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(54) Title: FUSED PYRIDINE AND PYRAZINE DERIVATIVES AS KINASE INHIBITORS

(57) Abstract: A series of amino-substituted fused pyridine and pyrazine derivatives, in particular amino-substituted quinoline and quinoxaline derivatives, being selective inhibitors of PI3 kinase enzymes, are accordingly of benefit in medicine, for example in the treatment of inflammatory, autoimmune, cardiovascular, neurodegenerative, metabolic, oncological, nociceptive or ophthalmic conditions.

FUSED PYRIDINE AND PYRAZINE DERIVATIVES AS KINASE INHIBITORS

The present invention relates to a class of fused pyridine and pyrazine 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.

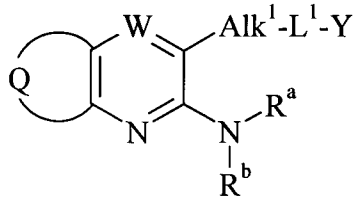
WO 2008/118454, WO 2008/118455 and WO 2008/118468 describe various series of quinoline and quinoxaline derivatives that are structurally related to each other and are stated to be useful to inhibit the biological activity of human PI3Kδ and to be of use in treating PI3K-mediated conditions or disorders.

Copending international patent application PCT/GB2008/004171, published on 2 July 2009 as WO 2009/081105, and copending international patent application PCT/GB2009/002504 (claiming priority from United Kingdom patent application 0819593.5) describe separate classes of fused bicyclic heteroaryl 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 fused pyridine and pyrazine derivatives as provided by the present invention. In particular, none of the available prior art publications provides for substitution by a non-cyclic amine moiety on the pyridine or pyrazine ring.

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

Q represents the residue of an optionally substituted phenyl ring; or an optionally substituted five-membered heteroaromatic ring selected from furyl, thienyl, pyrrolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl and triazolyl; or an optionally substituted six-membered heteroaromatic ring selected from pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl and triazinyl;

W represents C-R^1 or N;

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

L^1 represents oxygen, sulfur, N-R^2 or a covalent bond;

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

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

R^2 represents hydrogen or C_{1-6} alkyl;

R^a represents hydrogen or trifluoromethyl; or C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, heteroaryl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents; and

R^b represents hydrogen, C_{1-6} alkyl or C_{3-7} cycloalkyl.

The present invention also provides a compound of formula (I) as depicted above or an *N*-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof, wherein

R^a represents trifluoromethyl; or C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl-(C_{1-6})alkyl, heteroaryl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents; and

Q, W, Alk^1, L^1, Y, R^1, R^2 and R^b are as defined above.

The present invention further provides a compound of formula (I) as depicted above or an *N*-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof, wherein

R^a represents trifluoromethyl; or C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl-(C_{1-6})alkyl, aryl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, heteroaryl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents; and

Q, W, Alk^1, L^1, Y, R^1, R^2 and R^b are as defined above.

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.

Suitable alkenyl groups include straight-chained and branched C_{2-6} alkenyl groups. Typical examples include vinyl, allyl and dimethylallyl groups.

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, tetrahydrothienyl, pyrrolidinyl, indolinyl, thiazolidinyl, imidazolidinyl, tetrahydropyranyl, chromanyl, dioxanyl, piperidinyl, 1,2,3,4-tetrahydroquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, homopiperidinyl, piperazinyl, 1,2,3,4-tetrahydroquinoxalinyl, homopiperazinyl, morpholinyl, benzoxazinyl and thiomorpholinyl.

Suitable heteroaryl groups include furyl, benzofuryl, dibenzofuryl, thienyl, benzothienyl, dibenzothienyl, thienopyrimidinyl (including thieno[2,3-*d*]pyrimidinyl), pyrrolyl, indolyl, pyrrolopyridinyl (including pyrrolo[2,3-*b*]pyridinyl and pyrrolo[3,2-*c*]pyridinyl), pyrrolotriazinyl (including pyrrolo[2,1-*f*][1,2,4]triazinyl), pyrazolyl, indazolyl, pyrazolopyridinyl (including pyrazolo[1,5-*a*]pyridinyl), pyrazolopyrimidinyl (including pyrazolo[1,5-*a*]pyrimidinyl and pyrazolo[3,4-*d*]pyrimidinyl), pyrazolotriazinyl (including pyrazolo[1,5-*a*][1,3,5]triazinyl), oxazolyl, benzoxazolyl, isoxazolyl, thiazolyl, benzothiazolyl, isothiazolyl, imidazolyl, benzimidazolyl, imidazopyridinyl (including imidazo[1,2-*a*]pyridinyl and imidazo[4,5-*b*]pyridinyl), purinyl, imidazo[1,2-*a*]pyrimidinyl, imidazopyrazinyl (including imidazo[1,2-*a*]pyrazinyl), oxadiazolyl, thiadiazolyl, triazolyl, triazolopyrimidinyl (including [1,2,4]triazolo[1,5-*a*]pyrimidinyl), benzotriazolyl, tetrazolyl, pyridinyl, quinolinyl, isoquinolinyl, naphthyridinyl, pyridopyrimidinyl

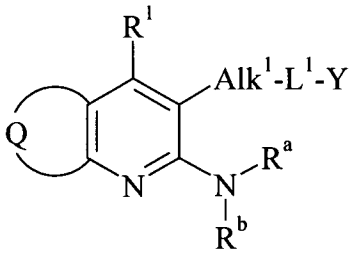
(including pyrido[3,2-*d*]pyrimidinyl), pyridazinyl, cinnolinyl, phthalazinyl, pyrimidinyl, quinazolinyl, pyrazinyl, quinoxalinyl, pteridinyl, triazinyl and chromenyl groups.

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

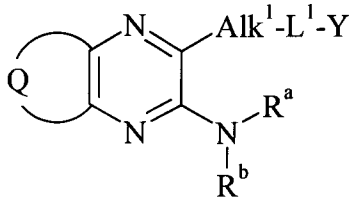
Where the compounds of formula (I) have one or more asymmetric centres, they may accordingly exist as enantiomers. Where the compounds of the invention possess two or more asymmetric centres, they may additionally exist as diastereomers. The invention is to be understood to extend to all such enantiomers 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 ^1H, ^2H (deuterium) or ^3H (tritium) atom, preferably ^1H. 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.

Specific sub-classes of compounds in accordance with the present invention are represented by the compounds of formula (IA) and (IB):



(IA)



(IB)

wherein Q, Alk^1, L^1, Y, R^1, R^a and R^b are as defined above.

In the compounds of formula (I), the moiety Q is defined as representing the residue of an optionally substituted phenyl ring, or of an optionally substituted five-membered or six-membered heteroaromatic ring as specified above. From this it is to be understood that the variable Q, when taken together with the two carbon atoms of the pyridine or pyrazine ring to which the Q-containing ring is fused, represents an optionally substituted phenyl ring, or an optionally substituted five-membered or six-membered heteroaromatic ring as specified above.

In one embodiment, the moiety Q in the compounds of formula (I) above represents the residue of an optionally substituted phenyl ring. In another embodiment, the moiety Q in the compounds of formula (I) above represents the residue of an optionally substituted five-membered heteroaromatic ring selected from furyl, thienyl, pyrrolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl and tetrazolyl. In a further embodiment, the moiety Q in the compounds of formula (I) above represents the residue of an optionally substituted six-membered heteroaromatic ring selected from pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl and triazinyl.

Suitably, the moiety Q represents the residue of a phenyl ring, which may be optionally substituted by one or two substitutents. In one embodiment, the moiety Q represents the residue of an unsubstituted phenyl ring. In another embodiment, the moiety Q represents the residue of a substituted phenyl ring. In one aspect of that embodiment, the moiety Q represents the residue of a monosubstituted phenyl ring. In another aspect of that embodiment, the moiety Q represents the residue of a disubstituted phenyl ring.

The ring of which the moiety Q is the residue may be unsubstituted, or may suitably be substituted, where possible, by one more, typically by one or two, substituents. In one embodiment, this ring is unsubstituted. In another embodiment, this ring is monosubstituted. In a further embodiment, this ring is disubstituted. Examples of typical substituents on the ring of which the moiety Q is the residue include C_{1-6} alkyl, C_{3-7}

cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, heteroaryl, heteroaryl(C_{1-6})alkyl, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulphinyl, C_{1-6} alkylsulphonyl, C_{2-6} alkylcarbonyl, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, halogen, cyano and trifluoromethyl.

Typically, the ring of which the moiety Q is the residue may optionally be substituted by C_{1-6} alkyl or halogen.

Suitably, the ring of which the moiety Q is the residue may optionally be substituted by C_{1-6} alkyl, especially methyl.

Suitably, the ring of which the moiety Q is the residue may optionally be substituted by halogen, especially fluoro or chloro. In one embodiment, the ring of which the moiety Q is the residue is optionally substituted by fluoro. In another embodiment, the ring of which the moiety Q is the residue is optionally substituted by chloro.

In one embodiment, W represents C-R^1. In another embodiment, W represents N.

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.

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.

Typically, Alk^1 represents methylene or (methyl)methylene.

A particular value of Alk^1 is (methyl)methylene, i.e. -$CH(CH_3)$-. Another value of Alk^1 is methylene, i.e. -CH_2-.

In one embodiment, L^1 represents oxygen. In another embodiment, L^1 represents sulfur. In a further embodiment, L^1 represents N-R^2. 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 of Y 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, any of which groups may be optionally substituted by one or more substituents. An additional example of Y is optionally substituted pyrazolotriazinyl. Further examples of Y include thieno-pyrimidinyl and pyrrolotriazinyl, either of which groups may be optionally substituted by one or more substituents.

Typically, Y may represent pyrrolyl, pyridin-2-yl, pyridin-3-yl, indolyl, isoquinolinyl, imidazolyl, pyrazolyl, triazolyl, pyridazinyl, pyrimidin-2-yl, pyrimidin-5-yl, pyrazinyl, triazinyl, indazolyl, furopyridinyl, thienopyridinyl, benzoxazolyl, benzothiazolyl, cinnolinyl, phthalazinyl, quinazolinyl, purin-1-yl, purin-2-yl, purin-3-yl, 7*H*-purin-6-yl, 9*H*-purin-6-yl, purin-7-yl, purin-8-yl, pyrazolo[3,4-*d*]pyrimidin-4-yl, triazolopyrimidinyl, pyridopyrimidin-4-yl, pyridopyrazinyl, pyridopyridazinyl, naphthyridinyl or pteridinyl, any of which groups may be optionally substituted by one or more substituents. Furthermore, Y may represent optionally substituted pyrazolotriazinyl. In addition, Y may represent pyrimidin-4-yl, pyrazolo[1,5-*a*]pyrimidinyl, thieno-pyrimidinyl or pyrrolotriazinyl, any of which groups may be optionally substituted by one or more substituents.

Selected values of Y include thienopyrimidinyl (especially thieno[2,3-*d*]pyrimidin-4-yl), pyrrolotriazinyl (especially pyrrolo[2,1-*f*][1,2,4]triazin-4-yl), pyrazolopyrimidinyl (especially pyrazolo[1,5-*a*]pyrimidin-7-yl and pyrazolo[3,4-*d*]pyrimidin-4-yl), pyrazolotriazinyl (especially pyrazolo[1,5-*a*][1,3,5]triazin-2-yl and pyrazolo[1,5-*a*][1,3,5]triazin-4-yl), purinyl (especially 9*H*-purin-6-yl), triazolo-pyrimidinyl (especially [1,2,4]triazolo[1,5-*a*]pyrimidin-7-yl), pyridopyrimidinyl (especially pyrido[3,2-*d*]pyrimidin-4-yl), pyrimidinyl (especially pyrimidin-2-yl and

pyrimidin-4-yl) and triazinyl (especially [1,3,5]triazin-2-yl), any of which groups may be optionally substituted by one or more substituents.

Typical values of Y include triazinyl, purinyl (especially 9*H*-purin-6-yl), pyrazolopyrimidinyl (especially pyrazolo[3,4-*d*]pyrimidin-4-yl) and pyrazolotriazinyl (especially pyrazolo[1,5-*a*][1,3,5]triazin-4-yl), any of which groups may be optionally substituted by one or more substituents.

Particular values of Y include purinyl (especially 9*H*-purin-6-yl) and pyrazolopyrimidinyl (especially pyrazolo[3,4-*d*]pyrimidin-4-yl), either of which groups may be optionally substituted by one or more substituents.

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.

Selected examples of optional substituents on the group Y include halogen, cyano, C_{1-6} alkyl, C_{1-6} alkylthio, C_{1-6} alkylsulphonyl, amino and C_{1-6} alkylamino.

Illustrative examples of optional substituents on the group Y include C_{1-6} alkyl, C_{1-6} alkylthio, C_{1-6} alkylsulphonyl and amino.

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.

Selected examples of particular substituents on the group Y include fluoro, cyano, methyl, methylthio, methylsulphonyl, amino and methylamino.

Illustrative examples of particular substituents on the group Y include methyl, methylthio, methylsulphonyl and amino.

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

In one embodiment, Y represents optionally substituted purinyl. In one aspect of that embodiment, Y represents unsubstituted purinyl, especially 9*H*-purin-6-yl. In another aspect of that embodiment, Y represents substituted purinyl, including halopurinyl, especially 2-fluoro-9*H*-purin-6-yl; and aminopurinyl, especially 2-amino-9*H*-purin-6-yl.

In another embodiment, Y represents optionally substituted pyrazolopyrimidinyl. In one aspect of that embodiment, Y represents pyrazolo[1,5-*a*]pyrimidin-4-yl. In another aspect of that embodiment, Y represents pyrazolo[3,4-*d*]pyrimidin-4-yl. In a further aspect of that embodiment, Y represents pyrazolopyrimidinyl substituted by C_{1-6} alkyl, especially 1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl.

In another embodiment, Y represents optionally substituted triazinyl. In one aspect of that embodiment, Y represents 4-amino-[1,3,5]triazin-2-yl. In another aspect of that embodiment, Y represents 4-(methylamino)-[1,3,5]triazin-2-yl. In a further aspect of that embodiment, Y represents 4-amino-6-methyl-[1,3,5]triazin-2-yl.

In another embodiment, Y represents optionally substituted pyrazolotriazinyl. In one aspect of that embodiment, Y represents pyrazolo[1,5-*a*][1,3,5]triazin-4-yl. In another aspect of that embodiment, Y represents 2-(methylthio)pyrazolo[1,5-*a*][1,3,5]-triazin-4-yl. In a further aspect of that embodiment, Y represents 2-(methylsulphonyl)-pyrazolo[1,5-*a*][1,3,5]triazin-4-yl. In a still further aspect of that embodiment, Y represents 4-aminopyrazolo[1,5-*a*][1,3,5]triazin-2-yl.

In another embodiment, Y represents optionally substituted thienopyrimidinyl, especially thieno[2,3-*d*]pyrimidin-4-yl.

In another embodiment, Y represents optionally substituted pyrrolotriazinyl, especially pyrrolo[2,1-*f*][1,2,4]triazin-4-yl.

In another embodiment, Y represents optionally substituted triazolopyrimidinyl. In one aspect of that embodiment, Y represents triazolopyrimidinyl substituted by C_{1-6} alkyl, especially 5-methyl-[1,2,4]triazolo[1,5-*a*]pyrimidin-7-yl.

In another embodiment, Y represents optionally substituted pyridopyrimidinyl, especially pyrido[3,2-*d*]pyrimidin-4-yl.

In another embodiment, Y represents optionally substituted pyrimidinyl. In one aspect of that embodiment, Y represents optionally substituted pyrimidin-2-yl, especially 4-amino-5-cyanopyrimidin-2-yl. In another aspect of that embodiment, Y represents optionally substituted pyrimidin-4-yl, especially 2-aminopyrimidin-4-yl and 2-amino-5-cyanopyrimidin-4-yl.

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

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

Suitable values of the group R^1 include hydrogen, fluoro, chloro, bromo, methyl and methoxy. Suitably, R^1 represents hydrogen or methyl. Typically, R^1 represents hydrogen.

In one embodiment, R^2 represents hydrogen. In another embodiment, R^2 represents C_{1-6} alkyl, especially methyl.

Suitable values of the group R^2 include hydrogen and methyl.

Suitably, R^a may represent trifluoromethyl; or C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, heteroaryl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents.

Generally, R^a may represent trifluoromethyl; or C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl-(C_{1-6})alkyl, heteroaryl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents.

Selected values of R^a include C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl-(C_{1-6})alkyl and heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents. In addition, R^a may represent hydrogen.

Illustrative values of R^a include C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-7} cycloalkyl, C_{3-7} heterocycloalkyl and C_{3-7} heterocycloalkyl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents.

Typical values of R^a include C_{1-6} alkyl and C_{3-7} cycloalkyl, either of which groups may be optionally substituted by one or more substituents.

Illustratively, R^a represents trifluoromethyl; or methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, 2-methylpropyl, *tert*-butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, phenyl, benzyl, phenylethyl, azetidinyl, tetrahydrofuryl, tetrahydrothienyl, pyrrolidinyl, piperidinyl, homopiperidinyl, morpholinyl, azetidinylmethyl, tetrahydrofurylmethyl, pyrrolidinylmethyl, pyrrolidinylethyl, pyrrolidinylpropyl, thiazolidinylmethyl, imidazolidinylethyl, piperidinylmethyl, piperidinylethyl, tetrahydroquinolinylmethyl, piperazinylpropyl, morpholinylmethyl, morpholinylethyl, morpholinylpropyl, pyridinyl, indolylmethyl, pyrazolylmethyl, pyrazolylethyl, imidazolylmethyl, imidazolylethyl, benzimidazolylmethyl, triazolylmethyl, pyridinylmethyl or pyridinylethyl, any of which groups may be optionally substituted by one or more substituents. Furthermore, R^a may represent optionally substituted allyl. In addition, R^a may represent hydrogen; or tetrahydropyranyl or dioxanylmethyl, either of which groups may be optionally substituted by one or more substituents.

Typically, R^a represents methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, 2-methyl-propyl, *tert*-butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, any of which groups may be optionally substituted by one or more substituents. Typically, R^a may also represent allyl, piperidinyl, tetrahydrofurylmethyl or imidazolidinylethyl, any of which groups may be optionally substituted by one or more substituents. Typically, R^a may further represent hydrogen; or cyclopropylmethyl, benzyl, tetrahydropyranyl, pyrrolidinylmethyl, pyrrolidinylpropyl, dioxanylmethyl, imidazolylmethyl or pyridinylmethyl, any of which groups may be optionally substituted by one or more substituents.

Desirably, R^a represents hydrogen; or methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, 2-methylpropyl, allyl, cyclopropyl, cyclopropylmethyl, benzyl, tetrahydropyranyl, piperidinyl, tetrahydrofurylmethyl, pyrrolidinylmethyl, pyrrolidinylpropyl, dioxanylmethyl, imidazolidinylethyl, imidazolylmethyl or pyridinylmethyl, any of which groups may be optionally substituted by one or more substituents.

Appositely, R^a represents methyl, ethyl, *n*-propyl, *n*-butyl, allyl, cyclopropyl, piperidinyl, tetrahydrofurylmethyl or imidazolidinylethyl, any of which groups may be optionally substituted by one or more substituents.

Typical examples of suitable substituents on R^a include halogen, C_{1-6} alkyl, C_{1-6} alkoxy, difluoromethoxy, trifluoromethoxy, C_{1-6} alkoxy(C_{1-6})alkyl, C_{1-6} alkylthio, C_{1-6} alkylsulphonyl, hydroxy, hydroxy(C_{1-6})alkyl, amino(C_{1-6})alkyl, cyano, trifluoromethyl, oxo, C_{2-6} alkylcarbonyl, carboxy, C_{2-6} alkoxycarbonyl, amino, C_{1-6} alkylamino, di(C_{1-6})-alkylamino, phenylamino, pyridinylamino, C_{2-6} alkylcarbonylamino, C_{2-6} alkoxycarbonyl-amino and aminocarbonyl. Additional examples of suitable substituents on R^a include (C_{1-6})alkylaminocarbonyl and di(C_{1-6})alkylaminocarbonyl.

Selected examples of suitable substituents on R^a include C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, hydroxy, oxo, C_{2-6} alkylcarbonyl, carboxy, C_{2-6} alkylcarbonylamino, (C_{1-6})alkylaminocarbonyl and di(C_{1-6})alkylaminocarbonyl.

Illustrative examples of suitable substituents on R^a include C_{1-6} alkoxy, hydroxy, oxo, C_{2-6} alkylcarbonyl, C_{2-6} alkylcarbonylamino and di(C_{1-6})alkylaminocarbonyl.

Typical examples of specific substituents on R^a include fluoro, chloro, bromo, methyl, ethyl, isopropyl, methoxy, isopropoxy, difluoromethoxy, trifluoromethoxy, methoxymethyl, methylthio, ethylthio, methylsulphonyl, hydroxy, hydroxymethyl, hydroxyethyl, aminomethyl, cyano, trifluoromethyl, oxo, acetyl, carboxy, methoxycarbonyl, ethoxycarbonyl, *tert*-butoxycarbonyl, amino, methylamino, ethylamino, dimethylamino, phenylamino, pyridinylamino, acetylamino, *tert*-butoxycarbonylamino and aminocarbonyl. Additional examples of specific substituents on R^a include ethoxy, methylaminocarbonyl and dimethylaminocarbonyl.

Selected examples of specific substituents on R^a include methyl, methoxy, ethoxy, methylthio, hydroxy, oxo, acetyl, carboxy, acetylamino, methylaminocarbonyl and dimethylaminocarbonyl.

Illustrative examples of specific substituents on R^a include methoxy, ethoxy, hydroxy, oxo, acetyl, acetylamino and dimethylaminocarbonyl.

Particular values of R^a include hydrogen, methyl, carboxymethyl, methylamino-carbonylmethyl, dimethylaminocarbonylmethyl, ethyl, methoxyethyl, ethoxyethyl, methylthioethyl, hydroxyethyl, acetylaminoethyl, methoxypropyl, dihydroxypropyl, methoxyprop-2-yl, *n*-butyl, 2-hydroxy-2-methylpropyl, allyl, cyclopropyl, hydroxy-cyclopropylmethyl, benzyl, tetrahydropyranyl, oxopiperidinyl, acetylpiperidinyl,

tetrahydrofurylmethyl, oxopyrrolidinylmethyl, acetylpyrrolidinylmethyl, oxopyrrolidinylpropyl, dioxanylmethyl, imidazolidinonylethyl, methylimidazolylmethyl and pyridinylmethyl.

Selected values of R^a include methyl, dimethylaminocarbonylmethyl, ethyl, methoxyethyl, ethoxyethyl, hydroxyethyl, acetylaminoethyl, methoxypropyl, *n*-butyl, allyl, cyclopropyl, oxopiperidinyl, acetylpiperidinyl, tetrahydrofurylmethyl and imidazolidinonylethyl.

In a particular embodiment, R^a represents C_{1-6} alkyl. In one aspect of that embodiment, R^a represents methyl. In another aspect of that embodiment, R^a represents *n*-butyl.

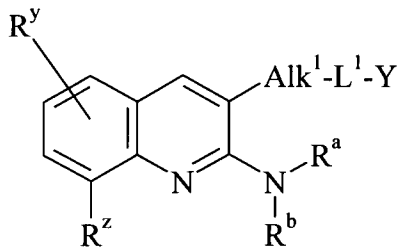
A particular value of R^a is oxopiperidinyl, especially 2-oxopiperidin-5-yl.

In a favoured embodiment, R^a represents oxopyrrolidinylmethyl, especially 2-oxopyrrolidin-5-ylmethyl.

Favourably, R^a represents pyridinylmethyl, especially the *N*-oxide derivative thereof.

Suitably, R^b represents hydrogen or C_{1-6} alkyl. In one embodiment, R^b is hydrogen. In another embodiment, R^b represents C_{1-6} alkyl, especially methyl or ethyl, particularly methyl. In one aspect of that embodiment, R^b represents methyl. In another aspect of that embodiment, R^b represents ethyl. In a further embodiment, R^b represents C_{3-7} cycloalkyl, e.g. cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

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 Alk^1, L^1, Y, R^a and R^b are as defined above; and

R^y and R^z independently represent hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, heteroaryl, heteroaryl(C_{1-6})alkyl, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulphinyl, C_{1-6} alkylsulphonyl, C_{2-6} alkylcarbonyl, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, halogen, cyano or trifluoromethyl.

Typically, R^y represents hydrogen or halogen. Suitably, R^y represents hydrogen.

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

Typically, R^z represents hydrogen, C_{1-6} alkyl or halogen. Appositely, R^z represents C_{1-6} alkyl or halogen. Suitably, R^z represents C_{1-6} alkyl, especially methyl.

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

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

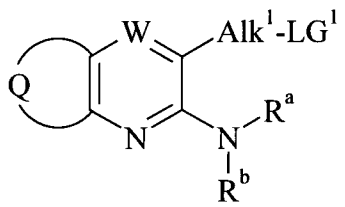
include, for example, mineral oil, liquid petroleum, propylene glycol, polyoxyethylene, polyoxypropylene, emulsifying wax and water. Alternatively, the compounds of use in the present invention may be formulated in a suitable lotion containing the active component suspended or dissolved in one or more 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 wherein L^1 represents oxygen, sulphur or N-R^2 may be prepared by a process which comprises reacting a compound of formula (III) with a compound of formula (IV):



(III)

H-L^{1a}-Y

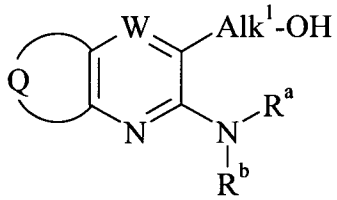
(IV)

wherein L^{1a} represents oxygen, sulphur or N-R^2, LG^1 represents a suitable leaving group, and Q, W, Alk^1, Y, R^2, R^a and R^b are as defined above.

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

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 or iodo may be prepared from a compound of formula (V):



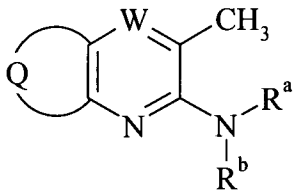
(V)

wherein Q, W, Alk^1, R^a and R^b are as defined above; by bromination or iodination.

The bromination 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.

The iodination reaction is conveniently effected by stirring compound (V) with an appropriate iodinating agent, e.g. elemental iodine, in a suitable solvent, e.g. a halogenated hydrocarbon such as dichloromethane, typically in the presence of triphenylphosphine and imidazole.

Alternatively, the intermediates of formula (III) above wherein Alk^1 represents methylene and LG^1 is bromo may be prepared from a compound of formula (VI):



(VI)

wherein Q, W, R^a and R^b are as defined above; by bromination.

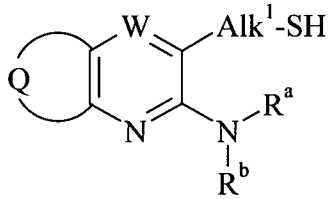
The reaction is conveniently effected at an elevated temperature in a suitable solvent, e.g. a halogenated solvent such as carbon tetrachloride, in the presence of a suitable brominating agent, e.g. *N*-bromosuccinimide, typically in the presence of a catalyst such as benzoyl peroxide.

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 or bromo. Alternatively, LG^2 may be a C_{1-6} alkylsulphonyl group, e.g. methylsulphonyl.

The reaction is conveniently effected by stirring compound (V), typically at an elevated temperature, with a compound LG^2-Y in a suitable solvent, e.g. *N,N*-dimethylformamide or 1,4-dioxane, 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 (VII):



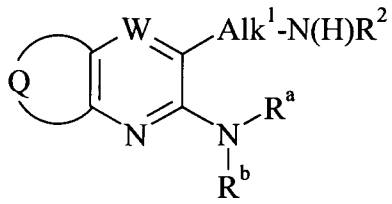
(VII)

wherein Q, W, Alk^1, Y, R^a, R^b and LG^2 are as defined above.

The reaction is conveniently effected by stirring compound (VII) 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 (VII) 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 N-R^2 may be prepared by a process which comprises reacting a compound of formula LG^2-Y with a compound of formula (VIII):



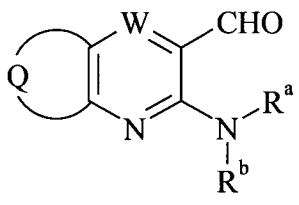
(VIII)

wherein Q, W, Alk^1, Y, R^2, R^a, R^b and LG^2 are as defined above.

The reaction is conveniently effected at an appropriate temperature, e.g. at ambient temperature or at an elevated temperature, in a suitable solvent, e.g. tetrahydrofuran, *n*-butanol, 1-methyl-2-pyrrolidinone (NMP) or 1,4-dioxane. 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 (VIII) wherein R^2 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 N-R^2 may be prepared by a process which comprises reacting a compound of formula Y-N(H)R^2 with a compound of formula (IX):



(IX)

wherein Q, W, Y, R^2, R^a and R^b are as defined above; under reducing conditions.

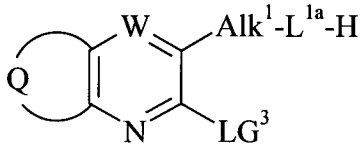
The reaction is conveniently effected by stirring compound (IX) with a compound Y-N(H)R^2 at an elevated temperature in a suitable solvent, e.g. a cyclic ether such as

tetrahydrofuran, in the presence of a reducing agent. A suitable reducing agent comprises a mixture of di-*n*-butyltin dichloride and phenylsilane.

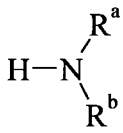
The intermediates of formula (VIII) wherein Alk^1 represents methylene and R^2 represents C_{1-6} alkyl, e.g. methyl, may be prepared by treating a suitable compound of formula (IX) above with a C_{1-6} alkylamine, e.g. methylamine, in the presence of titanium(IV) *n*-propoxide and a base, e.g. an organic 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 (IX) by treatment with a reducing agent, e.g. sodium borohydride.

The intermediates of formula (V), (VII) and (VIII) may be prepared by reacting a compound of formula (X) with a compound of formula (XI):



(X)



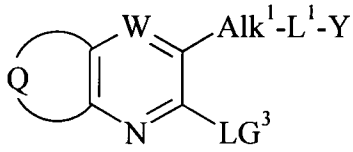
(XI)

wherein Q, W, Alk^1, L^{1a}, R^a and R^b are as defined above, and LG^3 represents a suitable leaving group.

The leaving group LG^3 is typically a halogen atom, e.g. chloro.

The reaction is conveniently effected at an elevated temperature in a suitable solvent, e.g. tetrahydrofuran, isopropanol, *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.

In a further procedure, the compounds of formula (I) may be prepared by a process which comprises reacting a compound of formula (XI) as defined above with a compound of formula (XII):



(XII)

wherein Q, W, Alk^1, L^1, Y and LG^3 are as defined above.

In a variant of the above procedure, the compounds of formula (I) wherein R^a and R^b both represent hydrogen may be prepared by a process which comprises reacting a compound of formula (XII) as defined above with trifluoroacetamide and a catalytic quantity of *trans-N,N'*-dimethylcyclohexane-1,2-diamine.

The above reaction, and the reaction between compounds (XI) and (XII), are both conveniently effected in the presence of a transition metal catalyst. A suitable transition metal catalyst is a copper(I) salt, e.g. a copper(I) halide such as copper(I) iodide.

Moreover, both reactions may be conveniently carried out at an elevated temperature in a suitable solvent, e.g. isopropanol, ethylene glycol or acetonitrile. The reactions may be performed in the presence of a suitable base, e.g. a phosphate salt such as potassium phosphate, or a carbonate salt such as caesium carbonate.

The intermediates of formula (XII) wherein L^1 represents oxygen, sulphur or N-R^2 may be prepared by reacting a compound of formula (X) as defined above with a compound of formula LG^2-Y, in which Y and LG^2 are as defined above, under conditions analogous to those described above for the reaction of a compound of formula (V), (VII) or (VIII) with a compound of formula LG^2-Y.

Where they are not commercially available, the starting materials of formula (IV), (VI), (IX), (X) and (XI) may be prepared by methods analogous to those described in the accompanying Examples, or by standard methods well known from the art.

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.

A compound of formula (I) wherein Y is substituted by C_{1-6} alkylthio, e.g. methylthio, may be converted into the corresponding compound wherein Y is substituted by C_{1-6} alkylsulphonyl, e.g. methylsulphonyl, by treatment with an oxidising agent, e.g. 3-chloroperoxybenzoic acid. Removal of the C_{1-6} alkylsulphonyl moiety from a compound of formula (I) wherein Y is substituted by C_{1-6} alkylsulphonyl, e.g. methylsulphonyl, may be effected by treatment with a reducing agent, e.g. sodium borohydride.

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

MeCN: acetonitrile
DCM: dichloromethane
Et_2O: diethyl ether
DIPEA: *N,N*-diisopropylethylamine
DMF: *N,N*-dimethylformamide
EtOAc: ethyl acetate
NMP: 1-methyl-2-pyrrolidinone
THF: tetrahydrofuran
TFA: trifluoroacetic acid
PPh_3: triphenylphosphine
Me: methyl
Ph: phenyl
MeOH: methanol
DMSO: dimethylsulfoxide
MCPBA: 3-chloroperoxybenzoic acid
TBAF: tetrabutylammonium fluoride
r.t.: room temperature
RT: retention time
SiO_2: silica
h: hour
br: broad
M: mass
HPLC: High Performance Liquid Chromatography
LCMS: Liquid Chromatography Mass Spectrometry
ES+: Electrospray Positive Ionisation

Analytical Conditions

All NMRs were obtained at 400 MHz.

Compounds were named with the aid of Beilstein Autonom or the Cambridgesoft Chemistry Cartridge (v. 9.0.0.182) software.

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.

Analytical Condition	Method	Description	
10cm_ESCI_AmmBicarb_MeCN 10cm_ESCI_Bicarb_MeCN 10cm_ESI_Bicarb 10cm_ESI_Bicarb_MeCN	1	Solvents:	Acetonitrile (far UV grade) Water (high purity via PureLab Option unit) with 10 mM ammonium hydrogencarbonate
		Column:	Waters Xterra MS 5 µm C18, 100

10cm_APCI_Formic			x 4.6 mm (Plus guard cartridge)	
		Flow Rate:	2 mL/min	
		Gradient:	A: Water/Bicarb	
			B: MeCN	
		Time	A%	B%
		0.00	95	5
		0.50	95	5
		4.00	5	95
		5.50	5	95
		5.60	95	5
		6.50	95	5
10cm_ESI_Formic 10cm_ESI_Formic_ MeCN	2	Solvents:	Acetonitrile (far UV grade) with 0.1% (v/v) formic acid Water (high purity via PureLab Option unit) with 0.1% formic acid	
		Column:	Phenomenex Luna 5 µm C18 (2), 100 x 4.6 mm (Plus guard cartridge)	
		Flow Rate:	2 mL/min	
		Gradient:	A: Water/formic acid	
			B: MeCN/formic acid	
		Time	A%	B%
		0.00	95	5
		3.50	5	95
		5.50	5	95
		5.60	95	5
		6.50	95	5
10cm_ESI_Formic_ MeOH	3	Solvents:	Methanol (LC-MS grade) with 0.1% (v/v) formic acid Water (high purity via PureLab Option unit) with 0.1% formic acid	
		Column:	Phenomenex Luna 5 µm C18 (2), 100 x 4.6 mm (Plus guard cartridge)	
		Flow Rate:	2 mL/min	
		Gradient:	A: Water/formic acid	
			B: MeOH/formic acid	
		Time	A%	B%
		0.00	95	5
		3.50	5	95
		7.00	5	95
		7.10	95	5
		8.00	95	5
15cm_Formic_Slow_ Sunfire_HPLC 15cm_Formic_Slow	4	Solvents:	Acetonitrile (far UV grade) with 0.1% (v/v) formic acid	

15cm_ESCI_Formic			Water (high purity via PureLab Ultra unit) with 0.1% formic acid	
		Column:	Waters Sunfire 5 µm C18, 150 x 4.6 mm	
		Flow Rate:	1 mL/min	
		Gradient:	A: Water/formic acid B: MeCN/formic acid	
		Time	A%	B%
		0.00	98	2
		4.00	98	2
		20.0	0	100
		22.0	0	100
		22.5	98	2
		24	98	2
15cm_Formic_Sunfire_ HPLC_MeCN	**5**	Solvents:	Acetonitrile (far UV grade) with 0.1% (v/v) formic acid Water (high purity via PureLab Ultra unit) with 0.1% formic acid	
		Column:	Waters Sunfire 5 µm C18, 150 x 4.6 mm	
		Flow Rate:	1 mL/min	
		Gradient:	A: Water/formic acid B: MeCN/formic acid	
		Time	A%	B%
		0.00	95	5
		1.00	95	5
		30.0	0	100
		40.0	0	100
		40.5	95	5
		45	95	5
25cm_Bicarb_Slow_ XBridge_HPLC_MeCN	**6**	Solvents:	Acetonitrile (far UV grade) Water (high purity via PureLab Option unit) with 10 mM ammonium hydrogencarbonate	
		Column:	Waters Xbridge 5 µm C18 (2), 250 x 4.6 mm	
		Flow Rate:	1 mL/min	
		Gradient:	A: Water/formic acid B: MeCN/formic acid	
		Time	A%	B%
		0.00	95	5
		2.5	95	5
		22	0	100
		25	0	100
		25.1	95	5
		26.5	95	5

25cm_Bicarb_Xbridge_ HPLC	7	Solvents:	Acetonitrile (far UV grade) Water (high purity via PureLab Option unit) with 10 mM ammonium hydrogencarbonate	
		Column:	Waters Xterra 5 µm C18 (2), 250 x 4.6 mm	
		Flow Rate:	1 mL/min	
		Gradient:	A: Water/formic acid B: MeCN/formic acid	
		Time	A%	B%
		0.00	95	5
		1.00	95	5
		30.0	0	100
		40.0	0	100
		40.5	95	5
		45	95	5
15cm_Formic_Ascentis_ HPLC_CH3CN	8	Solvents:	Acetonitrile (far UV grade) with 0.1% (v/v) formic acid Water (high purity via PureLab Option unit) with 0.1% formic acid	
		Column:	Supelco, Ascentis® Express C18, 2.7 µm C18, 150 x 4.6 mm	
		Flow Rate:	1 mL/min	
		Gradient:	A: Water/formic acid B: MeCN/formic acid	
		Time	A%	B%
		0.00	96	4
		3.00	96	4
		9.00	0	100
		13.6	0	100
		13.7	96	4
		15.0	96	4
15cm_Bicarb_ETERNITY _HPLC_CH3CN	9	Solvents:	100% Acetonitrile (far UV grade) Water (high purity via PureLab Ultra unit) with 10mM ammonium bicarbonate	
		Column:	Hichrom, Kromasil Eternity, 2.5 µm C18, 150 x 4.6 mm	
		Flow Rate:	1 mL/min	
		Gradient:	A: 10mM Ammonium bicarbonate in water B: 100% MeCN	
		Time	A%	B%
		0.00	95.5	4.5

3.00	95.5	4.4
9.00	0	100
13.6	0	10
13.7	95.5	4.5
15	95.5	4.5

INTERMEDIATE 1

[1-(2-Chloro-8-methylquinolin-3-yl)ethyl]carbamic acid *tert*-butyl ester

To a solution of 2-chloro-8-methylquinoline-3-carboxaldehyde (3.3 g, 16 mmol) in THF (100 mL) under nitrogen cooled to -78°C was added a solution of methyl-magnesium bromide (3M in Et_2O, 6.0 mL, 18 mmol). After stirring at -78°C for 1 h the mixture was allowed to warm to r.t. and 5% aqueous acetic acid (20 mL) added. The mixture was concentrated *in vacuo* and the aqueous residue extracted with EtOAc (2 x 150 mL). The organic layers were combined, dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The residue was purified by column chromatography (SiO_2, 33% EtOAc in heptane) to give the desired alcohol as a white solid. To a solution of this solid (2.6 g, 11.6 mmol) in DCM was added PPh_3 (3.0 g, 11.5 mmol), iodine (2.8 g, 11.0 mmol) and imidazole (1.0 g, 14.7 mmol). The reaction mixture was stirred at r.t. for 2 h, then washed with water (2 x 75 mL). The organic layer was separated, dried ($MgSO_4$), filtered through silica gel (20 g) and the silica washed with DCM. The filtrate was concentrated *in vacuo* to give the desired iodide as a brown solid. To a solution of this iodide (2.6 g, 7.85 mmol) in dry DMF (20 mL) under nitrogen was added sodium azide (1.0 g, 15.3 mmol), and the mixture was stirred at r.t. for 18 h. Water (100 mL) was added and the mixture was extracted with EtOAc (200 mL). The organic layer was washed with water (2 x 50 mL), separated, dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a pale yellow liquid. This was dissolved in THF (30 mL) and PPh_3 (2.8 g, 10.7 mmol) and water (5 mL) were added. The reaction was stirred at r.t. for 1 h and then heated at reflux for 1 h. After cooling to r.t., the organic solvent was removed *in vacuo* and the aqueous residue was acidified with 1M HCl and washed with EtOAc (50 mL). The aqueous layer was basified with 1M NaOH and extracted with DCM (2 x 75 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo* to give the desired amine as a colourless gum. To a solution of this amine (2.2 g, 9.95 mmol) in dry DCM (50 mL) was added di-*tert*-butyl dicarbonate (2.2 g, 10.1 mmol) and the reaction was stirred at r.t. for 72 h. The mixture was concentrated *in*

vacuo and the residue purified by column chromatography (SiO_2, 33% EtOAc in heptane) to give the *title compound* (2.6 g, 50%) as a white solid. δ_H ($CDCl_3$) 8.07 (s, 1H), 7.64 (d, *J* 8.0 Hz, 1H), 7.54 (d, *J* 7.2 Hz, 1H), 7.43 (t, *J* 7.6 Hz, 1H), 5.01-5.22 (m, 2H), 2.76 (s, 3H), 1.20-1.60 (m, 12H). LCMS (ES+) 321, 323 $(M+H)^+$.

INTERMEDIATE 2

{1-[2-(*N*-Butyl-*N*-methylamino)-8-methylquinolin-3-yl]ethyl}carbamic acid *tert*-butyl ester

To a solution of *Intermediate 1* (200 mg, 0.62 mmol) in NMP (4 mL) were added *N*-methylbutylamine (0.37 mL, 3.12 mmol) and DIPEA (0.56 mL, 3.12 mmol). The reaction mixture was heated at 140°C in a sealed tube overnight. Water (20 mL) was added and the mixture was extracted with EtOAc (150 mL). The organic layer was washed with water (3 x 25 mL), separated, dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The residue was purified by column chromatography (SiO_2, 5-10% EtOAc in petrol 40-60) to give the *title compound* (127 mg, 55%) as a yellow viscous oil. δ_H ($CDCl_3$) 7.90 (s, 1H), 7.52 (d, *J* 8.0 Hz, 1H), 7.42 (d, *J* 7.2 Hz, 1H), 7.23 (t, *J* 7.6 Hz, 1H), 5.10-5.20 (m, 1H), 4.95-5.05 (m, 1H), 2.97 (s, 3H), 2.70 (s, 3H), 1.62-1.69 (m, 2H), 1.30-1.50 (m, 16H), 0.93 (t, *J* 8.0 Hz, 3H). LCMS (ES+) 372 $(M+H)^+$.

INTERMEDIATE 3

(*R*)-2-Methylpropane-2-sulfinic acid 1-(2-chloro-8-methylquinolin-3-yl)meth-(*E*)-ylideneamide

To a solution of 2-chloro-8-methylquinoline-3-carboxaldehyde (2.05 g, 10 mmol) in dry THF (20 mL) under nitrogen was added titanium isopropoxide (5.68 g, 20 mmol) and the mixture stirred at r.t. for 10 minutes. (*R*)-(+)-2-Methyl-2-propanesulfinamide (1.21 g, 10 mmol) was added to the reaction which was stirred at r.t. for 72 h. Water (20 mL) was added and the mixture was extracted with DCM (150 mL). The organic layer was separated, dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to afford the *title compound* (2.4 g, 72%) as a pale yellow solid. δ_H ($CDCl_3$) 9.12 (s, 1H), 8.79 (s, 1H), 7.78 (d, *J* 8.4 Hz, 1H), 7.67 (d, *J* 6.8 Hz, 1H), 7.51 (t, *J* 7.8 Hz, 1H), 2.79 (s, 3H), 1.32 (s, 9H). LCMS (ES+) 309, 311 $(M+H)^+$.

INTERMEDIATE 4

(*R*)-2-Methylpropane-2-sulfinic acid [(*S*)-1-(2-chloro-8-methylquinolin-3-yl)ethyl]amide

To a solution of *Intermediate 3* (1.9 g, 6.15 mmol) in dry DCM (40 mL) under nitrogen cooled to -78°C was added dropwise over 10 minutes a solution of methyl-magnesium bromide (4.1 mL, 12.3 mmol, 3.0M in DCM). The reaction mixture was allowed to warm to r.t. and stirred for 18 h. Saturated NH_4Cl solution (50 mL) was added and the aqueous layer was extracted with DCM (100 mL). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow oil. This was crystallised from petrol 40-60 to afford the *title compound* (900 mg, 45%) as a pale yellow solid. δ_H ($CDCl_3$) 8.17 (s, 1H), 7.64 (d, *J* 8.0 Hz, 1H), 7.56 (d, *J* 7.2 Hz, 1H), 7.45 (t, *J* 7.6 Hz, 1H), 5.09-5.12 (m, 1H), 3.44 (d, *J* 4.8 Hz, 1H), 2.77 (s, 3H), 1.71 (d, *J* 6.8 Hz, 3H), 1.25 (s, 9H). LCMS (ES+) 325, 327 $(M+H)^+$.

INTERMEDIATE 5

N-{(*S*)-1-[2-(*N*-Allyl-*N*-methylamino)-8-methylquinolin-3-yl]ethyl}-(*R*)-2-methylpropane-2-sulfinamide

Intermediate 4 (1.0 g, 3 mmol) and *N*-methylallylamine (5 mL) were combined in a sealed tube and heated at 110°C for 5 days. The reaction mixture was cooled and partitioned between EtOAc and water. The organic layer was washed (water, brine), dried (phase separation cartridge) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, 50% EtOAc in isohexane) to give the *title compound* (1.0 g, 93%) as a brown solid. δ_H ($CDCl_3$) 8.02 (1H, s), 7.51 (1H, d, *J* 8.05 Hz), 7.44 (1H, d, *J* 6.89 Hz), 7.28-7.22 (1H, m), 6.09-5.99 (1H, m), 5.39 (1H, dq, *J* 17.17, 1.74 Hz), 5.23 (1H, dq, *J* 10.26, 1.62 Hz), 5.07-4.99 (1H, m), 3.97-3.89 (1H, m), 3.85-3.76 (1H, m), 3.47 (1H, d, *J* 4.61 Hz), 2.94 (3H, s), 2.71 (3H, s), 1.58 (3H, d, *J* 6.57 Hz), 1.21 (9H, s).

INTERMEDIATE 6

(*S*)-*N*-Allyl-3-(1-aminoethyl)-*N*,8-dimethylquinolin-2-amine

Intermediate 5 (1.1 g, 3.1 mmol) in MeOH (10 mL) was treated with 4M HCl in 1,4-dioxane (10 mL). The mixture was stirred at r.t. for 16 h and concentrated *in vacuo*. The residue was taken up in MeOH and placed on an SCX cartridge. The cartridge was washed through with MeOH and the target compound eluted with 7N NH_3/MeOH. The *title compound* (580 mg, 75%) was obtained as a yellow foam. δ_H ($CDCl_3$) 8.08 (1H, s), 7.54 (1H, d, *J* 8.05 Hz), 7.43 (1H, d, *J* 6.99 Hz), 7.28-7.20 (1H, m), 6.09-5.98 (1H, m), 5.35 (1H, dq, *J* 17.18, 1.72 Hz), 5.22 (1H, dq, *J* 10.23, 1.59 Hz), 4.52 (1H, q, *J* 6.51 Hz), 3.94-3.78 (2H, m), 2.93 (3H, s), 2.71 (3H, s), 1.48 (3H, d, *J* 6.52 Hz).

INTERMEDIATE 7

6-Chloro-9-{[2-(trimethylsilyl)ethoxy]methyl}-9*H*-purine

6-Chloropurine (5.0 g, 32 mmol) in DMF (75 mL) was treated with potassium carbonate (9.0 g, 65 mmol) and [2-(chloromethoxy)ethyl]trimethylsilane (7.0 g, 42 mmol) and stirred for 2 h. The reaction mixture was partitioned between EtOAc and water. The organic layer was dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (SiO_2, 20% EtOAc in isohexane) to give the *title compound* (4.9 g, 54%) as an off-white solid. δ_H ($CDCl_3$) 8.82 (1H, s), 8.32 (1H, s), 5.71 (2H, s), 3.71-3.61 (2H, m), 1.03-0.93 (2H, m), 0.00 (9H, s).

INTERMEDIATE 8

(*S*)-*N*-Allyl-*N*,8-dimethyl-3-[1-(9-{[2-(trimethylsilyl)ethoxy]methyl}-9*H*-purin-6-ylamino)ethyl]quinolin-2-amine

Intermediate 6 (580 mg, 2.3 mmol), *Intermediate 7* (840 mg, 2.95 mmol) and DIPEA (2.0 mL, 11 mmol) in *n*-butanol (2.0 mL) were combined in a sealed tube and heated under microwave irradiation to 150°C for 50 minutes. The reaction mixture was partitioned between DCM and water. The organic layer was dried (phase separation cartridge) and concentrated *in vacuo*. The resulting residue was purified by column chromatography (SiO_2, 40% EtOAc in isohexane) to give the *title compound* (1.0 g, 86%)

as a yellow solid. δ_H ($CDCl_3$) 8.39 (1H, s), 8.06 (1H, s), 7.96 (1H, s), 7.51 (1H, d, *J* 8.06 Hz), 7.46 (1H, d, *J* 7.05 Hz), 7.25 (1H, t, *J* 7.54 Hz), 6.22 (1H, br s), 6.22-6.06 (1H, m), 5.99-5.77 (1H, m), 5.61 (2H, s), 5.42 (1H, dd, *J* 17.20, 2.03 Hz), 5.24 (1H, dd, *J* 10.20, 1.90 Hz), 4.35 (1H, dd, *J* 15.53, 5.49 Hz), 3.91 (1H, dd, *J* 15.48, 6.01 Hz), 3.72-3.61 (2H, m), 3.09 (3H, s), 2.76 (3H, s), 1.66 (3H, d, *J* 6.64 Hz), 1.64-1.56 (1H, m), 1.50-1.34 (1H, m), 0.00 (9H, s).

INTERMEDIATE 9

N-(3-Fluoro-2-methylphenyl)acetamide

To a solution of 3-fluoro-2-methylaniline (6.00 g, 48 mmol) in dry DCM (100 mL) under nitrogen was added acetic anhydride (7.6 g, 75 mmol). The reaction mixture was stirred at r.t. for 18 h then washed with water (2 x 50 mL) and NaOH solution (1M, 2 x 50 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the *title compound* (8.0 g, 100%) as a white solid. δ_H ($CDCl_3$) 7.56 (1H, s), 7.16 (1H, q, *J* 7.6 Hz), 6.99 (1H, br s), 6.87 (1H, t, *J* 8.4 Hz), 2.27 (3H, s), 2.16 (3H, s).

INTERMEDIATE 10

2-Chloro-7-fluoro-8-methylquinoline-3-carbaldehyde

To dry DMF (12 mL) at 0°C was added $POCl_3$ (48 mL) over 30 minutes. The reaction mixture was warmed to r.t. and *Intermediate 9* (8.0 g, 48 mmol) was added portionwise. After being heated to 85°C for 18 h, the reaction mixture was cooled to r.t. and poured dropwise into ice/water (500 mL). The resulting precipitate was filtered, washed with water (500 mL) and dried to give the *title compound* (7.2 g, 67%) as a white solid. δ_H ($CDCl_3$) 10.56 (1H, s), 8.71 (1H, s), 7.82 (1H, q, *J* 7.6 Hz), 7.42 (1H, t, *J* 7.6 Hz), 2.67 (3H, s).

INTERMEDIATE 11

(*E*)-*N*-[(2-Chloro-7-fluoroquinolin-3-yl)methylidene]-(*R*)-2-methylpropane-2-sulfinamide

To a solution of 2-chloro-7-fluoroquinoline-3-carboxaldehyde (6.3 g, 30 mmol) in dry THF (200 mL) under nitrogen was added titanium isopropoxide (17.0 g, 60 mmol)

and the reaction mixture stirred at r.t. for 10 minutes. (*R*)-2-Methyl-2-propanesulfinamide (3.6 g, 30 mmol) was added to the reaction mixture which was stirred at r.t. for 72 h and partitioned between water (20 mL) and DCM (150 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the *title compound* (7.2 g, 76%) as a pale yellow solid. δ_H ($CDCl_3$) 9.09(1H, s), 8.83 (1H, s), 7.96 (1H, dd, *J* 6.0 Hz,), 7.69 (1H, d, *J* 7.2 Hz), 7.42 (1H, t, *J* 8.4 Hz), 1.32 (9H, s).

INTERMEDIATE 12

(*E*)-*N*-[(2-Chloro-7-fluoro-8-methylquinolin-3-yl)methylidene]-(*R*)-2-methylpropane-2-sulfinamide

Similarly, *Intermediate 10* (6.6 g, 29.5 mmol), titanium isopropoxide (17 g, 60 mmol), (*R*)-2-methyl-2-propanesulfinamide (3.6 g, 29.5 mmol) and THF (200 mL) gave the *title compound* (8.3 g, 86.4%) as a yellow solid. δ_H ($CDCl_3$) 9.12 (1H, s), 8.73 (1H, s), 7.71 (1H, dd, *J* 6.0 Hz), 7.40 (1H, t, *J* 8.2 Hz), 2.69 (3H, s), 1.32 (9H, s).

INTERMEDIATE 13

N-[(*S*)-1-(2-Chloro-7-fluoroquinolin-3-yl)ethyl]-(*R*)-2-methylpropane-2-sulfinamide

To a solution of *Intermediate 11* (7.2 g, 23.5 mmol) in dry DCM (40 mL) under nitrogen was added dropwise over 10 minutes at -78°C a solution of methylmagnesium bromide (16.0 mL, 48 mmol; 3.0M in Et_2O). After warming to r.t., the reaction mixture was stirred for 18 h and partitioned between a saturated solution of NH_4Cl (50 mL) and DCM (100 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow oil which was crystallised from 40-60 petroleum ether to give the *title compound* (4.0 g, 53%) as a pale yellow solid. δ_H ($CDCl_3$) 8.23 (1H, s), 7.16 (1H, dd, *J* 6.0 Hz), 7.65 (1H, d, *J* 7.2 Hz), 7.46 (1H, t, *J* 8.4 Hz), 5.16 (1H, q, *J* 6.8 Hz), 3.45 (1H, br s), 1.71 (3H, d, *J* 6.8 Hz), 1.26 (9H, s).

INTERMEDIATE 14

N-[(*S*)-1-(2-Chloro-7-fluoro-8-methylquinolin-3-yl)ethyl]-(*R*)-2-methylpropane-2-sulfinamide

Similarly, *Intermediate 12* (8.3 g, 25.4 mmol), methylmagnesium bromide (16.0 mL, 48 mmol; 3.0M in Et_2O), and DCM (100 mL) gave the *title compound* (4.2 g, 48%) as a yellow solid. δ_H ($CDCl_3$) 8.17 (1H, s), 7.63 (1H, dd, *J* 6.0 Hz), 7.32 (1H, t, *J* 8.8 Hz), 5.16 (1H, q, *J* 6.8 Hz), 3.45 (1H, d, *J* 6.8 Hz), 2.66 (3H, s) 1.70 (3H, d, *J* 6.8 Hz), 1.26 (9H, s).

INTERMEDIATE 15

(*S*)-*tert*-Butyl 1-(2-chloro-7-fluoroquinolin-3-yl)ethylcarbamate

To a solution of *Intermediate 13* (4.0 g, 12.17 mmol) in MeOH (20 mL) was added conc. HCl (1 mL) and the mixture stirred at r.t. for 2 h. The reaction mixture was partitioned between DCM (100 mL) and 2M NaOH solution (50 mL). The organic layer was dried ($MgSO_4$) and filtered. To this filtrate was added DIPEA (3.0 mL, 15.0 mmol) followed by a solution of di-*tert*-butyl dicarbonate (3.0 g, 13.76 mmol) in DCM (10 mL) dropwise. The reaction mixture was stirred at r.t. for 3 h, then diluted with DCM (10 mL) and washed with saturated $NaHCO_3$ solution (15 mL) and brine (15 mL). The organic layer was dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (SiO_2, 0-30% EtOAc in 40-60 petroleum ether) to give the *title compound* (3.4 g, 86%) as a white solid. δ_H ($CDCl_3$) 8.23 (1H, s), 7.16 (1H, dd, *J* 6.0 Hz), 7.65 (1H, d, *J* 7.2 Hz), 7.46 (1H, t, *J* 8.4 Hz), 5.18 (1H, br q, *J* 6.8 Hz), 3.49 (1H, d, *J* 6.8 Hz), 1.54 (3H, d, *J* 6.8 Hz), 1.48 (9H, s).

INTERMEDIATE 16

(*S*)-*tert*-Butyl 1-(2-chloro-7-fluoro-8-methylquinolin-3-yl)ethylcarbamate

Similarly, *Intermediate 14* (4.2 g, 12.2 mmol), conc. HCl (1 mL), di-*tert*-butyl dicarbonate (2.7 g, 12.2 mmol) and DIPEA (1.6 g, 12.2 mmol) gave the *title compound* (4.38 g, 90%) as a yellow solid. δ_H ($CDCl_3$) 8.07 (1H, s), 7.62 (1H, dd, *J* 6.0 Hz), 7.30

(1H, t, *J* 8.8 Hz), 5.17 (1H, m), 5.07 (1H, br s), 2.65(3H, s) 1.54 (3H, d, *J* 6.4 Hz), 1.42 (9H, s).

INTERMEDIATE 17

(*S*)-3-(1-Aminoethyl)-7-fluoro-*N*-(2-methoxyethyl)quinolin-2-amine hydrochloric acid salt

To a solution of *Intermediate 15* (0.28 g, 0.86 mmol) in *n*-butanol (2 mL) was added 2-methoxyethylamine (75 mg, 1.0 mmol) and DIPEA (0.42 mL, 2.33 mmol). The reaction mixture was heated at 110°C for 18 h and then concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, 0-3% MeOH in DCM) to give a pale orange oil (97 mg, 55%). To a solution of this oil in MeOH (2 mL) was added HCl (1.0 mL, 4.0M solution in 1,4-dioxane). The reaction mixture was stirred for 2 h and concentrated *in vacuo* to give the *title compound* (200 mg, 60%) as a beige solid. δ_H ($CDCl_3$) 7.67 (1H, s), 7.52 (1H, dd, *J* 6.8 Hz), 7.29 (1H, d, *J* 8.8 Hz), 6.90 (1H, t, *J* 6.8 Hz), 6.10 (1H, br s), 4.92 (1H, br s), 4.56 (1H, br d), 3.83 (1H, m, 1H), 3.73 (1H, m), 3.63 (2H, m), 3.45 (3H, s), 1.60 (3H, d, *J* 6.8 Hz).

INTERMEDIATE 18

(*S*)-3-(1-Aminoethyl)-7-fluoro-*N*-(3-methoxypropyl)quinolin-2-amine hydrochloric acid salt

Similarly, *Intermediate 15* (0.28 g, 0.86 mmol), 3-methoxypropylamine (80 mg, 1.0 mmol) and DIPEA (0.42 mL, 2.33 mmol) gave the *title compound* (140 mg, 50%) as a beige solid. δ_H ($CDCl_3$) 7.65 (1H, s), 7.49 (1H, dd, *J* 6.8 Hz), 7.65 (1H, d, *J* 8.8 Hz), 6.93 (1H, t, *J* 6.8 Hz), 6.10 (1H, br s), 4.88 (1H, br s), 4.56 (1H, br d), 3.63 (2H, m), 3.55 (2H, t, *J* 6.8 Hz), 3.38 (3H, s), 1.98 (2H, m), 1.60 (3H, d, *J* 6.8 Hz).

INTERMEDIATE 19

(*S*)-3-(1-Aminoethyl)-*N*,*N*-diethyl-7-fluoro-8-methylquinolin-2-amine hydrochloric acid salt

Similarly, *Intermediate 16* (0.28 g, 0.83 mmol), diethylamine (80 mg, 1.1 mmol) and DIPEA (0.42 mL, 2.33 mmol) gave the *title compound* (150 mg, 48%) as a beige solid. δ_H ($CDCl_3$) 7.88 (1H, s), 7.48 (1H, dd, *J* 6.8 Hz), 7.09 (1H, t, *J* 8.8 Hz), 5.10 (2H, br s), 3.46 (4H, q, *J* 6.8 Hz), 3.31 (1H, br s), 2.58 (3H, s), 1.41 (3H, d, *J* 6.8 Hz), 1.19 (6H, t, *J* 6.8 Hz).

INTERMEDIATE 20

(*R*,*E*)-*N*-[(2,8-Dichloroquinolin-3-yl)methylidene]-2-methylpropane-2-sulfinamide

To a solution of 2,8-dichloroquinoline-3-carboxaldehyde (43.0 g, 0.19 mol) in anhydrous THF (500 mL) was added titanium isopropoxide (114 mL, 0.38 mol) at r.t. After 15 minutes, (*R*)-2-methyl-2-propanesulfinamide (23.0 g, 0.19 mol) was added and stirring was continued for 17 h at r.t. Water (1 L) was added to the reaction mixture and the precipitate obtained was filtered and washed with DCM. The organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to give the *title compound* (61 g, 97%) as a pale yellow solid. δ_H ($CDCl_3$) 9.11 (1H, s), 8.83 (1H, s), 7.93 (1H, dd, *J* 7.54, 1.31 Hz), 7.88 (1H, dd, *J* 8.22, 1.31 Hz), 7.55 (1H, t, *J* 7.88 Hz), 1.33 (9H, s).

INTERMEDIATE 21

(*R*)-*N*-[(*S*)-1-(2,8-Dichloroquinolin-3-yl)ethyl]-2-methylpropane-2-sulfinamide

To a solution of *Intermediate 20* (61 g, 0.18 mol) was added dropwise methyl-magnesium bromide (123.5 mL, 0.37 mol; 3M in Et_2O) over 50 minutes in DCM (1.5 L) at -70°C under nitrogen. The reaction mixture was allowed to reach r.t. with stirring overnight. The mixture was cooled in ice-salt as saturated aqueous NH_4Cl (500 mL) was slowly added with stirring. The aqueous layer was extracted with DCM (2 x 500 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was triturated with Et_2O and the solid filtered, washed with Et_2O and dried under reduced pressure to give the *title compound* (32 g, 50%) as a pale pink solid. δ_H ($CDCl_3$)

8.26 (1H, s), 7.83 (1H, dd, *J* 7.52, 1.32 Hz), 7.74 (1H, dd, *J* 8.19, 1.32 Hz), 7.49 (1H, t, *J* 7.86 Hz), 5.16-5.07 (1H, m), 3.47 (1H, d, *J* 4.63 Hz), 1.71 (3H, d, *J* 6.75 Hz), 1.25 (9H, s).

INTERMEDIATE 22

(*S*)-1-(2,8-Dichloroquinolin-3-yl)ethanamine

To a solution of *Intermediate 21* (37.7 g, 0.11 mol) in MeOH (370 mL) was added 4N hydrogen chloride in 1,4-dioxane (58 mL) at r.t. The reaction mixture was stirred for 2 h and concentrated *in vacuo*. The residue was partitioned between 5N hydrochloric acid (300 mL) and DCM (300 mL). The organic layer was extracted with 5N hydrochloric acid (100 mL) and the combined aqueous layers basified with aqueous NaOH and extracted with DCM (3 x 500 mL) and chloroform (3 x 500 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to afford the *title compound* (23.7 g, 90%) as an amber oil. δ_H ($CDCl_3$) 8.40 (1H, s), 7.80 (1H, dd, *J* 7.51, 1.33 Hz), 7.75 (1H, dd, *J* 8.19, 1.33 Hz), 7.46 (1H, t, *J* 7.86 Hz), 4.67 (1H, q, *J* 6.52 Hz), 1.50 (3H, d, *J* 6.53 Hz).

INTERMEDIATE 23

(*S*)-*tert*-Butyl 1-(2,8-dichloroquinolin-3-yl)ethylcarbamate

To a stirred solution of *Intermediate 22* (23.7 g, 98 mmol) and DIPEA (51 mL, 0.3 mol) in DCM (1 L) was added di-*tert*-butyl dicarbonate (25.7 g, 118 mmol). The reaction mixture was allowed to stand at r.t. overnight and concentrated *in vacuo*. The residue was triturated with 40-60 petroleum ether, filtered, washed with 40-60 petroleum ether and dried under reduced pressure to give the *title compound* (28.4 g, 85%) as a colourless solid. δ_H ($CDCl_3$) 8.13 (1H, s), 7.80 (1H, dd, *J* 7.51, 1.32 Hz), 7.72 (1H, dd, *J* 8.18, 1.31 Hz), 7.46 (1H, t, *J* 7.85 Hz), 5.23-5.16 (1H, m), 5.10 (1H, br s), 1.55 (3H, br d, *J* 7.18 Hz), 1.42 (9H, br s).

INTERMEDIATE 24

(*S*)-*tert*-Butyl 1-[2-(1-acetylpiperidin-4-ylamino)-8-chloroquinolin-3-yl]ethylcarbamate

A mixture of *Intermediate 23* (0.34 g, 1 mmol), 1-(4-aminopiperidin-1-yl)-ethanone (0.25 g, 1.76 mmol) and DIPEA (0.84 mL, 5 mmol) in NMP (10 mL) was heated at 140°C for 18 h. After cooling, the reaction mixture was partitioned between Et_2O (200 mL) and water (100 mL). The organic layer was washed with water (3 x 100 mL), brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, 0-100% EtOAc in isohexane) to give the *title compound* (0.1 g, 22%) as a pale orange gum. δ_H ($CDCl_3$) 7.70 (1H, s), 7.62 (1H, dd, *J* 7.56, 1.40 Hz), 7.47 (1H, dd, *J* 7.93, 1.39 Hz), 7.08 (1H, t, *J* 7.74 Hz), 6.39 (1H, br s), 4.97-4.87 (1H, m), 4.59 (1H, br d, *J* 9.95 Hz), 4.50-4.42 (2H, m), 3.85-3.78 (1H, m), 3.37-3.27 (1H, m), 3.08-2.96 (1H, m), 2.40-2.25 (1H, m), 2.23-2.13 (1H, m), 2.12 (3H, d, *J* 3.80 Hz), 1.67-1.62 (3H, m), 1.60-1.47 (2H, m), 1.44 (9H, s).

INTERMEDIATE 25

(*S*)-1-{4-[3-(1-Aminoethyl)-8-chloroquinolin-2-ylamino]piperidin-1-yl}ethanone

To a solution of *Intermediate 24* (0.1 g, 0.22 mmol) in DCM (5 mL) was added TFA (2 mL). After 2 h at r.t. the mixture was concentrated *in vacuo* and the residue was dissolved in DCM and applied to a 2g SCX column. The column was washed with DCM, then 50% DCM in MeOH, then MeOH, then eluted with 1M ammonia in MeOH to give the *title compound* (62 mg, 85%) as a pale orange gum. δ_H ($CDCl_3$) 8.03 (1H, s), 7.59 (1H, dd, *J* 7.56, 1.45 Hz), 7.55 (1H, s), 7.44 (1H, dd, *J* 7.90, 1.41 Hz), 7.06 (1H, t, *J* 7.73 Hz), 4.45 (1H, br s), 4.37-4.24 (2H, m), 3.83-3.71 (1H, m), 3.41-3.31 (1H, m), 3.20-3.09 (1H, m), 2.41-2.30 (1H, m), 2.34-1.99 (1H, m), 2.13 (3H, s), 1.64-1.52 (4H, m), 1.50 (3H, d, *J* 6.59 Hz).

INTERMEDIATE 26

(*S*)-*tert*-Butyl 1-[8-chloro-2-(diethylamino)quinolin-3-yl]ethylcarbamate

A mixture of *Intermediate 23* (200 mg, 0.59 mmol), diethylamine (0.3 mL, 2.92 mmol) and DIPEA (0.52 mL, 2.92 mmol) in NMP (3 mL) was heated at 140°C overnight.

The reaction mixture was cooled and partitioned between water (10 mL) and EtOAc/Et_2O (100 mL). The organic layer was washed with water (2 x 10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, 5-10% EtOAc in 40-60 petroleum ether) to give the *title compound* (122 mg, 55%) as a yellow oil. δ_H ($CDCl_3$) 7.92 (1H, s), 7.66 (1H, dd, *J* 7.54, 1.39 Hz), 7.58 (1H, dd, *J* 8.01, 1.39 Hz), 7.23 (1H, t, *J* 7.78 Hz), 5.10 (1H, br s), 4.94 (1H, br s), 3.58-3.45 (2H, m), 3.37 (2H, br s), 1.47-1.36 (12H, m), 1.24 (6H, t, *J* 6.99 Hz).

INTERMEDIATE 27

(*S*)-*tert*-Butyl 1-[8-chloro-2-(2-methoxyethylamino)quinolin-3-yl]ethylcarbamate

Similarly, *Intermediate 23* (120 mg, 0.35 mmol), 2-methoxyethylamine (132 mg, 1.75 mmol) and DIPEA (0.3 mL, 1.75 mmol) in NMP (3 mL) gave the *title compound* (69 mg, 52%) as a pale yellow solid. δ_H ($CDCl_3$) 7.70 (1H, s), 7.62 (1H, dd, *J* 7.54, 1.42 Hz), 7.47 (1H, dd, *J* 7.91, 1.42 Hz), 7.08 (1H, t, *J* 7.73 Hz), 6.31 (1H, br s), 4.93 (1H, br s), 4.56 (1H, br d, *J* 9.31 Hz), 3.97-3.90 (1H, m), 3.86-3.78 (1H, m), 3.75-3.69 (2H, m), 3.43 (3H, s), 1.62 (3H, d, *J* 6.76 Hz), 1.45 (9H, s).

INTERMEDIATE 28

(*S*)-*tert*-Butyl 1-{8-chloro-2-[*N*-(2-methoxyethyl)-*N*-methylamino]quinolin-3-yl}ethyl carbamate

Similarly, *Intermediate 23* (120 mg, 0.35 mmol), *N*-(2-methoxyethyl)methylamine (156 mg, 1.75 mmol) and DIPEA (0.3 mL, 1.75 mmol) in NMP (3 mL) gave the *title compound* (115 mg, 83%) as a pale yellow solid. δ_H ($CDCl_3$) 7.95 (1H, s), 7.67 (1H, dd, *J* 7.47, 1.37 Hz), 7.58 (1H, dd, *J* 8.02, 1.35 Hz), 7.26-7.20 (1H, m), 5.18 (1H, br s), 5.03 (1H, br s), 3.86-3.77 (1H, m), 3.73 (2H, t, *J* 5.62 Hz), 3.52 (1H, s), 3.37 (3H, s), 3.12 (3H, s), 1.46-1.39 (12H, m).

INTERMEDIATE 29

(*S*)-*tert*-Butyl 1-[8-chloro-2-(methylamino)quinolin-3-yl]ethylcarbamate

Similarly, *Intermediate 23* (180 mg, 0.53 mmol), methylamine oxalate salt (424 mg, 2.63 mmol) and DIPEA (0.47 mL, 2.63 mmol) in NMP (3 mL) gave the *title compound* (72 mg, 41%) as a yellow oil. δ_H ($CDCl_3$) 7.68 (1H, s), 7.62 (1H, dd, *J* 7.54, 1.43 Hz), 7.47 (1H, dd, *J* 7.91, 1.42 Hz), 7.08 (1H, t, *J* 7.73 Hz), 4.92 (1H, br s), 4.53 (1H, d, *J* 9.73 Hz), 3.19 (3H, d, *J* 4.63 Hz), 1.64 (3H, d, *J* 6.81 Hz), 1.45 (9H, s).

Alternative procedure: A mixture of *Intermediate 23* (700 mg, 2.05 mmol) and 2N $MeNH_2$ in THF (4 mL) was heated at 70°C for 20 h. The reaction mixture was concentrated *in vacuo* onto silica gel and purified by column chromatography (SiO_2, 10-100% EtOAc in isohexane) to afford the *title compound* (649 mg, 94%) as a clear gum.

INTERMEDIATE 30

tert-Butyl (*S*)-1-(8-chloro-2-{[(*R*)-tetrahydrofur-2-ylmethyl]amino}quinolin-3-yl)ethyl-carbamate

Similarly, *Intermediate 23* (150 mg, 0.44 mmol), (*R*)-tetrahydrofurfurylamine (0.23 mL, 2.19 mmol) and DIPEA (0.39 mL, 2.19 mmol) in NMP (3 mL) gave the *title compound* (100 mg, 62%) as a yellow solid. δ_H ($CDCl_3$) 7.70 (1H, s), 7.61 (1H, dd, *J* 7.54, 1.40 Hz), 7.47 (1H, dd, *J* 7.92, 1.42 Hz), 7.08 (1H, t, *J* 7.75 Hz), 6.20 (1H, br s), 4.92 (1H, br s), 4.57 (1H, d, *J* 9.17 Hz), 4.32-4.24 (1H, m), 4.04-3.89 (2H, m), 3.83-3.75 (1H, m), 3.61-3.53 (1H, m), 2.11-2.02 (1H, m), 2.01-1.85 (2H, m), 1.80-1.70 (1H, m), 1.61 (3H, d, *J* 6.78 Hz), 1.45 (9H, s).

INTERMEDIATE 31

tert-Butyl (*S*)-1-(8-chloro-2-{[(*S*)-tetrahydrofur-2-ylmethyl]amino}quinolin-3-yl)ethyl-carbamate

Similarly, *Intermediate 23* (150 mg, 0.44 mmol), (*S*)-tetrahydrofurfurylamine (0.23 mL, 2.19 mmol) and DIPEA (0.39 mL, 2.19 mmol) in NMP (3 mL) gave the *title compound* (81 mg, 45%) as a yellow oil. δ_H ($CDCl_3$) 7.69 (1H, s), 7.61 (1H, dd, *J* 7.55, 1.40 Hz), 7.46 (1H, dd, *J* 7.91, 1.44 Hz), 7.11-7.04 (1H, m), 6.20 (1H, br s), 4.92 (1H, br

s), 4.58 (1H, d, *J* 9.09 Hz), 4.31-4.21 (1H, m), 3.99-3.91 (1H, m), 3.82-3.75 (3H, m), 2.09-1.85 (3H, m), 1.80-1.71 (1H, m), 1.64-1.56 (3H, m), 1.45 (9H, s).

INTERMEDIATE 32

(*S*)-3-(1-Aminoethyl)-8-chloro-*N*-(2-methoxyethyl)quinolin-2-amine bis hydrochloric acid salt

A solution of *Intermediate 27* (65 mg, 0.17 mmol) and hydrogen chloride (0.86 mL, 3.42 mmol; 4.0M in 1,4-dioxane) in 1,4-dioxane (5 mL) was stirred at r.t. overnight. The reaction mixture was concentrated *in vacuo* and purified by triturating in Et_2O to give the *title compound* (55 mg, 91%) as an off-white solid. δ_H (MeOD-d_4) 8.61 (1H, s), 8.06-7.98 (2H, m), 7.66-7.59 (1H, m), 3.99-3.89 (4H, m), 3.61 (3H, s), 1.79 (3H, d, *J* 6.73 Hz), 1H under H_2O.

INTERMEDIATE 33

(*S*)-3-(1-Aminoethyl)-8-chloro-*N*-(2-methoxyethyl)-*N*-methylquinolin-2-amine bis hydrochloric acid salt

Similarly, *Intermediate 28* (110 mg, 0.28 mmol) and hydrogen chloride (1.4 mL, 5.58 mmol; 4.0M in 1,4-dioxane) in 1,4-dioxane (5 mL) gave the *title compound* (97 mg, 95%) as a yellow solid. δ_H (MeOD-d_4) 8.82 (1H, s), 8.06-8.01 (2H, m), 7.65 (1H, t, *J* 7.93 Hz), 5.07 (1H, q, *J* 6.79 Hz), 4.03-3.82 (4H, m), 3.62 (3H, s), 3.41 (3H, s), 1.88 (3H, d, *J* 6.78 Hz).

INTERMEDIATE 34

(*S*)-3-(1-Aminoethyl)-8-chloro-*N*-methylquinolin-2-amine bis hydrochloric acid salt

Similarly, *Intermediate 29* (70 mg, 0.21 mmol) and hydrogen chloride (1.0 mL, 4.17 mmol; 4.0M in 1,4-dioxane) in 1,4-dioxane (5 mL) gave the *title compound* (56 mg, 87%) as a cream solid. δ_H (MeOD-d_4) 8.51 (1H, s), 7.99 (1H, dd, *J* 7.87, 1.24 Hz), 7.96 (1H, dd, *J* 8.01, 1.26 Hz), 7.58 (1H, t, *J* 7.93 Hz), 3.40 (3H, s), 1.77 (3H, d, *J* 6.73 Hz), 1H under H_2O.

INTERMEDIATE 35

3-[(*S*)-1-Aminoethyl]-8-chloro-*N*-{[(*R*)-tetrahydrofur-2-yl]methyl}quinolin-2-amine bis hydrochloric acid salt

Similarly, *Intermediate 30* (105 mg, 0.26 mmol) and hydrogen chloride (1.3 mL, 5.17 mmol; 4.0M in 1,4-dioxane) in 1,4-dioxane (5 mL) gave the *title compound* (90 mg, 92%) as an off-white solid. δ_H (MeOD-d_4) 8.68 (1H, s), 8.02 (2H, d, *J* 7.88 Hz), 7.63 (1H, t, *J* 7.88 Hz), 5.03-4.97 (1H, m), 4.41-4.33 (1H, m), 4.22-4.11 (1H, m), 4.11-3.94 (2H, m), 3.83 (1H, dd, *J* 15.30, 6.61 Hz), 2.28-2.19 (1H, m), 2.12-2.05 (2H, m), 1.96-1.82 (1H, m), 1.81 (3H, d, *J* 6.52 Hz).

INTERMEDIATE 36

(*S*)-1-(2-Chloro-8-methylquinolin-3-yl)ethylamine

To a solution of *Intermediate 4* (0.25 g, 0.77 mmol) in MeOH (2 mL) was added conc. HCl (1 mL) and the mixture was stirred at r.t. for 2 h. The reaction was poured into DCM (100 mL) and washed with 2M NaOH solution (50 mL). The organic layer was separated, dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to afford the *title compound* (0.16 g, 94%) as a white solid. δ_H ($CDCl_3$) 8.29 (s, 1H), 7.66 (d, *J* 8.4 Hz, 1H), 7.53 (d, *J* 6.8 Hz, 1H), 7.41-7.45 (m, 1H), 4.61-4.67 (m, 1H), 2.76 (s, 3H), 1.50 (d, *J* 4.0 Hz, 3H). LCMS (ES+) 221, 223 $(M+H)^+$.

INTERMEDIATE 37

[(*S*)-1-(2-Chloro-8-methylquinolin-3-yl)ethyl]carbamic acid *tert*-butyl ester

To a solution of *Intermediate 36* (1.83 g, 3.11 mmol) in dry DCM (10 mL) under nitrogen was added DIPEA (2.7 mL, 15.6 mmol) followed by a solution of di-*tert*-butyl dicarbonate in DCM (10 mL) dropwise. The reaction mixture was stirred at r.t. for 3 h, then diluted with DCM (10 mL) and washed with saturated $NaHCO_3$ solution (15 mL) and brine (15 mL). The organic layer was separated, dried (Na_2SO_4), filtered and the solvent removed *in vacuo*. Purification by column chromatography (SiO_2, 0-30% EtOAc in 40-60 petroleum ether) afforded the *title compound* (897 mg, 34%) as a white solid. δ_H ($CDCl_3$) 8.07 (s, 1H), 7.64 (d, *J* 8.0 Hz, 1H), 7.54 (d, *J* 7.2 Hz, 1H), 7.43 (t, *J* 7.6 Hz, 1H),

5.12-5.22 (m, 1H), 5.00-5.10 (m, 1H), 2.76 (s, 3H), 1.50-1.57 (m, 3H), 1.30-1.50 (m, 9H). LCMS (ES+) 321, 323 $(M+H)^+$.

INTERMEDIATE 38

(*S*)-3-(1-Aminoethyl)-8-chloro-*N*-methylquinolin-2-amine hydrochloride

A solution of *Intermediate 29* (649 mg, 1.93 mmol) and HCl (4 mL, 2.0M in Et_2O) in MeOH (5 mL) was stirred at r.t. overnight. The reaction mixture was concentrated *in vacuo* to afford the *title compound* (535 mg, 99%) as a white solid. δ_H (MeOD-d_4) as for *Intermediate 34*.

INTERMEDIATE 39

(*S*)-2-[3-(1-Aminoethyl)-8-chloroquinolin-2-ylamino]ethanol hydrochloride

A solution of *Intermediate 23* (700 mg, 2.05 mmol) and ethanolamine (1 mL) in *n*-butanol (5 mL) was heated at 120°C for 20 h. The reaction mixture was concentrated *in vacuo* onto silica gel and purified by column chromatography (SiO_2, 10-100% EtOAc in isohexane) to afford the required intermediate (711 mg, 95%). LCMS (ES+) 368 $(M+H)^+$. A solution of this material (711 mg, 1.94 mmol) and HCl (5 mL, 2.0M in Et_2O) in MeOH (5 mL) was stirred at r.t. overnight. The reaction mixture was concentrated *in vacuo* to afford the *title compound* (619 mg, 99%) as a white solid. δ_H (DMSO-d_6) 8.60 (3H, s), 8.21 (1H, s), 7.75 (1H, d, *J* 7.57 Hz), 7.68 (1H, d, *J* 7.92 Hz), 7.25 (1H, t, *J* 7.76 Hz), 4.78 (1H, t, *J* 6.77 Hz), 3.79-3.61 (4H, m), 1.59 (3H, d, *J* 6.54 Hz), 1H under water peak. LCMS (ES+) 268 $(M+H)^+$.

INTERMEDIATE 40

(*S*)-1-[3-(1-Aminoethyl)-8-chloroquinolin-2-ylamino]-2-methylpropan-2-ol hydrochloride

Similarly, *Intermediate 23* (700 mg, 2.05 mmol), 1-amino-2-methylpropan-2-ol (300 mg, 3.37 mmol) and DIPEA (2 mL) in *n*-butanol (10 mL) afforded a white solid (614 mg, 76%). This solid was dissolved in MeOH (8 mL) and treated with a solution of HCl (10 mL, 2N in Et_2O). The reaction mixture was stirred at r.t. overnight. The solvent

was evaporated *in vacuo* to give the *title compound* (573 mg, 99%) as a white solid. LCMS (ES+) 296 $(M+H)^+$.

INTERMEDIATE 41

(*S*)-1-{[3-(1-Aminoethyl)-8-chloroquinolin-2-ylamino]methyl}cyclopropanol hydrochloride

Similarly, *Intermediate 23* (480 mg, 1.40 mmol), 1-(aminomethyl)cyclopropanol (200 mg, 2.30 mmol) and DIPEA (2 mL) in *n*-butanol (8 mL) afforded an off-white solid (280 mg, 52%). This solid was dissolved in MeOH (5 mL) and treated with a solution of HCl (8 mL, 2N in Et_2O). The reaction mixture was stirred at r.t. overnight. The solvent was evaporated *in vacuo* to give the *title compound* (270 mg, 99%) as a tan glass. LCMS (ES+) 294 $(M+H)^+$.

INTERMEDIATE 42

(*S*)-1-{3-[3-(1-Aminoethyl)-8-chloroquinolin-2-ylamino]propyl}pyrrolidin-2-one hydrochloride

Similarly, *Intermediate 23* (150 mg, 0.44 mmol) and 1-(3-aminopropyl)pyrrolidin-2-one (1 mL) in *n*-butanol (5 mL) afforded the required intermediate. This was dissolved in MeOH (3 mL) and treated with a solution of HCl (3 mL, 2N in Et_2O). The reaction mixture was stirred at r.t. overnight. The solvent was evaporated *in vacuo* to give the *title compound* (169 mg, 99%). LCMS (ES+) 349 $(M+H)^+$.

INTERMEDIATE 43

(*S*)-5-({3-[(*S*)-1-Aminoethyl]-8-chloroquinolin-2-ylamino}methyl)pyrrolidin-2-one

Similarly, *Intermediate 23* (700 mg, 2.05 mmol), (*S*)-5-(aminomethyl)pyrrolidin-2-one (500 mg, 4.38 mmol) and DIPEA (2 mL) in *n*-butanol (12 mL) afforded a white solid (524 mg, 61%). The solid was dissolved in DCM (8 mL) and treated with TFA (3 mL). The reaction mixture was stirred at r.t. for 2 h, poured into 15% NaOH solution (20 mL) and extracted with EtOAc (50 mL). The organic phase was separated, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the *title compound* (398 mg, 99%)

as a clear glass. δ_H (DMSO-d_6) 8.28 (1H, t, *J* 5.58 Hz), 7.91-7.83 (1H, m), 7.79 (1H, s), 7.68-7.61 (3H, m), 7.20-7.11 (1H, m), 4.26 (1H, q, *J* 6.56 Hz), 4.00-3.89 (1H, m), 3.71-3.58 (2H, m), 2.32-2.08 (3H, m), 1.94-1.83 (1H, m), 1.51 (1H, d, *J* 6.59 Hz), 1.40 (3H, d, *J* 6.48 Hz). LCMS (ES+) 319 $(M+H)^+$.

INTERMEDIATE 44

1-[(*S*)-3-({3-[(*S*)-1-Aminoethyl]-8-chloroquinolin-2-ylamino}methyl)pyrrolidin-1-yl]ethanone hydrochloride

Similarly, *Intermediate 23* (700 mg, 2.05 mmol), (*S*)-1-[3-(aminomethyl)-pyrrolidin-1-yl]ethanone (710 mg, 4.02 mmol) and DIPEA (3 mL) in *n*-butanol (12 mL) afforded a white solid (189 mg, 20%). This was dissolved in MeOH (5 mL) and treated with a solution of HCl (5 mL, 2.0M in Et_2O). The reaction mixture was stirred at r.t. overnight. The solvent was evaporated *in vacuo* to give the *title compound* (186 mg, 88%) as a tan glass. LCMS (ES+) 347 $(M+H)^+$.

INTERMEDIATE 45

(*S*)-3-(1-Aminoethyl)-8-chloroquinolin-2-amine hydrochloride

A solution of *Intermediate 23* (700 mg, 2.05 mmol) and sodium azide (195 mg, 3.0 mmol) in DMF (8 mL) was heated in a sealed tube at 120°C for 20 h. The reaction mixture was diluted with EtOAc (50 mL) and washed with water (4 x 20 mL). The organic layer was separated, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a tan solid (610 mg, 86%). LCMS (ES+) 370 $(M+H)^+$. Zn dust (440 mg, 6.68 mmol) was added to this intermediate (464 mg, 1.33 mmol) in acetic acid (20 mL) and the reaction mixture stirred at r.t for 20 h. The reaction mixture was filtered and washed with MeOH (50 mL) and the filtrate was concentrated *in vacuo* to afford a yellow solid (380 mg, 88%). This solid was dissolved in MeOH (5 mL) and treated with a solution of HCl (10 mL, 2.0M in Et_2O). The reaction mixture was stirred at r.t. overnight. The solvent was evaporated *in vacuo* to give the *title compound* (260 mg, 98%) as a green gum. LCMS (ES+) 222 $(M+H)^+$.

INTERMEDIATE 46

(*S*)-2-{*N'*-[3-(1-Aminoethyl)-8-chloroquinolin-2-yl]-*N'*-methylamino}-*N*-methyl-acetamide

Following the procedure described for *Intermediate 39*, *Intermediate 23* (700 mg, 2.05 mmol), *N*-methyl-2-(methylamino)acetamide (209 mg, 2.05 mmol) and DIPEA (1 mL) in *n*-butanol (10 mL) afforded a white solid (284 mg, 34%). LCMS (ES+) 407 $(M+H)^+$. This solid (280 mg, 0.19 mmol) was dissolved in DCM (8 mL) and treated with TFA (4 mL). The reaction mixture was stirred at r.t. for 2 h., poured onto 15% NaOH solution (30 mL) and extracted with EtOAc (50 mL). The organic phase was separated, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the *title compound* (205 mg, 97%) as a clear glass. δ_H ($CDCl_3$) 8.89 (1H, s), 8.22 (1H, s), 7.71-7.62 (2H, m), 7.31-7.24 (1H, m), 4.52 (1H, q, *J* 6.44 Hz), 4.33 (1H, d, *J* 15.25 Hz), 4.08 (1H, d, *J* 15.25 Hz), 3.14 (3H, s), 2.86 (3H, d, *J* 4.87 Hz), 1.50 (3H, d, *J* 6.45 Hz). LCMS (ES+) 307 $(M+H)^+$.

INTERMEDIATE 47

(*S*)-3-(1-Aminoethyl)-8-chloro-*N*-[2-(methylthio)ethyl]quinolin-2-amine hydrochloride

Similarly, *Intermediate 23* (150 mg, 0.44 mmol) and 2-(methylthio)ethanamine (1 mL) in *n*-butanol (12 mL) afforded the required intermediate (174 mg). This was dissolved in MeOH (3 mL) and treated with a solution of HCl (3 mL, 2N in Et_2O). The reaction mixture was stirred at r.t. overnight. The solvent was evaporated *in vacuo* to give the *title compound* (118 mg, 90%) as a yellow solid. LCMS (ES+) 269 $(M+H)^+$.

INTERMEDIATE 48

(*S*)-3-(1-Aminoethyl)-8-chloro-*N*-[(1-methyl-1*H*-imidazol-4-yl)methyl]quinolin-2-amine hydrochloride

Similarly, *Intermediate 23* (700 mg, 2.05 mmol), (1-methyl-1*H*-imidazol-4-yl)methanamine (500 mg, 4.50 mmol) and DIPEA (4 mL) in *n*-butanol (10 mL) afforded a clear gum (701 mg, 82%). LCMS (ES+) 416 $(M+H)^+$. This was dissolved in MeOH (10 mL) and treated with a solution of HCl (8 mL, 2N in Et_2O). The reaction mixture was

stirred at r.t. overnight. The solvent was evaporated *in vacuo* to give the *title compound* (707 mg, 99%) as a pink foam. LCMS (ES+) 316 $(M+H)^+$.

INTERMEDIATE 49

tert-Butyl (*S*)-1-{8-chloro-2-[(*R*)-2,3-dihydroxypropylamino]quinolin-3-yl}ethyl-carbamate

A mixture of *Intermediate 23* (150 mg, 0.44 mmol), (*R*)-3-amino-1,2-propanediol (200 mg, 2.19 mmol) and DIPEA (0.4 mL, 2.19 mmol) in NMP (3 mL) was heated at 100°C overnight. The reaction mixture was cooled and partitioned between water (30 mL) and EtOAc (100 mL). The organic layer was washed with water (5 x 20 mL), separated, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, 75-100% EtOAc in isohexane) to give the *title compound* (147 mg, 85%) as a white solid. δ_H ($CDCl_3$) 7.75 (1H, s), 7.64 (1H, dd, *J* 7.6, 1.2 Hz), 7.49 (1H, dd, *J* 8.0, 1.2 Hz), 7.13 (1H, t, *J* 7.8 Hz), 7.00-6.90 (1H, m), 5.26-5.20 (1H, m), 4.98-4.90 (1H, m), 4.41 (1H, d, *J* 10.0 Hz), 3.90-3.75 (3H, m), 3.61-3.56 (2H, m), 3.38-3.32 (1H, m), 1.67 (3H, d, *J* 6.8 Hz), 1.45 (9H, s).

INTERMEDIATE 50

tert-Butyl (*S*)-1-{8-chloro-2-[(*S*)-2,3-dihydroxypropylamino]quinolin-3-yl}ethyl-carbamate

Similarly, *Intermediate 23* (150 mg, 0.44 mmol), (*S*)-3-amino-1,2-propanediol (200 mg, 2.19 mmol) and DIPEA (0.4 mL, 2.19 mmol) in NMP (3 mL) at 140°C gave the *title compound* (147 mg, 85%) as a white solid. δ_H ($CDCl_3$) 7.75 (1H, s), 7.63 (1H, dd, *J* 7.6, 1.6 Hz), 7.49 (1H, dd, *J* 8.0, 1.2 Hz), 7.13 (1H, t, *J* 7.8 Hz), 7.00-6.90 (1H, m), 4.99-4.90 (2H, m), 4.61 (1H, d, *J* 10.0 Hz), 3.92-3.80 (3H, m), 3.62-3.50 (3H, m), 1.67 (3H, d, *J* 6.8 Hz), 1.45 (9H, s).

INTERMEDIATE 51

(*S*)-*tert*-Butyl 1-[7-fluoro-2-(2-methoxyethylamino)-8-methylquinolin-3-yl]ethyl-carbamate

Similarly, *Intermediate 16* (150 mg, 0.44 mmol), 2-methoxyethylamine (0.38 mL, 4.42 mmol) and DIPEA (0.3 mL, 1.75 mmol) in NMP (2 mL) at 120°C gave the *title compound* (143 mg, 86%) as a yellow solid. δ_H ($CDCl_3$) 7.66 (1H, s), 7.37 (1H, dd, *J* 8.8, 6.4 Hz), 6.94 (1H, t, *J* 9.0 Hz), 6.19-6.10 (1H, m), 4.96-4.87 (1H, m), 4.58-4.52 (1H, m), 3.90-3.65 (4H, m), 3.42 (3H, s), 2.53 (3H, d, *J* 2.0 Hz), 1.61 (3H, d, *J* 6.4 Hz), 1.46 (9H, s).

INTERMEDIATE 52

(*S*)-*tert*-Butyl 1-{8-chloro-2-[2-(methylamino)-2-oxoethylamino]quinolin-3-yl}ethyl-carbamate

Similarly, *Intermediate 23* (150 mg, 0.44 mmol), 2-amino-*N*-methylacetamide hydrochloride (164 mg, 1.32 mmol) and DIPEA (0.47 mL, 2.63 mmol) in NMP (2 mL) at 120°C for 4 days gave the *title compound* (62 mg, 36%) as an off-white solid. δ_H ($CDCl_3$) 7.90 (1H, br m), 7.77 (1H, s), 7.66 (1H, dd, *J* 7.6, 1.2 Hz), 7.52 (1H, dd *J* 8.0, 1.2 Hz), 7.16 (1H, br s), 7.00-6.90 (1H, m), 4.99-4.91 (1H, m), 4.61 (1H, d, *J* 9.2 Hz), 4.33 (1H, dd, *J* 14.8, 5.2 Hz), 4.16 (1H, dd, *J* 14.8, 5.2 Hz), 2.79 (3H, d, *J* 4.8 Hz), 1.65 (3H, d, *J* 6.8 Hz), 1.44 (9H, s).

INTERMEDIATE 53

(*S*)-*tert*-Butyl 1-[7-fluoro-2-(2-hydroxyethylamino)-8-methylquinolin-3-yl]ethyl-carbamate

Similarly, *Intermediate 16* (1.0 g, 2.95 mmol) and ethanolamine (1.8 mL, 29.5 mmol) in NMP (10 mL) at 120°C gave the *title compound* (0.92 g, 86%) as a white solid. δ_H ($CDCl_3$) 7.69 (1H, s), 7.37 (1H, dd, *J* 8.8, 6.4 Hz), 6.96 (1H, t, *J* 9.0 Hz), 6.85-6.75 (1H, m), 5.66-5.63 (1H, m), 4.98-4.90 (1H, m), 4.60-4.56 (1H, m), 3.95-3.85 (2H, m), 3.80-3.72 (2H, m), 2.51 (3H, d, *J* 2.0 Hz), 1.65 (3H, d, *J* 6.8 Hz), 1.45 (9H, s), 1H exchanging.

INTERMEDIATE 54

(*S*)-*tert*-Butyl 1-{8-chloro-2-[2-(dimethylamino)-2-oxoethylamino]quinolin-3-yl}ethylcarbamate

Similarly, *Intermediate 23* (200 mg, 0.59 mmol), 2-amino-*N,N*-dimethylacetamide (179 mg, 1.75 mmol) and DIPEA (0.63 mL, 3.51 mmol) in NMP (2 mL) at 120°C gave the *title compound* (127 mg, 53%) as an off-white solid. δ_H ($CDCl_3$) 7.75 (1H, s), 7.62 (1H, dd, *J* 7.6, 1.2 Hz), 7.50 (1H, dd, *J* 8.0, 1.2 Hz), 7.11 (1H, br s), 6.50-6.40 (1H, m), 5.00-4.90 (1H, m), 4.80-4.70 (1H, m), 4.52 (1H, dd, *J* 17.2, 4.4 Hz), 4.16 (1H, dd, *J* 17.2, 4.4 Hz), 3.16 (3H, s), 3.04 (3H, s), 1.59 (3H, d, *J* 5.6 Hz), 1.43 (9H, s).

INTERMEDIATE 55

(*S*)-*tert*-Butyl 1-[8-chloro-2-(pyridin-2-ylmethylamino)quinolin-3-yl]ethylcarbamate

Similarly, *Intermediate 23* (250 mg, 0.73 mmol), 2-(aminomethyl)pyridine (0.38 mL, 3.65 mmol) and DIPEA (1.3 mL, 7.31 mmol) in NMP (2 mL) at 120°C gave the *title compound* (255 mg, 84%) as a lemon-yellow solid. δ_H ($CDCl_3$) 8.56 (1H, d, *J* 4.4 Hz), 7.74 (1H, s), 7.63-7.61 (2H, m), 7.54 (1H, d, *J* 7.6 Hz), 7.49 (1H, d, *J* 8.0 Hz), 7.16-7.13 (1H, m), 7.09 (1H, t, *J* 7.8 Hz), 6.95-6.85 (1H, m), 5.09-4.93 (3H, m), 4.71 (1H, d, *J* 8.8 Hz), 1.64 (3H, d, *J* 6.8 Hz), 1.40 (9H, s).

INTERMEDIATE 56

(*S*)-*tert*-Butyl 1-[8-chloro-2-(pyridin-3-ylmethylamino)quinolin-3-yl]ethylcarbamate

Similarly, *Intermediate 23* (500 mg, 1.46 mmol), 3-(aminomethyl)pyridine (0.75 mL, 7.31 mmol) and DIPEA (2.6 mL, 14.6 mmol) in NMP (4 mL) at 120°C gave the *title compound* (424 mg, 70%) as an off-white solid. δ_H ($CDCl_3$) 8.78 (1H, d, *J* 2.0 Hz), 8.47 (1H, dd, *J* 4.8, 1.6 Hz), 7.98-7.95 (1H, m), 7.71 (1H, s), 7.62 (1H, dd, *J* 7.6, 1.2 Hz), 7.47 (1H, dd, *J* 8.0, 1.2 Hz), 7.23-7.20 (1H, m), 7.09 (1H, t, *J* 7.8 Hz), 7.00-6.90 (1H, m), 5.00-4.90 (1H, m), 4.90-4.78 (2H, m), 4.57 (1H, d, *J* 9.6 Hz), 1.65 (3H, d, *J* 6.8 Hz), 1.39 (9H, s).

INTERMEDIATE 57

(*S*)-2-({3-[1-(*tert*-Butoxycarbonylamino)ethyl]-8-chloroquinolin-2-ylamino}methyl)-pyridine 1-oxide

A mixture of *Intermediate 55* (150 mg, 0.36 mmol) and MCPBA (137 mg, 0.44 mmol, 55%) in DCM (20 mL) was stirred at r.t. for 4 h. The solvent was removed *in vacuo* and the residue purified by column chromatography (SiO_2, 0-5% MeOH in EtOAc) to give the *title compound* (100 mg, 64%) as a cream solid. δ_H ($CDCl_3$) 8.23 (1H, d, *J* 6.0 Hz), 7.86-7.76 (1H, m), 7.73 (1H, s), 7.60 (1H, d, *J* 7.6 Hz), 7.48 (1H, dd, *J* 7.6, 0.8 Hz), 7.21-7.08 (3H, m), 6.98-6.84 (1H, m), 5.15 (1H, dd, *J* 15.2, 5.6 Hz), 5.03 (1H, dd, *J* 15.2, 6.0 Hz), 5.00-4.91 (1H, m), 4.80-4.70 (1H, m), 1.61 (3H, s), 1.42 (9H, s).

INTERMEDIATE 58

(*R*)-3-{3-[(*S*)-1-Aminoethyl]-8-chloroquinolin-2-ylamino}propane-1,2-diol bis hydrochloric acid salt

A solution of *Intermediate 49* (140 mg, 0.35 mmol) and HCl (1.8 mL, 7.07 mmol; 4.0M in 1,4-dioxane) in dry 1,4-dioxane (10 mL) was stirred at r.t. overnight. The reaction mixture was concentrated *in vacuo* to give the *title compound* (130 mg, quantitative) as a pale pink solid. δ_H (MeOD-d_4) 8.57 (1H, s), 8.00-7.96 (2H, m), 7.60 (1H, t, *J* 8.0 Hz), 4.96-4.84 (1H, m), 4.16-4.10 (1H, m), 3.98-3.83 (2H, m), 3.75-3.61 (2H, m), 1.79 (3H, d, *J* 6.8 Hz).

INTERMEDIATE 59

(*S*)-3-{3-[(*S*)-1-Aminoethyl]-8-chloroquinolin-2-ylamino}propane-1,2-diol bis hydrochloric acid salt

Similarly, *Intermediate 50* (60 mg, 0.15 mmol) and HCl (0.4 mL, 1.52 mmol; 4.0M in 1,4-dioxane) in dry 1,4-dioxane (5 mL) gave the *title compound* (56 mg, quantitative) as a dark pink solid. δ_H (MeOD-d_4) 8.57 (1H, s), 7.98-7.95 (2H, m), 7.59 (1H, t, *J* 8.0 Hz), 4.92-4.82 (1H, m), 4.17-4.10 (1H, m), 3.94-3.82 (2H, m), 3.72-3.54 (4H, m), 1.76 (3H, d, *J* 6.4 Hz).

INTERMEDIATE 60

(*S*)-3-(1-Aminoethyl)-7-fluoro-*N*-(2-methoxyethyl)-8-methylquinolin-2-amine bis hydrochloric acid salt

Similarly, *Intermediate 51* (140 mg, 0.37 mmol) and HCl (0.93 mL, 3.71 mmol; 4.0M in 1,4-dioxane) in dry 1,4-dioxane (5 mL) gave the *title compound* (144 mg, quantitative) as a white solid. δ_H (MeOD-d_4) 8.59 (1H, s), 7.96 (1H, dd, *J* 8.8, 5.6 Hz), 7.46 (1H, t, *J* 9.0 Hz), 4.96-4.86 (1H, m), 4.03-3.94 (4H, m), 3.66 (3H, s), 2.61 (3H, d, *J* 1.6 Hz), 1.80 (3H, d, *J* 6.4 Hz).

INTERMEDIATE 61

(*S*)-2-[3-(1-Aminoethyl)-8-chloroquinolin-2-ylamino]-*N*-methylacetamide bis hydrochloric acid salt

Similarly, *Intermediate 52* (60 mg, 0.15 mmol) and HCl (0.38 mL, 1.53 mmol; 4.0M in 1,4-dioxane) in dry 1,4-dioxane (5 mL) gave the *title compound* (54 mg, quantitative) as a white solid. δ_H (MeOD-d_4) 8.42 (1H, s), 7.92-7.87 (2H, m), 7.47 (1H, t, *J* 7.8 Hz), 4.94-4.84 (1H, m), 4.43 (1H, d, *J* 15.2 Hz), 4.30 (1H, d, *J* 15.6 Hz), 2.88 (3H, s), 1.81 (3H, d, *J* 6.4 Hz).

INTERMEDIATE 62

(*S*)-2-[3-(1-Aminoethyl)-7-fluoro-8-methylquinolin-2-ylamino]ethanol bis hydrochloric acid salt

Similarly, *Intermediate 53* (900 mg, 2.48 mmol) and HCl (6.2 mL, 24.8 mmol; 4.0M in 1,4-dioxane) in dry 1,4-dioxane (24 mL) gave the *title compound* (0.85 g, quantitative) as a white solid. δ_H (MeOD-d_4) 8.56 (1H, s), 7.93 (1H, dd, *J* 8.8, 5.6 Hz), 7.42 (1H, t, *J* 9.0 Hz), 4.94-4.85 (1H, m), 4.08-4.05 (2H, m), 3.93-3.91 (2H, m), 2.56 (3H, d, *J* 1.6 Hz), 1.78 (3H, d, *J* 6.8 Hz).

INTERMEDIATE 63

(*S*)-2-[3-(1-Aminoethyl)-8-chloroquinolin-2-ylamino]-*N*,*N*-dimethylacetamide bis hydrochloric acid salt

Similarly, *Intermediate 54* (120 mg, 0.30 mmol) and HCl (0.74 mL, 2.95 mmol; 4.0M in 1,4-dioxane) in dry 1,4-dioxane (5 mL) gave the *title compound* (120 mg, quantitative) as a white solid. δ_H (MeOD-d_4) 8.46 (1H, s), 7.87 (1H, d, *J* 8.0 Hz), 7.85 (1H, d, *J* 8.0 Hz), 7.43 (1H, t, *J* 8.0 Hz), 4.94-4.86 (1H, m), 4.76 (1H, d, *J* 12.0 Hz), 4.42 (1H, d, *J* 16.0 Hz), 3.10 (3H, d, *J* 8.0 Hz), 1.82 (3H, d, *J* 8.0 Hz).

INTERMEDIATE 64

(*S*)-3-(1-Aminoethyl)-8-chloro-*N*-(pyridin-2-ylmethyl)quinolin-2-amine tris hydrochloric acid salt

Similarly, *Intermediate 55* (100 mg, 0.24 mmol) and HCl (1.2 mL, 4.84 mmol; 4.0M in 1,4-dioxane) in dry 1,4-dioxane (5 mL) gave the *title compound* (143 mg, quantitative) as an off-white solid. δ_H (MeOD-d_4) 8.78-8.74 (1H, m), 8.55 (1H, td, *J* 7.92, 1.58 Hz), 8.25-8.19 (2H, m), 7.97-7.91 (1H, m), 7.73 (1H, dd, *J* 8.04, 1.33 Hz), 7.66 (1H, dd, *J* 7.61, 1.33 Hz), 7.27 (1H, t, *J* 7.82 Hz), 5.08 (2H, s), 4.98 (1H, q, *J* 6.74 Hz), 1.82 (3H, d, *J* 6.75 Hz).

INTERMEDIATE 65

(*S*)-3-(1-Aminoethyl)-8-chloro-*N*-(pyridin-3-ylmethyl)quinolin-2-amine tris hydrochloric acid salt

Similarly, *Intermediate 56* (100 mg, 0.24 mmol) and HCl (1.2 mL, 4.84 mmol; 4.0M in 1,4-dioxane) in dry 1,4-dioxane (5 mL) gave the *title compound* (143 mg, quantitative) as an off-white solid. δ_H (MeOD-d_4) 9.24 (1H, s), 8.88 (1H, d, *J* 8.17 Hz), 8.73 (1H, d, *J* 5.79 Hz), 8.11 (1H, s), 8.06 (1H, dd, *J* 8.11, 5.80 Hz), 7.71-7.67 (2H, m), 7.24 (1H, t, *J* 7.82 Hz), 1.76 (3H, d, *J* 6.74 Hz).

INTERMEDIATE 66

(*S*)-2-{[3-(1-Aminoethyl)-8-chloroquinolin-2-ylamino]methyl}pyridine 1-oxide bis hydrochloric acid salt

Similarly, *Intermediate 57* (100 mg, 0.23 mmol) and HCl (1.2 mL, 4.66 mmol; 4.0M in 1,4-dioxane) in dry 1,4-dioxane (5 mL) gave the *title compound* (103 mg, quantitative) as an off-white solid. δ_H (MeOD-d_4) 8.60 (1H, d, *J* 6.46 Hz), 8.47 (1H, s), 8.04 (1H, dd, *J* 7.87, 2.02 Hz), 7.92 (2H, ddd, *J* 10.68, 7.86, 1.32 Hz), 7.86-7.80 (1H, m), 7.72-7.65 (1H, m), 7.51 (1H, t, *J* 7.90 Hz), 5.20 (2H, s), 4.97 (1H, q, *J* 6.73 Hz), 1.78 (3H, d, *J* 6.73 Hz).

INTERMEDIATE 67

(*S*)-2-{7-Fluoro-8-methyl-3-[1-(9-{[2-(trimethylsilyl)ethoxy]methyl}-9*H*-purin-6-ylamino)ethyl]quinolin-2-ylamino}ethanol

A mixture of *Intermediate 62* (0.65 g, 1.93 mmol), *Intermediate 7* (0.83 g, 2.90 mmol) and DIPEA (1.7 mL, 9.67 mmol) in *n*-butanol (12 mL) was heated at 120°C under microwave irradiation for 3 h. The reaction mixture was concentrated *in vacuo* and the residue purified by column chromatography (SiO_2, 0-1% MeOH in EtOAc) to give the *title compound* (930 mg, 72%) as a cream solid. δ_H ($CDCl_3$) 8.49 (1H, s), 7.90 (2H, d, *J* 6.85 Hz), 7.48-7.39 (2H, m), 7.01 (1H, t, *J* 8.97 Hz), 5.93-5.78 (2H, m), 5.59 (2H, s), 3.94-3.74 (3H, m), 3.75-3.61 (3H, m), 2.54 (3H, d, *J* 2.26 Hz), 1.83 (3H, d, *J* 6.42 Hz), 1.01-0.92 (2H, m), 0.00 (9H, s).

INTERMEDIATE 68

(*S*)-2-{7-Fluoro-8-methyl-3-[1-(9-{[2-(trimethylsilyl)ethoxy]methyl}-9*H*-purin-6-ylamino)ethyl]quinolin-2-ylamino}acetaldehyde

To a solution of oxalyl chloride (0.95 mL, 1.91 mmol; 2.0M in DCM) in dry DCM (10 mL) cooled to -78°C was added dropwise dimethylsulphoxide (0.13 mL, 1.91 mmol) and the mixture stirred at -78°C for 15 minutes. The slow addition of a solution of *Intermediate 67* (650 mg, 1.27 mmol) in dry DCM (15 mL) took place and the mixture was stirred at -78°C for 30 minutes. Triethylamine (0.88 mL, 6.36 mmol) was added

dropwise and the reaction mixture was allowed to warm to 0°C and stirred for 45 minutes. Water (30 mL) was added and the mixture was diluted with DCM (50 mL). The organic layer was separated, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, 75-100% EtOAc in isohexane) to give the *title compound* (200 mg, 31%) as a yellow solid. δ_H ($CDCl_3$) 9.71 (1H, s), 8.51 (1H, s), 7.93 (2H, d, *J* 5.87 Hz), 7.55 (1H, br s), 7.48 (1H, dd, *J* 8.89, 6.14 Hz), 7.03 (1H, t, *J* 8.98 Hz), 5.98-5.84 (2H, m), 5.60 (2H, s), 4.24-4.17 (2H, m), 3.65 (2H, t, *J* 8.17 Hz), 2.48 (3H, m), 1.85 (3H, d, *J* 6.38 Hz), 0.96 (2H, t, *J* 8.17 Hz), 0.00 (9H, s).

INTERMEDIATE 69

(*S*)-2-{7-Fluoro-8-methyl-3-[1-(9-{[2-(trimethylsilyl)ethoxy]methyl}-9*H*-purin-6-ylamino)ethyl]quinolin-2-ylamino}acetic acid

A solution of *Intermediate 68* (250 mg, 0.49 mmol) in ethanol (10 mL) was treated with a solution of silver nitrate (210 mg, 1.22 mmol) in water (2 mL) followed by a solution of KOH in water (10 mL) and the mixture was stirred at r.t. for 30 minutes. The mixture was filtered through celite, washing with water (20 mL). The filtrate was washed with EtOAc (10 mL) and the aqueous layer was acidified to pH 3 with 2M HCl. This was extracted with DCM (2 x 50 mL), then the organic layers were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the *title compound* (82 mg, 32%) as a yellow solid. δ_H ($CDCl_3$) 8.51 (1H, s), 8.03 (1H, s), 8.02 (1H, br s), 7.96 (1H, s), 7.52 (1H, t, *J* 7.30 Hz), 7.08 (1H, t, *J* 9.00 Hz), 6.82-6.72 (1H, m), 5.88-5.78 (1H, m), 5.60 (2H, s), 4.35-4.22 (2H, m), 3.65 (2H, t, *J* 8.18 Hz), 2.53 (3H, s), 1.85 (3H, d, *J* 6.84 Hz), 0.96 (2H, t, *J* 8.14 Hz), 0.00 (9H, s), 1H exchanging.

INTERMEDIATE 70

N-[(*S*)-1-(2-Chloro-7-fluoro-8-methylquinolin-3-yl)ethyl]pyrazolo[1,5-*a*]pyrimidin-7-yl-amine

To a solution of *Intermediate 14* (4.0 g, 12.2 mmol) in MeOH (20 mL) was added conc. HCl (1 mL) and the mixture stirred at r.t. for 2 h. The reaction mixture was partitioned between DCM (100 mL) and 2M NaOH solution (50 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. A portion of the resulting

material (280 mg, 1.2 mmol), 7-chloropyrazolo[1,5-*a*]pyrimidine (310 mg, 1.9 mmol) and DIPEA (0.7 mL, 4 mmol) in *n*-butanol (3 mL) were combined and heated at 100°C for 64 h. The mixture was cooled and partitioned between EtOAc (50 mL) and water (50 mL). The aqueous layer was separated, extracted into EtOAc (20 mL) and the combined organics washed with water (15 mL), brine (15 mL), separated, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, 0-60% EtOAc in hexanes) to give the *title compound* (300 mg, 72%) as a pale yellow solid. δ_H ($CDCl_3$) 8.22 (1H, d, *J* 7.6 Hz), 8.11 (1H, s), 7.82 (1H, d, *J* 2.3 Hz), 7.57 (1H, dd, *J* 8.8, 6.1 Hz), 7.28 (1H, m), 6.06 (1H, d, *J* 2.0 Hz), 6.03 (1H, d, *J* 7.6 Hz), 5.51 (2H, m), 2.65 (3H, d, *J* 2.3 Hz), 1.69 (3H, d, *J* 6.8 Hz). LCMS (ES+) 356.2 $(M+H)^+$.

EXAMPLE 1

N-Butyl-*N*-methyl-*N*-{8-methyl-3-[1-(9*H*-purin-6-ylamino)ethyl]quinolin-2-yl}amine

To a solution of *Intermediate 2* (140 mg, 0.38 mmol) in DCM (7 mL) was added TFA (3 mL) and the mixture was stirred at r.t. for 1 h. The solvent was removed *in vacuo* to give a golden-yellow viscous oil (100 mg). Half of this oil (50 mg, 0.19 mmol) was dissolved in *n*-butanol (2 mL) and to this solution was added 6-chloropurine (43 mg, 0.28 mmol) and DIPEA (0.14 mL, 0.78 mmol). The reaction mixture was heated at 140°C in a microwave for 90 minutes. The solvent was removed *in vacuo* and the residue purified by preparative HPLC to give the *title compound* (44 mg, 75%) as a dark cream solid. δ_H (MeOD-d_4) 8.34 (s, 1H), 8.29 (s, 1H), 8.21 (s, 1H), 7.62 (d, *J* 8.0 Hz, 1H), 7.50 (d, *J* 6.8 Hz, 1H), 7.31 (t, *J* 7.6 Hz, 1H), 5.84-5.96 (m, 1H), 3.50-3.57 (m, 1H), 3.35-3.43 (m, 1H), 3.14 (s, 3H), 2.72 (s, 3H), 1.71-1.79 (m, 5H), 1.31-1.42 (m, 2H), 0.93 (t, *J* 7.4 Hz, 3H). LCMS (ES+) 390 $(M+H)^+$, RT 3.01 minutes (*Method 2*).

EXAMPLE 2

N-Butyl-*N*-methyl-*N*-{8-methyl-3-[1-(1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ylamino)ethyl]-quinolin-2-yl}amine

The *title compound* was prepared in a similar manner to *Example 1* using *Intermediate 2* (140 mg, 0.38 mmol) and was obtained as a brown solid (45 mg, 63%) after purification by preparative HPLC. δ_H (MeOD-d_4) 8.35 (br s, 2H), 8.24 (s, 1H), 7.62

(d, *J* 8.0 Hz, 1H), 7.49 (d, *J* 6.8 Hz, 1H), 7.30 (t, *J* 7.6 Hz, 1H), 5.90-6.00 (m, 1H), 3.48-3.57 (m, 1H), 3.13 (s, 3H), 2.72 (s, 3H), 1.67-1.76 (m, 5H), 1.34-1.42 (m, 2H), 0.92 (t, *J* 7.3 Hz, 3H). LCMS (ES+) 390 $(M+H)^+$, RT 3.20 minutes (*Method 2*).

EXAMPLE 3

(*S*)-3-[1-(9*H*-Purin-6-ylamino)ethyl]-*N*,*N*,8-trimethylquinolin-2-ylamine

To a solution of *Intermediate 4* (100 mg, 0.3 mmol) in *n*-butanol (4 mL) were added dimethylamine hydrochloride (125 mg, 1.5 mmol) and DIPEA (0.28 mL, 1.5 mmol). The reaction mixture was heated at 160°C in a microwave for 2 h. Conc. hydrochloric acid (1 mL) was added and the mixture was stirred at r.t. for 20 minutes. The mixture was poured into water (20 mL), basified with 5M NaOH solution (20 mL) and extracted with Et_2O (3 x 25 mL). The organic layers were combined, separated, dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The residue was dissolved in *n*-butanol (2.5 mL) and 6-chloro-9-[2-(trimethylsilanyl)ethoxymethyl]-9*H*-purine (100 mg, 0.35 mmol) and DIPEA (0.14 mL, 0.75 mmol) were added. The reaction mixture was heated at 160°C in a microwave for 1 h. HCl (2 mL, 4M solution in 1,4-dioxane) was added and the mixture was stirred for 20 minutes. The reaction mixture was poured into water (20 mL) basified with solid Na_2CO_3 and extracted with DCM (3 x 25 mL). The organic layers were combined, separated, dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The residue was purified by preparative HPLC to give the *title compound* (11 mg, 7.2%) as a white solid. δ_H ($CDCl_3$) 8.35 (s, 1H), 8.05 (s, 1H), 7.95 (s, 1H), 7.47 (d, *J* 8.8 Hz, 1H), 7.40 (d, *J* 8.8 Hz, 1H), 7.21 (t, *J* 8.8 Hz, 1H), 6.52 (br s, 1H), 5.92 (br s, 1H), 3.08 (s, 6H), 2.71 (s, 3H), 1.65 (d, *J* 6.4 Hz, 1H). LCMS (ES+) 348 $(M+H)^+$, RT 2.17 minutes (*Method 2*).

EXAMPLE 4

(*S*)-*N*-Allyl-*N*,8-dimethyl-3-[1-(9*H*-purin-6-ylamino)ethyl]quinolin-2-amine

Intermediate 8 (60 mg, 0.12 mmol) in THF (1 mL) was treated with 1.0M tetrabutylammonium fluoride (0.6 mL, 0.6 mmol) and heated at 50°C for 16 h. The reaction mixture was concentrated *in vacuo* and purified by column chromatography [SiO_2, 7M NH_3/MeOH (10%) in EtOAc] to give the *title compound* (31.9 mg, 71%) as a

white solid. δ_H ($CDCl_3$) 8.37 (1H, s), 8.03 (1H, s), 7.97 (1H, s), 7.43 (1H, d, *J* 8.04 Hz), 7.40 (1H, d, *J* 7.03 Hz), 7.18 (1H, t, *J* 7.52 Hz), 6.55 (1H, br d, *J* 7.12 Hz), 6.16-6.03 (1H, m), 5.85 (1H, br s), 5.38 (1H, d, *J* 17.21 Hz), 5.20 (1H, d, *J* 10.22 Hz), 4.32 (1H, dd, *J* 15.51, 5.41 Hz), 3.87 (1H, dd, *J* 15.48, 6.00 Hz), 3.04 (3H, s), 2.70 (3H, s), 1.62 (3H, d, *J* 6.68 Hz), 1H under H_2O. LCMS (ES+) 374 $(M+H)^+$, RT 15.05 minutes (*Method 5*).

EXAMPLE 5

(*S*)-*N*,*N*-Diethyl-7-fluoro-3-[1-(9*H*-purin-6-ylamino)ethyl]quinolin-2-amine

To a solution of *Intermediate 15* (0.32 g, 1.0 mmol) in *n*-butanol (2 mL) were added diethylamine (80 mg, 1.1 mmol) and DIPEA (0.42 mL, 2.33 mmol). The reaction mixture was heated at 110°C for 18 h and then concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, 0-3% MeOH in DCM) to give a pale orange oil (97 mg, 55%). To a solution of this oil in MeOH (2 mL) was added HCl (1.0 mL, 4.0M solution in 1,4-dioxane). The reaction mixture was stirred for 2 h and concentrated *in vacuo* to give a beige solid (150 mg, 48%). To a solution of this solid (0.1 g, 0.38 mmol) in *n*-butanol (2 mL) were added 6-chloropurine (66 mg, 0.42 mmol) and DIPEA (100 mg, 0.78 mmol). The reaction mixture was heated at 110°C for 18 h and then concentrated *in vacuo*. The residue was purified by preparative HPLC to give the *title compound* (30 mg, 21%) as a white solid. δ_H ($CDCl_3$) 8.35 (1H, s), 8.03 (1H, s), 7.96 (1H, s), 7.57 (1H, dd, *J* 8.88, 6.15 Hz), 7.47 (1H, dd, *J* 10.62, 2.57 Hz), 7.08 (1H, td, *J* 8.62, 2.58 Hz), 6.50 (1H, s), 5.81 (1H, s), 3.60-3.40 (4H, m), 1.64 (3H, d, *J* 6.66 Hz), 1.21 (6H, t, *J* 6.98 Hz). LCMS (ES+) 380 $(M+H)^+$, RT 19.26 minutes (*Method 6*).

EXAMPLE 6

(*S*)-N^2-{1-[2-(Diethylamino)-7-fluoroquinolin-3-yl]ethyl}-[1,3,5]triazine-2,4-diamine

Similarly *Intermediate 15* (0.122 g, 0.38 mmol), 2-amino-4-chloro-[1,3,5]triazine (0.055 mg, 0.43 mmol) and DIPEA (100 mg, 0.78 mmol) in *n*-butanol (2 mL) gave the *title compound* (33.6 mg, 25%) as a white solid. δ_H ($CDCl_3$) 8.10 (1H, s), 7.92 (1H, s), 7.59 (1H, dd, *J* 8.88, 6.16 Hz), 7.47 (1H, dd, *J* 10.60, 2.56 Hz), 7.10 (1H, td, *J* 8.62, 2.58 Hz), 6.14-4.89 (4H, m), 3.54-3.46 (2H, m), 3.42-3.29 (2H, m), 1.49 (3H, d, *J* 6.70 Hz), 1.18 (6H, t, *J* 6.91 Hz). LCMS (ES+) 356 $(M+H)^+$, RT 3.04 minutes (*Method 1*).

EXAMPLE 7

(*S*)-N^2-{1-[2-(Diethylamino)-7-fluoroquinolin-3-yl]ethyl}-6-methyl-[1,3,5]triazine-2,4-diamine

Similarly, *Intermediate 15* (0.073 g, 0.23 mmol), 2-amino-4-chloro-6-methyl-[1,3,5]triazine (36 mg, 0.25 mmol) and DIPEA (100 mg, 0.78 mmol) in *n*-butanol (2 mL) gave the *title compound* (11.2 mg, 14%) as a white solid. δ_H ($CDCl_3$) 7.91 (1H, s), 7.59 (1H, dd, *J* 8.86, 6.14 Hz), 7.47 (1H, dd, *J* 10.62, 2.57 Hz), 7.13-7.06 (1H, m), 5.74-5.06 (4H, m), 3.53 (2H, s), 3.39 (2H, s), 2.39-2.04 (3H, m), 1.46 (3H, s), 1.19 (6H, t, *J* 7.01 Hz). LCMS (ES+) 370 $(M+H)^+$, RT 3.33 minutes (*Method 1*).

EXAMPLE 8

(*S*)-N^2-{1-[7-Fluoro-2-(2-methoxyethylamino)quinolin-3-yl]ethyl}-6-methyl-[1,3,5]-triazine-2,4-diamine

To a solution of *Intermediate 17* (35 mg, 0.13 mmol) in *n*-butanol (2 mL) were added 2-amino-4-chloro-6-methyl-[1,3,5]triazine (23 mg, 0.16 mmol) and DIPEA (45 mg, 0.35 mmol). The reaction mixture was heated at 110°C for 18 h and then concentrated *in vacuo*. The residue was purified by preparative HPLC to give the *title compound* (12.3 mg, 25%) as a white solid. δ_H ($CDCl_3$) 7.78 (1H, d, *J* 1.68 Hz), 7.52 (1H, dd, *J* 8.79, 6.30 Hz), 7.29 (1H, dd, *J* 10.95, 2.50 Hz), 6.95 (1H, td, *J* 8.62, 2.55 Hz), 6.33 (1H, br d, *J* 8.70 Hz), 5.28 (1H, br t, *J* 7.86 Hz), 4.03 (1H, br s), 3.79 (2H, br s), 3.62-3.70 (2H, m), 3.53-3.61 (2H, m), 3.45 (3H, s), 2.22 (3H, s), 1.65 (3H, d, *J* 6.83 Hz). LCMS (ES+) 372 $(M+H)^+$, RT 2.33 minutes (*Method 1*).

EXAMPLE 9

(*S*)-7-Fluoro-*N*-(2-methoxyethyl)-3-[1-(9*H*-purin-6-ylamino)ethyl]quinolin-2-amine

Similarly, *Intermediate 17* (35 mg, 0.133 mmol), 6-chloropurine (25 mg, 0.16 mmol) and DIPEA (45 mg, 0.35 mmol) in *n*-butanol (2 mL) gave the *title compound* (7.6 mg, 15%) as a white solid. δ_H ($CDCl_3$) 8.48 (1H, s), 7.92 (1H, s), 7.85 (1H, s), 7.55 (1H, dd, *J* 8.80, 6.28 Hz), 7.30 (1H, dd, *J* 10.99, 2.54 Hz), 6.95 (1H, td, *J* 8.61, 2.57 Hz), 6.71

(1H, br s), 6.13 (1H, br d, *J* 9.19 Hz), 5.84 (1H, br s), 3.80-3.70 (2H, m), 3.62-3.48 (2H, m), 3.22 (3H, s), 1.78 (3H, d, *J* 6.77 Hz). LCMS (ES+) 382 $(M+H)^+$, RT 6.96 minutes (*Method 8*).

EXAMPLE 10

(*S*)-7-Fluoro-*N*-(3-methoxypropyl)-3-[1-(9*H*-purin-6-ylamino)ethyl]quinolin-2-amine

Similarly, *Intermediate 18* (60 mg, 0.21 mmol), 6-chloropurine (37 mg, 0.24 mmol) and DIPEA (100 mg, 0.78 mmol) in *n*-butanol (2 mL) gave the *title compound* (13.3 mg, 16%) as a pale yellow solid. δ_H ($CDCl_3$) 8.44 (1H, s), 7.96 (1H, s), 7.83 (1H, s), 7.51 (1H, dd, *J* 8.77, 6.14 Hz), 7.31 (1H, dd, *J* 11.00, 2.53 Hz), 6.93 (1H, td, *J* 8.60, 2.57 Hz), 6.63 (2H, d, *J* 9.76 Hz), 5.78 (1H, s), 3.71-3.53 (2H, m), 3.48-3.33 (2H, m), 3.25 (3H, s), 1.97-1.80 (2H, m), 1.77 (3H, d, *J* 6.71 Hz). LCMS (ES+) 396 $(M+H)^+$, RT 7.01 minues (*Method 8*).

EXAMPLE 11

(*S*)-N^2-{1-[2-(Diethylamino)-7-fluoro-8-methylquinolin-3-yl]ethyl}-6-methyl-[1,3,5]-triazine-2,4-diamine

Similarly, *Intermediate 19* (70 mg, 0.25 mmol), 2-amino-4-chloro-6-methyl-[1.3.5]triazine (40 mg, 0.27 mmol) and DIPEA (100 mg, 0.78 mmol) in *n*-butanol (2 mL) gave the *title compound* (30 mg, 30%) as a white solid. δ_H ($CDCl_3$) 7.87 (1H, s), 7.43 (1H, t, *J* 7.31 Hz), 7.07 (1H, t, *J* 9.01 Hz), 5.62 (1H, s), 5.49 (1H, s), 5.06 (2H, s), 3.57-3.48 (2H, m), 3.45-3.36 (2H, m), 2.59 (3H, d, *J* 2.40 Hz), 2.27 (2H, s), 2.18 (1H, s), 1.46 (3H, d, *J* 6.80 Hz), 1.22 (6H, t, *J* 6.99 Hz). LCMS (ES+) 384 $(M+H)^+$, RT 3.73 minutes (*Method 1*).

EXAMPLE 12

(*S*)-1-(4-{3-[1-(4-Amino-[1,3,5]triazin-2-ylamino)ethyl]-8-chloroquinolin-2-ylamino}piperidin-1-yl)ethanone

A mixture of *Intermediate 25* (62 mg, 0.18 mmol), 2-amino-4-chloro-[1,3,5]-triazine (47 mg, 0.36 mmol) and DIPEA (0.15 mL, 0.89 mmol) in 1,4-dioxane (3 mL)

was heated at 130°C under microwave irradiation for 1.5 h. The reaction mixture was concentrated *in vacuo* and the residue purified by preparative HPLC to give the *title compound* (28.7 mg, 36%). δ_H (DMSO-d_6) 8.14-7.90 (2H, m), 7.73-7.64 (3H, m), 7.17 (1H, t, *J* 7.75 Hz), 7.28-6.72 (2H, m), 6.65-6.54 (1H, m), 5.33 (1H, br s), 4.33 (2H, br s), 3.92-3.79 (1H, m), 3.23 (1H, t, *J* 13.52 Hz), 2.92-2.70 (1H, m), 2.30-1.70 (5H, m), 1.56 (3H, s), 1.50-1.33 (2H, m). LCMS (ES+) 441 $(M+H)^+$, RT 7.85 minutes (*Method 5*).

EXAMPLE 13

(*S*)-8-Chloro-*N*,*N*-diethyl-3-[1-(9*H*-purin-6-ylamino)ethyl]quinolin-2-amine

A solution of *Intermediate 26* (60 mg, 0.16 mmol) and hydrogen chloride (0.8 mL, 3.17 mmol; 4.0M in 1,4-dioxane) in 1,4-dioxane (5 mL) was stirred at r.t. overnight. The reaction mixture was concentrated *in vacuo* to give a yellow solid (64 mg). A solution of this solid (64 mg, 0.18 mmol) in *n*-butanol (5 mL) with DIPEA (0.2 mL, 0.91 mmol) and 6-bromopurine (54 mg, 2.7 mmol) was heated at 80°C overnight and then heated at 120°C for 10 h. The reaction mixture was concentrated *in vacuo* and purified by preparative HPLC to give the *title compound* (25 mg, 34%) as a beige solid. δ_H (MeOD-d_4) 8.26-8.15 (3H, m), 8.13 (1H, s), 7.67 (1H, dd, *J* 7.50, 1.39 Hz), 7.64 (1H, dd, *J* 8.08, 1.41 Hz), 7.26 (1H, t, *J* 7.79 Hz), 5.85 (1H, s), 3.67-3.51 (5H, m), 1.65 (3H, d, *J* 6.71 Hz), 1.27 (6H, t, *J* 6.97 Hz). LCMS (ES+) 396 $(M+H)^+$, RT 16.58 minutes (*Method 5*).

EXAMPLE 14

(*S*)-8-Chloro-*N*-(2-methoxyethyl)-3-[1-(9*H*-purin-6-ylamino)ethyl]quinolin-2-amine

A solution of *Intermediate 32* (50 mg, 0.14 mmol), 6-bromopurine (42 mg, 0.21 mmol) and DIPEA (0.13 mL, 0.71 mmol) in *n*-butanol (1.5 mL) was heated at 120°C in the microwave for 3 h. The reaction mixture was concentrated *in vacuo* and purified by preparative HPLC to afford the *title compound* (9 mg, 16%) as a yellow solid. δ_H (MeOD-d_4) 8.35 (1H, s), 8.10 (1H, s), 8.04 (1H, s), 7.60 (2H, d, *J* 7.75 Hz), 7.12 (1H, t, *J* 7.74 Hz), 5.80 (1H, br s), 3.89-3.73 (2H, m), 3.72-3.56 (2H, m), 3.22 (3H, s), 1.77 (3H, d, *J* 6.78 Hz), 3 NH not visible. LCMS (ES+) 398 $(M+H)^+$, RT 3.01 minutes (*Method 1*).

EXAMPLE 15

(*S*)-8-Chloro-*N*-(2-methoxyethyl)-*N*-methyl-3-[1-(9*H*-purin-6-ylamino)ethyl]quinolin-2-amine

Similarly, *Intermediate 33* (45 mg, 0.12 mmol), 6-bromopurine (37 mg, 0.18 mmol) and DIPEA (0.13 mL, 0.71 mmol) in *n*-butanol (1.5 mL) gave the *title compound* (9 mg, 18%) as an orange-yellow solid. δ_H (MeOD-d_4) 8.29-8.18 (2H, m), 8.13 (1H, s), 7.68 (1H, dd, *J* 7.49, 1.39 Hz), 7.65 (1H, dd, *J* 8.10, 1.38 Hz), 7.26 (1H, t, *J* 7.80 Hz), 5.92 (1H, s), 3.86-3.68 (4H, m), 3.35 (3H, s), 3.23 (3H, s), 1.65 (3H, d, *J* 6.70 Hz), 2 NH not visible. LCMS (ES+) 412 $(M+H)^+$, RT 2.31 minutes (*Method 2*).

EXAMPLE 16

(*S*)-8-Chloro-*N*-methyl-3-[1-(9*H*-purin-6-ylamino)ethyl]quinolin-2-amine

Similarly, *Intermediate 34* (50 mg, 0.16 mmol), 6-bromopurine (48 mg, 0.24 mmol) and DIPEA (0.14 mL, 0.81 mmol) in *n*-butanol (1.5 mL) gave the *title compound* (12 mg, 21%) as a dark cream solid. δ_H (MeOD-d_4) 8.30 (1H, s), 8.12 (1H, s), 7.97 (1H, s), 7.59 (1H, dd, *J* 7.56, 1.40 Hz), 7.55 (1H, dd, *J* 7.98, 1.41 Hz), 7.10 (1H, t, *J* 7.77 Hz), 5.71 (1H, s), 3.14 (3H, s), 1.73 (3H, d, *J* 6.81 Hz). LCMS (ES+) 354 $(M+H)^+$, RT 2.00 minutes (*Method 2*).

EXAMPLE 17

8-Chloro-3-[(*S*)-1-(9*H*-purin-6-ylamino)ethyl]-*N*-{[(*R*)-tetrahydrofur-2-yl]methyl}-quinolin-2-amine

Similarly, *Intermediate 35* (80 mg, 0.21 mmol), 6-bromopurine (63 mg, 0.32 mmol) and DIPEA (0.19 mL, 1.06 mmol) in *n*-butanol (2 mL) gave the *title compound* (30 mg, 34%) as a yellow solid. δ_H (MeOD-d_4) 8.25 (1H, s), 7.99 (1H, s), 7.94 (1H, s), 7.53-7.46 (2H, m), 7.02 (1H, t, *J* 7.77 Hz), 5.71 (1H, br s), 4.16-4.08 (1H, m), 3.74-3.56 (2H, m), 3.52 (2H, t, *J* 6.75 Hz), 1.88-1.76 (1H, m), 1.75-1.60 (5H, m), 1.56-1.46 (1H, m), 3 NH not visible. LCMS (ES+) 424 $(M+H)^+$, RT 7.40 minutes (*Method 8*).

EXAMPLE 18

8-Chloro-3-[(*S*)-1-(9*H*-purin-6-ylamino)ethyl]-*N*-{[(*S*)-tetrahydrofur-2-yl]methyl}-quinolin-2-amine

A solution of *Intermediate 31* (80 mg, 0.20 mmol) and hydrogen chloride (1.0 mL, 3.94 mmol; 4.0M in 1,4-dioxane) in 1,4-dioxane (5 mL) was stirred at r.t. overnight. The reaction mixture was concentrated *in vacuo* to give an off-white semi-solid (75 mg). A solution of this material (75 mg, 0.20 mmol) in *n*-butanol (2 mL) with DIPEA (0.18 mL, 0.99 mmol) and 6-bromopurine (59 mg, 3.0 mmol) was heated at 130°C in the microwave for 2 h. The reaction mixture was concentrated *in vacuo* and purified by preparative HPLC to give the *title compound* (14 mg, 17%) as a fawn solid. δ_H (MeOD-d_4) 8.35 (1H, s), 8.10 (1H, s), 8.04 (1H, s), 7.60 (2H, d, *J* 7.77 Hz), 7.12 (1H, t, *J* 7.77 Hz), 5.80 (1H, br s), 4.16-4.09 (1H, m), 3.84-3.76 (2H, m), 3.73-3.60 (2H, m), 2.00-1.80 (3H, m), 1.78 (3H, d, *J* 6.79 Hz), 1.77-1.65 (1H, m), 3 NH not visible. LCMS (ES+) 424 $(M+H)^+$, RT 7.41 minutes (*Method 8*).

EXAMPLE 19

(*S*)-8-Chloro-*N*-(2-methoxyethyl)-3-{1-[2-(methylthio)pyrazolo[1,5-*a*][1,3,5]triazin-4-ylamino]ethyl}quinolin-2-amine

To a solution of *Intermediate 27* (310 mg, 0.82 mmol) in DCM (3 mL) was added TFA (1 mL). The reaction mixture was stirred for 2 h and concentrated *in vacuo*. The residue was dissolved in MeOH and passed though an SCX cartridge [eluents: MeOH, MeOH/7N NH_3 (10:1)] to give crude deprotected amine. To a solution of the amine in dry THF (5 mL) were added DIPEA (0.36 mL, 2 mmol) and 4-chloro-2-(methylthio)-pyrazolo[1,5-*a*][1,3,5]triazine (196 mg, 0.98 mmol). The reaction mixture was stirred for 6 h and concentrated *in vacuo*. The residue was partitioned between DCM (50 mL) and water (10 mL). The organic layer was washed with water (2 x 10 mL) and brine, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 0-20% EtOAc in isohexane) afforded the *title compound* (213 mg, 58%) as a clear glass. δ_H ($CDCl_3$) 7.86 (1H, s), 7.84 (1H, d, *J* 2.11 Hz), 7.64 (1H, dd, *J* 7.56, 1.38 Hz), 7.51 (1H, dd, *J* 7.96, 1.39 Hz), 7.11 (1H, t, *J* 7.76 Hz), 6.50 (1H, d, *J* 9.57 Hz), 6.25 (1H, d, *J* 2.10 Hz), 6.21 (1H, t, *J* 5.31 Hz), 5.68-5.58 (1H, m), 3.96-3.87 (1H, m), 3.85-3.76 (1H, m),

3.67-3.53 (2H, m), 3.16 (3H, s), 2.59 (3H, s), 1.83 (3H, d, *J* 6.76 Hz). LCMS (ES+) 444 $(M+H)^+$, RT 3.84 minutes (*Method 1*).

EXAMPLE 20

(*S*)-8-Chloro-*N*-(2-methoxyethyl)-3-{1-[2-(methylsulfonyl)pyrazolo[1,5-*a*][1,3,5]triazin-4-ylamino]ethyl}quinolin-2-amine

To a solution of *Example 19* (160 mg, 0.36 mmol) in DCM (4 mL) was added MCPBA (125 mg, 0.72 mmol). The reaction mixture was stirred for 3 h and concentrated *in vacuo*. Purification by preparative HPLC followed by trituration with Et_2O gave the *title compound* (60 mg, 35%) as a white solid. δ_H ($CDCl_3$) 8.07 (1H, d, *J* 2.14 Hz), 7.92 (1H, s), 7.65 (1H, dd, *J* 7.54, 1.35 Hz), 7.53 (1H, dd, *J* 7.99, 1.35 Hz), 7.13 (1H, t, *J* 7.77 Hz), 6.85 (1H, br s), 6.67 (1H, d, *J* 2.14 Hz), 6.10 (1H, br s), 5.81 (1H, br t, *J* 7.06 Hz), 4.04-3.97 (1H, m), 3.74-3.65 (1H, m), 3.59-3.47 (2H, m), 3.37 (3H, s), 2.96 (3H, s), 1.91 (3H, d, *J* 6.75 Hz). LCMS (ES+) 476 $(M+H)^+$, RT 3.00 minutes (*Method 1*).

EXAMPLE 21

(*S*)-8-Chloro-*N*-(2-methoxyethyl)-3-[1-(pyrazolo[1,5-*a*][1,3,5]triazin-4-ylamino)ethyl]-quinolin-2-amine

To a solution of *Example 20* (60 mg, 0.12 mmol) in EtOH/$CHCl_3$ (1:1; 1.2 mL) was added portionwise $NaBH_4$ (9.6 mg, 0.25 mmol). After 10 minutes of stirring, water (1 mL) was added and the reaction mixture was concentrated *in vacuo*. The residue was partitioned between DCM and water. The organic layer was washed with water (2 x 10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The resulting gum was freeze-dried to give the *title compound* (30 mg, 60%) as an off-white solid. δ_H ($CDCl_3$) 8.28 (1H, s), 7.96 (1H, d, *J* 2.14 Hz), 7.90 (1H, s), 7.65 (1H, dd, *J* 7.56, 1.39 Hz), 7.52 (1H, dd, *J* 7.97, 1.41 Hz), 7.12 (1H, t, *J* 7.76 Hz), 6.59 (1H, br d, *J* 9.42 Hz), 6.48-6.46 (2H, m), 5.75-5.66 (1H, m), 3.94-3.85 (1H, m), 3.83-3.74 (1H, m), 3.65-3.51 (2H, m), 3.18 (3H, s), 1.86 (3H, d, *J* 6.80 Hz). LCMS (ES+) 398 $(M+H)^+$, RT 19.67 minutes (*Method 6*).

EXAMPLE 22

(*S*)-8-Chloro-*N*-cyclopropyl-3-[1-(9*H*-purin-6-ylamino)ethyl]quinolin-2-amine

Intermediate 23 (200 mg, 0.58 mmol), cyclopropylamine (0.2 mL, 2.93 mmol), DIPEA (0.52 mL, 2.93 mmol) and NMP (2 mL) were combined in a sealed tube and heated to 140°C overnight. After cooling, the mixture was dissolved in a 1:1 mixture of Et_2O and EtOAc (100 mL) and washed with saturated brine (3 x 25 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 10% EtOAc in isohexane) gave a yellow gum (68 mg, 32%). LCMS (ES+) 362, 364 $(M+H)^+$. The yellow gum (68 mg, 0.19 mmol) was dissolved in DCM (3 mL) and TFA (2 mL) and the solution obtained was left to stand at r.t. for 2 h. The excess solvent was removed *in vacuo* and azeotroped with toluene to give a residue (60 mg). To this was added 6-chloropurine (92 mg, 0.37 mmol), DIPEA (0.22 mL, 1.25 mmol) and NMP (2 mL) and the reaction mixture was heated under microwave irradiation to 150°C for 1 h. After cooling, the mixture was dissolved in a 1:1 mixture of Et_2O and EtOAc (100 mL) and washed with saturated brine (3 x 25 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by preparative HPLC gave the *title compound* (6 mg, 6%) as a light yellow solid. δ_H (DMSO-d_6) 8.37-8.14 (2H, m), 8.19 (1H, s), 8.00 (1H, s), 7.67-7.63 (2H, m), 7.37 (1H, d, *J* 3.94 Hz), 7.15 (1H, t, *J* 7.75 Hz), 5.66 (1H, br s), 3.22-3.12 (1H, m), 1.62 (3H, d, *J* 6.72 Hz), 0.83-0.72 (2H, m), 0.56-0.48 (2H, m). LCMS (ES+) 380 $(M+H)^+$, RT 7.09 minutes (*Method 5*).

EXAMPLE 23

(*R*)-5-{3-[(*S*)-1-(4-Amino-6-methyl-[1,3,5]triazin-2-ylamino)ethyl]-8-chloroquinolin-2-ylamino}piperidin-2-one

Intermediate 23 (250 mg, 0.73 mmol), (*R*)-5-aminopiperidin-2-one (275 mg, 1.83 mmol), DIPEA (0.81 mL, 3.65 mmol) and NMP (1.5 mL) were combined in a sealed tube and heated to 140°C for 48 h. After cooling, the mixture was dissolved in a 1:1 mixture of Et_2O and EtOAc (200 mL) and washed with saturated brine (3 x 50 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 0-8% MeOH in DCM) gave a yellow oil (100 mg, 33%). LCMS (ES+) 419, 421 $(M+H)^+$. The yellow oil (100 mg, 0.24 mmol) was dissolved in DCM (3

mL) and TFA (2 mL) and the solution was left to stand at r.t. for 2 h. The excess solvent was removed *in vacuo* and the residue azeotroped with toluene. Purification by ion exchange chromatography (SCX cartridge eluting with NH_3 in MeOH) gave a cream solid (50 mg, 66%). LCMS (ES+) 319, 321 $(M+H)^+$. The cream solid (50 mg, 0.16 mmol), 2-amino-4-chloro-6-methyl-[1,3,5]triazine (27 mg, 0.19 mmol), DIPEA (0.086 mL, 0.48 mmol) and NMP (1.5 mL) were combined and heated under microwave irradiation to 150°C for 1 h. After cooling, the mixture was dissolved in a 1:1 mixture of Et_2O and EtOAc (100 mL) and washed with saturated brine (3 x 10 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by preparative HPLC gave the *title compound* (9.3 mg, 14%) as a brown glass. δ_H ($CDCl_3$) 7.82 (1H, s), 7.66 (1H, dd, *J* 7.56, 1.36 Hz), 7.53 (1H, dd, *J* 8.02, 1.39 Hz), 7.15 (1H, t, *J* 7.76 Hz), 6.89 (1H, br s), 6.69 (1H, s), 5.44-5.35 (2H, m), 5.30-5.23 (1H, m), 4.13-4.08 (1H, m), 4.04-3.97 (1H, m), 3.52-3.44 (1H, m), 2.40-2.32 (2H, m), 2.30 (3H, s), 2.29-2.19 (1H, m), 2.03-1.95 (1H, m), 1.69 (3H, d, *J* 6.71 Hz). LCMS (ES+) 427 $(M+H)^+$, RT 15.05 minutes (*Method 6*).

EXAMPLE 24

(*S*)-1-(4-{8-Chloro-3-[1-(9*H*-purin-6-ylamino)ethyl]quinolin-2-ylamino}piperidin-1-yl)ethanone

Intermediate 23 (200 mg, 0.58 mmol), 1-(4-aminopiperidin-1-yl)ethanone (416 mg, 2.93 mmol), DIPEA (0.52 mL, 2.93 mmol) and NMP (2 mL) were combined in a sealed tube and heated to 140°C overnight. After cooling, the mixture was dissolved in a 1:1 mixture of Et_2O and EtOAc (100 mL) and washed with saturated brine (3 x 25 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 50% EtOAc in isohexane) gave a yellow gum (140 mg, 54%). LCMS (ES+) 447, 449 $(M+H)^+$. The yellow gum (140 mg, 0.31 mmol) was dissolved in DCM (6 mL) and TFA (4 mL) and the solution was left to stand at r.t. for 2 h. The excess solvent was removed *in vacuo* and the residue azeotroped with toluene. Purification by ion exchange chromatography (SCX cartridge eluting with NH_3 in MeOH) gave a yellow gum (100 mg, 90%). LCMS (ES+) 347, 349 $(M+H)^+$. The yellow gum (55 mg, 0.16 mmol), 6-chloropurine (47 mg, 0.19 mmol), DIPEA (0.086 mL, 0.48 mmol) and NMP (1.5 mL) were combined and heated under microwave irradiation to 150°C for 1 h.

After cooling, the mixture was dissolved in a 1:1 mixture of Et_2O and EtOAc (100 mL) and washed with saturated brine (3 x 25 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by preparative HPLC gave the *title compound* (15.8 mg, 21%) as a light brown solid. δ_H ($CDCl_3$) 8.37 (1H, s), 8.08 (1H, s), 7.97 (1H, s), 7.68 (1H, dd, *J* 7.52, 1.33 Hz), 7.55 (1H, dd, *J* 8.09, 1.35 Hz), 7.26-7.22 (1H, m), 6.34 (1H, br s), 5.83 (1H, br s), 5.48 (1H, d, *J* 7.91 Hz), 4.11-4.00 (2H, m), 3.76-3.67 (1H, m), 3.51-3.41 (1H, m), 3.05 (1H, t, *J* 11.81 Hz), 2.19-2.05 (2H, m), 2.01 (3H, s), 1.93-1.78 (2H, m), 1.73-1.61 (4H, m). LCMS (ES+) 465 $(M+H)^+$, RT 2.47 minutes (*Method 2*).

EXAMPLE 25

(*S*)-5-{8-Chloro-3-[(*S*)-1-(9*H*-purin-6-ylamino)ethyl]quinolin-2-ylamino}piperidin-2-one

Intermediate 23 (200 mg, 0.58 mmol), (*S*)-5-aminopiperidin-2-one (220 mg, 1.46 mmol), DIPEA (0.52 mL, 2.93 mmol) and NMP (1.5 mL) were combined in a sealed tube and heated to 140°C for 72 h. After cooling, the mixture was dissolved in a 1:1 mixture of Et_2O and EtOAc (200 mL) and washed with saturated brine (3 x 50 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography (0-5% MeOH in DCM) gave a yellow gum (65 mg, 35%). LCMS (ES+) 319, 321 $(M+H)^+$. The yellow gum (65 mg, 0.20 mmol), 6-chloropurine (60 mg, 0.24 mmol), DIPEA (0.110 mL, 0.61 mmol) and NMP (1.5 mL) were combined and heated under microwave irradiation to 150°C for 1 h. After cooling, the mixture was dissolved in a 1:1 mixture of Et_2O and EtOAc (100 mL) and washed with saturated brine (3 x 10 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by preparative HPLC gave the *title compound* (7.2 mg, 8%) as a yellow solid. δ_H (DMSO-d_6) 8.26-8.20 (2H, m), 8.16 (1H, s), 7.98 (1H, s), 7.71 (1H, s), 7.63-7.57 (2H, m), 7.36 (1H, t, *J* 5.43 Hz), 7.10 (1H, t, *J* 7.75 Hz), 5.70 (1H, br s), 3.94 (1H, br s), 3.67-3.56 (2H, m), 2.20-1.99 (3H, m), 1.84-1.80 (1H, m), 1.60 (3H, d, *J* 6.63 Hz). LCMS (ES+) 437 $(M+H)^+$, RT 7.8 minutes (*Method 5*).

EXAMPLE 26

2-(*N'*-{3-[(4-Amino-6-methyl-[1,3,5]triazin-2-yloxy)methyl]-8-methylquinolin-2-yl}-*N'*-methylamino)-*N,N*-dimethylacetamide

(2-Chloro-8-methylquinolin-3-yl)methanol (250 mg, 1.13 mmol), *N,N*-dimethyl-2-(methylamino)acetamide (658 mg, 5.66 mmol), DIPEA (1 mL, 5.66 mmol) and NMP (3 mL) were combined in a sealed tube and heated to 140°C for 5 h. After cooling, the mixture was dissolved in a 1:1 mixture of Et_2O and EtOAc (100 mL) and washed with saturated brine (3 x 25 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 0-5% MeOH in DCM) gave a yellow solid (195 mg, 60%). LCMS (ES+) 288 $(M+H)^+$. To the yellow solid (90 mg, 0.31 mmol) in 1,4-dioxane (3 mL) was added NaH (31 mg, 0.78 mmol; 60% dispersion in mineral oil). The reaction mixture was stirred at r.t. for 5 minutes. 2-Amino-4-chloro-6-methyl-[1,3,5]triazine (50 mg, 0.34 mmol) was added and the mixture was heated in a sealed tube at 80°C overnight. After cooling, the mixture was diluted with H_2O (10 mL) and extracted with DCM (3 x 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography (0-5% MeOH in DCM) gave the *title compound* (25 mg, 21%) as an off-white solid. δ_H ($CDCl_3$) 8.14 (1H, s), 7.50 (1H, d, *J* 8.07 Hz), 7.41 (1H, d, *J* 7.06 Hz), 7.18 (1H, t, *J* 7.57 Hz), 5.56 (2H, s), 4.32 (2H, s), 3.18 (3H, s), 3.13 (3H, s), 2.97 (3H, s), 2.61 (3H, s), 2.39 (3H, s). LCMS (ES+) 396 $(M+H)^+$, RT 2.76 minutes (*Method 1*).

EXAMPLE 27

2-(*N'*-{3-[(4-Amino-[1,3,5]triazin-2-yloxy)methyl]-8-methylquinolin-2-yl}-*N'*-methyl-amino)-*N,N*-dimethylacetamide

(2-Chloro-8-methylquinolin-3-yl)methanol (250 mg, 1.13 mmol), *N,N*-dimethyl-2-(methylamino)acetamide (658 mg, 5.66 mmol), DIPEA (1 mL, 5.66 mmol) and NMP (3 mL) were combined in a sealed tube and heated to 140°C for 5 h. After cooling, the mixture was dissolved in a 1:1 mixture of Et_2O and EtOAc (100 mL) and washed with saturated brine (3 x 25 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by chromatography (0-5% MeOH in DCM) gave a yellow solid (195 mg, 60%). LCMS (ES+) 288 $(M+H)^+$. To the yellow solid (90 mg,

0.31 mmol) in 1,4-dioxane (3 mL) was added NaH (31 mg, 0.78 mmol; 60% dispersion in mineral oil). The reaction mixture was stirred at r.t. for 5 minutes. 2-Amino-4-chloro-[1,3,5]triazine (45 mg, 0.34 mmol) was added and the mixture was heated in a sealed tube at 80°C overnight. After cooling, the mixture was diluted with water (10 mL) and extracted with DCM (3 x 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 0-5% MeOH in DCM) gave the *title compound* (28 mg, 24%) as a white solid. δ_H (DMSO-d_6) 8.35 (1H, s), 8.20 (1H, s), 7.66-7.62 (3H, m), 7.47 (1H, d, *J* 6.99 Hz), 7.22 (1H, t, *J* 7.52 Hz), 5.48 (2H, s), 4.35 (2H, s), 3.20 (3H, s), 3.05 (3H, s), 2.86 (3H, s), 3H under H_2O. LCMS (ES+) 382 $(M+H)^+$, RT 3.07 minutes (*Method 1*).

EXAMPLE 28

(*S*)-1-(4-{8-Methyl-3-[1-(9*H*-purin-6-ylamino)ethyl]quinolin-2-ylamino}piperidin-1-yl)ethanone

Intermediate 37 (150 mg, 0.47 mmol), 1-(4-aminopiperidin-1-yl)ethanone (332 mg, 2.34 mmol), DIPEA (0.42 mL, 2.34 mmol) and NMP (3 mL) were combined in a sealed tube and heated to 140°C overnight. After cooling, the mixture was dissolved in a 1:1 mixture of Et_2O and EtOAc (100 mL) and washed with saturated brine (3 x 25 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by chromatography (SiO_2, 0-5% MeOH in DCM) gave a yellow gum (94 mg, 47%). LCMS (ES+) 427 $(M+H)^+$. The yellow gum (75 mg, 0.176 mmol) was dissolved in DCM (3 mL) and TFA (2 mL) and the solution obtained was stirred at r.t. for 2 h. The excess solvent was removed *in vacuo* and the residue azeotroped with toluene (3 x 10 mL). To the residue obtained were added 6-chloropurine (65 mg, 0.26 mmol), DIPEA (0.16 mL, 0.88 mmol) and *n*-butanol (2.5 mL) and the reaction mixture was heated under microwave irradiation at 120°C for 1 h. After cooling, the mixture was dissolved in a 1:1 mixture of Et_2O and EtOAc (100 mL) and washed with saturated brine (3 x 25 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to dryness. Purification by preparative HPLC gave the *title compound* (29.6 mg, 38%) as a brown gum. δ_H ($CDCl_3$) 8.35 (1H, s), 8.06 (1H, s), 7.95 (1H, s), 7.51 (1H, d, *J* 8.18 Hz), 7.44 (1H, d, *J* 7.05 Hz), 6.47 (1H, br s), 5.85 (1H, br s), 5.46 (1H, d, *J* 8.00 Hz), 4.05 (1H, br s), 3.90 (1H, d, *J* 12.75 Hz), 3.65-3.43 (1H, m), 3.41-3.34 (1H, m), 2.97 (1H, d, *J* 8.22 Hz), 2.71 (3H, s), 2.13 (1H, d, *J*

11.43 Hz), 2.06 (1H, d, *J* 9.97 Hz), 2.01 (3H, s), 1.87-1.70 (2H, m), 1.66 (3H, d, *J* 6.72 Hz), 1H under $CHCl_3$. LCMS (ES+) 445 $(M+H)^+$, RT 2.33 minutes (*Method 2*).

EXAMPLE 29

(*S*)-*N*-(2-{8-Chloro-3-[1-(9*H*-purin-6-ylamino)ethyl]quinolin-2-ylamino}ethyl)acetamide

Intermediate 23 (150 mg, 0.44 mmol), *N*-acetylethylenediamine (100 mg, 1 mmol), NMP (3 mL) and DIPEA (0.5 mL) were combined in a sealed tube. The reaction mixture was heated to 100°C for 60 h. After cooling to r.t. the reaction mixture was partitioned between EtOAc and water. The organic layer was washed with water (3 x 5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography to give an off-white foam (95 mg, 53%). The foam (95 mg, 0.23 mmol) was combined with MeOH (3 mL) and 2N HCl in Et_2O (3 mL) and stirred at r.t. for 18 h. The reaction mixture was concentrated *in vacuo* and the residue was combined with 6-chloropurine (31 mg, 0.2 mmol), *n*-butanol (3 mL) and DIPEA (0.5 mL) in a sealed tube and heated to 120°C for 20 h. The reaction mixture was concentrated *in vacuo* and purified by preparative HPLC to give the *title compound* (16 mg, 8%) as a yellow solid. δ_H (DMSO-d_6) 8.32 (1H, br s), 8.24-8.16 (2H, m), 8.02 (1H, t, *J* 5.48 Hz), 7.99 (1H, s), 7.64 (1H, dd, *J* 7.54, 1.36 Hz), 7.61 (1H, dd, *J* 7.99, 1.43 Hz), 7.37 (1H, t, *J* 5.20 Hz), 7.13 (1H, t, *J* 7.75 Hz), 5.65 (1H, br s), 3.78-3.68 (1H, m), 3.59-3.49 (1H, m), 3.48-3.36 (3H, m), 1.82 (3H, s), 1.63 (3H, d, *J* 6.70 Hz). LCMS (ES+) 425 $(M+H)^+$, RT 7.50 minutes (*Method 8*).

EXAMPLE 30

(*S*)-1-(2-{8-Chloro-3-[1-(9*H*-purin-6-ylamino)ethyl]quinolin-2-ylamino}ethyl)-imidazolidin-2-one

Similarly, *Intermediate 23* (150 mg, 0.44 mmol) and 1-(2-aminoethyl)-imidazolidin-2-one (129 mg, 1 mmol) gave the *title compound* (16.4 mg, 8%) as a yellow solid. δ_H (DMSO-d_6) 8.26 (1H, d, *J* 7.81 Hz), 8.24-8.15 (2H, m), 7.96 (1H, s), 7.64 (1H, dd, *J* 7.54, 1.37 Hz), 7.59 (1H, dd, *J* 7.94, 1.38 Hz), 7.34 (1H, t, *J* 5.31 Hz), 7.12 (1H, t, *J* 7.75 Hz), 6.26 (1H, s), 5.65 (1H, s), 3.86-3.79 (1H, m), 3.63-3.53 (1H, m), 3.50 (2H, t, *J*

7.87 Hz), 3.42 (2H, t, *J* 6.43 Hz), 3.21-3.14 (3H, m), 1.61 (3H, d, *J* 6.73 Hz). LCMS (ES+) 452 $(M+H)^+$, RT 2.31 minutes (*Method 2*).

EXAMPLE 31

(*S*)-8-Chloro-*N*-(3-methoxypropyl)-3-[1-(9*H*-purin-6-ylamino)ethyl]quinolin-2-amine

Similarly, *Intermediate 23* (150 mg, 0.44 mmol) and 3-methoxypropylamine (89 mg, 1 mmol) gave the *title compound* (15.4 mg, 8%) as a tan solid. δ_H (DMSO-d_6) 8.31-8.19 (2H, m), 8.19 (1H, s), 7.99 (1H, s), 7.65-7.61 (2H, m), 7.21 (1H, t, *J* 5.24 Hz), 7.12 (1H, t, *J* 7.74 Hz), 5.69 (1H, br s), 3.65-3.57 (2H, m), 3.18 (3H, s), 1.99-1.83 (2H, m), 1.65 (3H, d, *J* 6.72 Hz), 3H under H_2O. LCMS (ES+) 412 $(M+H)^+$, RT 7.68 minutes (*Method 8*).

EXAMPLE 32

(*S*)-8-Chloro-*N*-(2-ethoxyethyl)-3-[1-(9*H*-purin-6-ylamino)ethyl]quinolin-2-amine

Similarly, *Intermediate 23* (150 mg, 0.44 mmol) and 2-ethoxyethylamine (89 mg, 1 mmol) gave the *title compound* (13.1 mg, 7%) as a tan solid. δ_H (DMSO-d_6) 8.25 (1H, s), 8.22 (1H, d, *J* 8.91 Hz), 8.18 (1H, s), 8.01 (1H, s), 7.66-7.61 (2H, m), 7.27 (1H, br s), 7.14 (1H, t, *J* 7.74 Hz), 5.69 (1H, br s), 3.80-3.66 (2H, m), 3.67-3.61 (2H, m), 3.42 (2H, qd, *J* 6.98, 1.19 Hz), 1.65 (3H, d, *J* 6.71 Hz), 1.02 (3H, t, *J* 6.98 Hz), 1H under H_2O. LCMS (ES+) 412 $(M+H)^+$, RT 2.82 minutes (*Method 1*).

EXAMPLE 33

(*S*)-2-{8-Chloro-3-[1-(9*H*-purin-6-ylamino)ethyl]quinolin-2-ylamino}ethanol

Similarly, *Intermediate 23* (150 mg, 0.44 mmol) and 2-aminoethanol (61 mg, 1 mmol) gave the *title compound* (29.8 mg, 17%) as an off-white solid. δ_H (DMSO-d_6) 8.24 (2H, s), 8.18 (1H, br s), 8.00 (1H, s), 7.65-7.60 (2H, m), 7.37 (1H, br s), 7.13 (1H, t, *J* 7.75 Hz), 5.70 (1H, br s), 4.87 (1H, t, *J* 4.98 Hz), 3.77-3.68 (3H, m), 3.60-3.53 (1H, m), 1.64 (3H, d, *J* 6.73 Hz), 1H under H_2O. LCMS (ES+) 384 $(M+H)^+$, RT 6.91 minutes (*Method 8*).

EXAMPLE 34

(*S*)-8-Chloro-*N*-methyl-3-[1-(pyrrolo[2,1-*f*][1,2,4]triazin-4-ylamino)ethyl]quinolin-2-amine

A solution of *Intermediate 38* (75 mg, 0.275 mmol), 4-bromopyrrolo[2,1-*f*][1,2,4]-triazine (55 mg, 0.275 mmol) and DIPEA (1.0 mL, 5.46 mmol) in *n*-butanol (4 mL) was heated at 140°C under microwave irradiation for 1 h. The reaction mixture was concentrated *in vacuo* and purified by preparative HPLC to afford the *title compound* (39.2 mg, 40%) as a yellow solid. δ_H (DMSO-d_6) 8.63 (1H, d, *J* 7.61 Hz), 7.92 (1H, s), 7.89 (1H, s), 7.66 (1H, dd, *J* 2.65, 1.56 Hz), 7.63 (2H, d, *J* 7.74 Hz), 7.20-7.16 (1H, m), 7.13-7.06 (2H, m), 6.67 (1H, dd, *J* 4.37, 2.61 Hz), 5.64-5.58 (1H, m), 3.05 (3H, d, *J* 4.34 Hz), 1.60 (3H, d, *J* 6.75 Hz). LCMS (ES+) 353 $(M+H)^+$, 3.02 minutes (*Method 2*).

EXAMPLE 35

(*S*)-8-Chloro-3-[1-(2-fluoro-9*H*-purin-6-ylamino)ethyl]-*N*-methylquinolin-2-amine

Similarly, *Intermediate 38* (75 mg, 0.275 mmol), 6-chloro-2-fluoro-9*H*-purine (47 mg, 0.275 mmol) and DIPEA (1.0 mL, 5.46 mmol) in *n*-butanol (4 mL) afforded the *title compound* (8.4 mg, 8%) as a white solid. δ_H (DMSO-d_6) 8.92-8.75 (1H, m), 8.19 (1H, s), 7.92 (1H, s), 7.66-7.56 (2H, m), 7.12 (1H, t, *J* 7.77 Hz), 5.55-5.45 (1H, m), 3.08 (3H, d, *J* 4.31 Hz), 1.59 (3H, d, *J* 6.73 Hz), 2H missing. LCMS (ES+) 372 $(M+H)^+$, 2.43 minutes (*Method 2*).

EXAMPLE 36

(*S*)-N^2-{1-[8-Chloro-2-(methylamino)quinolin-3-yl]ethyl}-6-methyl-[1,3,5]triazine-2,4-diamine

Similarly, *Intermediate 38* (75 mg, 0.275 mmol), 2-amino-4-chloro-6-methyl-[1,3,5]triazine (40 mg, 0.275 mmol) and DIPEA (1.0 mL, 5.46 mmol) in *n*-butanol (4 mL) afforded the *title compound* (45 mg, 48%) as a white solid. δ_H (DMSO-d_6) 7.92-7.73 (2H, m), 7.64 (2H, d, *J* 7.73 Hz), 7.20-7.09 (1H, m), 6.85-6.71 (2H, m), 5.38-5.16 (1H, m), 3.05 (3H, d, *J* 4.36 Hz), 2.16-2.12 (3H, m), 1.50 (3H, d, *J* 6.63 Hz), 1H under H_2O. LCMS (ES+) 344 $(M+H)^+$, 3.03 minutes (*Method 1*).

EXAMPLE 37

(*S*)-N^2-{1-[8-Chloro-2-(methylamino)quinolin-3-yl]ethyl}-[1,3,5]triazine-2,4-diamine

Similarly, *Intermediate 38* (75 mg, 0.275 mmol), 2-amino-4-chloro-[1,3,5]triazine (35.7 mg, 0.275 mmol) and DIPEA (1.0 mL, 5.46 mmol) in *n*-butanol (4 mL) afforded the *title compound* (35.9 mg, 40%) as a white solid. δ_H (DMSO-d_6) 8.04-7.98 (1H, m), 7.91-7.68 (2H, m), 7.64 (2H, d, *J* 7.52 Hz), 7.13 (1H, t, *J* 7.78 Hz), 6.95-6.76 (2H, m), 5.35-5.13 (1H, m), 3.06 (3H, d, *J* 4.27 Hz), 2.11 (1H, s), 1.53-1.42 (3H, m). LCMS (ES+) 330 $(M+H)^+$, 9.16 minutes (*Method 9*).

EXAMPLE 38

(*S*)-2-{8-Chloro-3-[1-(pyrrolo[2,1-*f*][1,2,4]triazin-4-ylamino)ethyl]quinolin-2-ylamino}ethanol

A solution of *Intermediate 39* (75 mg, 0.248 mmol), 4-bromopyrrolo[2,1-*f*][1,2,4]-triazine (49 mg, 0.248 mmol) and DIPEA (1.0 mL, 5.46 mmol) in *n*-butanol (5 mL) was stirred at r.t. for 3 days. The reaction mixture was concentrated *in vacuo* and purified by preparative HPLC to give the *title compound* (39.0 mg, 41%) as a white solid. δ_H (DMSO-d_6) 8.61 (1H, d, *J* 7.92 Hz), 8.00 (1H, s), 7.92 (1H, s), 7.70-7.63 (3H, m), 7.30-7.24 (1H, m), 7.15 (1H, t, *J* 7.75 Hz), 7.05 (1H, d, *J* 4.19 Hz), 6.68 (1H, dd, *J* 4.37, 2.61 Hz), 5.69 (1H, t, *J* 7.19 Hz), 4.85 (1H, t, *J* 4.97 Hz), 3.75-3.68 (3H, m), 3.60-3.53 (1H, m), 1.66 (3H, d, *J* 6.73 Hz). LCMS (ES+) 383 $(M+H)^+$, 3.22 minutes (*Method 1*).

EXAMPLE 39

(*S*)-2-{8-Chloro-3-[1-(pyrazolo[1,5-*a*]pyrimidin-7-ylamino)ethyl]quinolin-2-ylamino}ethanol

A solution of *Intermediate 39* (75 mg, 0.248 mmol), 7-chloropyrazolo[1,5-*a*]pyrimidine (38 mg, 0.248 mmol) and DIPEA (1.0 mL, 5.46 mmol) in *n*-butanol (5 mL) was heated at 140°C under microwave irradiation for 1 h. The reaction mixture was concentrated *in vacuo* and purified by preparative HPLC to afford the *title compound* (26.1 mg, 28%) as an off-white solid. δ_H (DMSO-d_6) 8.41 (1H, s), 8.21 (1H, d, *J* 2.29

Hz), 8.10 (1H, d, *J* 5.20 Hz), 8.03 (1H, s), 7.65 (1H, d, *J* 7.52 Hz), 7.58 (1H, d, *J* 7.89 Hz), 7.20 (1H, d, *J* 5.73 Hz), 7.12 (1H, t, *J* 7.73 Hz), 6.51 (1H, d, *J* 2.28 Hz), 5.87 (1H, d, *J* 5.27 Hz), 5.19 (1H, d, *J* 6.85 Hz), 3.82-3.62 (5H, m), 1.69 (3H, d, *J* 6.57 Hz). LCMS (ES+) 383 $(M+H)^+$, 13.2 minutes (*Method 6*).

EXAMPLE 40

(*S*)-2-{8-Chloro-3-[1-(2-fluoro-9*H*-purin-6-ylamino)ethyl]quinolin-2-ylamino}ethanol

Similarly, *Intermediate 39* (75 mg, 0.248 mmol), 6-chloro-2-fluoro-9*H*-purine (42.8 mg, 0.248 mmol) and DIPEA (1.0 mL, 5.46 mmol) in *n*-butanol (5 mL) afforded the *title compound* (13.2 mg, 13%) as an off-white solid. δ_H (DMSO-d_6) 13.14 (1H, s), 8.20-8.15 (1H, m), 7.98 (1H, s), 7.63 (2H, dd, *J* 13.06, 7.57 Hz), 7.17-7.11 (2H, m), 7.02 (1H, s), 5.56-5.48 (1H, m), 4.85-4.80 (1H, m), 3.75-3.69 (3H, m), 3.65-3.58 (1H, m), 1.62 (3H, d, *J* 6.62 Hz). LCMS (ES+) 402 $(M+H)^+$, 7.22 minutes (*Method 8*).

EXAMPLE 41

(*S*)-2-{3-[1-(4-Amino-[1,3,5]triazin-2-ylamino)ethyl]-8-chloroquinolin-2-ylamino}-ethanol

Similarly, *Intermediate 39* (75 mg, 0.248 mmol), 2-amino-4-chloro-[1,3,5]triazine (32 mg, 0.248 mmol) and DIPEA (1.0 mL, 5.46 mmol) in *n*-butanol (5 mL) afforded the *title compound* (42.4 mg, 48%) as an off-white solid. δ_H (DMSO-d_6) 8.07-7.82 (2H, m), 7.69-7.61 (2H, m), 7.23-7.10 (2H, m), 7.00-6.70 (2H, m), 5.34-5.20 (1H, m), 3.80-3.68 (3H, m), 3.61-3.54 (1H, m), 1.56-1.48 (3H, m), 2H under H_2O. LCMS (ES+) 360 $(M+H)^+$, 8.45 minutes (*Method 6*).

EXAMPLE 42

(*S*)-2-{3-[1-(4-Amino-6-methyl-[1,3,5]triazin-2-ylamino)ethyl]-8-chloroquinolin-2-ylamino}ethanol

Similarly, *Intermediate 39* (75 mg, 0.248 mmol), 2-amino-4-chloro-6-methyl-[1,3,5]triazine (36 mg, 0.248 mmol) and DIPEA (1.0 mL, 5.46 mmol) in *n*-butanol (5 mL) afforded the *title compound* (45.6 mg, 49%) as an off-white solid. δ_H (DMSO-d_6) 7.93

(1H, s), 7.79 (1H, d, *J* 8.23 Hz), 7.68-7.63 (2H, m), 7.36-7.26 (1H, m), 7.18-7.12 (1H, m), 7.00-6.40 (2H, m), 6.80 (1H, s), 5.41-5.19 (1H, m), 3.80-3.65 (3H, m), 3.60-3.51 (1H, m), 2.23-2.07 (3H, m), 1.53 (3H, d, *J* 6.70 Hz). LCMS (ES+) 374 $(M+H)^+$, 2.65 minutes (*Method 1*).

EXAMPLE 43

(*S*)-2-{8-Chloro-3-[1-(5-methyl-[1,2,4]triazolo[1,5-*a*]pyrimidin-7-ylamino)ethyl]-quinolin-2-ylamino}ethanol

Similarly, *Intermediate 39* (75 mg, 0.248 mmol), 7-chloro-5-methyl-[1,2,4]triazolo[1,5-*a*]pyrimidine (42 mg, 0.248 mmol) and DIPEA (1.0 mL, 5.46 mmol) in *n*-butanol (5 mL) afforded the *title compound* (61.4 mg, 62%) as a tan solid. δ_H (DMSO-d_6) 8.85-8.63 (1H, m), 8.50 (1H, s), 8.05 (1H, s), 7.66 (1H, dd, *J* 7.54, 1.36 Hz), 7.60 (1H, dd, *J* 7.98, 1.39 Hz), 7.17-7.09 (2H, m), 6.06 (1H, s), 5.23-5.17 (1H, m), 4.90-4.80 (1H, m), 3.78-3.67 (4H, m), 2.38 (3H, s), 1.68 (3H, d, *J* 6.54 Hz). LCMS (ES+) 398 $(M+H)^+$, 7.12 minutes (*Method 8*).

EXAMPLE 44

(*S*)-2-{3-[1-(2-Amino-9*H*-purin-6-ylamino)ethyl]-8-chloroquinolin-2-ylamino}ethanol

Similarly, *Intermediate 39* (75 mg, 0.248 mmol), 6-chloro-9*H*-purin-2-amine (42 mg, 0.248 mmol) and DIPEA (1.0 mL, 5.46 mmol) in *n*-butanol (5 mL) afforded the *title compound* (11.9 mg, 12%) as a tan solid. δ_H (DMSO-d_6) 8.14 (1H, s), 7.93 (1H, s), 7.60-7.48 (4H, m), 7.02 (1H, t, *J* 7.75 Hz), 5.83 (2H, s), 5.55-5.40 (1H, m), 5.05-4.83 (1H, m), 3.72-3.54 (3H, m), 3.42-3.32 (1H, m), 1.54 (3H, d, *J* 6.72 Hz). LCMS (ES+) 399 $(M+H)^+$, 6.67 minutes (*Method 8*).

EXAMPLE 45

(*S*)-2-Methyl-1-{3-[1-(9*H*-purin-6-ylamino)ethyl]-8-chloroquinolin-2-ylamino}propan-2-ol

Similarly, *Intermediate 40* (50 mg, 0.17 mmol), 6-bromopurine (50 mg, 0.25 mmol) and DIPEA (1.0 mL, 5.46 mmol) in *n*-butanol (6 mL) afforded the *title compound*

(13.9 mg, 20%) as a yellow glass. δ_H (DMSO-d_6) 8.25 (1H, br s), 8.17 (1H, br s), 8.04 (1H, s), 7.64 (2H, d, *J* 7.71 Hz), 7.28 (1H, br s), 7.15 (1H, t, *J* 7.78 Hz), 5.17 (1H, s), 3.72-3.64 (1H, m), 3.53-3.45 (1H, m), 3.20 (1H, s), 1.67 (3H, d, *J* 6.67 Hz), 1.14 (6H, s), 2H under H_2O. LCMS (ES+) 412 $(M+H)^+$, 7.39 minutes (*Method 8*).

EXAMPLE 46

(*S*)-1-{8-Chloro-3-[1-(pyrrolo[2,1-*f*][1,2,4]triazin-4-ylamino)ethyl]quinolin-2-ylamino}-2-methylpropan-2-ol

Similarly, *Intermediate 40* (50 mg, 0.17 mmol), 4-bromopyrrolo[2,1-*f*][1,2,4]-triazine (100 mg, 0.51 mmol) and DIPEA (1.0 mL, 5.46 mmol) in *n*-butanol (6 mL) afforded the *title compound* (9.2 mg, 13%) as a clear glass. δ_H (DMSO-d_6) 8.62 (1H, d, *J* 8.10 Hz), 8.06 (1H, s), 7.93 (1H, s), 7.73-7.63 (3H, m), 7.20-7.12 (2H, m), 7.03-7.00 (1H, m), 6.68-6.65 (1H, m), 5.77-5.70 (1H, m), 5.08 (1H, s), 3.68 (1H, dd, *J* 13.43, 5.71 Hz), 3.48 (1H, dd, *J* 13.42, 5.28 Hz), 1.70 (3H, d, *J* 6.69 Hz), 1.15 (3H, s), 1.14 (3H, s). LCMS (ES+) 411 $(M+H)^+$, 7.99 minutes (*Method 8*).

EXAMPLE 47

(*S*)-1-{3-[1-(4-Amino-6-methyl-[1,3,5]triazin-2-ylamino)ethyl]-8-chloroquinolin-2-ylamino}-2-methylpropan-2-ol

Similarly, *Intermediate 40* (50 mg, 0.17 mmol), 2-amino-4-chloro-6-methyl-[1,3,5]triazine (50 mg, 0.35 mmol) and DIPEA (1.0 mL, 5.46 mmol) in *n*-butanol (6 mL) afforded the *title compound* (26.8 mg, 39%) as a clear glass. δ_H (DMSO-d_6) 7.96 (1H, s), 7.83-7.52 (3H, m), 7.34-7.05 (1H, m), 7.00-6.50 (3H, m), 5.47-5.15 (2H, m), 3.75-3.21 (2H, m), 2.20-2.09 (3H, m), 1.56 (3H, d, *J* 6.72 Hz), 1.20-1.11 (6H, m). LCMS (ES+) 402 $(M+H)^+$, 6.91 minutes (*Method 8*).

EXAMPLE 48

(*S*)-1-(8-Chloro-3-{1-[4-(methylamino)-[1,3,5]triazin-2-ylamino]ethyl}quinolin-2-ylamino)-2-methylpropan-2-ol

Similarly, *Intermediate 40* (50 mg, 0.17 mmol), 4-chloro-2-(methylamino)-[1,3,5]triazine (50 mg, 0.28 mmol) and DIPEA (1.0 mL, 5.46 mmol) in *n*-butanol (6 mL) afforded the *title compound* (20.1 mg, 30%) as an off-white solid. δ_H (DMSO-d_6) 8.20-7.80 (2H, m) 7.68-7.59 (2H, m), 7.30 (1H, br s), 7.20-7.00 (2.5H, m), 6.91 (0.5H, br s), 5.45-5.10 (2H, m), 3.70-3.40 (2H, m), 2.80-2.65 (3H, m), 1.55 (3H, d, *J* 6.79 Hz), 1.27-1.09 (6H, m). LCMS (ES+) 402 $(M+H)^+$, 7.07 minutes (*Method 8*).

EXAMPLE 49

(*S*)-1-{3-[1-(4-Amino-[1,3,5]triazin-2-ylamino)ethyl]-8-chloroquinolin-2-ylamino}-2-methylpropan-2-ol

Similarly, *Intermediate 40* (50 mg, 0.17 mmol), 2-amino-4-chloro-[1,3,5]triazine (50 mg, 0.30 mmol) and DIPEA (1.0 mL, 5.46 mmol) in *n*-butanol (6 mL) afforded the *title compound* (14.8 mg, 22%) as an off-white solid. δ_H (DMSO-d_6) 8.12-7.81 (2H, m), 7.71-7.62 (2H, m), 7.33-6.85 (3H, m), 5.44-5.11 (2H, m), 3.72-3.63 (1H, m), 3.65-3.41 (1H, m), 1.57 (3H, s), 1.16 (6H, d, *J* 6.30 Hz), 2H under H_2O. LCMS (ES+) 388 $(M+H)^+$, 8.80 minutes (*Method 9*).

EXAMPLE 50

(*S*)-1-{8-Chloro-3-[1-(pyrido[3,2-*d*]pyrimidin-4-ylamino)ethyl]quinolin-2-ylamino}-2-methylpropan-2-ol

Similarly, *Intermediate 40* (50 mg, 0.17 mmol), 4-chloropyrido[3,2-*d*]pyrimidine (50 mg, 0.30 mmol) and DIPEA (1.0 mL, 5.46 mmol) in *n*-butanol (6 mL) afforded the *title compound* (24.5 mg, 34%) as a brown solid. δ_H (DMSO-d_6) 9.02 (1H, d, *J* 8.34 Hz), 8.88 (1H, dd, *J* 4.25, 1.57 Hz), 8.55 (1H, s), 8.17 (1H, dd, *J* 8.45, 1.58 Hz), 8.11 (1H, s), 7.89 (1H, dd, *J* 8.47, 4.24 Hz), 7.66 (2H, d, *J* 7.75 Hz), 7.22-7.11 (2H, m), 5.80-5.71 (1H, m), 5.11 (1H, s), 3.67 (1H, dd, *J* 13.42, 5.72 Hz), 3.55-3.47 (1H, m), 1.76 (3H, d, *J* 6.75 Hz), 1.13 (6H, d, *J* 11.92 Hz). LCMS (ES+) 423 $(M+H)^+$, 9.72 minutes (*Method 9*).

EXAMPLE 51

(*S*)-1-{3-[1-(2-Amino-9*H*-purin-6-ylamino)ethyl]-8-chloroquinolin-2-ylamino}-2-methylpropan-2-ol

Similarly, *Intermediate 40* (50 mg, 0.17 mmol), 6-chloro-9*H*-purin-2-amine (50 mg, 0.29 mmol) and DIPEA (1.0 mL, 5.46 mmol) in *n*-butanol (6 mL) at 150°C afforded the *title compound* (10.1 mg, 14%) as a white solid. δ_H (DMSO-d_6) 8.44 (1H, s), 8.07 (1H, s), 8.00-7.88 (1H, m), 7.76-7.57 (4H, m), 7.15 (1H, t, *J* 7.75 Hz), 6.02-5.92 (2H, m), 5.70-5.58 (1H, m), 5.46-5.37 (1H, m), 3.79-3.69 (1H, m), 1.69 (3H, d, *J* 6.68 Hz), 1.16 (3H, s), 1.08 (3H, s), 1H under H_2O. LCMS (ES+) 427 $(M+H)^+$, 6.86 minutes (*Method 8*).

EXAMPLE 52

(*S*)-1-{8-Chloro-3-[1-(thieno[2,3-*d*]pyrimidin-4-ylamino)ethyl]quinolin-2-ylamino}-2-methylpropan-2-ol

Similarly, *Intermediate 40* (50 mg, 0.17 mmol), 4-chlorothieno[2,3-*d*]pyrimidine (50 mg, 0.29 mmol) and DIPEA (1.0 mL, 5.46 mmol) in *n*-butanol (6 mL) afforded the *title compound* (6 mg, 8%) as a brown solid. δ_H (DMSO-d_6) 8.41-8.33 (2H, m), 8.05 (1H, s), 7.77 (1H, d, *J* 5.96 Hz), 7.72-7.62 (3H, m), 7.19-7.13 (1H, m), 7.11-7.06 (1H, m), 5.75-5.70 (1H, m), 5.12 (1H, s), 3.69 (1H, dd, *J* 13.33, 5.50 Hz), 3.48 (1H, dd, *J* 13.35, 5.17 Hz), 1.69 (3H, d, *J* 6.58 Hz), 1.15 (3H, s), 1.12 (3H, s). LCMS (ES+) 428 $(M+H)^+$, 1.84 minutes (*Method 2*).

EXAMPLE 53

(*S*)-1-{8-Chloro-3-[1-(pyrazolo[1,5-*a*]pyrimidin-7-ylamino)ethyl]quinolin-2-ylamino}-2-methylpropan-2-ol

Similarly, *Intermediate 40* (50 mg, 0.17 mmol), 7-chloropyrazolo[1,5-*a*]-pyrimidine (100 mg, 0.51 mmol) and DIPEA (1.0 mL, 5.46 mmol) in *n*-butanol (6 mL) afforded the *title compound* (15.1 mg, 22%) as a tan glass. δ_H (DMSO-d_6) 8.20 (1H, d, *J* 2.28 Hz), 8.11 (1H, d, *J* 5.21 Hz), 8.06 (1H, s), 7.66 (1H, dd, *J* 7.55, 1.35 Hz), 7.60 (1H,

dd, *J* 7.99, 1.38 Hz), 7.16-7.09 (2H, m), 6.51 (1H, d, *J* 2.28 Hz), 5.91 (1H, d, *J* 5.27 Hz), 5.27-5.19 (2H, m), 3.77 (1H, dd, *J* 13.45, 5.77 Hz), 3.57 (1H, dd, *J* 13.46, 5.60 Hz), 1.73 (3H, d, *J* 6.59 Hz), 1.21 (3H, s), 1.19 (3H, s), 1H under H_2O. LCMS (ES+) 411 $(M+H)^+$, 2.99 minutes (*Method 1*).

EXAMPLE 54

(*S*)-1-({3-[1-(4-Amino-[1,3,5]triazin-2-ylamino)ethyl]-8-chloroquinolin-2-ylamino}methyl)cyclopropanol

Similarly, *Intermediate 41* (50 mg, 0.15 mmol), 2-amino-4-chloro-[1,3,5]triazine (50 mg, 0.38 mmol) and DIPEA (1.0 mL, 5.46 mmol) in *n*-butanol (1 mL) afforded the *title compound* (6.0 mg, 10%) as a clear glass. δ_H (DMSO-d_6) 8.15-7.70 (2H, m), 7.67 (3H, t, *J* 8.97 Hz), 7.28 (1H, t, *J* 5.23 Hz), 7.16 (1H, t, *J* 7.70 Hz), 7.10-6.70 (2H, m), 5.95 (0.5H, br s), 5.75 (0.5H, br s), 5.40-5.20 (1H, m), 3.75-3.50 (2H, m), 1.56 (3H, br s), 0.63 (4H, br s). LCMS (ES+) 386 $(M+H)^+$, 8.80 minutes (*Method 9*).

EXAMPLE 55

(*S*)-1-[(8-Chloro-3-{1-[4-(methylamino)-[1,3,5]triazin-2-ylamino]ethyl}quinolin-2-ylamino)methyl]cyclopropanol

Similarly, *Intermediate 41* (50 mg, 0.15 mmol), 4-chloro-2-(methylamino)-[1,3,5]triazine (50 mg, 0.35 mmol) and DIPEA (1.0 mL, 5.46 mmol) in *n*-butanol (1 mL) afforded the *title compound* (10.3 mg, 17%) as a clear glass. δ_H (DMSO-d_6) 8.14-7.84 (3H, m), 7.70-7.62 (3H, m), 7.34-6.97 (2H, m), 5.95-5.65 (1H, m), 5.40-5.20 (1H, m), 3.83-3.48 (3H, m), 3.20 (1H, s), 2.80-2.70 (4H, m), 1.56-1.52 (4H, m). LCMS (ES+) 400 $(M+H)^+$, 7.11 minutes (*Method 8*).

EXAMPLE 56

(*S*)-1-({3-[1-(4-Amino-6-methyl-[1,3,5]triazin-2-ylamino)ethyl]-8-chloroquinolin-2-ylamino}methyl)cyclopropanol

Similarly, *Intermediate 41* (50 mg, 0.15 mmol), 2-amino-4-chloro-6-methyl-[1,3,5]triazine (50 mg, 0.35 mmol) and DIPEA (1.0 mL, 5.46 mmol) in *n*-butanol (1 mL)

afforded the *title compound* (14.1 mg, 24%) as an off-white solid. δ_H (DMSO-d_6) 7.84 (1H, s), 7.67 (1H, d, *J* 8.29 Hz), 7.58-7.51 (2H, m), 7.26 (1H, s), 7.08-7.02 (1H, m), 6.60-6.64 (1H, m), 5.30-5.08 (1H, m), 3.70-3.12 (8H, m), 2.10-1.98 (3H, m), 1.44 (3H, d, *J* 6.55 Hz). LCMS (ES+) 400 $(M+H)^+$, 8.92 minutes (*Method 9*).

EXAMPLE 57

(*S*)-1-({8-Chloro-3-[1-(9*H*-purin-6-ylamino)ethyl]quinolin-2-ylamino}methyl)-cyclopropanol

Similarly, *Intermediate 41* (50 mg, 0.15 mmol), 6-chloropurine (50 mg, 0.32 mmol) and DIPEA (1.0 mL, 5.46 mmol) in *n*-butanol (6 mL) afforded the *title compound* (6.0 mg, 10%) as an off-white solid. δ_H (DMSO-d_6) 8.26 (1H, s), 8.18 (1H, s), 8.04 (1H, s), 7.64 (2H, d, *J* 7.72 Hz), 7.50-7.42 (1H, m), 7.19-7.11 (1H, m), 5.80-5.70 (2H, m), 3.82 (1H, dd, *J* 13.97, 5.57 Hz), 3.57 (1H, dd, *J* 14.05, 4.71 Hz), 1.68 (3H, d, *J* 6.75 Hz), 0.71-0.54 (4H, m), 2H under H_2O. LCMS (ES+) 410 $(M+H)^+$, 7.21 minutes (*Method 8*).

EXAMPLE 58

(*S*)-1-(3-{8-Chloro-3-[1-(9*H*-purin-6-ylamino)ethyl]quinolin-2-ylamino}propyl)-pyrrolidin-2-one

A solution of *Intermediate 42* (169 mg, 0.44 mmol), 6-chloropurine (61 mg, 0.40 mmol) and DIPEA (1.0 mL, 5.46 mmol) in *n*-butanol (3 mL) was heated at 120°C for 20 h. The reaction mixture was concentrated *in vacuo* and the residue was purified by preparative HPLC to afford the *title compound* (26.6 mg, 14%) as a brown solid. δ_H (DMSO-d_6) 8.31-8.14 (3H, m), 7.97 (1H, s), 7.65-7.56 (2H, m), 7.32-7.25 (1H, m), 7.11 (1H, t, *J* 7.72 Hz), 5.75-5.60 (1H, m), 3.70-3.46 (3H, m), 2.25 (2H, t, *J* 8.01 Hz), 2.00-1.83 (4H, m), 1.64 (3H, d, *J* 6.69 Hz), 3H under H_2O. LCMS (ES+) 465 $(M+H)^+$, 2.20 minutes (*Method 1*).

EXAMPLE 59

(*S*)-5-({8-Chloro-3-[(*S*)-1-(pyrrolo[2,1-*f*][1,2,4]triazin-4-ylamino)ethyl]quinolin-2-ylamino}methyl)pyrrolidin-2-one

Following the procedure described for *Example 39*, *Intermediate 43* (50 mg, 0.16 mmol), 4-bromopyrrolo[2,1-*f*][1,2,4]triazine (40 mg, 0.28 mmol) and DIPEA (1.0 mL, 5.46 mmol) in *n*-butanol (6 mL) at 160°C afforded the *title compound* (16.9 mg, 24%) as an off-white solid. δ_H (DMSO-d_6) 8.65 (1H, d, *J* 7.86 Hz), 8.02 (1H, s), 7.95 (1H, s), 7.77 (1H, s), 7.70-7.65 (3H, m), 7.32-7.26 (1H, m), 7.16 (1H, t, *J* 7.76 Hz), 7.08-7.05 (1H, m), 6.69 (1H, dd, *J* 4.37, 2.61 Hz), 5.74-5.66 (1H, m), 4.00-3.91 (1H, m), 3.86-3.77 (1H, m), 3.56-3.47 (1H, m), 2.25-2.01 (3H, m), 1.91-1.79 (1H, m), 1.66 (3H, d, *J* 6.72 Hz). LCMS (ES+) 436 $(M+H)^+$, 3.03 minutes (*Method 1*).

EXAMPLE 60

(*S*)-5-({8-Chloro-3-[(*S*)-1-(pyrido[3,2-*d*]pyrimidin-4-ylamino)ethyl]quinolin-2-ylamino}methyl)pyrrolidin-2-one

Similarly, *Intermediate 43* (50 mg, 0.16 mmol), 4-chloropyrido[3,2-*d*]pyrimidine (40 mg, 0.27 mmol) and DIPEA (1.0 mL, 5.46 mmol) in *n*-butanol (6 mL) at 160°C afforded the *title compound* (26.4 mg, 37%) as a brown solid. δ_H (DMSO-d_6) 9.06 (1H, d, *J* 8.09 Hz), 8.91 (1H, dd, *J* 4.26, 1.58 Hz), 8.56 (1H, s), 8.17 (1H, dd, *J* 8.45, 1.58 Hz), 8.09 (1H, s), 7.90 (1H, dd, *J* 8.48, 4.25 Hz), 7.77 (1H, s), 7.67-7.61 (2H, m), 7.33 (1H, t, *J* 5.52 Hz), 7.14 (1H, t, *J* 7.76 Hz), 5.75-5.69 (1H, m), 4.01-3.95 (1H, m), 3.81-3.74 (1H, m), 3.61-3.53 (1H, m), 2.25-2.02 (3H, m), 1.90-1.83 (1H, m), 1.72 (3H, d, *J* 6.76 Hz). LCMS (ES+) 448 $(M+H)^+$, 2.87 minutes (*Method 1*).

EXAMPLE 61

(*S*)-5-({8-Chloro-3-[(*S*)-1-(9*H*-purin-6-ylamino)ethyl]quinolin-2-ylamino}methyl)-pyrrolidin-2-one

Similarly, *Intermediate 43* (250 mg, 0.78 mmol), 6-chloropurine (121 mg, 0. 87 mmol) and DIPEA (1.0 mL, 5.46 mmol) in *n*-butanol (6 mL) at 150°C afforded the *title compound* (56.2 mg, 17%) as a pale yellow solid. δ_H (DMSO-d_6) 13.02 (1H, s), 8.29-8.15

(2H, m), 8.02 (1H, s), 7.77-7.68 (1H, m), 7.66-7.60 (2H, m), 7.43-7.35 (1H, m), 7.39 (1H, s), 7.14 (1H, t, *J* 7.75 Hz), 5.82-5.62 (1H, m), 4.03-3.93 (1H, m), 3.98 (1H, s), 3.78-3.54 (2H, m), 2.26-2.02 (2H, m), 1.90-1.81 (1H, m), 1.64 (3H, d, *J* 6.67 Hz). LCMS (ES+) 437 $(M+H)^+$, 7.98 minutes (*Method 8*).

EXAMPLE 62

(*S*)-5-({3-[(*S*)-1-(4-Amino-6-methyl-[1,3,5]triazin-2-ylamino)ethyl]-8-chloroquinolin-2-ylamino}methyl)pyrrolidin-2-one

Similarly, *Intermediate 43* (50 mg, 0.16 mmol), 2-amino-4-chloro-6-methyl-[1,3,5]triazine (40 mg, 0.28 mmol) and DIPEA (1.0 mL, 5.46 mmol) in *n*-butanol (6 mL) at 140°C afforded the *title compound* (9.2 mg, 13%) as a pale yellow solid. δ_H (DMSO-d_6) 7.93 (1H, s), 7.73-7.61 (3H, m), 7.19-7.12 (1H, m), 6.90-6.66 (2H, m), 5.34-5.20 (1H, m), 4.00-3.88 (1H, m), 3.78-3.70 (1H, m), 3.61-3.53 (1H, m), 2.27-2.01 (6H, m), 1.90-1.80 (1H, m), 1.52 (3H, d, *J* 6.71 Hz), 1H under H_2O. LCMS (ES+) 427 $(M+H)^+$, 2.24 minutes (*Method 2*).

EXAMPLE 63

(*S*)-5-({3-[(*S*)-1-(2-Amino-9*H*-purin-6-ylamino)ethyl]-8-chloroquinolin-2-ylamino}-methyl)pyrrolidin-2-one

Similarly, *Intermediate 43* (50 mg, 0.16 mmol), 6-chloro-9*H*-purin-2-amine (40 mg, 0.28 mmol) and DIPEA (1.0 mL, 5.46 mmol) in *n*-butanol (6 mL) at 160°C afforded the *title compound* (6.9 mg, 10%) as an off-white solid. δ_H (DMSO-d_6) 8.03 (1H, s), 7.75-7.62 (5H, m), 7.44-7.39 (1H, m), 7.19-7.13 (1H, m), 5.94-5.45 (2H, m), 3.98-3.92 (1H, m), 3.66-3.58 (3H, m), 2.19-1.91 (3H, m), 1.75-1.58 (4H, m), 1H under H_2O. LCMS (ES+) 452 $(M+H)^+$, 7.32 minutes (*Method 8*).

EXAMPLE 64

1-[(*S*)-3-({8-Chloro-3-[(*S*)-1-(9*H*-purin-6-ylamino)ethyl]quinolin-2-ylamino}methyl)-pyrrolidin-1-yl]ethanone

Similarly, *Intermediate 44* (50 mg, 0.44 mmol), 6-chloropurine (50 mg, 0.32 mmol) and DIPEA (1.0 mL, 5.46 mmol) in *n*-butanol (6 mL) at 160°C afforded the *title compound* (7.2 mg, 11%) as an off-white solid. δ_H (DMSO-d_6) 13.1-12.6 (1H, br s), 8.27-8.12 (3H, m), 7.97 (1H, d, *J* 7.19 Hz), 7.63-7.56 (2H, m), 7.40-7.29 (1H, m), 7.13-7.07 (1H, m), 5.78-5.55 (1H, m), 3.65-3.29 (4H, m), 3.22-3.07 (2H, m), 2.76-2.60 (1H, m), 1.98-1.75 (4H, m), 1.74-1.56 (4H, m). LCMS (ES+) 465 $(M+H)^+$, 2.48 minutes (*Method 2*).

EXAMPLE 65

(*S*)-5-({3-[(*S*)-1-(2-Aminopyrimidin-4-ylamino)ethyl]-8-chloroquinolin-2-ylamino}methyl)pyrrolidin-2-one

A solution of *Intermediate 43* (50 mg, 0.157 mmol), 2-amino-4-chloropyrimidine (40.7 mg, 0.314 mmol) and DIPEA (0.109 mL, 0.628 mmol) in *n*-butanol (1.5 mL) was heated under microwave irradiation at 170°C for 2.5 h. After cooling, the mixture was dissolved in EtOAc (75 mL) and washed with saturated brine (3 x 15 mL). The organic layer was separated, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by preparative HPLC gave the *title compound* (3.7 mg, 6%) as a white solid. δ_H (MeOD-d_4) 8.55 (2H, br s), 7.95 (1H, s), 7.70-7.60 (3H, m), 7.18 (1H, t, *J* 7.78 Hz), 6.05 (1H, d, *J* 6.58 Hz), 5.47 (1H, d, *J* 7.79 Hz), 5.00-4.80 (3H, m, masked by H_2O), 4.22-4.15 (1H, m), 3.89 (1H, dd, *J* 13.83, 4.67 Hz), 3.78 (1H, dd, *J* 13.83, 4.98 Hz), 2.40-2.20 (3H, m), 2.05-1.95 (1H, m), 1.68 (3H, d, *J* 6.49 Hz). LCMS (ES+) 412 $(M+H)^+$, 2.69 minutes (*Method 1*).

EXAMPLES 66 & 67

4-Amino-2-[(*S*)-1-(8-chloro-2-{[(*S*)-5-oxopyrrolidin-2-yl]methylamino}quinolin-3-yl)ethylamino]pyrimidine-5-carbonitrile and 2-Amino-4-[(*S*)-1-(8-chloro-2-{[(*S*)-5-oxopyrrolidin-2-yl]methylamino}quinolin-3-yl)ethylamino]pyrimidine-5-carbonitrile

A solution of *Intermediate 43* (100 mg, 0.314 mmol), 2,4-dichloro-5-cyano-pyrimidine (81.9 mg, 0.471 mmol) and DIPEA (0.164 mL, 0.941 mmol) in *n*-butanol (2 mL) was stirred at r.t. for 72 h. The mixture was dissolved in EtOAc (150 mL) and washed with saturated brine (3 x 30 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 97:2:1 DCM/ MeOH/NH_3 solution in MeOH) gave an off-white glass (60 mg, 42%). LCMS (ES+) 456 $(M+H)^+$ (mixture of regioisomers). The off-white glass (60 mg, 0.132 mmol), 7M NH_3 in MeOH (1.5 mL) and NH_4OH (1 mL) were combined and heated under microwave irradiation at 120°C for 1 h. After addition of saturated brine (20 mL) the reaction mixture was extracted with EtOAc (3 x 60 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by preparative HPLC gave the *title compounds* (9.7 mg, 17%; and 22.2 mg, 39%) as white solids. δ_H (DMSO-d_6) 8.23 (1H, s), 8.01 (1H, s), 7.86 (1H, d, *J* 8.07 Hz), 7.73-7.64 (3H, m), 7.30-7.20 (1H, br s), 7.18 (2H, t, *J* 7.76 Hz), 6.88 (1H, t, *J* 5.30 Hz), 5.55-5.47 (1H, m), 3.98-3.92 (1H, m), 3.73-3.57 (2H, m), 2.22-1.96 (3H, m), 1.83-1.72 (1H, m), 1.63 (3H, d, *J* 6.74 Hz). δ_H (DMSO-d_6; T = 125°C) 8.23 (1H, s), 8.00 (1H, s), 7.65 (1H, s), 7.63 (1H, s), 7.45 (1H, d, *J* 8.00 Hz), 7.17 (1H, t, *J* 8.00 Hz), 7.09 (1H, br s), 6.70-6.57 (3H, m), 5.40-5.30 (1H, m), 4.02-3.95 (1H, m), 3.80-3.68 (2H, m), 2.25-2.10 (3H, m), 1.96-1.87 (1H, m), 1.63 (3H, d, *J* 8.00 Hz). LCMS (ES+) 412 $(M+H)^+$, 3.11 minutes (*Method 1*). LCMS (ES+) 412 $(M+H)^+$, 1.70 minutes (*Method 2*).

EXAMPLE 68

(*S*)-N^6-[1-(2-Amino-8-chloroquinolin-3-yl)ethyl]-9*H*-purine-2,6-diamine

Following the procedure described for *Example 39*, *Intermediate 45* (55 mg, 0.25 mmol), 6-chloro-9*H*-purin-2-amine (44 mg, 0.26 mmol) and DIPEA (0.5 mL, 2.23 mmol) in *n*-butanol (4 mL) at 140°C afforded the *title compound* (30.1 mg, 34%) as an off-white solid. δ_H (DMSO-d_6) 8.05 (1H, s), 7.72 (1H, s), 7.68-7.60 (3H, m), 7.14 (1H, t, *J* 7.74

Hz), 6.80 (2H, s), 5.78 (2H, s), 5.60-5.45 (1H, m), 1.63 (3H, d, *J* 6.75 Hz), 1H under H_2O. LCMS (ES+) 355 $(M+H)^+$, 6.37 minutes (*Method 8*).

EXAMPLE 69

(*S*)-N^2-[1-(2-Amino-8-chloroquinolin-3-yl)ethyl]-[1,3,5]triazine-2,4-diamine

Similarly, *Intermediate 45* (55 mg, 0.25 mmol), 2-amino-4-chloro-[1,3,5]triazine (35 mg, 0.26 mmol) and DIPEA (0.5 mL, 2.23 mmol) in *n*-butanol (4 mL) at 140°C afforded the *title compound* (5.2 mg, 6%) as a white solid. δ_H (DMSO-d_6) 8.59 (1H, s), 8.00 (1H, br s), 7.92 (1H, s), 7.80 (0.5H, m), 7.70 (0.5H, m), 7.64 (1H, t, *J* 6.66 Hz), 7.14 (1H, s), 7.00-6.60 (4H, m), 5.30-5.10 (1H, m), 1.50 (3H, s). LCMS (ES+) 316 $(M+H)^+$, 8.28 minutes (*Method 9*).

EXAMPLE 70

(*S*)-*N*-[1-(2-Amino-8-chloroquinolin-3-yl)ethyl]pyrido[3,2-*d*]pyrimidin-4-amine

Similarly, *Intermediate 45* (55 mg, 0.25 mmol), 4-chloropyrido[3,2-*d*]pyrimidine (44 mg, 0.26 mmol) and DIPEA (0.5 mL, 2.23 mmol) in *n*-butanol (4 mL) at 140°C afforded the *title compound* (6.4 mg, 7%) as an off-white solid. δ_H (DMSO-d_6) 9.03 (1H, d, *J* 7.98 Hz), 8.92-8.89 (1H, m), 8.51 (1H, s), 8.20-8.14 (1H, m), 8.06 (1H, s), 7.90 (1H, dd, *J* 8.46, 4.25 Hz), 7.65-7.58 (2H, m), 7.11 (1H, t, *J* 7.74 Hz), 6.85 (2H, s), 5.69-5.62 (1H, m), 1.71 (3H, d, *J* 6.80 Hz). LCMS (ES+) 351 $(M+H)^+$, 6.71 minutes (*Method 8*).

EXAMPLE 71

(*S*)-8-Chloro-3-[1-(pyrrolo[2,1-*f*][1,2,4]triazin-4-ylamino)ethyl]quinolin-2-amine

Following the procedure described for *Example 38*, *Intermediate 45* (70 mg, 0.26 mmol), 4-bromopyrrolo[2,1-*f*][1,2,4]triazine (52 mg, 0.26 mmol) and DIPEA (1.0 mL, 5.46 mmol) in *n*-butanol (5 mL) at r.t. for 20 h afforded the *title compound* (2.6 mg) as an off-white solid. δ_H (DMSO-d_6) 8.62-8.57 (1H, m), 8.00 (1H, s), 7.89 (1H, s), 7.69-7.63 (3H, m), 7.17-7.11 (1H, m), 7.08 (1H, d, *J* 4.27 Hz), 6.79 (2H, br s), 6.69 (1H, dd, *J* 4.35, 2.60 Hz), 5.67-5.61 (1H, m), 1.64 (3H, d, *J* 6.76 Hz). LCMS (ES+) 339 $(M+H)^+$, 3.19 minutes (*Method 1*).

EXAMPLE 72

(*S*)-2-(*N'*-{8-Chloro-3-[1-(9*H*-purin-6-ylamino)ethyl]quinolin-2-yl}-*N'*-methylamino)-*N*-methylacetamide

Following the procedure described for *Example 39*, *Intermediate 46* (65 mg, 0.21 mmol), 6-chloropurine (50 mg, 0.32 mmol) and DIPEA (1.0 mL, 4.56 mmol) in *n*-butanol (6 mL) at 150°C afforded the *title compound* (10.7 mg, 12%) as a clear glass. δ_H (DMSO-d_6) 13.04-12.76 (1H, br s), 8.29 (2H, d, *J* 17.68 Hz), 8.11 (2H, d, *J* 9.46 Hz), 8.05 (1H, d, *J* 5.25 Hz), 7.70-7.63 (2H, m), 7.24 (1H, t, *J* 7.78 Hz), 5.72-5.54 (1H, m), 4.42 (1H, d, *J* 16.19 Hz), 3.86 (1H, d, *J* 16.18 Hz), 3.13 (3H, s), 2.62 (3H, d, *J* 4.61 Hz), 1.56 (3H, d, *J* 6.70 Hz). LCMS (ES+) 425 $(M+H)^+$, 2.31 minutes (*Method 2*).

EXAMPLE 73

(*S*)-2-(*N'*-{3-[1-(4-Amino-6-methyl-[1,3,5]triazin-2-ylamino)ethyl]-8-chloroquinolin-2-yl}-*N'*-methylamino)-*N*-methylacetamide

Similarly, *Intermediate 46* (65 mg, 0.21 mmol), 2-amino-4-chloro-6-methyl-[1,3,5]triazine (50 mg, 0.35 mmol) and DIPEA (1.0 mL, 4.56 mmol) in *n*-butanol (6 mL) at 150°C afforded the *title compound* (44.9 mg, 52%) as a clear glass. δ_H (DMSO-d_6) 8.30-8.21 (1H, m), 8.14-8.07 (1H, m), 7.99 (1H, d, *J* 7.66 Hz), 7.79-7.73 (2H, m), 7.37-7.31 (1H, m), 5.41-5.33 (1H, m), 4.62-4.48 (1H, m), 3.92-3.81 (1H, m), 3.20 (2H, s), 3.14 (3H, s), 2.71 (3H, d, *J* 4.35 Hz), 1.40 (3H, s), 3H under H_2O. LCMS (ES+) 415 $(M+H)^+$, 7.47 minutes (*Method 7*).

EXAMPLE 74

(*S*)-2-(*N'*-{3-[1-(4-Amino-[1,3,5]triazin-2-ylamino)ethyl]-8-chloroquinolin-2-yl}-*N'*-methylamino)-*N*-methylacetamide

Similarly, *Intermediate 46* (65 mg, 0.21 mmol), 2-amino-4-chloro-[1,3,5]triazine (50 mg, 0.38 mmol) and DIPEA (1.0 mL, 4.56 mmol) in *n*-butanol (6 mL) at 150°C afforded the *title compound* (32.4 mg, 39%) as a white solid. δ_H (DMSO-d_6) 8.26 (1H, s), 8.15-8.05 (1H, m), 7.99 (1H, d, *J* 8.67 Hz), 7.77 (2H, d, *J* 7.49 Hz), 7.38-7.30 (1H, m),

5.42-5.32 (1H, m), 4.55-4.39 (1H, m), 3.90-3.83 (1H, m), 3.20-3.11 (3H, m), 2.73-2.67 (3H, m), 1.49-1.39 (3H, m), 3H under H_2O. LCMS (ES+) 401 $(M+H)^+$, 7.56 minutes (*Method 8*).

EXAMPLE 75

(*S*)-2-(*N'*-{8-Chloro-3-[1-(thieno[2,3-*d*]pyrimidin-4-ylamino)ethyl]quinolin-2-yl}-*N'*-methylamino)-*N*-methylacetamide

Similarly, *Intermediate 46* (50 mg, 0.16 mmol), 4-chlorothieno[2,3-*d*]pyrimidine (50 mg, 0.23 mmol) and DIPEA (1.0 mL, 4.56 mmol) in *n*-butanol (6 mL) at 160°C afforded the *title compound* (7.5 mg, 11%) as a yellow solid. δ_H (DMSO-d_6) 8.45 (1H, d, *J* 6.69 Hz), 8.32 (1H, s), 8.29 (1H, s), 8.06 (1H, d, *J* 5.15 Hz), 7.88 (1H, d, *J* 5.99 Hz), 7.80-7.74 (2H, m), 7.67 (1H, d, *J* 5.98 Hz), 7.34-7.29 (1H, m), 5.72-5.67 (1H, m), 4.45 (1H, d, *J* 16.27 Hz), 3.96 (1H, d, *J* 16.32 Hz), 3.20 (3H, s), 2.69 (3H, d, *J* 4.62 Hz), 1.62 (3H, d, *J* 6.69 Hz). LCMS (ES+) 441 $(M+H)^+$, 3.12 minutes (*Method 1*).

EXAMPLE 76

(*S*)-2-(*N'*-{8-Chloro-3-[1-(pyrrolo[2,1-*f*][1,2,4]triazin-4-ylamino)ethyl]quinolin-2-yl)}-*N'*-methylamino)-*N*-methylacetamide

Similarly, *Intermediate 46* (50 mg, 0.16 mmol), 4-bromopyrrolo[2,1-*f*][1,2,4]-triazine (50 mg, 0.25 mmol) and DIPEA (1.0 mL, 4.56 mmol) in *n*-butanol (6 mL) at 160°C afforded the *title compound* (17.8 mg, 26%) as a beige solid. δ_H (DMSO-d_6) 8.61 (1H, d, *J* 6.86 Hz), 8.19 (1H, s), 7.96 (1H, d, *J* 5.33 Hz), 7.74-7.64 (3H, m), 7.57 (1H, dd, *J* 2.62, 1.56 Hz), 7.24 (1H, t, *J* 7.80 Hz), 7.04 (1H, dd, *J* 4.37, 1.60 Hz), 6.60 (1H, dd, *J* 4.37, 2.60 Hz), 5.65-5.57 (1H, m), 4.31 (1H, d, *J* 16.27 Hz), 3.86 (1H, d, *J* 16.27 Hz), 3.08 (3H, s), 2.59 (3H, d, *J* 4.61 Hz), 1.53 (3H, d, *J* 6.70 Hz). LCMS (ES+) 424 $(M+H)^+$, 3.25 minutes (*Method 1*).

EXAMPLE 77

(*S*)-2-(*N'*-{8-Chloro-3-[1-(pyrazolo[1,5-*a*]pyrimidin-7-ylamino)ethyl]quinolin-2-yl}-*N'*-methylamino)-*N*-methylacetamide

Similarly, *Intermediate 46* (50 mg, 0.16 mmol), 7-chloropyrazolo[1,5-*a*]-pyrimidine (50 mg, 0.32 mmol) and DIPEA (1.0 mL, 4.56 mmol) in *n*-butanol (6 mL) at 160°C afforded the *title compound* (35.7 mg, 53%) as a brown glass. δ_H (DMSO-d_6) 8.59 (1H, s), 8.40-8.34 (1H, m), 8.14-8.05 (3H, m), 7.79-7.70 (2H, m), 7.34-7.28 (1H, m), 6.44 (1H, d, *J* 2.28 Hz), 6.35 (1H, d, *J* 5.26 Hz), 5.28-5.21 (1H, m), 4.14 (1H, d, *J* 15.88 Hz), 3.98 (1H, d, *J* 15.88), 3.17 (3H, s), 2.70 (3H, d, *J* 4.53 Hz), 1.87 (3H, d, *J* 6.62 Hz). LCMS (ES+) 424 $(M+H)^+$, 7.55 minutes (*Method 8*).

EXAMPLE 78

(*S*)-2-(*N'*-{8-Chloro-3-[1-(pyrido[3,2-*d*]pyrimidin-4-ylamino)ethyl]quinolin-2-yl}-*N'*-methylamino)-*N*-methylacetamide

Similarly, *Intermediate 46* (50 mg, 0.16 mmol), 4-chloropyrido[3,2-*d*]pyrimidine (50 mg, 0.30 mmol) and DIPEA (1.0 mL, 4.56 mmol) in *n*-butanol (6 mL) at 160°C afforded the *title compound* (38.8 mg, 56%) as a white solid. δ_H (DMSO-d_6) 9.00-8.93 (1H, m), 8.89 (1H, dd, *J* 4.26, 1.58 Hz), 8.46 (2H, s), 8.14 (1H, dd, *J* 8.46, 1.58 Hz), 8.08-8.04 (1H, m), 7.88 (1H, dd, *J* 8.47, 4.26 Hz), 7.75-7.69 (2H, m), 7.29 (1H, t, *J* 7.80 Hz), 5.80-5.69 (1H, m), 4.42 (1H, d, *J* 16.32 Hz), 3.92 (1H, d, *J* 16.32 Hz), 3.18 (3H, s), 2.67 (3H, d, *J* 4.64 Hz), 1.68 (3H, d, *J* 6.76 Hz). LCMS (ES+) 436 $(M+H)^+$, 2.98 minutes (*Method 1*).

EXAMPLE 79

(*S*)-2-(*N'*-{3-[1-(2-Amino-9*H*-purin-6-ylamino)ethyl]-8-chloroquinolin-2-yl}-*N'*-methylamino)-*N*-methylacetamide

Similarly, *Intermediate 46* (50 mg, 0.16 mmol), 6-chloro-9*H*-purin-2-amine (50 mg, 0.30 mmol) and DIPEA (1.0 mL, 4.56 mmol) in *n*-butanol (6 mL) at 160°C afforded the *title compound* (3.11 mg, 1%) as a brown glass. δ_H (DMSO-d_6) 12.13 (1H, s), 8.41-8.31 (1H, m), 8.14-8.10 (1H, m), 7.91 (1H, s), 7.75-7.67 (3H, m), 7.30 (1H, t, *J* 7.79 Hz),

5.70-5.54 (2H, m), 4.76 (1H, s), 3.87-3.75 (1H, m), 3.22-3.10 (3H, m), 2.69 (3H, d, *J* 4.63 Hz), 1.49 (3H, d, *J* 6.63 Hz), 1H under H_2O. LCMS (ES+) 440 $(M+H)^+$, 2.55 minutes (*Method 1*).

EXAMPLE 80

(*S*)-8-Chloro-*N*-[2-(methylthio)ethyl]-3-[1-(9*H*-purin-6-ylamino)ethyl]quinolin-2-amine

Similarly, *Intermediate 47* (132 mg, 0.40 mmol), 6-chloropurine (62 mg, 0.40 mmol) and DIPEA (1.0 mL, 4.56 mmol) in *n*-butanol (5 mL) at 120°C afforded the *title compound* (24.4 mg, 15%) as a brown glass. δ_H (DMSO-d_6) 8.33-8.15 (3H, m), 7.99 (1H, s), 7.67-7.59 (2H, m), 7.49-7.42 (1H, m), 7.16-7.10 (1H, m), 5.71-5.60 (1H, m), 3.90-3.79 (1H, m), 3.78-3.67 (1H, m), 2.87-2.79 (2H, m), 2.16 (3H, s), 1.64 (3H, d, *J* 6.73 Hz), 1H under H_2O. LCMS (ES+) 414 $(M+H)^+$, 3.06 minutes (*Method 2*).

EXAMPLE 81

(*S*)-N^2-(1-{8-Chloro-2-[(1-methyl-1*H*-imidazol-4-yl)methylamino]quinolin-3-yl}ethyl)pyrazolo[1,5-*a*][1,3,5]triazine-2,4-diamine

Similarly, *Intermediate 48* (50 mg, 0.16 mmol), 2-(methylsulfonyl)pyrazolo[1,5-*a*][1,3,5]triazin-4-amine (50 mg, 0.23 mmol) and DIPEA (1.0 mL, 4.56 mmol) in *n*-butanol (6 mL) at 130°C afforded the *title compound* (2.6 mg, 4%) as an off-white solid. δ_H (MeOD-d_4): 7.97 (1H, s), 7.79 (1H, d, *J* 2.04 Hz), 7.61 (2H, d, *J* 7.76 Hz), 7.38 (1H, s), 7.13 (1H, t, *J* 7.77 Hz), 6.98 (1H, s), 5.72 (1H, s), 5.42 (1H, m), 4.76 (1H, d, *J* 14.70 Hz), 4.62 (1H, d, *J* 14.74 Hz), 3.58 (3H, s), 1.67 (3H, d, *J* 6.81 Hz). LCMS (ES+) 448 $(M+H)^+$, 7.38 minutes (*Method 8*).

EXAMPLE 82

(*S*)-*N*-(1-{8-Chloro-2-[(1-methyl-1*H*-imidazol-4-yl)methylamino]quinolin-3-yl}ethyl)thieno[2,3-*d*]pyrimidin-4-amine formate salt

Similarly, *Intermediate 48* (50 mg, 0.16 mmol), 4-chlorothieno[2,3-*d*]pyrimidine (50 mg, 0.29 mmol) and DIPEA (1.0 mL, 4.56 mmol) in *n*-butanol (6 mL) at 130°C for 20 h afforded the *title compound* (13.4 mg, 19%) as a tan solid. δ_H (DMSO-d_6) 8.34-8.24

(2H, m), 8.18 (1H, s), 8.03 (1H, s), 7.75 (1H, d, *J* 6.00 Hz), 7.68 (2H, m), 7.63 (1H, d, *J* 5.97 Hz), 7.47 (1H, s), 7.37 (1H, t, *J* 5.06 Hz), 7.15 (1H, t, *J* 7.75 Hz), 7.02 (1H, s), 5.73-5.65 (1H, m), 4.60 (2H, d, *J* 4.89 Hz), 3.60 (3H, s), 1.66 (3H, d, *J* 6.75 Hz). LCMS (ES+) 450 $(M+H)^+$, 3.17 minutes (*Method 1*).

EXAMPLE 83

(*S*)-*N*-(1-{8-chloro-2-[(1-methyl-1*H*-imidazol-4-yl)methylamino]quinolin-3-yl}ethyl)pyrido[3,2-*d*]pyrimidin-4-amine formate salt

Similarly, *Intermediate 48* (50 mg, 0.16 mmol), 4-chloropyrido[3,2-*d*]pyrimidine (50 mg, 0.30 mmol) and DIPEA (1.0 mL, 4.56 mmol) in *n*-butanol (6 mL) at 130°C afforded the *title compound* (30.1 mg, 6%) as a tan solid. δ_H (DMF-d_7) 9.37 (1H, d, *J* 8.43 Hz), 9.26 (1H, dd, *J* 4.24, 1.56 Hz), 8.71 (2H, d, *J* 6.63 Hz), 8.54 (1H, dd, *J* 8.47, 1.57 Hz), 8.48 (1H, s), 8.27 (1H, dd, *J* 8.47, 4.24 Hz), 7.90-7.82 (2H, m), 7.54 (1H, t, *J* 7.75 Hz), 7.43 (1H, s), 6.14-6.05 (1H, m), 5.04-4.93 (2H, m), 3.98 (3H, s), 3.59 (1H, s), 2.12 (3H, d, *J* 6.78 Hz). LCMS (ES+) 445 $(M+H)^+$, 3.06 minutes (*Method 1*).

EXAMPLE 84

(*S*)-7-Fluoro-8-methyl-3-[1-(9*H*-purin-6-ylamino)ethyl]-*N*-(tetrahydro-2*H*-pyran-4-yl)quinolin-2-amine

A solution of *Intermediate 16* (151 mg, 0.45 mmol), 4-aminotetrahydro-2*H*-pyran (325 mg, 3.22 mmol) and DIPEA (0.388 mL, 2.23 mmol) in NMP (4 mL) and isopropanol (4 mL) was heated under microwave irradiation at 160°C for 2 h. After cooling, the mixture was dissolved in a 1:1 mixture of Et_2O and EtOAc (200 mL) and washed with saturated brine (3 x 50 mL). The organic layer was separated, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 5% EtOAc in DCM) gave a colourless oil (27 mg, 15%). LCMS (ES+) 404 $(M+H)^+$. The colourless oil (27 mg, 0.067 mmol) was dissolved in DCM (3.5 mL) and TFA (0.345 mL) and the solution was stirred at r.t. for 1.5 h. The excess solvent was removed *in vacuo* and the residue obtained was basified with 0.4M NaOH (10 mL) and extracted with EtOAc (3 x 20 mL). The organic layer was separated, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a colourless residue (19 mg, 93%). LCMS

(ES+) 304 $(M+H)^+$. This compound (19 mg, 0.062 mmol), 6-chloropurine (13.8 mg, 0.089 mmol), DIPEA (0.031 mL, 0.179 mmol) and *n*-butanol (1 mL) were combined and heated under microwave irradiation at 130°C for 1 h. Purification by preparative HPLC gave the *title compound* (3.7 mg, 14%) as a white solid. δ_H ($CDCl_3$) 12.20 (1H, br s), 8.48 (1H, s), 7.95 (1H, s), 7.84 (1H, s), 7.41 (1H, dd, *J* 8.77, 6.25 Hz), 6.95 (1H, t, *J* 8.97 Hz), 6.54 (1H, s), 5.95 (1H, d, *J* 9.64 Hz) 5.88 (1H, br s), 4.42-4.30 (1H, m), 4.05-3.99 (1H, m), 3.95-3.89 (1H, m), 3.56 (2H, dtd, *J* 29.99, 11.44, 2.45 Hz), 2.50 (3H, s), 2.25 (1H, d, *J* 12.90 Hz), 1.90 (1H, d, *J* 12.99 Hz), 1.79 (3H, d, *J* 6.49 Hz), 1.70-1.55 (1H, m, masked by H_2O), 1.37-1.29 (1H, m). LCMS (ES+) 422 $(M+H)^+$, 2.66 minutes (*Method 2*).

EXAMPLE 85

8-Chloro-*N*-(1-methoxyprop-2-yl)-3-[(*S*)-1-(9*H*-purin-6-ylamino)ethyl]quinolin-2-amine and 8-Chloro-*N*-[(*R*)-1-methoxyprop-2-yl]-3-[(*S*)-1-(9*H*-purin-6-ylamino)ethyl]quinolin-2-amine

A solution of *Intermediate 23* (200 mg, 0.59 mmol), 2-amino-1-methoxypropane (0.15 mL, 1.47 mmol) and DIPEA (0.5 mL, 2.23 mmol) in NMP (3 mL) was stirred at 140°C for 20 h. The reaction mixture was diluted with water (20 mL) and extracted with Et_2O (100 mL). The organic layer was washed with water (20 mL) and brine (20 mL), separated, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the required intermediate (300 mg). A solution of this compound (300 mg, 0.79 mmol) and HCl (2 mL, 4 mmol; 2.0M in Et_2O) in MeOH (2 mL) was stirred at r.t. over a weekend. The reaction mixture was concentrated *in vacuo*. The resulting material (250 mg, 0.59 mmol), 6-chloropurine (117 mg, 0.76 mmol) and DIPEA (0.28 mL, 1.52 mmol) in *n*-butanol (5.0 mL) were stirred at 120°C overnight. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between DCM (100 mL) and water (30 mL). The organic layer was dried (phase separation cartridge) and concentrated *in vacuo*. The residue was purified by preparative HPLC to give the *title compounds* (24 mg, 9%; and 23 mg, 9%) as white solids. δ_H (DMSO-d_6) 8.29 (1H, s), 8.18 (2H, s), 8.04 (1H, s), 7.66 (2H, t, *J* 6.80 Hz), 7.15 (1H, t, *J* 7.89 Hz), 7.10-7.00 (1H, m), 5.80-5.62 (1H, m), 4.66-4.60 (1H, m), 3.61-3.55 (1H, m), 2.11-2.10 (2H, m), 1.68 (3H, d, *J* 6.61 Hz), 1.09 (3H, d, *J* 6.63 Hz), 3H under solvent peak. LCMS (ES+) 412 $(M+H)^+$, 1.70 minutes (*Method 2*). δ_H

(DMSO-d_6) 8.30-8.25 (1H, m), 8.19-8.14 (2H, m), 8.04 (1H, s), 7.71-7.63 (2H, m), 7.20-7.13 (1H, m), 5.80-5.65 (0.5H, m), 4.66-4.58 (1H, m), 3.03 (2H, s), 1.68 (3H, d, *J* 6.68 Hz), 1.29 (3H, d, *J* 6.69 Hz), 3H and 2 geminal protons under solvent peak. LCMS (ES+) 412 $(M+H)^+$, 1.70 minutes (*Method 2*).

EXAMPLE 86

(*R*)-3-{8-Chloro-3-[(*S*)-1-(9*H*-purin-6-ylamino)ethyl]quinolin-2-ylamino}propane-1,2-diol

A solution/suspension of *Intermediate 58* (60 mg, 0.16 mmol), 6-bromopurine (49 mg, 0.25 mmol) and DIPEA (0.15 mL, 0.82 mmol) in *n*-butanol (2 mL) was heated at 130°C under microwave irradiation for 3 h. The reaction mixture was concentrated *in vacuo* and purified by preparative HPLC to afford the *title compound* (10 mg, 15%) as a cream solid. δ_H (MeOD-d_4) 8.23 (1H, s), 8.02 (1H, s), 7.97 (1H, s), 7.54-7.48 (2H, m), 7.05 (1H, t, *J* 7.78 Hz), 5.75-5.60 (1H, m), 3.81-3.70 (3H, m), 3.47-3.32 (2H, m), 1.67 (3H, d, *J* 6.80 Hz). LCMS (ES+) 414, 416 $(M+H)^+$, 1.80 minutes (*Method 2*).

EXAMPLE 87

(*S*)-3-{8-Chloro-3-[(*S*)-1-(9*H*-purin-6-ylamino)ethyl]quinolin-2-ylamino}propane-1,2-diol

Similarly, *Intermediate 59* (50 mg, 0.14 mmol), 6-bromopurine (41 mg, 0.20 mmol) and DIPEA (0.12 mL, 0.68 mmol) in *n*-butanol (2 mL) gave the *title compound* (14 mg, 25%) as a pale yellow solid. δ_H (MeOD-d_4) 8.32 (1H, s), 8.12 (1H, s), 8.07 (1H, s), 7.64-7.59 (2H, m), 7.16 (1H, t, *J* 7.78 Hz), 5.76 (1H, s), 3.93-3.81 (2H, m), 3.80-3.73 (1H, m), 3.58-3.47 (2H, m), 2.68 (1H, s), 1.76 (3H, d, *J* 6.78 Hz). LCMS (ES+) 414, 416 $(M+H)^+$, 9.70 minutes (*Method 4*).

EXAMPLE 88

(*R*)-3-(8-Chloro-3-{(*S*)-1-[4-(methylamino)-[1,3,5]triazin-2-ylamino]ethyl}quinolin-2-ylamino)propane-1,2-diol

Similarly, *Intermediate 58* (60 mg, 0.16 mmol), 4-chloro-2-(methylamino)-[1,3,5]triazine (36 mg, 0.25 mmol) and DIPEA (0.15 mL, 0.82 mmol) in *n*-butanol (2 mL) gave the *title compound* (30 mg, 45%) as a white solid. δ_H (MeOD-d_4) 8.16-7.90 (1H, br s), 8.01 (1H, s), 7.64 (1H, d, *J* 7.6 Hz), 7.63 (1H, d, *J* 8.0 Hz), 7.19 (1H, t, *J* 7.8 Hz), 5.50-5.30 (1H, br s), 3.93-3.78 (3H, m), 3.60-3.43 (2H, m), 2.90-2.86 (3H, m), 1.58 (3H, d, *J* 6.8 Hz). LCMS (ES+) 404, 406 $(M+H)^+$, 2.40 minutes (*Method 1*).

EXAMPLE 89

(*S*)-N^6-{1-[7-Fluoro-2-(2-methoxyethylamino)-8-methylquinolin-3-yl]ethyl}-9*H*-purine-2,6-diamine

Similarly, *Intermediate 60* (60 mg, 0.17 mmol), 6-chloro-9*H*-purin-2-amine (44 mg, 0.26 mmol) and DIPEA (0.15 mL, 0.86 mmol) in *n*-butanol (2 mL) gave the *title compound* (24 mg, 34%) as a cream solid. δ_H (MeOD-d_4) 7.98 (1H, s), 7.72 (1H, s), 7.51 (1H, dd, *J* 8.80, 6.33 Hz), 6.95 (1H, t, *J* 9.10 Hz), 5.73-5.65 (1H, m), 3.92-3.84 (1H, m), 3.79-3.63 (3H, m), 2.50 (3H, d, *J* 2.34 Hz), 1.74 (3H, d, *J* 6.81 Hz), 3H under solvent peak. LCMS (ES+) 411 $(M+H)^+$, 2.40 minutes (*Method 4*).

EXAMPLE 90

(*S*)-2-{8-Chloro-3-[1-(9*H*-purin-6-ylamino)ethyl]quinolin-2-ylamino}-*N*-methyl-acetamide

Similarly, *Intermediate 61* (50 mg, 0.14 mmol), 6-bromopurine (41 mg, 0.21 mmol) and DIPEA (0.12 mL, 0.68 mmol) in *n*-butanol (2 mL) gave the *title compound* (14 mg, 25%) as a yellow solid. δ_H (MeOD-d_4) 8.26 (1H, s), 8.11 (1H, s), 8.02 (1H, s), 7.60-7.56 (2H, m), 7.11 (1H, t, *J* 7.78 Hz), 5.72-5.63 (1H, m), 4.28 (1H, d, *J* 16.08 Hz), 4.17 (1H, d, *J* 16.09 Hz), 2.74 (3H, s), 1.74 (3H, d, *J* 6.79 Hz). LCMS (ES+) 411 $(M+H)^+$, 2.43 minutes (*Method 1*).

EXAMPLE 91

(*S*)-2-{8-Chloro-3-[1-(9*H*-purin-6-ylamino)ethyl]quinolin-2-ylamino}-*N*,*N*-dimethyl-acetamide

Similarly, *Intermediate 63* (60 mg, 0.16 mmol), 6-bromopurine (47 mg, 0.24 mmol) and DIPEA (0.14 mL, 0.79 mmol) in *n*-butanol (2 mL) gave the *title compound* (15.3 mg, 23%) as a yellow solid. δ_H (MeOD-d_4) 8.32 (1H, s), 8.10 (1H, s), 8.07 (1H, s), 7.61 (2H, d, *J* 8.0 Hz), 7.14 (1H, t, *J* 7.8 Hz), 5.90-5.80 (1H, m), 4.57 (1H, d, *J* 16.63 Hz), 4.34 (1H, d, *J* 16.58 Hz), 3.23 (3H, s), 2.99 (3H, s), 1.80 (3H, d, *J* 6.80 Hz). LCMS (ES+) 425 $(M+H)^+$, 2.67 minutes (*Method 1*).

EXAMPLE 92

(*S*)-8-Chloro-3-[1-(9*H*-purin-6-ylamino)ethyl]-*N*-(pyridin-2-ylmethyl)quinolin-2-amine

Similarly, *Intermediate 64* (70 mg, 0.17 mmol), 6-bromopurine (49 mg, 0.25 mmol) and DIPEA (0.18 mL, 0.99 mmol) in *n*-butanol (2 mL) gave the *title compound* (10.8 mg, 21%) as a yellow solid. δ_H (MeOD-d_4) 8.38 (1H, d, *J* 5.04 Hz), 8.15 (1H, s), 8.10-8.05 (2H, m), 7.69-7.56 (3H, m), 7.51 (1H, d, *J* 7.89 Hz), 7.26-7.20 (1H, m), 7.12 (1H, t, *J* 7.78 Hz), 5.90-5.80 (1H, m), 5.02 (1H, d, *J* 15.57 Hz), 1.80 (3H, d, *J* 6.80 Hz), 1H under H_2O. LCMS (ES+) 431 $(M+H)^+$, 1.98 minutes (*Method 2*).

EXAMPLE 93

(*S*)-2-({8-Chloro-3-[1-(9*H*-purin-6-ylamino)ethyl]quinolin-2-ylamino}methyl)pyridine 1-oxide

Similarly, *Intermediate 66* (50 mg, 0.11 mmol), 6-bromopurine (34 mg, 0.17 mmol) and DIPEA (0.12 mL, 0.68 mmol) in *n*-butanol (2 mL) gave the *title compound* (6.8 mg, 15%) as a yellow solid. δ_H (MeOD-d_4) 8.30-8.25 (2H, m), 8.06 (1H, s), 8.02 (1H, s), 7.70 (1H, d, *J* 7.75 Hz), 7.52 (2H, t, *J* 8.42 Hz), 7.41-7.33 (2H, m), 7.07 (1H, t, *J* 7.78 Hz), 5.85-5.50 (1H, m), 5.08 (1H, d, *J* 16.58 Hz), 4.96 (1H, d, *J* 16.57 Hz), 1.75 (3H, d, *J* 6.81 Hz). LCMS (ES+) 431, 433 $(M+H)^+$, 1.98 minutes (*Method 2*).

EXAMPLE 94

(*S*)-2-{3-[1-(4-Aminopyrazolo[1,5-*a*][1,3,5]triazin-2-ylamino)ethyl]-8-chloroquinolin-2-ylamino}-*N*,*N*-dimethylacetamide

Similarly, *Intermediate 63* (60 mg, 0.16 mmol), 2-chloropyrazolo[1,5-*a*][1,3,5]-triazin-4-amine (50 mg, 0.24 mmol) and DIPEA (0.17 mL, 0.95 mmol) in *n*-butanol (2 mL) gave the *title compound* (8 mg, 12%) as a white solid. δ_H (MeOD-d_4) 7.95 (1H, s), 7.74 (1H, d, *J* 2.11 Hz), 7.55 (2H, d, *J* 7.75 Hz), 7.09 (1H, t, *J* 7.73 Hz), 5.79-5.75 (1H, m), 5.42-5.38 (1H, m), 4.54-4.39 (2H, m), 3.21 (3H, s), 2.96 (3H, s), 1.64 (3H, d, *J* 6.82 Hz). LCMS (ES+) 440 $(M+H)^+$, 2.96 minutes (*Method 1*).

EXAMPLE 95

(*S*)-8-Chloro-3-[1-(9*H*-purin-6-ylamino)ethyl]-*N*-(pyridin-3-ylmethyl)quinolin-2-amine

Similarly, *Intermediate 65* (100 mg, 0.24 mmol), 6-bromopurine (72 mg, 0.36 mmol) and DIPEA (0.43 mL, 2.42 mmol) in *n*-butanol (3 mL) gave the *title compound* (7 mg, 7%) as a yellow solid. δ_H (MeOD-d_4) 8.60 (1H, s), 8.34-8.30 (1H, m), 8.19 (1H, s), 8.10 (1H, s), 7.89 (1H, s), 8.03 (1H, s), 7.93-7.90 (1H, m), 7.61-7.57 (2H, m), 7.29-7.23 (1H, m), 7.12 (1H, t, *J* 7.76 Hz), 5.88-5.74 (1H, m), 4.96 (1H, d, *J* 15 Hz), 4.76 (1H, d, *J* 14.68 Hz), 1.74 (3H, d, *J* 6.77 Hz). LCMS (ES+) 431 $(M+H)^+$, 2.01 minutes (*Method 2*).

EXAMPLE 96

(*S*)-N^2-{1-[7-Fluoro-2-(2-methoxyethylamino)-8-methylquinolin-3-yl]ethyl}-6-methyl-[1,3,5]triazine-2,4-diamine

Similarly, *Intermediate 60* (65 mg, 0.23 mmol), 2-amino-4-chloro-6-methyl-[1,3,5]triazine (40 mg, 0.27 mmol) and DIPEA (100 mg, 0.78 mmol) in *n*-butanol (2 mL) gave the *title compound* (16 mg, 20%) as a white solid. δ_H ($CDCl_3$) 7.76 (1H, s), 7.38 (1H, dd, *J* 8.79, 6.25 Hz), 6.97-6.90 (1H, m), 6.00-5.93 (1H, m), 5.30 (1H, d, *J* 8.63 Hz), 4.10-4.02 (1H, m), 3.89-3.56 (4H, m), 3.66-3.21 (5H, m), 2.52 (3H, d, *J* 2.38 Hz), 2.31-2.18 (3H, m), 1.66-1.59 (3H, m). LCMS (ES+) 386 $(M+H)^+$, 2.56 minutes (*Method 1*).

EXAMPLE 97

(*S*)-*N*,*N*-Diethyl-7-fluoro-8-methyl-3-[1-(9*H*-purin-6-ylamino)ethyl]quinolin-2-amine

Similarly, *Intermediate 19* (70 mg, 0.25 mmol), 6-bromopurine (42 mg, 0.27 mmol) and DIPEA (100 mg, 0.78 mmol) in *n*-butanol (2 mL) gave the *title compound* (22.2 mg, 22%) as a white solid. δ_H ($CDCl_3$) 8.37 (1H, s), 7.99 (2H, d, *J* 5.28 Hz), 7.44-7.36 (1H, m), 7.04 (1H, t, *J* 9.00 Hz), 6.60-6.53 (1H, m), 5.87-5.76 (1H, m), 3.61-3.41 (4H, m), 2.63 (1H, s), 2.60 (3H, d, *J* 2.38 Hz), 1.64 (3H, d, *J* 6.62 Hz), 1.23 (6H, t, *J* 6.96 Hz). LCMS (ES+) 394 $(M+H)^+$, 9.05 minutes (*Method 8*).

EXAMPLE 98

(*S*)-N^2-{1-[7-Fluoro-2-(3-methoxypropylamino)-8-methylquinolin-3-yl]ethyl}-[1,3,5]-triazine-2,4-diamine

A mixture of *Intermediate 16* (280 mg, 0.83 mmol), 3-methoxypropylamine (98 mg, 1.1 mmol) and DIPEA (0.4 mL, 2.19 mmol) in *n*-butanol (2 mL) was heated at 120°C for 5 days. The reaction mixture was cooled and partitioned between water (30 mL) and EtOAc (100 mL). The organic layer was washed with water (5 x 20 mL), separated, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was then purified by column chromatography (SiO_2, 75-100% EtOAc in isohexane) to give an off-white solid. This was dissolved in 1,4-dioxane (10 mL) and treated with HCl (2 mL; 4.0M in 1,4-dioxane) and the mixture was stirred at r.t. overnight. The reaction mixture was concentrated *in vacuo* to give an orange oil (200 mg, 81%). A portion of this oil (70 mg, 0.25 mmol), 2-amino-4-chloro-[1,3,5]triazine (35 mg, 0.27 mmol) and DIPEA (100 mg, 0.78 mmol) in *n*-butanol (2 mL) was heated at 110°C overnight. The solvent was removed *in vacuo* and the residue purified by preparative HPLC to give the *title compound* (31.5 mg, 34%) as a white solid. δ_H ($CDCl_3$) 7.72 (1H, s), 7.37 (1H, dd, *J* 8.76, 6.25 Hz), 6.93 (1H, t, *J* 8.99 Hz), 6.43 (1H, s), 5.56-5.06 (4H, m), 3.89-3.34 (5H, m), 3.34 (3H, s), 2.53 (3H, d, *J* 2.39 Hz), 2.03-1.92 (2H, m), 1.66 (3H, d, *J* 6.69 Hz). LCMS (ES+) 386 $(M+H)^+$, 2.20 minutes (*Method 2*).

EXAMPLE 99

(*S*)-7-Fluoro-*N*-(3-methoxypropyl)-8-methyl-3-[1-(9*H*-purin-6-ylamino)ethyl]quinolin-2-amine

A mixture of *Intermediate 16* (280 mg, 0.83 mmol), 3-methoxypropylamine (98 mg, 1.1 mmol) and DIPEA (0.4 mL, 2.19 mmol) in *n*-butanol (2 mL) was heated at 120°C for 5 days. The reaction mixture was cooled and partitioned between water (30 mL) and EtOAc (100 mL). The organic layer was washed with water (5 x 20 mL), separated, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was then purified by column chromatography (SiO_2, 75-100% EtOAc in isohexane) to give an off-white solid. This was dissolved in 1,4-dioxane (10 mL) and treated with HCl (2 mL; 4.0M in 1,4-dioxane) and the mixture was stirred at r.t. overnight. The reaction mixture was concentrated *in vacuo* to give an orange oil (200 mg, 81%). A portion of this oil (70 mg, 0.25 mmol), 6-bromopurine (39 mg, 0.27 mmol) and DIPEA (100 mg, 0.78 mmol) in *n*-butanol (2 mL) was heated at 110°C overnight. The solvent was removed *in vacuo* and the residue purified by preparative HPLC to give the *title compound* (17.2 mg, 18%) as a white solid. δ_H ($CDCl_3$) 8.47 (1H, s), 7.94 (1H, s), 7.81 (1H, s), 7.39 (1H, dd, *J* 8.81, 6.23 Hz), 6.96-6.89 (1H, m), 6.52 (1H, s), 6.00 (1H, d, *J* 9.12 Hz), 5.81 (1H, s), 3.71-3.58 (2H, m), 3.47-3.32 (2H, m), 3.24 (3H, s), 2.53 (3H, d, *J* 2.36 Hz), 2.02-1.82 (3H, m), 1.78 (3H, d, *J* 6.67 Hz). LCMS (ES+) 410 $(M+H)^+$, 2.30 minutes (*Method 2*).

EXAMPLE 100

N-[(1,4-Dioxan-2-yl)methyl]-7-fluoro-3-[(*S*)-1-(9*H*-purin-6-ylamino)ethyl]quinolin-2-amine

A mixture of *Intermediate 15* (280 mg, 0.83 mmol), (1,4-dioxan-2-yl)-methanamine (117 mg, 1.0 mmol) and DIPEA (0.42 mL, 2.33 mmol) in *n*-butanol (2 mL) was heated at 120°C for 3 days. The reaction mixture was cooled and partitioned between water (30 mL) and EtOAc (100 mL). The organic layer was washed with water (5 x 20 mL), separated, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, 75-100% EtOAc in isohexane) to give an off-white solid. This was dissolved in 1,4-dioxane (10 mL) and treated with HCl (2 mL; 4.0M in 1,4-dioxane) and the mixture was stirred at r.t. overnight. The reaction mixture was

concentrated *in vacuo* to give a yellow oil (120 mg). A portion of this oil (60 mg, 0.19 mmol), 6-bromopurine (37 mg, 0.24 mmol) and DIPEA (100 mg, 0.78 mmol) in *n*-butanol (2 mL) was heated at 110°C overnight. The solvent was removed *in vacuo* and the residue purified by preparative HPLC to give the *title compound* (5.2 mg, 7%) as a white solid. δ_H ($CDCl_3$) 8.50-8.45 (1H, m), 7.97-7.91 (1H, m), 7.88-7.86 (1H, m), 7.56 (1H, dd, *J* 8.83, 6.18 Hz), 6.99-6.93 (1H, m), 6.76-6.62 (1H, m), 6.33-6.23 (1H, m), 5.92-5.78 (1H, m), 3.86-3.24 (9H, m), 1.79 (3H, d, *J* 6.71 Hz), 2H under H_2O. LCMS (ES+) 424 $(M+H)^+$, 2.20 minutes (*Method 1*).

EXAMPLE 101

N^2-[(*S*)-1-{2-[(1,4-Dioxan-2-yl)methylamino]-7-fluoroquinolin-3-yl}ethyl]-6-methyl-[1,3,5]triazine-2,4-diamine

A mixture of *Intermediate 15* (280 mg, 0.83 mmol), (1,4-dioxan-2-yl)-methanamine (117 mg, 1.0 mmol) and DIPEA (0.42 mL, 2.33 mmol) in *n*-butanol (2 mL) was heated at 120°C for 3 days. The reaction mixture was cooled and partitioned between water (30 mL) and EtOAc (100 mL). The organic layer was washed with water (5 x 20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, 75-100% EtOAc in isohexane) to give an off-white solid. This was dissolved in 1,4-dioxane (10 mL) and treated with HCl (2 mL; 4.0M in 1,4-dioxane) and the mixture was stirred at r.t. overnight. The reaction mixture was concentrated *in vacuo* to give a yellow oil (120 mg). A portion of this oil (60 mg, 0.19 mmol), 2-amino-4-chloro-6-methyl-[1,3,5]triazine (35 mg, 0.24 mmol) and DIPEA (100 mg, 0.78 mmol) in *n*-butanol (2 mL) was heated at 110°C overnight. The solvent was removed *in vacuo* and the residue purified by preparative HPLC to give the *title compound* (6 mg, 9%) as a white solid. δ_H ($CDCl_3$) 7.82-7.75 (1H, m), 7.53 (1H, dd, *J* 8.78, 6.26 Hz), 7.31-7.24 (2H, m), 7.18-7.07 (1H, m), 6.99-6.93 (1H, m), 6.21-6.09 (1H, m), 5.34-5.22 (2H, m), 4.02-3.49 (9H, m), 2.24 (3H, s), 1.67 (3H, d, *J* 6.71 Hz). LCMS (ES+) 414 $(M+H)^+$, 2.17 minutes (*Method 1*).

EXAMPLE 102

(*S*)-N^2-{1-[7-Fluoro-2-(3-methoxypropylamino)quinolin-3-yl]ethyl}-6-methyl-[1,3,5]-triazine-2,4-diamine

Similarly, *Intermediate 18* (60 mg, 0.21 mmol), 2-amino-4-chloro-6-methyl-[1,3,5]triazine (35 mg, 0.24 mmol) and DIPEA (100 mg, 0.78 mmol) in *n*-butanol (2 mL) gave the *title compound* (18 mg, 22%) as a white solid. δ_H ($CDCl_3$) 7.74 (1H, s), 7.52 (1H, dd, *J* 8.78, 6.29 Hz), 7.31 (1H, dd, *J* 11.05, 2.55 Hz), 6.96-6.89 (1H, m), 6.49 (1H, s), 6.58-5.89 (3H, m), 5.40-5.20 (1H, m), 4.75 (1H, br s), 3.82-3.42 (4H, m), 3.36 (3H, s), 2.40-2.22 (3H, m), 1.98-1.90 (2H, m), 1.66 (3H, d, *J* 6.72 Hz). LCMS (ES+) 386 $(M+H)^+$, 6.64 minutes (*Method 8*).

EXAMPLE 103

(*S*)-7-Fluoro-*N*-(3-methoxypropyl)-8-methyl-3-[1-(pyrazolo[1,5-*a*]pyrimidin-7-ylamino)ethyl]quinolin-2-amine

A mixture of *Intermediate 16* (280 mg, 0.83 mmol), 3-methoxypropylamine (98 mg, 1.1 mmol) and DIPEA (0.4 mL, 2.19 mmol) in *n*-butanol (2 mL) was heated at 120°C for 5 days. The reaction mixture was cooled and partitioned between water (30 mL) and EtOAc (100 mL). The organic layer was washed with water (5 x 20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, 75-100% EtOAc in isohexane) to give an off-white solid. This was dissolved in 1,4-dioxane (10 mL) and treated with HCl (2 mL; 4.0M in 1,4-dioxane) and the mixture was stirred at r.t. overnight. The reaction mixture was concentrated *in vacuo* to give an orange oil (200 mg, 81%). A portion of this oil (70 mg, 0.25 mmol), 7-chloropyrazolo[1,5-*a*]-pyrimidine (38 mg, 0.25 mmol) and DIPEA (100 mg, 0.78 mmol) in *n*-butanol (2 mL) was heated at 110°C overnight. The solvent was removed *in vacuo* and the residue purified by preparative HPLC to give the *title compound* (29 mg, 30%) as a white solid. δ_H ($CDCl_3$) 8.11 (1H, d, *J* 5.12 Hz), 8.05 (1H, d, *J* 2.32 Hz), 7.76 (1H, s), 7.34 (1H, dd, *J* 8.81, 6.23 Hz), 6.94 (1H, t, *J* 9.00 Hz), 6.66 (1H, d, *J* 5.60 Hz), 6.55 (1H, d, *J* 2.32 Hz), 5.74 (1H, d, *J* 5.14 Hz), 5.69 (1H, t, *J* 4.76 Hz), 4.80-4.70 (1H, m), 3.79 (2H, q, *J* 5.57 Hz), 3.59-3.53 (2H, m), 3.27 (3H, s), 2.56 (3H, d, *J* 2.40 Hz), 2.06-1.93 (2H, m), 1.79 (3H, d, *J* 6.70 Hz). LCMS (ES+) 409 $(M+H)^+$, 3.41 minutes (*Method 1*).

EXAMPLE 104

(*S*)-7-Fluoro-*N*-(2-methoxyethyl)-8-methyl-3-[1-(pyrazolo[1,5-*a*]pyrimidin-7-ylamino)ethyl]quinolin-2-amine

Similarly, *Intermediate 60* (65 mg, 0.23 mmol), 7-chloropyrazolo[1,5-*a*]-pyrimidine (38 mg, 0.25 mmol) and DIPEA (100 mg, 0.78 mmol) in *n*-butanol (2 mL) gave the *title compound* (11 mg, 12%) as a white solid. δ_H ($CDCl_3$) 8.14 (1H, d, *J* 5.12 Hz), 8.05 (1H, d, *J* 2.32 Hz), 7.81 (1H, s), 7.38 (1H, dd, *J* 8.82, 6.20 Hz), 6.98 (1H, t, *J* 8.99 Hz), 6.63 (1H, d, *J* 5.77 Hz), 6.56 (1H, d, *J* 2.32 Hz), 5.80 (1H, d, *J* 5.15 Hz), 5.33-5.28 (1H, m), 4.86-4.77 (1H, m), 3.93-3.79 (2H, m), 3.64-3.60 (2H, m), 3.19 (3H, s), 2.55 (3H, d, *J* 2.40 Hz), 1.81 (3H, d, *J* 6.74 Hz). LCMS (ES+) 395 $(M+H)^+$, 3.28 minutes (*Method 1*).

EXAMPLE 105

(*S*)-N^2-{1-[2-(Diethylamino)-7-fluoro-8-methylquinolin-3-yl]ethyl}-[1,3,5]triazine-2,4-diamine

Similarly, *Intermediate 19* (70 mg, 0.25 mmol), 2-amino-4-chloro-[1,3,5]triazine (35 mg, 0.27 mmol) and DIPEA (100 mg, 0.78 mmol) in *n*-butanol (2 mL) gave the *title compound* (19.5 mg, 21%) as a white solid. δ_H ($CDCl_3$) 8.13 (1H, s), 7.88 (1H, s), 7.45 (1H, dd, *J* 8.86, 6.14 Hz), 7.08 (1H, t, *J* 9.01 Hz), 5.75-5.62 (1H, m), 5.51-5.35 (1H, m), 5.00-4.85 (2H, m), 3.59-3.42 (2H, m), 3.44-3.33 (2H, m), 2.60 (3H, d, *J* 2.41 Hz), 1.49 (3H, d, *J* 6.50 Hz), 1.21 (6H, t, *J* 6.94 Hz). LCMS (ES+) 370 $(M+H)^+$, 3.20 minutes (*Method 2*).

EXAMPLE 106

(*S*)-N^2-{1-[7-Fluoro-2-(3-methoxypropylamino)-8-methylquinolin-3-yl]ethyl}-6-methyl-[1,3,5]triazine-2,4-diamine

A mixture of *Intermediate 16* (280 mg, 0.83 mmol), 3-methoxypropylamine (98 mg, 1.1 mmol) and DIPEA (0.4 mL, 2.19 mmol) in *n*-butanol (2 mL) was heated at 120°C for 5 days. The reaction mixture was cooled and partitioned between water (30 mL) and

EtOAc (100 mL). The organic layer was washed with water (5 x 20 mL), separated, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was then purified by column chromatography (SiO_2, 75-100% EtOAc in isohexane) to give an off-white solid. This was dissolved in 1,4-dioxane (10 mL) and treated with HCl (2 mL; 4.0M in 1,4-dioxane) and the mixture was stirred at r.t. overnight. The reaction mixture was concentrated *in vacuo* to give an orange oil (200 mg, 81%). A portion of this oil (70 mg, 0.25 mmol), 2-amino-4-chloro-6-methyl-[1,3,5]triazine (36 mg, 0.25 mmol) and DIPEA (100 mg, 0.78 mmol) in *n*-butanol (2 mL) was heated at 110°C overnight. The solvent was removed *in vacuo* and the residue purified by preparative HPLC to give the *title compound* (19.8 mg, 21%) as a white solid. δ_H ($CDCl_3$) 7.71 (1H, s), 7.37 (1H, dd, *J* 8.76, 6.27 Hz), 6.93 (1H, t, *J* 8.99 Hz), 6.58-5.89 (3H, m), 5.54-4.82 (4H, m), 3.87-3.41 (4H, m), 3.34 (3H, br s), 2.53 (3H, d, *J* 2.38 Hz), 2.30-2.20 (3H, m), 1.70-1.63 (3H, m). LCMS (ES+) 400 $(M+H)^+$, 2.14 minutes (*Method 2*).

EXAMPLE 107

(*S*)-1-(2-{8-Chloro-3-[1-(pyrido[3,2-*d*]pyrimidin-4-ylamino)ethyl]quinolin-2-ylamino}ethyl)imidazolidin-2-one

A mixture of *Intermediate 23* (1.0 g, 2.9 mmol), 1-(2-aminoethyl)imidazolidin-2-one (0.5 g, 3.9 mmol) and DIPEA (0.8 mL, 5.8 mmol) in *n*-butanol (10 mL) was heated at 120°C for 72 h. After cooling, the reaction mixture was partitioned between Et_2O (200 mL) and water (100 mL). The organic layer was washed with water (3 x 100 mL) and brine (100 mL), separated, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, 5% MeOH in DCM) to give a pale yellow solid. This was dissolved in DCM (20 mL), treated with TFA (5 mL) and stirred for 4 h at r.t. After quenching with 2M NaOH solution (30 mL), the organic layer was washed with water (3 x 10 mL), separated, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give an orange oil (0.8 g, 82%). A portion of this oil (100 mg, 0.3 mmol), 4-chloropyrido[3,2-*d*]pyrimidine (55 mg, 0.33 mmol) and DIPEA (100 mg, 0.78 mmol) in *n*-butanol (2 mL) was heated at 120°C for 18 h. The solvent was removed *in vacuo* and the residue was purified by preparative HPLC to give the *title compound* (70 mg, 48%) as a pale yellow solid. δ_H ($CDCl_3$) 8.70-8.66 (2H, m), 8.15-8.09 (1H, m), 7.90 (1H, s), 7.67 (1H, dd, *J* 8.48, 4.25 Hz), 7.62 (1H, dd, *J* 7.54, 1.39 Hz), 7.53-7.46 (1H, m), 7.33 (1H, d,

J 9.01 Hz), 7.10 (1H, t, *J* 7.75 Hz), 6.74 (1H, s), 5.75-5.64 (1H, m), 4.55 (1H, s), 3.98-3.87 (1H, m), 3.76-3.65 (1H, m), 3.63-3.42 (4H, m), 3.29-3.13 (2H, m), 1.82 (3H, d, *J* 6.78 Hz). LCMS (ES+) 463 $(M+H)^+$, 2.98 minutes (*Method 1*).

EXAMPLE 108

(*S*)-1-(2-{8-Chloro-3-[1-(pyrrolo[2,1-*f*][1,2,4]triazin-4-ylamino)ethyl]quinolin-2-ylamino}ethyl)imidazolidin-2-one

A mixture of *Intermediate 23* (1.0 g, 2.9 mmol), 1-(2-aminoethyl)imidazolidin-2-one (0.5 g, 3.9 mmol) and DIPEA (0.8 mL, 5.8 mmol) in *n*-butanol (10 mL) was heated at 120°C for 72 h. After cooling, the reaction mixture was partitioned between Et_2O (200 mL) and water (100 mL). The organic layer was washed with water (3 x 100 mL) and brine (100 mL), separated, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, 5% MeOH in DCM) to give a pale yellow solid. This was dissolved in DCM (20 mL), treated with TFA (5 mL) and stirred for 4 h at r.t. After quenching with 2M NaOH solution (30 mL), the organic layer was washed with water (3 x 10 mL), separated, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give an orange oil (0.8 g, 82%). A portion of this oil (100 mg, 0.3 mmol), 4-bromopyrrolo[2,1-*f*][1,2,4]triazine (66 mg, 0.33 mmol) and DIPEA (100 mg, 0.78 mmol) in *n*-butanol (2 mL) was heated at 120°C for 18 h. The solvent was removed *in vacuo* and the residue was purified by preparative HPLC to give the *title compound* (100 mg, 74%) as a white solid. δ_H ($CDCl_3$) 7.97 (1H, s), 7.89 (1H, s), 7.63 (1H, dd, *J* 7.56, 1.38 Hz), 7.55-7.52 (2H, m), 7.14-7.09 (1H, m), 6.89 (1H, dd, *J* 4.40, 1.54 Hz), 6.81 (1H, d, *J* 7.26 Hz), 6.61 (1H, dd, *J* 4.41, 2.61 Hz), 6.16 (1H, s), 5.57-5.52 (1H, m), 4.09-4.03 (1H, m), 3.86 (1H, s), 3.77 (1H, dd, *J* 16.66, 8.33 Hz), 3.64-3.35 (4H, m), 3.21-3.05 (2H, m), 1.79 (3H, d, *J* 6.81 Hz). LCMS (ES+) 451 $(M+H)^+$, 2.94 minutes (*Method 1*).

EXAMPLE 109

(*S*)-1-(2-{3-[1-(2-Amino-9*H*-purin-6-ylamino)ethyl]-8-chloroquinolin-2-ylamino}ethyl)imidazolidin-2-one

A mixture of *Intermediate 23* (1.0 g, 2.9 mmol), 1-(2-aminoethyl)imidazolidin-2-one (0.5 g, 3.9 mmol) and DIPEA (0.8 mL, 5.8 mmol) in *n*-butanol (10 mL) was heated at

120°C for 72 h. After cooling, the reaction mixture was partitioned between Et_2O (200 mL) and water (100 mL). The organic layer was washed with water (3 x 100 mL) and brine (100 mL), separated, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, 5% MeOH in DCM) to give a pale yellow solid. This was dissolved in DCM (20 mL), treated with TFA (5 mL) and stirred for 4 h at r.t. After quenching with 2M NaOH solution (30 mL), the organic layer was washed with water (3 x 10 mL), separated, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give an orange oil (0.8 g, 82%). A portion of this oil (100 mg, 0.3 mmol), 2-amino-6-chloropurine (56 mg, 0.33 mmol) and DIPEA (100 mg, 0.78 mmol) in *n*-butanol (2 mL) was heated at 120°C for 18 h. The solvent was removed *in vacuo* and the residue was purified by preparative HPLC to give the *title compound* (41.8 mg, 35%) as a white solid. δ_H (MeOD-d_4) 7.96 (1H, s), 7.76 (1H, s), 7.59-7.53 (2H, m), 7.08 (1H, t, *J* 7.77 Hz), 5.70-5.64 (1H, m), 3.99-3.89 (1H, m), 3.82-3.48 (4H, m), 3.39-3.31 (2H, m), 3.16-3.07 (2H, m), 1.70-1.66 (3H, m). LCMS (ES+) 467 $(M+H)^+$, 2.58 minutes (*Method 1*).

EXAMPLE 110

(*S*)-1-(2-{8-Chloro-3-[1-(pyrazolo[1,5-*a*]pyrimidin-7-ylamino)ethyl]quinolin-2-ylamino}ethyl)imidazolidin-2-one

A mixture of *Intermediate 23* (1.0 g, 2.9 mmol), 1-(2-aminoethyl)imidazolidin-2-one (0.5 g, 3.9 mmol) and DIPEA (0.8 mL, 5.8 mmol) in *n*-butanol (10 mL) was heated at 120°C for 72 h. After cooling, the reaction mixture was partitioned between Et_2O (200 mL) and water (100 mL). The organic layer was washed with water (3 x 100 mL) and brine (100 mL), separated, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, 5% MeOH in DCM) to give a pale yellow solid. This was dissolved in DCM (20 mL), treated with TFA (5 mL) and stirred for 4 h at r.t. After quenching with 2M NaOH solution (30 mL), the organic layer was washed with water (3 x 10 mL), separated, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give an orange oil (0.8 g, 82%). A portion of this oil (100 mg, 0.3 mmol), 7-chloropyrazolo[1,5-*a*]pyrimidine (50 mg, 0.33 mmol) and DIPEA (100 mg, 0.78 mmol) in *n*-butanol (2 mL) was heated at 120°C for 18 h. The solvent was removed *in vacuo* and the residue was purified by preparative HPLC to give the *title compound* (57 mg, 42%) as a clear glass. δ_H ($CDCl_3$) 8.09 (1H, d, *J* 5.17 Hz), 8.04 (1H, d, *J* 2.33 Hz), 7.81 (1H, s),

7.63 (1H, dd, *J* 7.56, 1.36 Hz), 7.46 (1H, dd, *J* 7.98, 1.36 Hz), 7.14-7.04 (1H, m), 6.92 (1H, d, *J* 5.76 Hz), 6.53 (1H, d, *J* 2.32 Hz), 6.37 (1H, s), 5.80 (1H, d, *J* 5.21 Hz), 4.94-4.84 (1H, m), 4.59 (1H, s), 3.98-3.89 (1H, m), 3.86-3.77 (1H, m), 3.68-3.52 (4H, m), 3.38-3.24 (2H, m), 1.80 (3H, d, *J* 6.76 Hz). LCMS (ES+) 451 $(M+H)^+$, 3.41 minutes (*Method 1*).

EXAMPLE 111

(*S*)-1-(2-{8-Chloro-3-[1-(1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ylamino)ethyl]-quinolin-2-ylamino}ethyl)imidazolidin-2-one

A mixture of *Intermediate 23* (1.0 g, 2.9 mmol), 1-(2-aminoethyl)imidazolidin-2-one (0.5 g, 3.9 mmol) and DIPEA (0.8 mL, 5.8 mmol) in *n*-butanol (10 mL) was heated at 120°C for 72 h. After cooling, the reaction mixture was partitioned between Et_2O (200 mL) and water (100 mL). The organic layer was washed with water (3 x 100 mL) and brine (100 mL), separated, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, 5% MeOH in DCM) to give a pale yellow solid. This was dissolved in DCM (20 mL), treated with TFA (5 mL) and stirred for 4 h at r.t. After quenching with 2M NaOH solution (30 mL), the organic layer was washed with water (3 x 10 mL), separated, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give an orange oil (0.8 g, 82%). A portion of this oil (100 mg, 0.3 mmol), 4-chloro-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (34 mg, 0.2 mmol) and DIPEA (100 mg, 0.78 mmol) in *n*-butanol (2 mL) was heated at 120°C for 18 h. The solvent was removed *in vacuo* and the residue was purified by preparative HPLC to give the *title compound* (22 mg, 26%) as a white solid. δ_H ($CDCl_3$) 8.44 (1H, s), 8.19-8.10 (1H, m), 7.89 (1H, s), 7.62 (1H, dd, *J* 7.57, 1.35 Hz), 7.53 (1H, d, *J* 7.68 Hz), 7.13-7.08 (1H, m), 6.05-5.94 (1H, m), 5.51-5.43 (1H, m), 4.20-4.11 (1H, m), 4.02 (3H, s), 3.95-3.86 (2H, m), 3.59-3.50 (3H, m), 3.36-3.10 (1H, m), 3.23 (1H, s), 1.79 (3H, d, *J* 6.75 Hz). LCMS (ES+) 466 $(M+H)^+$, 8.86 minutes (*Method 9*).

EXAMPLE 112

(*S*)-1-(2-{7-Fluoro-3-[1-(pyrazolo[1,5-*a*]pyrimidin-7-ylamino)ethyl]quinolin-2-ylamino}ethyl)imidazolidin-2-one

Intermediate 15 (324 mg, 1.0 mmol), 1-(2-aminoethyl)imidazolidin-2-one (260 mg, 2.0 mmol), DIPEA (270 mg, 2.0 mmol) and *n*-butanol (5.0 mL) were combined in a sealed tube and heated to 120°C for 72 h. After cooling, the mixture was dissolved in a 1:1 mixture of Et_2O and EtOAc (200 mL) and washed with saturated brine (3 x 50 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 0-5% MeOH in DCM) gave a yellow solid (76 mg, 17%). This was dissolved in DCM (5 mL) and treated with TFA (1 mL) and the mixture stirred for 4 h at r.t. before being quenched with 2M NaOH solution (30 mL). The organic layer was washed with water (2 x 10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a pale orange gum (55 mg, 94%). This was combined with 7-chloropyrazolo[1,5-*a*]-pyrimidine (38 mg, 0.22 mmol) and DIPEA (100 mg, 0.78 mmol) in *n*-butanol (2 mL) and the mixture heated at 120°C for 16 h. After cooling, the mixture was dissolved in a 1:1 mixture of Et_2O and EtOAc (100 mL) and washed with saturated brine (3 x 10 mL). The organic layer was separated, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by preparative HPLC gave the *title compound* (6 mg, 7.8%) as a white solid. δ_H (MeOD-d_4) 8.16 (1H, d, *J* 2.32 Hz), 8.10 (1H, d, *J* 5.40 Hz), 7.95 (1H, s), 7.60 (1H, dd, *J* 8.85, 6.33 Hz), 7.31 (1H, dd, *J* 11.11, 2.53 Hz), 6.97 (1H, td, *J* 8.72, 2.56 Hz), 6.49 (1H, d, *J* 2.33 Hz), 5.93 (1H, d, *J* 5.43 Hz), 5.06 (1H, q, *J* 6.73 Hz), 4.00-3.90 (1H, m), 3.83-3.73 (1H, m), 3.72-3.52 (4H, m), 3.32-3.26 (2H, m), 1.78 (3H, d, *J* 6.74 Hz). LCMS (ES+) 435 $(M+H)^+$, 8.93 minutes (*Method 9*).

EXAMPLE 113

(*S*)-1-(2-{8-Chloro-3-[1-(pyrazolo[1,5-*a*][1,3,5]triazin-4-ylamino)ethyl]quinolin-2-ylamino}ethyl)imidazolidin-2-one

A mixture of *Intermediate 23* (1.0 g, 2.9 mmol), 1-(2-aminoethyl)imidazolidin-2-one (0.5 g, 3.9 mmol) and DIPEA (0.8 mL, 5.8 mmol) in *n*-butanol (10 mL) was heated at 120°C for 72 h. After cooling, the reaction mixture was partitioned between Et_2O (200 mL) and water (100 mL). The organic layer was washed with water (3 x 100 mL) and

brine (100 mL), separated, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, 5% MeOH in DCM) to give a pale yellow solid. This was dissolved in DCM (20 mL), treated with TFA (5 mL) and stirred for 4 h at r.t. After quenching with 2M NaOH solution (30 mL), the organic layer was washed with water (3 x 10 mL), separated, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give an orange oil (0.8 g, 82%). A portion of this oil (333 mg, 1.0 mmol), 4-chloro-2-(methylthio)pyrazolo[1,5-*a*][1,3,5]triazine (220 mg, 1.1 mmol), DIPEA (270 mg, 2.0 mmol) and *n*-butanol (5 mL) were combined in a sealed tube and heated to 120°C for 16 h. After cooling, the mixture was dissolved in a 1:1 mixture of Et_2O and EtOAc (200 mL) and washed with saturated brine (3 x 50 mL). The organic layer was separated, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 0-5% MeOH in DCM) gave a yellow solid (360 mg, 80%). This was dissolved in DCM (50 mL) and treated with MCPBA (480 mg, 1.2 mmol) and the mixture was stirred for 4 h at r.t. After quenching with 2M NaOH solution (30 mL), the organic layer was washed with water (2 x 10 mL), separated, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a pale yellow gum (300 mg, 94%). To a solution of this gum (150 mg, 0.27 mmol) in EtOH (5 mL) was added portionwise $NaBH_4$ (22 mg, 0.58 mmol). After 10 minutes, water (10 mL) was added and the reaction mixture was concentrated *in vacuo*. The residue was partitioned between DCM (30 mL) and water (10 mL). The organic layer was washed with water (2 x 10 mL) and brine (10 mL), separated, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2, 0-5% MeOH in DCM) gave the *title compound* (24.6 mg, 20%) as an off-white solid. δ_H ($CDCl_3$) 8.22 (1H, s), 8.00-7.90 (2H, m), 7.63 (1H, dd, *J* 7.52, 1.43 Hz), 7.53 (1H, dd, *J* 7.93, 1.42 Hz), 7.43-7.36 (1H, m), 7.11 (1H, t, *J* 7.74 Hz), 6.69-6.59 (1H, m), 6.44 (1H, d, *J* 2.18 Hz), 5.60-5.51 (1H, m), 4.54 (1H, s), 3.89-3.72 (2H, m), 3.71-3.44 (4H, m), 3.35-3.24 (2H, m), 1.85 (3H, d, *J* 14.20 Hz). LCMS (ES+) 452 $(M+H)^+$, 9.08 minutes (*Method 9*).

EXAMPLE 114

(*S*)-2-{8-Chloro-3-[1-(9*H*-purin-6-ylamino)ethyl]quinolin-2-ylamino}acetic acid

A solution of *Intermediate 69* (60 mg, 0.11 mmol) in dry THF (5 mL) was treated with a solution of TBAF (0.57 mL, 0.57 mmol; 1.0M in THF) and the mixture heated at

50°C for 24 h. The solvent was removed *in vacuo* and the residue was purified by preparative HPLC to afford the *title compound* (10.7 mg, 24%) as a white solid. δ_H (MeOD-d_4) 8.33-8.31 (1H, m), 8.10 (1H, s), 8.03 (1H, s), 7.51 (1H, dd, *J* 8.83, 6.22 Hz), 7.01-6.95 (1H, m), 5.81-5.75 (1H, m), 4.30 (1H, d, *J* 17.2 Hz), 4.21 (1H, d, *J* 17.2 Hz), 2.49 (3H, d, *J* 2.32 Hz), 1.78 (3H, d, *J* 6.80 Hz). LCMS (ES+) 396 $(M+H)^+$, 2.29 minutes (*Method 2*).

EXAMPLE 115

N-Benzyl-*N*-{7-fluoro-8-methyl-3-[(*S*)-1-(pyrazolo[1,5-*a*]pyrimidin-7-ylamino)ethyl]-quinolin-2-yl}amine

A mixture of *Intermediate 70* (150 mg, 0.4 mmol), benzylamine (0.08 mL, 0.7 mmol), copper(I) iodide (12 mg, 0.06 mmol), potassium phosphate (170 mg, 0.8 mmol) and ethylene glycol (62 mg, 1 mmol) in isopropanol (2 mL) was degassed and heated at 90°C overnight. The mixture was cooled to r.t. and extra benzylamine (0.05 mL, 0.4 mmol), copper(I) iodide (10 mg, 0.05 mmol) and ethylene glycol (62 mg, 1 mmol) were added. The mixture was degassed and heated at 90°C overnight. The reaction mixture was cooled to r.t., diluted with EtOAc (2 0 mL) and water (10 mL) and stirred for 15 minutes. The aqueous layer was separated and extracted into EtOAc (10 mL). The combined organic layers were washed with water (3 x 5 mL), brine (5 mL), separated, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a brown oil. This was passed through a SiO_2 plug (0-50% EtOAc in hexane) and concentrated *in vacuo*. The clear residue was purified by preparative HPLC to give the *title compound* (12.5 mg, 7.5%) as a white foam. δ_H (DMSO-d_6) 8.49 (1H, dd, *J* 7.6, 0.5 Hz), 7.95 (1H, d, *J* 7.6 Hz), 7.87 (1H, s), 7.74 (1H, d, *J* 2.0 Hz), 7.57 (1H, t, *J* 5.8 Hz), 7.51 (1H dd, *J* 8.6, 6.6 Hz), 7.39 (2H, d, *J* 7.3 Hz), 7.26 (2H, m), 7.17 (1H, m), 6.97 (1H, t, *J* 9.1 Hz), 6.33 (1H, d, *J* 7.6 Hz), 5.82 (1H, dd, *J* 2.3, 0.8 Hz), 5.43 (1H, t, *J* 7.1 Hz), 4.75 (2H, d, *J* 5.6 Hz), 2.36 (3H, d, *J* 2.0 Hz), 1.54 (3H, d, *J* 6.6 Hz). LCMS (ES+) 427 $(M+H)^+$, 2.58 minutes.

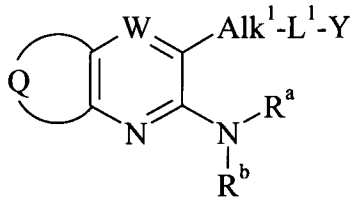
EXAMPLE 116

7-Fluoro-8-methyl-3-[(*S*)-1-(pyrazolo[1,5-*a*]pyrimidin-7-ylamino)ethyl]quinolin-2-ylamine

Intermediate 70 (150 mg, 0.4 mmol), copper(I) iodide (15 mg, 0.08 mmol), Cs_2CO_3 (400 mg, 1.2 mmol) and trifluoroacetamide (100 mg, 0.9 mmol) were added to degassed acetonitrile (3 mL). *trans-N,N'*-Dimethylcyclohexane-1,2-diamine (4 drops) was added and the mixture heated at 90°C overnight. The reaction mixture was cooled to r.t., diluted with EtOAc (15 mL) and washed with water (2 x 5 mL). The organics were separated, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a crude oil which was purified by preparative HPLC to give the *title compound* (7.4 mg, 5%) as an off-white solid. δ_H (DMSO-d_6) 8.49 (1H, m), 7.88 (2H, m), 7.75 (1H, d, *J* 2.0 Hz), 7.51 (1H, dd, *J* 8.3, 6.6 Hz), 6.98 (1H, t, *J* 9.1 Hz), 6.48 (2H, s), 6.33 (1H, d, *J* 7.6 Hz), 5.91 (1H, dd, *J* 2.3, 0.8 Hz), 5.31 (1H, t, *J* 7.1 Hz,), 2.42 (3H, d, *J* 2.0 Hz), 1.50 (3H, d, *J* 6.8 Hz). LCMS (ES+) 337 $(M+H)^+$, 1.99 minutes.

Claims:

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



(I)

wherein

Q represents the residue of an optionally substituted phenyl ring; or an optionally substituted five-membered heteroaromatic ring selected from furyl, thienyl, pyrrolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl and triazolyl; or an optionally substituted six-membered heteroaromatic ring selected from pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl and triazinyl;

W represents C-R^1 or N;

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

L^1 represents oxygen, sulfur, N-R^2 or a covalent bond;

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

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

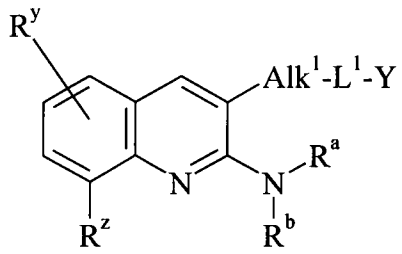
R^2 represents hydrogen or C_{1-6} alkyl;

R^a represents hydrogen or trifluoromethyl; or C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, heteroaryl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents; and

R^b represents hydrogen, C_{1-6} alkyl or C_{3-7} cycloalkyl.

2. A compound as claimed in claim 1 wherein Q represents the residue of a phenyl ring, which is unsubstituted, or substituted by one or two substituents.

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



(IIA)

wherein Alk^1, L^1, Y, R^a and R^b are as defined in claim 1; and

R^y and R^z independently represent hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, heteroaryl, heteroaryl(C_{1-6})alkyl, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulphinyl, C_{1-6} alkylsulphonyl, C_{2-6} alkylcarbonyl, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, halogen, cyano or trifluoromethyl.

4. A compound as claimed in claim 3 wherein R^y represents hydrogen or halogen.

5. A compound as claimed in claim 3 or claim 4 wherein R^z represents hydrogen, C_{1-6} alkyl or halogen.

6. A compound as claimed in any one of the preceding claims wherein Alk^1 represents methylene or (methyl)methylene.

7. A compound as claimed in any one of the preceding claims wherein L^1 represents oxygen or N-R^2, in which R^2 is as defined in claim 1.

8. A compound as claimed in any one of the preceding claims wherein Y represents thienopyrimidinyl, pyrrolotriazinyl, pyrazolopyrimidinyl, pyrazolotriazinyl, purinyl, triazolopyrimidinyl, pyridopyrimidinyl, pyrimidinyl or triazinyl, any of which groups may be optionally substituted by one or more substituents independently selected

from halogen, cyano, C_{1-6} alkyl, C_{1-6} alkylthio, C_{1-6} alkylsulphonyl, amino and C_{1-6} alkylamino.

9. A compound as claimed in any one of the preceding claims wherein R^a represents C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl-(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl or heteroaryl-(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, hydroxy, oxo, C_{2-6} alkylcarbonyl, carboxy, C_{2-6} alkylcarbonylamino, (C_{1-6})alkylaminocarbonyl and di(C_{1-6})alkylaminocarbonyl.

10. A compound as claimed in any one of the preceding claims wherein R^b represents hydrogen or C_{1-6} alkyl.

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

12. 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.

13. 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.

14. 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.

15. 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.

16. 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/GB2010/000243

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/12 C07D401/14 C07D471/04 C07D487/04 C07D495/04
A61K31/4709 A61K31/52 A61P29/00 A61P37/00
ADD.
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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	V. SINGH ET AL.: "Reductive-Cyclization-Mediated Synthesis of Fused Polycyclic Quinolines from Baylis-Hillman Adducts of Acrylonitrile: Scope and Limitations" EUROPEAN JOURNAL OF ORGANIC CHEMISTRY, no. 20, 2009, pages 3454-3466, XP002576761 ISSN: 1434-193X DOI: 10.1002/ejoc.200900336 * Compound of formula 6 *; page 3456	1-6
X	US 2006/178514 A1 (BARUAH ANIMA [IN] ET AL) 10 August 2006 (2006-08-10) * Compounds of formula Ie, Io *example 10	1-6

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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"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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 April 2010	04/05/2010

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Herz, Claus

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 2010/027097 A1 (MITSUBISHI TANABE PHARMA CORP [JP]; KAWANISHI EIJI; MATSUMURA TAKEHIKO) 11 March 2010 (2010-03-11) claims 1-11; example 4.001	1-6
X	WO 2006/073973 A2 (REDDY US THERAPEUTICS INC [US]; BARUAH ANIMA [IN]; DE DIBYENDU [US]; K) 13 July 2006 (2006-07-13) * Compounds of formula Ie, Io *example 10	1-6
X	J. R. AHUJA ET AL.: "A new short synthesis of 3,3'-methylenebis[coumarins] and 3,3-methylenebis[2-diethylaminoquinolines] " SYNTHETIC COMMUNICATIONS, vol. 17, no. 16, 1987, pages 1951-1958, XP009131702 ISSN: 0039-7911 DOI: 10.1080/00397918708057807 * Compounds of formula 5a & 5b *; page 1952	1-6
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