compound of formula LG^2-Y, in which Y is as defined above and LG^2 represents a suitable leaving group.

The leaving group LG^2 is typically a halogen atom, e.g. chloro.

The reaction is conveniently effected by stirring compound (V) with a compound LG^2-Y in a suitable solvent, e.g. *N,N*-dimethylformamide, typically under basic conditions, e.g. in the presence of an inorganic base such as sodium hydride.

In another procedure, the compounds of formula (I) wherein L^1 represents sulfur may be prepared by a process which comprises reacting a compound of formula LG^2-Y with a compound of formula (VI):



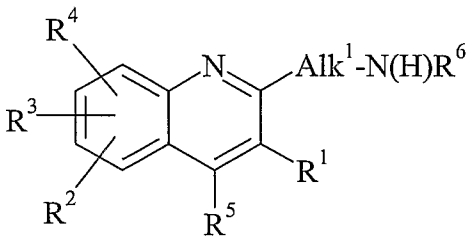
(VI)

wherein Alk^1, Y, R^1, R^2, R^3, R^4, R^5 and LG^2 are as defined above.

The reaction is conveniently effected by stirring compound (VI) with a compound LG^2-Y in a suitable solvent, e.g. a lower alkanol such as methanol, typically under basic conditions, e.g. in the presence of an alkali metal alkoxide such as sodium methoxide.

The intermediates of formula (VI) may typically be prepared by treating a suitable compound of formula (III) above with thiolacetic acid; followed by treatment of the resulting compound with a base, e.g. an alkali metal alkoxide such as sodium methoxide.

In another procedure, the compounds of formula (I) wherein L^1 represents NR^6 may be prepared by a process which comprises reacting a compound of formula LG^2-Y with a compound of formula (VII):



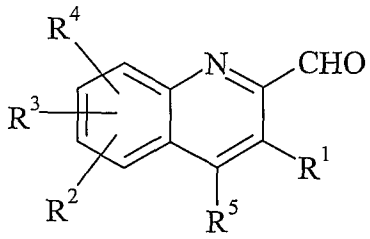
(VII)

wherein Alk^1, Y, R^1, R^2, R^3, R^4, R^5, R^6 and LG^2 are as defined above.

The reaction is conveniently effected at an elevated temperature in a suitable solvent, e.g. tetrahydrofuran, *n*-butanol or 1-methyl-2-pyrrolidinone (NMP). The reaction may be performed in the presence of a suitable base, e.g. an organic base such as *N,N*-diisopropylethylamine.

The intermediates of formula (VII) wherein R^6 represents hydrogen may be prepared by treating a suitable compound of formula (III) above with potassium phthalimide; followed by treatment of the resulting compound with hydrazine. Alternatively, they may be prepared by treating a suitable compound of formula (III) above with sodium azide; followed by treatment of the resulting compound with triphenylphosphine.

In an additional procedure, the compounds of formula (I) wherein Alk^1 represents methylene and L^1 represents NR^6 may be prepared by a process which comprises reacting a compound of formula Y-N(H)R^6 with a compound of formula (VIII):



(VIII)

wherein Y, R^1, R^2, R^3, R^4, R^5 and R^6 are as defined above; under reducing conditions.

The reaction is conveniently effected by stirring compound (VIII) with a compound Y-N(H)R^6 at an elevated temperature in a suitable solvent, e.g. a cyclic ether such as tetrahydrofuran, in the presence of a reducing agent. A suitable reducing agent comprises a mixture of di-*n*-butyltin dichloride and phenylsilane.

The intermediates of formula (VII) wherein Alk^1 represents methylene and R^6 represents C_{1-6} alkyl, e.g. methyl, may be prepared by treating a suitable compound of formula (VIII) above with a C_{1-6} alkylamine, e.g. methylamine, in the presence of titanium(IV) *n*-propoxide and a base, e.g. an organic base such as *N,N*-diisopropylamine; followed by treatment of the resulting compound with a reducing agent, e.g. sodium triacetoxyborohydride.

The intermediates of formula (V) wherein Alk^1 represents methylene may be prepared from the corresponding compound of formula (VIII) by treatment with a reducing agent, e.g. sodium borohydride.

Where they are not commercially available, the starting materials of formula (IV) and (VIII) may be prepared by methods analogous to those described in the accompanying Examples, or by standard methods well known from the art. By way of illustration, the group R^1 may be introduced into the molecule by standard techniques, such as Suzuki conditions.

It will be understood that any compound of formula (I) initially obtained from any of the above processes may, where appropriate, subsequently be elaborated into a further compound of formula (I) by techniques known from the art. By way of illustration, a compound of formula (I) wherein the moiety Y is substituted by a halogen atom, e.g. chloro, may be converted into the corresponding compound wherein Y is substituted by amino (-NH_2) by treatment with ammonia. Similarly, a compound of formula (I) wherein the moiety Y is substituted by a halogen atom, e.g. chloro, may be converted into the

corresponding compound wherein Y is substituted by C_{1-6} alkylamino (e.g. methylamino or *tert*-butylamino), di(C_{1-6})alkylamino (e.g. dimethylamino) or arylamino (e.g. phenylamino) by treatment with the appropriate C_{1-6} alkylamine (e.g. methylamine or *tert*-butylamine), di(C_{1-6})alkylamine (e.g. dimethylamine) or arylamine (e.g. aniline) respectively.

Where a mixture of products is obtained from any of the processes described above for the preparation of compounds according to the invention, the desired product can be separated therefrom at an appropriate stage by conventional methods such as preparative HPLC; or column chromatography utilising, for example, silica and/or alumina in conjunction with an appropriate solvent system.

Where the above-described processes for the preparation of the compounds according to the invention give rise to mixtures of stereoisomers, these isomers may be separated by conventional techniques. In particular, where it is desired to obtain a particular enantiomer of a compound of formula (I) this may be produced from a corresponding mixture of enantiomers using any suitable conventional procedure for resolving enantiomers. Thus, for example, diastereomeric derivatives, e.g. salts, may be produced by reaction of a mixture of enantiomers of formula (I), e.g. a racemate, and an appropriate chiral compound, e.g. a chiral base. The diastereomers may then be separated by any convenient means, for example by crystallisation, and the desired enantiomer recovered, e.g. by treatment with an acid in the instance where the diastereomer is a salt. In another resolution process a racemate of formula (I) may be separated using chiral HPLC. Moreover, if desired, a particular enantiomer may be obtained by using an appropriate chiral intermediate in one of the processes described above. Alternatively, a particular enantiomer may be obtained by performing an enantiomer-specific enzymatic biotransformation, e.g. an ester hydrolysis using an esterase, and then purifying only the enantiomerically pure hydrolysed acid from the unreacted ester antipode. Chromatography, recrystallisation and other conventional separation procedures may also be used with intermediates or final products where it is desired to obtain a particular geometric isomer of the invention.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry*, ed. J.F.W. McOmie, Plenum Press, 1973; and

T.W. Greene & P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 3rd edition, 1999. The protecting groups may be removed at any convenient subsequent stage utilising methods known from the art.

The following Examples illustrate the preparation of compounds according to the invention.

The compounds in accordance with this invention potently inhibit the activity of human PI3Kα and/or PI3Kβ and/or PI3Kγ and/or PI3Kδ.

Enzyme Inhibition Assays

Measurement of the ability of compounds to inhibit the lipid kinase activity of the four class 1 PI3 kinase isoforms (α, β, γ and δ) was performed using a commercially available homogeneous time-resolved fluorescence assay as described by Gray *et al.*, *Anal. Biochem.*, 2003, **313**, 234-245, according to the manufacturer's instructions (Upstate). All assays were performed at 2 μM ATP and a concentration of purified class 1 PI3 kinase known to generate product within the linear range of the assay. Dilutions of inhibitor in DMSO were added to the assay and compared with assays run in the presence of 2% (v/v) DMSO alone (100% activity). The concentration of inhibitor required to inhibit the enzyme activity by 50% is quoted as the IC_{50}.

When tested in the above assay, the compounds of the accompanying Examples were all found to possess IC_{50} values for inhibition of activity of human PI3Kα and/or PI3Kβ and/or PI3Kγ and/or PI3Kδ of 50 μM or better.

EXAMPLES

Abbreviations

DCM: dichloromethane	DMF: *N,N*-dimethylformamide
DMSO: dimethylsulphoxide	EtOAc: ethyl acetate
MeCN: acetonitrile	MeOH: methanol
THF: tetrahydrofuran	SiO_2: silica
br: broad	h: hour(s)
M: mass	r.t.: room temperature
RT: retention time	

ES+: electrospray positive ionisation

HPLC: high performance liquid chromatography

LCMS: liquid chromatography mass spectrometry

Analytical Conditions

All NMRs were obtained either at 300 MHz or 400 MHz.

Compounds were named with the aid of Beilstein Autonom.

All reactions involving air- or moisture-sensitive reagents were performed under a nitrogen atmosphere using dried solvents and glassware. Degassing was performed by bubbling nitrogen through the reaction mixture.

Compounds that required preparative HPLC were purified using *Method 1* or *Method 2* below.

Method 1: Phenomenex Luna C18(2) 250 × 21.2 mm, 5 μm column. Mobile phase A: 99.92% water, 0.08% formic acid. Mobile phase B: 99.92% MeCN, 0.08% formic acid. Gradient program (flow rate 25.0 mL/min), column temperature: ambient, variable gradient.

Method 2: Phenomenex Luna C18(2) 250 × 21.2 mm, 5 μm column. Mobile phase A: 10 mM ammonium acetate in water. Mobile Phase B: 10 mM ammonium acetate in MeCN. Gradient program (flow rate 25.0 mL/min), column temperature: ambient, variable gradient.

Analytical methods used for LCMS were *Method 3* and *Method 4* below.

Method 3: Phenomenex Luna C18(2) 100 × 4.6 mm, 5 μm column. Mobile phase A: 99.92% water, 0.08% formic acid. Mobile phase B: 99.92% MeCN, 0.08% formic acid. Gradient program (flow rate 3.0 mL/min, column temperature 35°C):

Time	A %	B %
0.00	95.0	5.0
4.40	5.0	95.0
5.30	5.0	95.0
5.32	95.0	5.0
6.50	95.0	5.0

Method 4: Phenomenex Luna C18(2) 100 × 4.6 mm, 5 μm column. Mobile phase A: 5 mM NH_4OAc, pH 5.8. Mobile phase B: 95:5 MeCN:100 mM NH_4OAc, pH 5.8. Gradient program (flow rate 3.0 mL/min, column temperature 35°C):

Time	A %	B %
0.00	95.0	5.0
4.40	5.0	95.0
5.30	5.0	95.0
5.32	95.0	5.0
6.50	95.0	5.0

INTERMEDIATE 1

4-Methyl-3-phenylquinoline-2-carboxylic acid methyl ester

To a solution of 2-chloro-4-methyl-3-phenylquinoline (200 mg, 0.78 mmol) in MeOH (5 mL) was added triethylamine (0.5 mL) and [1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium(II), dichloromethane adduct (10 mg). The reaction mixture was heated at 100°C under an atmosphere of carbon monoxide in a Parr bomb for 24 h. The solvent was removed *in vacuo* and the residue purified by column chromatography (SiO_2, 0-10% EtOAc in heptane) to give the *title compound* as an off-white solid (220 mg, quantitative). δ_H (DMSO-d_6) 8.24-8.26 (m, 1H), 8.09-8.11 (m, 1H), 7.70-7.80 (m, 2H), 7.40-7.50 (m, 3H), 7.23-7.33 (m, 2H), 3.55 (s, 3H), 2.48 (s, 3H). LCMS (ES+) 278.0 $(M+H)^+$, RT 3.88 minutes (*Method 3*).

INTERMEDIATE 2

2-Bromomethyl-4-methyl-3-phenylquinoline

To a suspension of sodium borohydride (180 mg, 4.76 mmol) in dry THF (8 mL) was added *Intermediate 1* (220 mg, 0.79 mmol) and the mixture heated at reflux for 15 minutes. The reaction was allowed to cool to r.t., saturated NH_4Cl solution (10 mL) was added and the mixture extracted with EtOAc (40 mL). The organic layer was separated, dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Purification was by column chromatography (SiO_2, 0-10% MeOH in DCM) to give the desired intermediate. To a solution of this intermediate (30 mg, 0.12 mmol) in DCM (0.5 mL) was added

phosphorus tribromide (0.022 mL, 0.24 mmol) and the reaction was stirred at r.t. for 2 h. 10% aqueous K_2CO_3 solution (10 mL) was added cautiously to the mixture which was then extracted with DCM (3 x 20 mL). The organic layers were combined, dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the *title compound* (40 mg, 16%) as a brown glass. δ_H ($CDCl_3$) 8.00-8.20 (m, 2H), 7.25-7.75 (m, 7H), 4.50 (s, 2H), 2.40 (s, 3H). LCMS (ES+) 312.1, 314.1 $(M+H)^+$, RT 4.29 minutes (*Method 3*).

INTERMEDIATE 3

(3-Phenylquinolin-2-yl)methanol

To a solution of 3-phenylquinoline-2-carboxylic acid methyl ester (226 mg, 0.86 mmol) in THF (15 mL) under nitrogen was added ethanol (1.5 mL) followed by sodium borohydride (72 mg, 1.89 mmol) and lithium chloride (81 mg, 1.93 mmol). The reaction mixture was stirred at r.t. for 18 h. Water (30 mL) was added and the mixture extracted with DCM (2 x 30 mL). The organic layers were combined, dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Purification of the residue by column chromatography (SiO_2, 2% MeOH in DCM) gave the *title compound* (147 mg, 73%) as an orange gum. δ_H (DMSO-d_6) 8.27 (s, 1H), 8.08 (d, *J* 8.5 Hz, 1H), 8.04 (d, *J* 7.4 Hz, 1H), 7.76-7.84 (m, 1H), 7.44-7.68 (m, 6H), 5.26 (t, *J* 5.5 Hz, 1H), 4.64 (d, *J* 5.5 Hz, 2H). LCMS (ES+) 236.1 $(M+H)^+$, RT 2.35 minutes (*Method 3*).

INTERMEDIATE 4

2-Bromomethyl-3-phenylquinoline

To a solution of *Intermediate 3* (224 mg, 0.95 mmol) in DCM (0.5 mL) was added phosphorus tribromide (0.45 mL, 4.75 mmol) and the reaction was stirred at r.t. for 2 h. The mixture was poured into aqueous K_2CO_3 solution (60 mL) and extracted with DCM (2 x 50 mL). The organic layers were combined, washed with aqueous K_2CO_3 solution (100 mL), separated, dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the *title compound* (154 mg, 54%) as a beige solid. δ_H ($CDCl_3$) 8.15 (d, *J* 8.5 Hz, 1H), 8.05 (s, 1H), 7.81-7.86 (m, 1H), 7.72-7.79 (m, 1H), 7.45-7.63 (m, 6H), 4.69 (s, 2H). LCMS (ES+) 298.1, 300.1 $(M+H)^+$, RT 4.19 minutes (*Method 3*).

EXAMPLE 1

4-Methyl-3-phenyl-2-(9*H*-purin-6-ylsulfanylmethyl)quinoline

To a solution of *Intermediate 2* (40 mg, 0.13 mmol) in dry DMF (0.5 mL) under nitrogen at r.t. was added 6-mercaptopurine (21.8 mg, 0.13 mmol). The reaction mixture was stirred at r.t. for 18 h. Purification by preparative HPLC *(Method 2)* gave the *title compound* (16 mg, 33%) as an off-white glass. δ_H ($CDCl_3$) 8.58 (br s, 1H), 8.27 (br s, 1H), 8.11 (d, *J* 6 Hz, 1H), 8.06 (d, *J* 6 Hz, 1H), 7.72 (t, *J* 6 Hz, 1H), 7.60 (t, *J* 6 Hz, 1H), 7.25-7.45 (m, 5H), 4.70 (br s, 2H), 2.44 (s, 3H). LCMS (ES+) 384.2 $(M+H)^+$, RT 3.49 minutes (*Method 4*).

EXAMPLE 2

4-Methyl-6-(4-methyl-3-phenylquinolin-2-ylmethoxy)pyrimidin-2-ylamine formate salt

To a suspension of sodium borohydride (180 mg, 4.76 mmol) in dry THF (8 mL) was added *Intermediate 1* (220 mg, 0.79 mmol) and the mixture heated at reflux for 15 minutes. The reaction was allowed to cool to r.t., saturated NH_4Cl solution (10 mL) added and the mixture extracted with EtOAc (40 mL). The organic layer was separated, dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Purification was by column chromatography (SiO_2, 0-10% MeOH in DCM) to give the desired intermediate (30 mg, 15%). The reaction was repeated to provide more material. To a solution of this intermediate (100 mg, 0.4 mmol) in dry DMF (2 mL) was added sodium hydride (15.4 mg, 0.4 mmol, 60% dispersion in mineral oil) followed by 2-amino-4-chloro-6-methyl-pyrimidine (57 mg, 0.4 mmol). The reaction mixture was stirred at r.t. for 18 h. Purification by preparative HPLC *(Method 1)* gave the *title compound* (17 mg, 12%) as a pale yellow glass. δ_H ($CDCl_3$) 8.41 (br s, 1H), 8.14 (d, *J* 6 Hz, 1H), 8.05 (d, *J* 6 Hz, 1H), 7.70-7.77 (m, 1H), 7.58-7.64 (m, 1H), 7.37-7.46 (m, 3H), 7.21-7.24 (m, 2H), 6.48 (br s, 2H), 5.92 (s, 1H), 5.30 (s, 2H), 2.44 (s, 3H), 2.39 (s, 3H). LCMS (ES+) 357.1 $(M+H)^+$, RT 2.21 minutes (*Method 3*).

EXAMPLE 3

4-(4-Methyl-3-phenylquinolin-2-ylmethoxy)pyrimidin-2-ylamine formate salt

To a suspension of sodium borohydride (180 mg, 4.76 mmol) in dry THF (8 mL) was added *Intermediate 1* (220 mg, 0.79 mmol) and the mixture heated at reflux for 15 minutes. The reaction was allowed to cool to r.t., saturated NH_4Cl solution (10 mL) added and the mixture extracted with EtOAc (40 mL). The organic layer was separated, dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Purification was by column chromatography (SiO_2, 0-10% MeOH in DCM) to give the desired intermediate (30 mg, 15%). The reaction was repeated to provide more material. To a solution of this intermediate (100 mg, 0.4 mmol) in dry DMF (2 mL) was added sodium hydride (15.4 mg, 0.4 mmol, 60% dispersion in mineral oil) followed by 2-amino-4-chloropyrimidine (52 mg, 0.4 mmol). The reaction mixture was stirred at r.t. for 18 h. Purification by preparative HPLC *(Method 1)* gave the *title compound* as a pale yellow foam (28 mg, 20%). δ_H ($CDCl_3$) 9.70 (br s, 2H), 8.31 (br s, 1H), 8.14 (d, *J* 6 Hz, 1H), 8.05 (d, *J* 6 Hz, 1H), 7.84 (d, *J* 6 Hz, 1H), 7.70-7.77 (m, 1H), 7.58-7.64 (m, 1H), 7.36-7.45 (m, 3H), 7.22-7.27 (m, 2H), 6.08 (d, *J* 6 Hz, 1H), 5.32 (s, 2H), 2.45 (s, 3H), 2.39 (s, 3H). LCMS (ES+) 343.1 $(M+H)^+$, RT 2.17 minutes (*Method 3*).

EXAMPLE 4

4-Methyl-6-(4-methyl-3-phenylquinolin-2-ylmethoxy)-[1,3,5]triazin-2-ylamine

To a solution of *Intermediate 2* (125 mg, 0.4 mmol) in MeCN (4 mL) was added 4-amino-6-methyl-[1,3,5]triazin-2-ol (50 mg, 0.4 mmol) and K_2CO_3 (110 mg, 0.8 mmol) and the mixture heated at reflux for 18 h. The solvent was removed *in vacuo* and the residue purified by preparative HPLC *(Method 1)* to give the *title compound* (9 mg, 6%) as an off-white solid. δ_H ($CDCl_3$) 8.12 (d, *J* 6 Hz, 1H), 8.03 (d, *J* 6 Hz, 1H), 7.68-7.75 (m, 1H), 7.57-7.63 (m, 1H), 7.35-7.45 (m, 3H), 7.24-7.30 (m, 2H), 5.33 (s, 2H), 5.22 (br s, 2H), 2.43 (s, 3H), 2.33 (s, 3H). LCMS (ES+) 358.1 $(M+H)^+$, RT 2.74 minutes (*Method 3*).

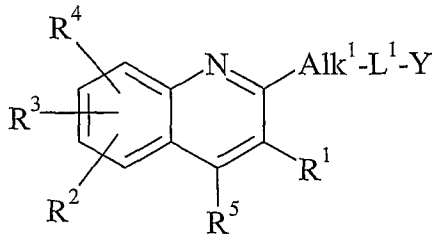
EXAMPLE 5

3-Phenyl-2-(9*H*-purin-6-ylsulfanylmethyl)quinoline

To a solution of 6-mercaptopurine (78 mg, 0.46 mmol) in dry DMF (1 mL) under nitrogen was added slowly a solution of *Intermediate 4* (153 mg, 0.61 mmol) in DMF (2 mL). The reaction mixture was stirred at r.t. for 18 h. Purification by preparative HPLC *(Method 1)* gave the *title compound* (49 mg, 26%) as a white solid. δ_H (DMSO-d_6) 8.54 (s, 1H), 8.42 (s, 1H), 8.28 (s, 1H), 8.04 (d, *J* 7.5 Hz, 1H), 7.75-7.84 (m, 1H), 7.56-7.60 (m, 3H), 7.40-7.53 (m, 1H), 4.95 (s, 2H). LCMS (ES+) 370.1 $(M+H)^+$, RT 3.02 minutes (*Method 3*).

Claims:

1. A compound of formula (I) or an *N*-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof:



(I)

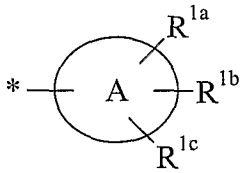
wherein

Alk^1 represents an optionally substituted straight or branched C_{1-3} alkylene chain;

L^1 represents oxygen, sulfur, NR^6 or a covalent bond;

Y represents an optionally substituted mono- or bicyclic heteroaryl group containing at least one nitrogen atom;

R^1 represents a group of formula (a):



(a)

in which the asterisk (*) represents the point of attachment of the ring A to the remainder of the molecule;

A represents a saturated, partially saturated or unsaturated 4-, 5-, 6- or 7-membered monocyclic ring containing 0, 1, 2, 3 or 4 heteroatoms selected from N, O and S, but containing no more than one O or S atom;

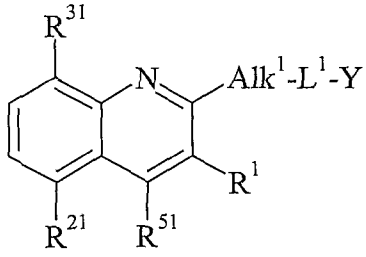
R^{1a}, R^{1b} and R^{1c} independently represent hydrogen, halogen, cyano, nitro, oxo, C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, C_{3-7} heterocycloalkyl (optionally substituted by C_{1-6} alkyl), heteroaryl, trifluoromethyl, hydroxy, C_{1-6} alkoxy, difluoromethoxy, trifluoromethoxy, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, C_{2-6} alkylcarbonylamino, C_{2-6} alkoxycarbonylamino, C_{1-6} alkylsulfonylamino, formyl, C_{2-6} alkylcarbonyl, carboxy, C_{2-6} alkoxycarbonyl,

aminocarbonyl, C_{1-6} alkylaminocarbonyl, di(C_{1-6})alkylaminocarbonyl, aminosulfonyl, C_{1-6} alkylaminosulfonyl or di(C_{1-6})alkylaminosulfonyl;

R^2, R^3, R^4 and R^5 independently represent hydrogen, halogen, cyano, nitro, C_{1-6} alkyl, trifluoromethyl, aryl(C_{1-6})alkyl, hydroxy, C_{1-6} alkoxy, difluoromethoxy, trifluoromethoxy, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, C_{2-6} alkylcarbonylamino, C_{2-6} alkoxycarbonylamino, C_{1-6} alkylsulfonylamino, formyl, C_{2-6} alkylcarbonyl, carboxy, C_{2-6} alkoxycarbonyl, aminocarbonyl, C_{1-6} alkylaminocarbonyl, di(C_{1-6})alkylaminocarbonyl, aminosulfonyl, C_{1-6} alkylaminosulfonyl or di(C_{1-6})alkylaminosulfonyl; and

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

2. A compound as claimed in claim 1 represented by formula (IIA) or an *N*-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof:



(IIA)

wherein

R^{21} represents hydrogen, halogen, C_{1-6} alkyl, aryl(C_{1-6})alkyl or C_{1-6} alkoxy;

R^{31} represents hydrogen or halogen;

R^{51} represents hydrogen or C_{1-6} alkyl; and

Alk^1, L^1, Y and R^1 are as defined in claim 1.

3. A compound as claimed in claim 1 or claim 2 wherein Alk^1 represents methylene, (methyl)methylene or (ethyl)methylene.

4. A compound as claimed in any one of the preceding claims wherein L^1 represents oxygen or sulfur.

5. A compound as claimed in any one of the preceding claims wherein Y represents pyrimidinyl, triazinyl or purinyl, any of which groups may be optionally substituted by one or more substituents.

6. A compound as claimed in any one of the preceding claims wherein Y is unsubstituted, or substituted by one or more substituents selected from C_{1-6} alkyl and amino.

7. A compound as claimed in any one of the preceding claims wherein R^1 represents phenyl.

8. A compound as herein specifically disclosed in any one of the Examples.

9. A compound of formula (I) as defined in claim 1 or an *N*-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof, for use in therapy.

10. A compound of formula (I) as defined in claim 1 or an *N*-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof, for use in the treatment and/or prevention of a disorder for which the administration of a selective PI3K inhibitor is indicated.

11. A pharmaceutical composition comprising a compound of formula (I) as defined in claim 1 or an *N*-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof, in association with a pharmaceutically acceptable carrier.

12. The use of a compound of formula (I) as defined in claim 1 or an *N*-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof, for the manufacture of a medicament for the treatment and/or prevention of a disorder for which the administration of a selective PI3K inhibitor is indicated.

13. A method for the treatment and/or prevention of a disorder for which the administration of a selective PI3K inhibitor is indicated which comprises administering to a patient in need of such treatment an effective amount of a compound of formula (I) as

defined in claim 1 or an *N*-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2009/002741

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D401/12 C07D473/38 A61K31/506 A61K31/52 A61K31/53
A61P3/00 A61P9/00 A61P25/00 A61P27/00 A61P29/00
A61P35/00 A61P37/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, BEILSTEIN Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/118468 A1 (AMGEN INC [US]) 2 October 2008 (2008-10-02) cited in the application abstract claim 1 page 1, line 4 - line 6 page 93; example 43 page 224, line 4 - line 5 page 91; example 40 page 51; example 5 page 58; example 12	1-13

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 February 2010	10/02/2010

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2009/002741

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008118468 A1	02-10-2008	AU 2008231304 A1	02-10-2008
		CA 2681136 A1	02-10-2008
		CR 11053 A	23-10-2009
		EP 2137186 A1	30-12-2009
		US 2009137581 A1	28-05-2009