(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
14 May 2010 (14.05.2010)

PCT

(10) International Publication Number
WO 2010/052448 A2

(51) International Patent Classification:
C07D 241/42 (2006.01) *C07D 403/10* (2006.01)
C07D 401/04 (2006.01) *C07D 471/04* (2006.01)
C07D 401/12 (2006.01) *A61K 31/498* (2006.01)

(21) International Application Number:
PCT/GB2009/002514

(22) International Filing Date:
22 October 2009 (22.10.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0820275.6 5 November 2008 (05.11.2008) GB
0911965.2 9 July 2009 (09.07.2009) GB

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

WO 2010/052448 A2

(54) Title: FUSED PYRAZINE DERIVATIVES AS KINASE INHIBITORS

(57) Abstract: A series of quinoxaline derivatives, and analogues thereof, which are functionalised further by a substituted phenyl or pyridinyl moiety, being selective inhibitors of PO 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 PYRAZINE DERIVATIVES AS KINASE INHIBITORS

The present invention relates to a class of fused pyrazine derivatives, and to their use in therapy. More particularly, the invention provides a family of quinoxaline derivatives, and analogues thereof, which are functionalised further by a substituted phenyl or pyridinyl moiety. 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).

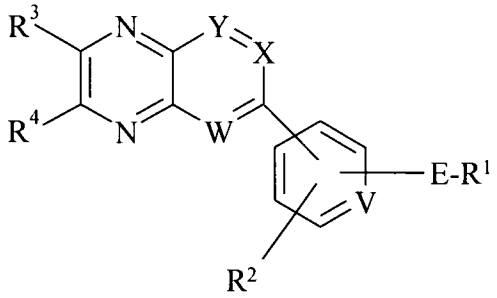
In addition, the compounds in accordance with the present invention may be beneficial as pharmacological standards for use in the development of new biological tests and in the search for new pharmacological agents. Thus, the compounds of this invention may be useful as radioligands in assays for detecting compounds capable of binding to human PI3K enzymes.

WO 98/54158 describes a class of substituted quinoline and quinoxaline derivatives which are stated to act as inhibitors of PDGF-R tyrosine kinase activity and/or Lck tyrosine kinase activity.

WO 2008/141065, published on 20 November 2008, relates to a class of quinoxaline derivatives that are substituted in the 6-position by *inter alia* a pyridinyl moiety. The compounds described therein are stated to be suitable for the modulation, notably the inhibition, of the activity of PI3 kinases, suitably PI3Kα.

The compounds in accordance with 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 a pharmaceutically acceptable salt or solvate thereof:



(I)

wherein

V represents N or CH;

W represents N or C-R^5;

X represents N or C-R^6; and

Y represents N or C-R^7; provided that no more than one of W, X and Y represents N at any one time;

E represents a covalent bond, -O-, -N(R^8)-, -C(O)-, -C(=N-OR^9)-, -C(O)N(R^8)-, -N(R^8)C(O)-, -S-, -S(O)-, -S$(O)_2$-, -S$(O)_2$N(R^8)- or -N(R^8)S$(O)_2$-; or E represents an optionally substituted straight-chained or branched alkylene chain containing 1 to 5 carbon atoms; or E represents an optionally substituted straight-chained or branched heteroalkylene chain containing 1 to 5 carbon atoms and one or more heteroatoms independently selected from O, S and -N(R^8)-;

R^1 represents -OR^9, -N$R^c R^d$, -N(R^8)(OR^9), -NR^dCOR^a, -CO_2R^b, -N$R^d CO_2R^b$, -CON$R^c R^d$, -NHCON$R^c R^d$ or -SR^e; or R^1 represents C_{3-7} cycloalkyl, aryl, C_{3-7} heterocycloalkyl or heteroaryl, any of which groups may be optionally substituted by one or more substituents;

R^2 represents hydrogen, halogen, cyano, trifluoromethyl, difluoromethoxy, trifluoromethoxy, -N$R^c R^d$, -COR^a, -CO_2R^b, -CON$R^c R^d$ or -NR^dCOR^a; or R^2 represents C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, 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;

R^3 and R^4 independently represent hydrogen or C_{1-6} alkyl;

R^5, R^6 and R^7 independently represent hydrogen, halogen or C_{1-6} alkyl;

R^8 represents hydrogen, trifluoromethyl, -COR^a, -CO_2R^b, -CON$R^c R^d$ or -SO_2R^e; or R^8 represents 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;

R^9 represents hydrogen; or C_{1-6} alkyl, aryl(C_{1-6})alkyl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents;

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

R^b represents hydrogen; or optionally substituted C_{1-6} alkyl;

R^c represents hydrogen; or C_{1-6} alkyl, aryl, aryl(C_{1-6})alkyl, heteroaryl, heteroaryl(C_{1-6})alkyl or (aryl)(heteroaryl)(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents;

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

R^e represents C_{1-6} alkyl.

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

E represents a covalent bond, -O-, -N(R^8)-, -C(O)-, -C(O)N(R^8)-, -N(R^8)C(O)-, -$S(O)_2$-, -$S(O)_2$N(R^8)- or -N(R^8)$S(O)_2$-; or E represents an optionally substituted straight-chained or branched alkylene chain containing 1 to 5 carbon atoms; or E represents an optionally substituted straight-chained or branched heteroalkylene chain containing 1 to 5 carbon atoms and one or more heteroatoms independently selected from O, S and -N(R^8)-;

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

V, W, X, Y, R^2, R^3, R^4 and R^8 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, where possible, by one or more substituents. Typically, such groups will be unsubstituted, or substituted, where possible, by one or two substituents. Suitably, such groups will be unsubstituted or, where possible, monosubstituted.

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.

Typical C_{2-6} alkenyl groups include vinyl and allyl.

Typical C_{2-6} alkynyl groups include ethynyl, prop-1-yn-1-yl, prop-2-yn-1-yl, but-1-yn-1-yl and 3-methylbut-1-yn-1-yl.

Suitable C_{3-7} cycloalkyl groups, which may comprise benzo-fused analogues thereof, include cyclopropyl, cyclobutyl, cyclopentyl, indanyl, cyclohexyl and cycloheptyl.

Suitable aryl groups include phenyl and naphthyl, preferably phenyl.

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

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

Suitable heteroaryl groups include furyl, benzofuryl, dibenzofuryl, thienyl, benzothienyl, dibenzothienyl, pyrrolyl, indolyl, pyrrolo[2,3-*b*]pyridinyl, pyrrolo[3,2-*c*]-pyridinyl, pyrazolyl, pyrazolo[1,5-*a*]pyridinyl, indazolyl, oxazolyl, benzoxazolyl, isoxazolyl, thiazolyl, benzothiazolyl, isothiazolyl, imidazolyl, benzimidazolyl, imidazo[1,2-*a*]pyridinyl, imidazo[4,5-*b*]pyridinyl, imidazo[1,2-*a*]pyrimidinyl,

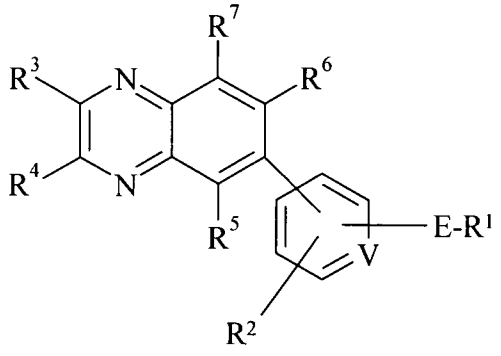
imidazo[1,2-*a*]pyrazinyl, oxadiazolyl, thiadiazolyl, triazolyl, benzotriazolyl, tetrazolyl, pyridinyl, quinolinyl, isoquinolinyl, pyridazinyl, cinnolinyl, pyrimidinyl, pyrazinyl, quinoxalinyl and chromenyl groups.

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

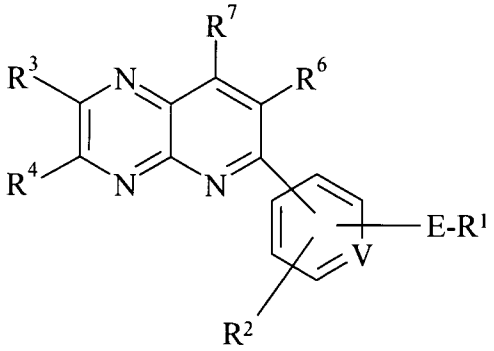
Where the compounds of formula (I) have one or more asymmetric centres, they may accordingly exist as enantiomers. Where the compounds of the invention possess two or more asymmetric centres, they may additionally exist as diastereomers. The invention is to be understood to extend to all such enantiomers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

It is to be understood that each individual atom present in formula (I), or in the formulae depicted hereinafter, may in fact be present in the form of any of its naturally occurring isotopes, with the most abundant isotope(s) being preferred. Thus, by way of example, each individual hydrogen atom present in formula (I), or in the formulae depicted hereinafter, may be present as a ^{1}H, ^{2}H (deuterium) or ^{3}H (tritium) atom, preferably ^{1}H. Similarly, by way of example, each individual carbon atom present in formula (I), or in the formulae depicted hereinafter, may be present as a ^{12}C, ^{13}C or ^{14}C atom, preferably ^{12}C.

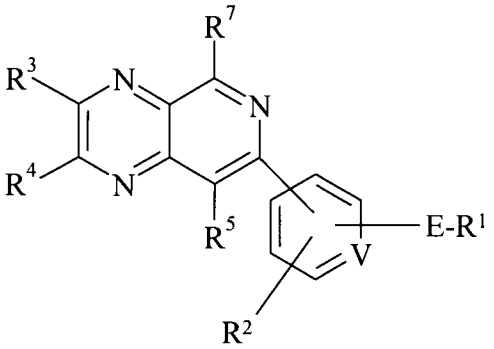
Specific sub-classes of compounds in accordance with the present invention are represented by the compounds of formula (IA), (IB), (IC) and (ID):



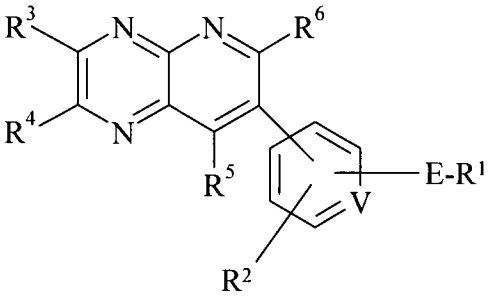
(IA)



(IB)



(IC)



(ID)

wherein V, E, R^1, R^2, R^3, R^4, R^5, R^6 and R^7 are as defined above.

In one aspect, the present invention provides a compound of formula (IA) as depicted above, or a pharmaceutically acceptable salt or solvate thereof, wherein

V represents CH;

R^3 and R^4 both represent hydrogen; and

E, R^1, R^2, R^5, R^6 and R^7 are as defined above.

In another aspect, the present invention provides a compound of formula (IB), (IC) or (ID) as depicted above, or a pharmaceutically acceptable salt or solvate thereof, wherein V, E, R^1, R^2, R^3, R^4, R^5, R^6 and R^7 are as defined above.

In one embodiment, V represents N. In another embodiment, V represents CH.

In a first embodiment, W represents C-R^5, X represents C-R^6 and Y represents C-R^7, in which R^5, R^6 and R^7 are as defined above. In a second embodiment, W represents N, X represents C-R^6 and Y represents C-R^7, in which R^6 and R^7 are as defined above. In

a third embodiment, W represents C-R^5, X represents N and Y represents C-R^7, in which R^5 and R^7 are as defined above. In a fourth embodiment, W represents C-R^5, X represents C-R^6 and Y represents N, in which R^5 and R^6 are as defined above.

Typically, E represents a covalent bond, -O-, -N(R^8)-, -C(O)-, -C(O)N(R^8)-, -N(R^8)C(O)-, -S$(O)_2$-, -S$(O)_2$N(R^8)- or -N(R^8)S$(O)_2$-; or E represents an optionally substituted straight-chained or branched alkylene chain containing 1 to 5 carbon atoms; or E represents an optionally substituted straight-chained or branched heteroalkylene chain containing 1 to 5 carbon atoms and one or more heteroatoms independently selected from O, S and -N(R^8)-.

Appositely, E represents a covalent bond, -N(R^8)-, -C(O)-, -C(=N-OR^9)-, -C(O)N(R^8)-, -S-, -S$(O)_2$- or -S$(O)_2$N(R^8)-; or E represents an optionally substituted straight-chained or branched alkylene chain containing 1 to 5 carbon atoms; or E represents an optionally substituted straight-chained or branched heteroalkylene chain containing 1 to 5 carbon atoms and one or more heteroatoms independently selected from O, S and -N(R^8)-.

Suitably, E represents a covalent bond, -N(R^8)-, -C(O)-, -S$(O)_2$- or -S$(O)_2$N(R^8)-; or E represents an optionally substituted straight-chained or branched alkylene chain containing 1 to 5 carbon atoms; or E represents an optionally substituted straight-chained or branched heteroalkylene chain containing 1 to 5 carbon atoms and one or more heteroatoms independently selected from O, S and -N(R^8)-.

In a first embodiment, E represents a covalent bond, in which case R^1 is directly attached to the aromatic ring containing the variable V. In a second embodiment, E represents -O-. In a third embodiment, E represents -N(R^8)-, in which R^8 is as defined above. In a fourth embodiment, E represents -C(O)-. In a fifth embodiment, E represents -C(=N-OR^9)-, in which R^9 is as defined above. In a sixth embodiment, E represents -C(O)N(R^8)-, in which R^8 is as defined above. In a seventh embodiment, E represents -N(R^8)C(O)-, in which R^8 is as defined above. In an eighth embodiment, E represents -S-. In a ninth embodiment, E represents -S(O)-. In a tenth embodiment, E represents -S$(O)_2$-. In an eleventh embodiment, E represents -S$(O)_2$N(R^8)-, in which R^8 is as defined above. In a twelfth embodiment, E represents -N(R^8)S$(O)_2$-, in which R^8 is as defined above. In a thirteenth embodiment, E represents an optionally substituted straight-chained or branched alkylene chain containing 1 to 5 carbon atoms, typically 1 to 4 carbon atoms. In a fourteenth embodiment, E represents an optionally substituted straight-chained or

branched heteroalkylene chain containing 1 to 5 carbon atoms, suitably 1, 2 or 3 carbon atoms, typically 1 or 2 carbon atoms, and one or more heteroatoms independently selected from O, S and -N(R^8)-, in which R^8 is as defined above.

Examples of typical substituents on the alkylene or heteroalkylene chain represented by E include oxo, aryl, C_{3-7} heterocycloalkyl, hydroxy, C_{1-6} alkoxy, heteroaryl(C_{1-6})alkoxy, (C_{1-6})alkylheteroaryl(C_{1-6})alkoxy, C_{2-6} alkoxycarbonyl(C_{1-6})alkoxy, aminocarbonyl(C_{1-6})alkoxy, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, C_{2-6} alkylcarbonylamino and (C_{1-6})alkylaminocarbonylamino.

Examples of suitable substituents on the alkylene or heteroalkylene chain represented by E include oxo, aryl, C_{1-6} alkoxy, C_{2-6} alkoxycarbonyl(C_{1-6})alkoxy and aminocarbonyl(C_{1-6})alkoxy.

Examples of illustrative substituents on the alkylene or heteroalkylene chain represented by E include oxo, phenyl, pyrrolidinyl, hydroxy, ethoxy, pyridinylmethoxy, methylisoxazolylmethoxy, ethoxycarbonylmethoxy, aminocarbonylmethoxy, amino, dimethylamino, acetylamino and ethylaminocarbonylamino.

Examples of particular substituents on the alkylene or heteroalkylene chain represented by E include oxo, phenyl, ethoxy, ethoxycarbonylmethoxy and aminocarbonylmethoxy.

Where E represents an optionally substituted straight-chained or branched alkylene chain, typical chains 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.

Where E represents an optionally substituted straight-chained or branched alkylene chain, illustrative chains include methylene (-CH_2-), (phenyl)methylene, (pyrrolidinyl)-methylene, (hydroxy)methylene, (ethoxy)methylene, (pyridinylmethoxy)methylene, (methylisoxazolylmethoxy)methylene, (ethoxycarbonylmethoxy)methylene, (aminocarbonylmethoxy)methylene, (amino)methylene, (dimethylamino)methylene, (acetylamino)methylene, (ethylaminocarbonylamino)methylene, (methyl)methylene, (hydroxy)(methyl)methylene, ethylene (-CH_2CH_2-), (oxy)ethylene, (ethyl)methylene, (dimethyl)methylene, (methyl)ethylene, (dimethyl)ethylene and (dimethyl)(oxy)ethylene.

Where E represents an optionally substituted straight-chained or branched alkylene chain, particular chains include methylene (-CH_2-), (phenyl)methylene, (ethoxy)-methylene, (ethoxycarbonylmethoxy)methylene, (aminocarbonylmethoxy)methylene, (methyl)methylene, ethylene (-CH_2CH_2-), (oxy)ethylene, (ethyl)methylene, (dimethyl)-methylene, (methyl)ethylene, (dimethyl)ethylene and (dimethyl)(oxy)ethylene.

Where E represents an optionally substituted straight-chained or branched heteroalkylene chain, such chain comprises an alkylene chain as defined above interrupted at some point along its length by one or more heteroatoms independently selected from O, S and -$N(R^8)$-. Typically, the heteroalkylene chain E contains one or two heteroatoms. Suitably, the heteroalkylene chain E contains one heteroatom.

In one embodiment, the heteroalkylene chain E contains O. In another embodiment, the heteroalkylene chain E contains S. In a preferred embodiment, the heteroalkylene chain E contains -$N(R^8)$-.

Typical examples of the heteroalkylene chain E include -$CH_2N(R^8)$-, -$CH_2N(R^8)CH(CH_3)$- and -$CH_2N(R^8)CH_2CH_2$-.

Selected examples of the heteroalkylene chain E include -$CH_2N(R^8)$- and -$CH_2N(R^8)CH(CH_3)$-.

Appositely, R^1 represents -OR^9, -NR^cR^d, -NR^dCOR^a, -CO_2R^b, -$NR^dCO_2R^b$, -$NHCONR^cR^d$ or -SR^e; or R^1 represents C_{3-7} cycloalkyl, aryl, C_{3-7} heterocycloalkyl or heteroaryl, any of which groups may be optionally substituted by one or more substituents.

Typically, R^1 represents C_{3-7} cycloalkyl, aryl, C_{3-7} heterocycloalkyl or heteroaryl, any of which groups may be optionally substituted by one or more substituents.

Suitably, R^1 represents C_{3-7} cycloalkyl, aryl or C_{3-7} heterocycloalkyl, any of which groups may be optionally substituted by one or more substituents.

In a first embodiment, R^1 represents -OR^9. In a second embodiment, R^1 represents -NR^cR^d. In a third embodiment, R^1 represents -$N(R^8)(OR^9)$. In a fourth embodiment, R^1 represents -NR^dCOR^a. In a fifth embodiment, R^1 represents -CO_2R^b. In a sixth embodiment, R^1 represents -$NR^dCO_2R^b$. In a seventh embodiment, R^1 represents -$CONR^cR^d$. In an eighth embodiment, R^1 represents -$NHCONR^cR^d$. In a ninth embodiment, R^1 represents -SR^e. In a tenth embodiment, R^1 represents optionally substituted C_{3-7} cycloalkyl. In an eleventh embodiment, R^1 represents optionally substituted aryl. In a twelfth embodiment, R^1 represents optionally substituted C_{3-7}

heterocycloalkyl. In a thirteenth embodiment, R^1 represents optionally substituted heteroaryl.

Apposite values of R^1 include $-OR^9$, $-NR^cR^d$, $-NR^dCOR^a$, $-CO_2R^b$, $-NR^dCO_2R^b$, $-NHCONR^cR^d$ and $-SR^e$; and cyclopropyl, cyclobutyl, cyclopentyl, indanyl, cyclohexyl, phenyl, azetidinyl, tetrahydrofuranyl, pyrrolidinyl, isoindolinyl, tetrahydropyranyl, piperidinyl, azepanyl, piperazinyl, morpholinyl and pyrazolyl, any of which groups may be optionally substituted by one or more substituents.

Suitable values of R^1 include cyclopropyl, cyclobutyl, cyclopentyl, indanyl, cyclohexyl, phenyl, azetidinyl, tetrahydrofuranyl, pyrrolidinyl, isoindolinyl, tetrahydropyranyl, piperidinyl, azepanyl, piperazinyl, morpholinyl and pyrazolyl, any of which groups may be optionally substituted by one or more substituents.

Typical values of R^1 include cyclopropyl, cyclopentyl, cyclohexyl, phenyl, azetidinyl, tetrahydrofuranyl, pyrrolidinyl, tetrahydropyranyl, piperidinyl, azepanyl, piperazinyl and morpholinyl, any of which groups may be optionally substituted by one or more substituents.

Examples of illustrative substituents on R^1 include halogen, hydroxy, oxo, C_{1-6} alkyl, difluoroethyl, C_{1-6} alkoxy(C_{1-6})alkyl, C_{2-6} alkylcarbonylamino, C_{3-7} cycloalkyl-carbonylamino, carboxy, aminocarbonyl, C_{3-7} cycloalkylaminocarbonyl and hydroxy-(C_{3-7})heterocycloalkylcarbonyl.

Examples of suitable substituents on R^1 include halogen, hydroxy, oxo, C_{1-6} alkyl, difluoroethyl, C_{1-6} alkoxy(C_{1-6})alkyl, C_{3-7} cycloalkylcarbonylamino, carboxy, amino-carbonyl, C_{3-7} cycloalkylaminocarbonyl and hydroxy(C_{3-7})heterocycloalkylcarbonyl.

Examples of apposite substituents on R^1 include fluoro, hydroxy, oxo, methyl, difluoroethyl, methoxymethyl, acetylamino, cyclopentylcarbonylamino, carboxy, aminocarbonyl, cyclopentylaminocarbonyl and hydroxypyrrolidinylcarbonyl.

Examples of particular substituents on R^1 include fluoro, hydroxy, oxo, methyl, difluoroethyl, methoxymethyl, cyclopentylcarbonylamino, carboxy, aminocarbonyl, cyclopentylaminocarbonyl and hydroxypyrrolidinylcarbonyl.

Representative values of R^1 include hydroxy, methoxy, ethoxy, amino, (methoxy)-(methyl)amino, acetylamino, carboxy, methoxycarbonyl, *tert*-butoxycarbonylamino, ethylaminocarbonylamino, methylthio, cyclopropyl, cyclopentylcarbonylamino-cyclopropyl, carboxycyclopropyl, cyclopentylaminocarbonylcyclopropyl, hydroxypyrrolidinylcarbonylcyclopropyl, cyclobutyl, cyclopentyl, aminocarbonyl-

cyclopentyl, indanyl, cyclohexyl, hydroxycyclohexyl, aminocarbonylcyclohexyl, phenyl, azetidinyl, hydroxyazetidinyl, (dimethyl)(hydroxy)tetrahydrofuranyl, (methoxymethyl)-(methyl)tetrahydrofuranyl, pyrrolidinyl, hydroxypyrrolidinyl, oxopyrrolidinyl, dioxopyrrolidinyl, acetylaminopyrrolidinyl, isoindolinyl, tetrahydropyranyl, piperidinyl, fluoropiperidinyl, difluoropiperidinyl, methylpiperidinyl, aminocarbonylpiperidinyl, azepanyl, oxopiperazinyl, difluoroethylpiperazinyl, morpholinyl and pyrazolyl.

Idealised values of R^1 include cyclopropyl, cyclopentylcarbonylamino-cyclopropyl, carboxycyclopropyl, cyclopentylaminocarbonylcyclopropyl, hydroxypyrrolidinylcarbonylcyclopropyl, cyclobutyl, cyclopentyl, aminocarbonyl-cyclopentyl, indanyl, cyclohexyl, hydroxycyclohexyl, aminocarbonylcyclohexyl, phenyl, azetidinyl, hydroxyazetidinyl, (dimethyl)(hydroxy)tetrahydrofuranyl, (methoxymethyl)-(methyl)tetrahydrofuranyl, pyrrolidinyl, hydroxypyrrolidinyl, oxopyrrolidinyl, dioxopyrrolidinyl, acetylaminopyrrolidinyl, isoindolinyl, tetrahydropyranyl, piperidinyl, fluoropiperidinyl, difluoropiperidinyl, methylpiperidinyl, aminocarbonylpiperidinyl, azepanyl, oxopiperazinyl, difluoroethylpiperazinyl, morpholinyl and pyrazolyl.

Selected values of R^1 include cyclopropyl, cyclopentylcarbonylaminocyclopropyl, carboxycyclopropyl, cyclopentylaminocarbonylcyclopropyl, hydroxypyrrolidinylcarbonyl-cyclopropyl, cyclopentyl, cyclohexyl, phenyl, hydroxyazetidinyl, (dimethyl)(hydroxy)-tetrahydrofuranyl, (methoxymethyl)(methyl)tetrahydrofuranyl, pyrrolidinyl, hydroxy-pyrrolidinyl, oxopyrrolidinyl, tetrahydropyranyl, piperidinyl, fluoropiperidinyl, difluoro-piperidinyl, methylpiperidinyl, aminocarbonylpiperidinyl, azepanyl, difluoroethyl-piperazinyl and morpholinyl.

Suitably, R^2 represents hydrogen, halogen, trifluoromethoxy, $-NR^cR^d$ or $-NR^dCOR^a$; or R^2 represents C_{1-6} alkyl, C_{1-6} alkoxy, aryl or C_{3-7} heterocycloalkyl, any of which groups may be optionally substituted by one or more substituents.

In a particular embodiment, R^2 represents hydrogen.

In a particular embodiment, R^2 is unsubstituted.

Selected values of R^2 include hydrogen, fluoro, bromo, trifluoromethoxy, amino, acetylamino, methyl, methoxy, phenyl and morpholinyl.

In one embodiment, R^3 represents hydrogen. In another embodiment, R^3 represents C_{1-6} alkyl, especially methyl.

In one embodiment, R^4 represents hydrogen. In another embodiment, R^4 represents C_{1-6} alkyl, especially methyl.

In one embodiment, R^5 represents hydrogen. In another embodiment, R^5 represents halogen, especially fluoro. In a further embodiment, R^5 represents C_{1-6} alkyl, especially methyl.

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

In one embodiment, R^7 represents hydrogen. In another embodiment, R^7 represents halogen, especially fluoro. In a further embodiment, R^7 represents C_{1-6} alkyl, especially methyl.

Typically, R^8 represents hydrogen, $-COR^a$, $-CO_2R^b$, $-CONR^cR^d$ or $-SO_2R^e$; or R^8 represents C_{1-6} alkyl or heteroaryl, either of which groups may be optionally substituted by one or more substituents.

Suitably, R^8 represents hydrogen, $-COR^a$ or $-SO_2R^e$; or R^8 represents C_{1-6} alkyl or heteroaryl, either of which groups may be optionally substituted by one or more substituents.

In one embodiment, R^8 represents hydrogen. In another embodiment, R^8 represents $-COR^a$. In another embodiment, R^8 represents $-CO_2R^b$. In another embodiment, R^8 represents $-CONR^cR^d$. In another embodiment, R^8 represents $-SO_2R^e$. In a further embodiment, R^8 represents optionally substituted C_{1-6} alkyl. In an additional embodiment, R^8 represents optionally substituted heteroaryl.

Suitably, R^8 is unsubstituted or monosubstituted.

In a particular embodiment, R^8 is unsubstituted. In another embodiment, R^8 is monosubstituted.

Examples of typical substituents on R^8 include hydroxy and aminocarbonyl.

Typical values of R^8 include hydrogen, $-COR^a$, $-CO_2R^b$, $-CONR^cR^d$, $-SO_2R^e$, methyl, aminocarbonylmethyl, ethyl, hydroxyethyl and pyridinyl.

Selected values of R^8 include hydrogen, $-COR^a$, $-SO_2R^e$, methyl and pyridinyl.

Typically, R^9 represents hydrogen, C_{1-6} alkyl or heteroaryl(C_{1-6})alkyl.

In one embodiment, R^9 represents hydrogen. In another embodiment, R^9 represents C_{1-6} alkyl, preferably methyl or ethyl, especially ethyl. In a further embodiment, R^9 represents heteroaryl(C_{1-6})alkyl, typically pyridinylmethyl.

Suitably, R^a represents C_{1-6} alkyl or aryl.

In one embodiment, R^a represents C_{1-6} alkyl. In another embodiment, R^a represents aryl.

Selected values of R^a include methyl, isopropyl and phenyl.

In one embodiment, R^b represents hydrogen. In another embodiment, R^b represents C_{1-6} alkyl, typically methyl, ethyl or *tert*-butyl, especially methyl or ethyl.

Typical values of R^c include hydrogen, methyl, ethyl, phenyl, benzyl, pyridinylmethyl and (phenyl)(pyridinyl)methyl.

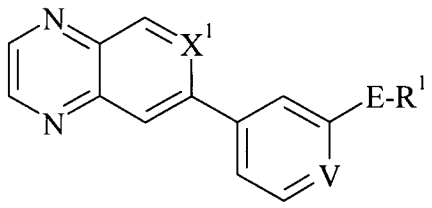
Particular values of R^c include hydrogen, phenyl, benzyl, pyridinylmethyl and (phenyl)(pyridinyl)methyl.

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

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

Suitably, R^e represents methyl.

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



(IIA)

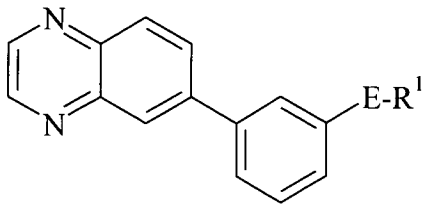
wherein

X^1 represents N or C-R^6; and

V, E, R^1 and R^6 are as defined above.

In one embodiment, X^1 represents N. In another embodiment, X^1 represents C-R^6.

One defined subset of the compounds of formula (IIA) above is represented by the compounds of formula (IIB), and pharmaceutically acceptable salts and solvates thereof:

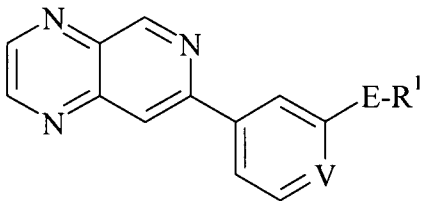


(IIB)

wherein

E and R^1 are as defined above.

Another defined subset of the compounds of formula (IIA) above is represented by the compounds of formula (IIC), and pharmaceutically acceptable salts and solvates thereof:



(IIC)

wherein

V, E and R^1 are as defined above.

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.

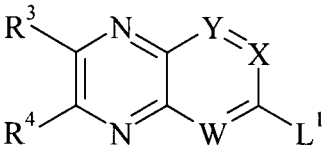
For topical administration the compounds according to the present invention may be conveniently formulated in a suitable ointment containing the active component suspended or dissolved in one or more pharmaceutically acceptable carriers. Particular carriers include, for example, mineral oil, liquid petroleum, propylene glycol, polyoxyethylene, polyoxypropylene, emulsifying wax and water. Alternatively, the compounds according to 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 according to the present invention may be conveniently formulated as microionized 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.

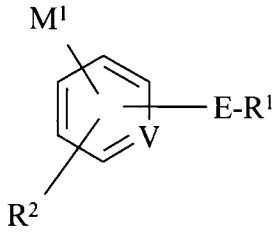
For rectal administration the compounds according to the present invention may be conveniently formulated as suppositories. These can be prepared by mixing the active component with a suitable non-irritating excipient which is solid at room temperature but liquid at rectal temperature and so will melt 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 the invention required for the prophylaxis or treatment of a particular condition will vary depending on the compound chosen and the condition of the patient to be treated. In general, however, daily dosages may range from around 10 ng/kg to 1000 mg/kg, typically from 100 ng/kg to 100 mg/kg, e.g. around 0.01 mg/kg to 40 mg/kg body weight, for oral or buccal administration, from around 10 ng/kg to 50 mg/kg body weight for parenteral administration, and from around 0.05 mg to around 1000 mg, e.g. from around 0.5 mg to around 1000 mg, for nasal administration or administration by inhalation or insufflation.

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



(III)



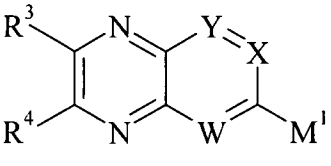
(IV)

wherein V, W, X, Y, E, R^1, R^2, R^3 and R^4 are as defined above, L^1 represents a suitable leaving group, and M^1 represents a boronic acid moiety $-B(OH)_2$ or a cyclic ester thereof formed with an organic diol, e.g. pinacol, 1,3-propanediol or neopentyl glycol; in the presence of a transition metal catalyst.

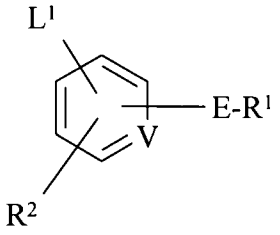
The leaving group L^1 is typically a halogen atom, e.g. chloro, bromo or iodo.

The transition metal catalyst of use in the reaction between compounds (III) and (IV) is suitably tetrakis(triphenylphosphine)palladium(0). The reaction is conveniently effected at an elevated temperature in a suitable solvent, e.g. an ethereal solvent such as ethylene glycol dimethyl ether (DME) or 1,4-dioxane, generally under basic conditions, e.g. in the presence of an inorganic base such as sodium carbonate, potassium carbonate, caesium carbonate or potassium phosphate.

Conversely, the compounds of formula (I) above may be prepared by a process which comprises reacting a compound of formula (V) with a compound of formula (VI):



(V)

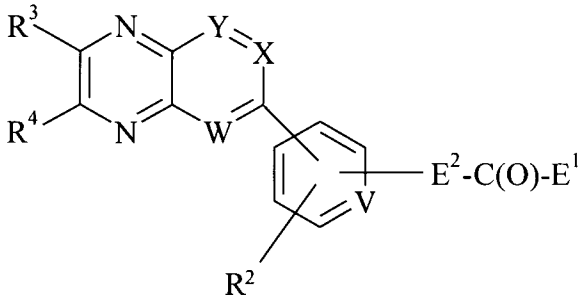


(VI)

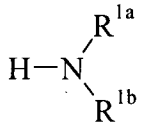
wherein V, W, X, Y, E, R^1, R^2, R^3, R^4, L^1 and M^1 are as defined above; in the presence of a transition metal catalyst; under conditions analogous to those described above for the reaction between compounds (III) and (IV).

The compounds of formula (I) above wherein E-R^1 contains the motif -CH-N- may be prepared by a process which comprises reacting the appropriate aldehyde or ketone derivative with the appropriate amine derivative in the presence of a reducing agent.

Thus, by way of illustration, the compounds of formula (I) above wherein R^1 represents an optionally substituted *N*-linked C_{3-7} heterocycloalkyl group containing at least one nitrogen atom may be prepared by a process which comprises reacting a compound of formula (VII) with a compound of formula (VIIIA):

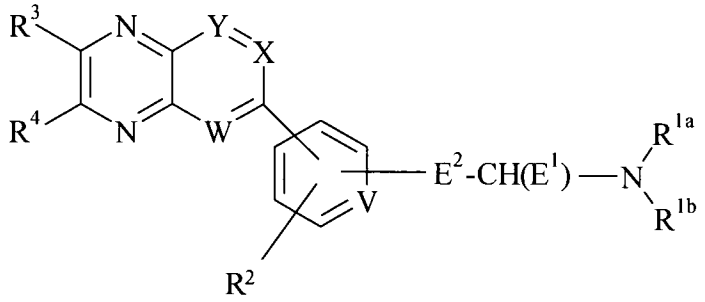


(VII)



(VIIIA)

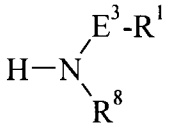
wherein V, W, X, Y, R^2, R^3 and R^4 are as defined above, -E^2-CH(E^1)- corresponds to the moiety E as specified above, and R^{1a} and R^{1b}, when taken together with the nitrogen atom to which they are both attached, represent an optionally substituted C_{3-7} heterocycloalkyl group; in the presence of a reducing agent; to provide a compound of formula (IR):



(IR)

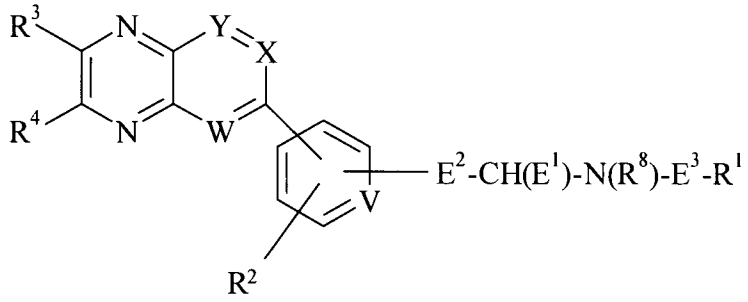
wherein V, W, X, Y, R^2, R^3, R^4, E^1, E^2, R^{1a} and R^{1b} are as defined above.

Similarly, also by way of illustration, the compounds of formula (I) above may be prepared by a process which comprises reacting a compound of formula (VII) as defined above with a compound of formula (VIIIB):



(VIIIB)

wherein R^1 and R^8 are as defined above, and $-E^2-CH(E^1)-N(R^8)-E^3-$ corresponds to the moiety E as specified above; in the presence of a reducing agent; to provide a compound of formula (IS):



(IS)

wherein V, W, X, Y, R^1, R^2, R^3, R^4, R^8, E^1, E^2 and E^3 are as defined above.

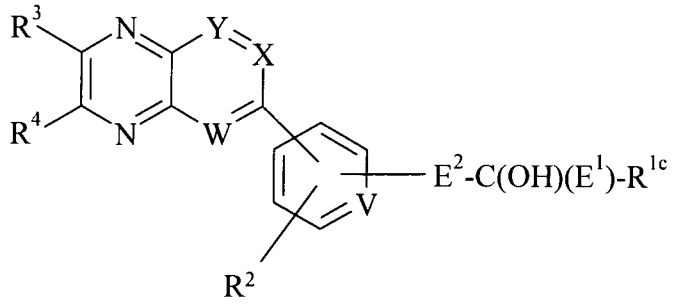
Suitably, E^1 represents hydrogen, methyl or ethyl.

Suitably, E^2 represents a covalent bond or a methylene linkage.

Suitably, E^3 represents a covalent bond, or a methylene or (methyl)methylene linkage.

The reducing agent of use in the reaction between compound (VII) and compound (VIIIA) or (VIIIB) is suitably sodium triacetoxyborohydride or (polystyrylmethyl)-trimethylammonium cyanoborohydride. The reaction is conveniently effected at ambient temperature in a suitable solvent, e.g. a chlorinated solvent such as dichloromethane or 1,2-dichloroethane and/or an ethereal solvent such as tetrahydrofuran, in the presence of trimethyl orthoformate or acetic acid.

The compounds of formula (I) above wherein R^1 represents an optionally substituted C_{3-7} cycloalkyl, aryl, C_{3-7} heterocycloalkyl or heteroaryl group may be prepared by a process which comprises reacting a compound of formula (VII) as defined above with a compound of formula R^{1c}-Mg-Hal; to provide a compound of formula (IT):



(IT)

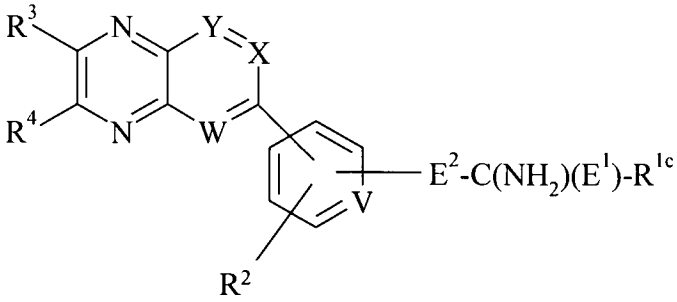
wherein V, W, X, Y, R^2, R^3 and R^4 are as defined above, $-E^2-C(OH)(E^1)-$ corresponds to the moiety E as specified above, R^{1c} represents an optionally substituted C_{3-7} cycloalkyl, aryl, C_{3-7} heterocycloalkyl or heteroaryl group, and Hal represents a halogen atom.

Suitable values of R^{1c} include methyl and phenyl.

The halogen atom Hal is suitably chloro or bromo.

The reaction is conveniently performed at ambient temperature in a suitable solvent, e.g. a cyclic ether such as tetrahydrofuran.

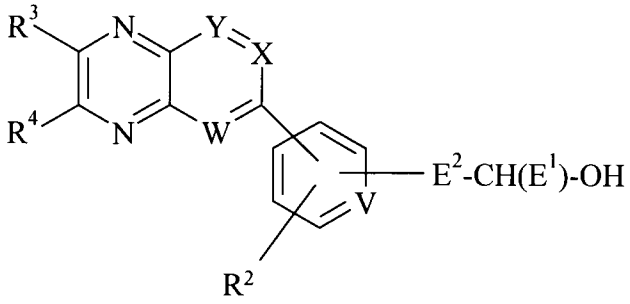
In another procedure, the compounds of formula (I) above may be prepared by a process which comprises reacting a compound of formula (VII) as defined above with 2-methyl-2-propanesulfinamide in the presence of titanium(IV) isopropoxide; followed by treatment of the resulting compound with a compound of formula R^{1c}-Mg-Hal as defined above; followed by treatment of the resulting compound with a mineral acid such as hydrochloric acid; to provide a compound of formula (IU):



(IU)

wherein V, W, X, Y, R^2, R^3, R^4 and R^{1c} are as defined above, and $-E^2-C(NH_2)(E^1)-$ corresponds to the moiety E as specified above.

The compounds of formula (I) above wherein R^1 represents hydroxy (-OH) may be prepared by a process which comprises treating a compound of formula (VII) as defined above with a reducing agent; to provide a compound of formula (IW):

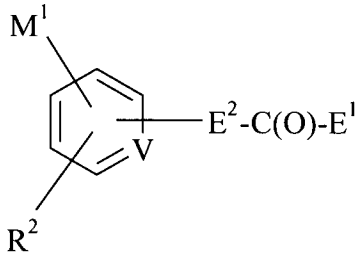


(IW)

wherein V, W, X, Y, R^2, R^3, R^4, E^1 and E^2 are as defined above.

The reducing agent is suitably sodium borohydride, in which case the reaction is conveniently effected in a suitable solvent, e.g. a lower alkanol such as methanol.

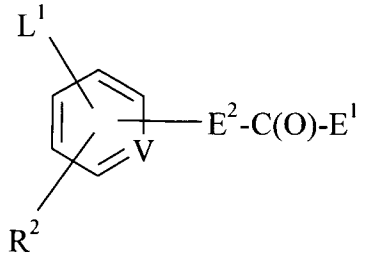
The intermediates of formula (VII) above may be prepared by reacting a compound of formula (III) as defined above with a compound of formula (IX):



(IX)

wherein V, R^2, M^1, E^1 and E^2 are as defined above; in the presence of a transition metal catalyst; under conditions analogous to those described above for the reaction between compounds (III) and (IV).

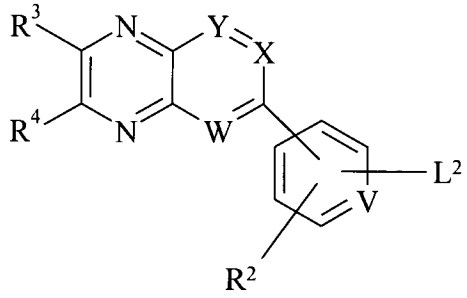
Conversely, the intermediates of formula (VII) above may be prepared by reacting a compound of formula (V) as defined above with a compound of formula (X):



(X)

wherein V, R^2, L^1, E^1 and E^2 are as defined above; in the presence of a transition metal catalyst; under conditions analogous to those described above for the reaction between compounds (III) and (IV).

The compounds of formula (I) wherein E represents $-N(R^8)-E^3-$ may be prepared by a process which comprises reacting a compound of formula (VIIIB) as defined above with a compound of formula (XI):



(XI)

wherein V, W, X, Y, R^2, R^3 and R^4 are as defined above, and L^2 represents a suitable leaving group; in the presence of a transition metal catalyst.

Similarly, the compounds of formula (I) wherein E represents a covalent bond, and R^1 represents an optionally substituted *N*-linked C_{3-7} heterocycloalkyl group containing at least one nitrogen atom, may be prepared by a process which comprises reacting a compound of formula (VIIIA) as defined above with a compound of formula (XI) as defined above; in the presence of a transition metal catalyst.

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

The transition metal catalyst of use in the reaction between compound (XI) and the compound of formula (VIIIA) or (VIIIB) is suitably di-μ-bromobis(tri-*tert*-butyl-phosphine)dipalladium(I). The reaction is conveniently effected at an elevated

temperature in a suitable solvent, e.g. a hydrocarbon solvent such as toluene, generally under basic conditions, e.g. in the presence of a base such as sodium *tert*-butoxide or sodium *tert*-pentoxide.

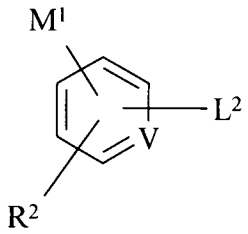
Alternatively, the compounds of formula (I) wherein E represents a covalent bond, and R^1 represents an optionally substituted *N*-linked C_{3-7} heterocycloalkyl group containing at least one nitrogen atom, may be prepared by a process which comprises reacting a compound of formula (VIIIA) as defined above directly with a compound of formula (XI) as defined above. Similarly, the compounds of formula (I) wherein E represents $-N(R^8)-E^3-$ may be prepared by a process which comprises reacting a compound of formula (VIIIB) directly with a compound of formula (XI) as defined above. In both those circumstances, the reaction is conveniently effected at an elevated temperature in a suitable solvent, e.g. dimethylsulfoxide.

The compounds of formula (I) wherein E represents -S- may be prepared by a process which comprises reacting a compound of formula R^1-SH with a compound of formula (XI) as defined above. The reaction is typically effected in the presence of a base, e.g. sodium hydride.

Similarly, the compounds of formula (I) wherein R^1 represents $-SR^e$ may be prepared by a process which comprises reacting the sodium salt of a compound of formula R^e-SH, e.g. sodium thiomethoxide, with a compound of formula (XI) as defined above.

In both cases, the reaction is conveniently performed at an elevated temperature in a suitable solvent, e.g. a cyclic ether such as tetrahydrofuran.

The intermediates of formula (XI) above may be prepared by reacting a compound of formula (III) as defined above with a compound of formula (XII):



(XII)

wherein V, R^2, M^1 and L^2 are as defined above; in the presence of a transition metal catalyst; under conditions analogous to those described above for the reaction between compounds (III) and (IV).

Where they are not commercially available, the starting materials of formula (III), (IV), (V), (VI), (VIIIA), (VIIIB), (IX), (X) and (XII) 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 example, a compound of formula (I) wherein E represents -C(O)- may be converted into the corresponding compound wherein E represents $-C(CH_3)(OH)-$ by treatment with a methylating agent such as methylmagnesium chloride. Similarly, a compound of formula (I) wherein E-R^1 represents $-CO_2R^b$ may be converted into the corresponding compound wherein E-R^1 represents $-C(CH_3)_2OH$ by treatment with a methylating agent such as methylmagnesium chloride. A compound of formula (I) wherein E represents -C(O)- may be converted into the corresponding compound wherein E represents $-C(CH_3)_2-$ by treatment with a methylating agent, e.g. methylmagnesium bromide, in the presence of zirconium tetrachloride.

A compound of formula (I) wherein E contains a hydroxy (-OH) moiety may be converted into the corresponding compound wherein E contains an optionally substituted alkoxy moiety, e.g. ethoxy, ethoxycarbonylmethoxy, aminocarbonylmethoxy, pyridin-3-ylmethoxy or 5-methylisoxazol-3-ylmethoxy, by treatment with the appropriate alkyl halide, e.g. ethyl iodide, ethyl bromoacetate, 2-bromoacetamide, 3-picolyl chloride or 3-(bromomethyl)-5-methylisoxazole, typically in the presence of a base such as sodium hydride.

A compound of formula (I) wherein E contains a hydroxy (-OH) moiety may be converted into the corresponding compound wherein the hydroxy substituent has been removed by treatment with a reducing agent typically comprising a mixture of triethylsilane and an organic acid such as trifluoroacetic acid.

A compound of formula (I) wherein E contains an amino ($-NH_2$) moiety may be converted into the corresponding compound wherein E contains a dimethylamino moiety by treatment with formaldehyde, typically at an elevated temperature in the presence of formic acid.

A compound of formula (I) wherein E contains an amino ($-NH_2$) moiety may be converted into the corresponding compound wherein E contains a pyrrolidin-1-yl moiety

by treatment with 1,4-dibromobutane, typically at an elevated temperature in the presence of a base such as potassium carbonate.

A compound of formula (I) wherein E contains an amino ($-NH_2$) moiety may be converted into the corresponding compound wherein E contains a C_{2-6} alkylcarbonylamino moiety, e.g. acetylamino, by treatment with the appropriate C_{2-6} alkylcarbonyl halide, e.g. acetyl chloride, typically in the presence of an organic base such as triethylamine.

A compound of formula (I) wherein E contains an amino ($-NH_2$) moiety may be converted into the corresponding compound wherein E contains a (C_{1-6})alkylamino-carbonylamino moiety, e.g. ethylaminocarbonylamino, by treatment with the appropriate C_{1-6} alkyl isocyanate, e.g. ethyl isocyanate.

A compound of formula (I) wherein E represents -C(O)- may be converted into the corresponding compound wherein E represents -C(=N-OH)- by treatment with hydroxyl-amine hydrochloride.

A compound of formula (I) wherein E represents -S- may be converted into the corresponding compound wherein E represents $-S(O)_2-$ by treatment with an oxidizing agent such as 3-chloroperoxybenzoic acid.

A compound of formula (I) wherein R^1 contains an amino ($-NH_2$) moiety may be converted into the corresponding compound wherein R^1 contains a C_{3-7} cycloalkyl-carbonylamino moiety, e.g. cyclopentylcarbonylamino, by treatment with the appropriate C_{3-7} cycloalkylcarbonyl halide, e.g. cyclopentylcarbonyl chloride, typically in the presence of an organic base such as *N*,*N*-diisopropylethylamine.

A compound of formula (I) wherein R^1 comprises a hydroxy (-OH) moiety may be converted into the corresponding compound wherein R^1 comprises a 2-oxopyrrolidin-1-yl moiety by treatment with methanesulfonyl chloride; followed by treatment of the resulting mesylate with 2-pyrrolidinone in the presence of a base, e.g. sodium hydride.

A compound of formula (I) wherein R^1 comprises an amino ($-NH_2$) moiety may be converted into the corresponding compound wherein R^1 comprises a 2,5-dioxopyrrolidin-1-yl moiety by treatment with succinic anhydride, typically at an elevated temperature in the presence of an organic acid such as acetic acid.

A compound of formula (I) wherein R^1 represents amino ($-NH_2$) may be converted into the corresponding compound wherein R^1 represents $-NHCONHR^c$ by treatment with the appropriate isocyanate $R^c-N=C=O$, e.g. ethyl isocyanate.

A compound of formula (I) wherein R^1 comprises an amino ($-NH_2$) moiety may be converted into the corresponding compound wherein R^1 comprises a *tert*-butoxycarbonyl-amino moiety by treatment with di-*tert*-butyl dicarbonate.

A compound of formula (I) wherein R^1 contains a *tert*-butoxycarbonyl moiety may be converted into the corresponding compound wherein R^1 contains a carboxy moiety by treatment with trifluoroacetic acid.

A compound of formula (I) wherein R^1 contains a carboxy moiety may be converted into the corresponding compound wherein R^1 contains a C_{3-7} cycloalkyl-aminocarbonyl moiety, e.g. cyclopentylaminocarbonyl, or an optionally substituted C_{3-7} heterocycloalkylcarbonyl moiety, e.g. 3-hydroxypyrrolidin-1-ylcarbonyl, by treatment with thionyl chloride; followed by treatment of the resulting acid chloride with the appropriate amine, e.g. cyclopentylamine or 3-hydroxypyrrolidine.

A compound of formula (I) wherein R^2 represents halogen, e.g. bromo, may be converted into the corresponding compound wherein R^2 represents an optionally substituted aryl moiety, e.g. phenyl, by treatment with the appropriate aryl boronic acid or a cyclic ester thereof, e.g. a pinacol ester thereof, in the presence of a catalyst. The catalyst may typically be a transition metal catalyst. A suitable catalyst is tetrakis-(triphenylphosphine)palladium(0), in which case the transformation may conveniently be effected at an elevated temperature in the presence of a base such as sodium carbonate, potassium carbonate or potassium phosphate, in an inert solvent such as 1,2-dimethoxy-ethane, tetrahydrofuran or 1,4-dioxane, optionally in the presence of tetra-*n*-butyl-ammonium bromide.

A compound of formula (I) wherein R^2 represents halogen, e.g. bromo, may be converted into the corresponding compound wherein R^2 represents an optionally substituted *N*-linked C_{3-7} heterocycloalkyl moiety containing at least one nitrogen atom, e.g. morpholin-4-yl, by treatment with the appropriate heterocycle, e.g. morpholine, in the presence of a catalyst. The catalyst may typically be a transition metal catalyst. A suitable catalyst is di-μ-bromobis(tri-*tert*-butylphosphine)dipalladium(I). The reaction is conveniently effected at an elevated temperature in a suitable solvent, e.g. a hydrocarbon solvent such as toluene, generally under basic conditions, e.g. in the presence of a base such as sodium *tert*-butoxide.

A compound of formula (I) wherein R^2 represents $-NHR^d$ may be converted into the corresponding compound wherein R^2 represents $-NR^dCOR^a$ by treatment with the

appropriate acyl halide, e.g. acetyl chloride, typically in the presence of an organic base such as *N*,*N*-diisopropylethylamine.

A compound of formula (I) wherein R^8 represents hydrogen may be converted into the corresponding compound wherein R^8 represents $-COR^a$ by treatment with the appropriate acyl halide, e.g. acetyl chloride, isobutyryl chloride or benzoyl chloride, typically in the presence of an organic base such as triethylamine.

A compound of formula (I) wherein R^8 represents hydrogen may be converted into the corresponding compound wherein R^8 represents $-CO_2R^b$ by treatment with the appropriate haloformate, e.g. methyl chloroformate, typically in the presence of an organic base such as triethylamine.

A compound of formula (I) wherein R^8 represents hydrogen may be converted into the corresponding compound wherein R^8 represents $-CONHR^c$ by treatment with the appropriate isocyanate R^c-N=C=O, e.g. ethyl isocyanate.

A compound of formula (I) wherein R^8 represents hydrogen may be converted into the corresponding compound wherein R^8 represents $-SO_2R^e$ by treatment with the appropriate sulfonyl halide, e.g. methylsulfonyl chloride, typically in the presence of an organic base such as triethylamine.

A compound of formula (I) wherein R^8 represents hydrogen may be converted into the corresponding compound wherein R^8 represents an optionally substituted heteroaryl moiety, e.g. pyridin-2-yl, by treatment with the appropriate halogenated heterocycle, e.g. 2-chloropyridine, in the presence of a catalyst. The catalyst may typically be a transition metal catalyst. A suitable catalyst is [1,1'-bis(di-*tert*-butylphosphino)ferrocene]-palladium(II) dichloride. The reaction is conveniently effected at an elevated temperature in a suitable solvent, e.g. a hydrocarbon solvent such as toluene, generally under basic conditions, e.g. in the presence of a base such as sodium *tert*-butoxide.

A compound of formula (I) wherein R^9 represents hydrogen may be converted into the corresponding compound wherein R^9 is other than hydrogen, e.g. ethyl or pyridin-3-ylmethyl, by treatment with the appropriate alkyl halide, e.g. ethyl iodide or 3-picolyl chloride, typically in the presence of a base such as sodium hydride.

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

Ac: acetyl
DCM: dichloromethane
DIPEA: *N,N*-diisopropylethylamine
DMAP: 4-(dimethylamino)pyridine
DME: ethylene glycol dimethyl ether
DMF: *N,N*-dimethylformamide
DMSO: dimethylsulfoxide
Et: ethyl
EtOAc: ethyl acetate
Me: methyl
MeOH: methanol
NMP: 1-methyl-2-pyrrolidinone
Ph: phenyl
TFA: trifluoroacetic acid
THF: tetrahydrofuran
mCPBA: 3-chloroperoxybenzoic acid
AcOH: acetic acid
br: broad
h: hour
M: mass
r.t.: room temperature
sat. saturated
SiO_2: silica
RT: retention time
brine: saturated aqueous sodium chloride solution
HBTU: *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate
$Pd(PPh_3)_4$: tetrakis(triphenylphosphine)palladium(0)

HPLC: High Performance Liquid Chromatography

LCMS: Liquid Chromatography Mass Spectrometry

ES+: Electrospray Positive Ionisation

Analytical Conditions

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

Compounds were named with the aid of ACD Labs Name (v. 9.0 or 10.0) supplied by Advanced Chemical Development, Toronto, Canada; 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 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	**4**	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 4.6mm	
		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 4.6mm	
		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	
		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

INTERMEDIATE 1

3-(Quinoxalin-6-yl)benzaldehyde

A mixture of 6-bromoquinoxaline (210 mg, 1.01 mmol), 3-formylphenylboronic acid (301 mg, 2.01 mmol), 2M aqueous sodium carbonate solution (1.7 mL, 14.4 mmol) and $Pd(PPh_3)_4$ (35 mg, 0.03 mmol) in DME (3.5 mL) was heated to 120°C in a sealed tube, under microwave irradiation, for 20 minutes. After cooling, the organic phase was adsorbed onto silica and purified by column chromatography (SiO_2, 10-100% EtOAc in heptane) to give the *title compound* (340 mg) as a beige solid. δ_H ($CDCl_3$) 10.15 (s, 1H), 8.91 (d, 1H), 8.89 (d, 1H), 8.38 (d, 1H), 8.26-8.31 (m, 1H), 8.24 (d, 1H), 8.10 (dd, 1H), 8.02-8.07 (m, 1H), 7.94-8.00 (dd, 1H), 7.72 (t, 1H). LCMS (ES+) 235 $(M+H)^+$, RT 2.99 minutes.

INTERMEDIATE 2

1-[3-(Quinoxalin-6-yl)phenyl]ethanone

A mixture of 6-bromoquinoxaline (314 mg, 1.50 mmol), 3-acetylphenylboronic acid (246 mg, 1.50 mmol), 2M aqueous sodium carbonate solution (1.7 mL, 14.4 mmol) and $Pd(PPh_3)_4$ (35 mg, 0.03 mmol) in DME (3.5 mL) was heated to 120°C in a sealed tube, under microwave irradiation, for 20 minutes. After cooling, the organic phase was adsorbed onto silica and purified by column chromatography (SiO_2, 10-100% EtOAc in heptane) to give the *title compound* (280 mg, 75%) as a pale orange-cream solid. δ_H ($CDCl_3$) 8.91 (d, 1H), 8.87 (d, 1H), 8.34-8.39 (m, 2H), 8.23 (d, 1H), 8.09 (dd, 1H), 8.04 (d, 1H), 7.97 (d, 1H), 7.64 (t, 1H), 2.71 (s, 3H). LCMS (ES+) 249 $(M+H)^+$, RT 3.32 minutes.

INTERMEDIATE 3

(3-Bromophenyl)(pyrrolidin-1-yl)methanone

3-Bromobenzoyl chloride (658 mg, 3 mmol) was added to a stirred solution of pyrrolidine (1 mL) in DCM (10 mL), pre-cooled in an ice-water bath. The reaction mixture was stirred, then allowed to warm to r.t. After 3 h the mixture was partitioned between water and DCM (10 mL each), and the aqueous phase further extracted with

DCM (20 mL). The combined organic phases were dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified by column chromatography (SiO_2, 20-100% EtOAc in heptane) to give the *title compound* (625 mg, 82%) as a colourless oil. δ_H ($CDCl_3$) 8.66 (t, 1H), 7.55 (m, 1H), 7.44 (m, 1H), 7.28 (t, 1H), 3.64 (t, 2H), 3.41 (t, 2H), 2.03-1.84 (m, 4H). LCMS (ES+) 254 $(M+H)^+$, RT 3.01 minutes.

INTERMEDIATE 4

2-(3-Bromophenyl)-1-(pyrrolidin-1-yl)ethanone

HBTU (1.24 g, 3.28 mmol) was added to a solution of 3-bromophenylacetic acid (642 mg, 2.99 mmol) and DIPEA (847 mg, 6.57 mmol) in DMF (5 mL). The mixture was stirred for 5 minutes. Pyrrolidine (254 mg, 3.58 mmol) was added and the resulting solution allowed to stand for 18 h. The mixture was partitioned between water and EtOAc (50 mL each). The organic phase was washed with water (20 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified by column chromatography (SiO_2, 20-100% EtOAc in heptane, and then, on another column, 0-5% MeOH in DCM) to give the *title compound* (235 mg, 29%) as a brown oil. δ_H ($CDCl_3$) 7.44 (s, 1H), 7.38 (dt, 1H), 7.14-7.26 (m, 2H), 3.62 (s, 2H), 3.37-3.56 (m, 4H), 1.77-2.02 (m, 4H). LCMS (ES+) 268 $(M+H)^+$, RT 3.19 minutes.

INTERMEDIATE 5

1-[3-(Quinoxalin-6-yl)phenyl]propan-2-one

A mixture of 3-bromophenylacetone (213 mg, 1 mmol), benzopyrazine-6-boronic acid hydrochloride (210 mg, 1 mmol), 2M aqueous sodium carbonate solution (1.5 mL, 3 mmol) and $Pd(PPh_3)_4$ (35 mg, 0.03 mmol) in DME (3 mL) was heated to 120°C in a sealed tube, under microwave irradiation, for 20 minutes. After cooling, the mixture was partitioned between saturated ammonium chloride solution and EtOAc (2 mL each), and the organic phase adsorbed onto silica and purified by column chromatography (SiO_2, 20-100% EtOAc in heptane) to give the *title compound* (153 mg, 58%) as a pale orange-brown gum. δ_H ($CDCl_3$) 8.88 (d, 1H), 8.85 (d, 1H), 8.31 (d, 1H), 8.19 (d, 1H), 8.05 (dd, 1H), 7.68 (d, 1H), 7.60 (s, 1H), 7.50 (t, 1H), 7.29 (d, 1H), 3.83 (s, 2H), 2.24 (s, 3H). LCMS (ES+) 263 $(M+H)^+$, RT 3.03 minutes.

INTERMEDIATE 6

(3-Bromophenyl)acetic acid methyl ester

Acetyl chloride (0.5 mL) was added to MeOH (100 mL). 3-Bromophenylacetic acid (15 g, 69.8 mmol) was added, and the mixture refluxed for 2 h. The solvent was removed *in vacuo* and the residue partitioned between DCM and water (50 mL each). The aqueous phase was extracted with DCM (20 mL) and the combined organic phases were dried ($MgSO_4$) and the solvent removed *in vacuo* to give the *title compound* (15.85 g, 99%) as a colourless oil. δ_H ($CDCl_3$) 7.44 (s, 1H), 7.37-7.43 (m, 1H), 7.15-7.24 (m, 2H), 3.70 (s, 3H), 3.59 (s, 2H).

INTERMEDIATE 7

2-(3-Bromophenyl)-2-methylpropionic acid methyl ester

A solution of *Intermediate 6* (15.85 g, 69.2 mmol) in THF (50 mL) was added as a steady stream over about 5 minutes to a suspension of sodium hydride (60% dispersion in mineral oil, 8.32 g, 208 mmol) in THF (100 mL) under nitrogen in an ice-water bath whilst maintaining the internal temperature between 10°C and 20°C. After the addition was complete, the mixture was stirred at r.t. for 1 h. The mixture was cooled again in an ice-water bath, and a solution of methyl iodide (10.6 mL, 24.6 g, 173 mmol) in THF (100 mL) was added slowly so as to maintain the temperature of the reaction at <25°C. After the addition was complete the mixture was stirred for a further 15 minutes with the ice-water bath, and then for 18 h. The mixture was poured slowly (over a period of about 2 minutes) onto a mixture of ice (approximately 100 g) and saturated ammonium chloride solution (100 mL). The resulting mixture was evaporated and extracted with DCM (2 x 50 mL). The combined organic phases were dried ($MgSO_4$), the solvent removed *in vacuo* and purified by column chromatography (SiO_2, 10-100% EtOAc in heptane) to give the *title compound* (17.3 g) as a pale straw-coloured oil. δ_H ($CDCl_3$) 7.48 (t, 1H), 7.38 (m, 1H), 7.23-7.29 (m, 1H), 7.19 (t, 1H), 3.66 (s, 3H), 1.56 (s, 6H).

INTERMEDIATE 8

2-(3-Bromophenyl)-2-methylpropionic acid

Sodium hydroxide (2M, 20 mL) was added to a solution of *Intermediate 7* (6.5 g) in MeOH (20 mL) and THF (20 mL). The resulting mixture was refluxed for 2 h. The mixture was evaporated, and the residue partitioned between water and DCM (100 mL each). The aqueous phase was acidified (2M hydrochloric acid) and extracted with DCM (100 mL then 50 mL). The combined organic phases were dried ($MgSO_4$) and the solvent removed *in vacuo* to give the *title compound* (4.55 g, 68% over two steps) as a cream solid. δ_H ($CDCl_3$) 7.54 (s, 1H), 7.40 (d, 1H), 7.33 (d, 1H), 7.21 (t, 1H), 1.59 (s, 6H).

INTERMEDIATE 9

2-(3-Bromophenyl)-2-methyl-1-(pyrrolidin-1-yl)propan-1-one

Oxalyl chloride (3 mL) was added to a solution of *Intermediate 8* (1.6 g, 6.58 mmol) in DCM (20 mL) at r.t. The mixture was stirred for 30 minutes and then allowed to stand for 18 h. The mixture was concentrated *in vacuo*, adding DCM (2 x 10 mL) to assist removal of oxalyl chloride. Half this residue was dissolved in DCM (10 mL) and added to a stirred solution of pyrrolidine (257 mg, 3.62 mmol) and triethylamine (366 mg, 3.62 mmol) in DCM (10 mL), pre-cooled in an ice-water bath. The mixture was allowed to warm to r.t., and after 15 minutes the mixture was partitioned between water (20 mL) and DCM (10 mL). The aqueous phase was extracted with further DCM (10 mL), and the combined organic phases dried ($MgSO_4$) and concentrated *in vacuo* to give the *title compound* (980 mg, essentially quantitative) as a pale yellow-orange solid. δ_H ($CDCl_3$) 7.41 (t, 1H), 7.34-7.38 (dt, 1H), 7.12-7.23 (m, 2H), 3.52 (t, 2H), 2.75 (t, 2H), 1.56-1.80 (m, 4H), 1.52 (s, 6H). LCMS (ES+) 297 $(M+H)^+$, RT 3.67 minutes.

INTERMEDIATE 10

4-(Quinoxalin-6-yl)pyridine-2-carbaldehyde

A mixture of 4-bromo-2-formylpyridine (186 mg, 1 mmol), benzopyrazine-6-boronic acid hydrochloride (211 mg, 0.3 mmol), 2M aqueous sodium carbonate solution (1.5 mL, 3 mmol) and $Pd(PPh_3)_4$ (35 mg, 0.03 mmol) in DME (3 mL) was heated to

120°C in a sealed tube, under microwave irradiation, for 20 minutes. The mixture was partitioned between water/brine (1:1, 30 mL) and EtOAc (30 mL). The organic phase was dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified by column chromatography (SiO_2, 10-100% EtOAc in heptane) to give the *title compound* (120 mg, 51%) as a cream solid. δ_H ($CDCl_3$) 10.20 (s, 1H), 8.92-8.96 (m, 3H), 8.46 (d, 1H), 8.36 (d, 1H), 8.28 (d, 1H), 8.11 (dd, 1H), 7.92 (dd, 1H). LCMS (ES+) 236 $(M+H)^+$, RT 2.48 minutes.

INTERMEDIATE 11

(3,5-Dibromophenyl)(pyrrolidin-1-yl)methanone

Oxalyl chloride (3 mL) was added to a solution/suspension of 3,5-dibromobenzoic acid (2 g, 7.14 mmol) in DCM (20 mL) in an ice-water bath. Two drops of DMF were added, and the mixture stirred, then allowed to warm to r.t. After 15 minutes, THF (5 mL) was added. After 2 h, the mixture was concentrated *in vacuo*, adding DCM (20 mL) to assist removal of oxalyl chloride. The residue was dissolved in DCM (20 mL) and added to a stirred solution of pyrrolidine (3 mL) in DCM (20 mL), pre-cooled in an ice-water bath. The mixture was stirred, allowed to warm to r.t., and then left to stand for 18 h. The mixture was washed with water (20 mL) and adsorbed onto silica. The residue was purified by column chromatography (SiO_2, 20 to 100% EtOAc in heptane) to give the *title compound* (2.1 g, 88%) as a pale orange-brown solid. δ_H ($CDCl_3$) 7.72 (t, 1H), 7.58 (d, 2H), 3.62 (t, 2H), 3.41 (t, 2H), 1.86-2.04 (m, 4H). LCMS (ES+) 334 $(M+H)^+$, RT 3.58 minutes.

INTERMEDIATE 12

[3-Bromo-5-(trifluoromethoxy)phenyl](pyrrolidin-1-yl)methanone

Oxalyl chloride (3 mL) was added to a solution/suspension of 3-bromo-5-(trifluoromethoxy)benzoic acid (1.5 g, 5.26 mmol) and DMF (2 drops) in DCM (20 mL) at r.t. The mixture was stirred for 2 h. The mixture was concentrated *in vacuo*, adding DCM (20 mL) to assist removal of oxalyl chloride. The residue was dissolved in DCM (20 mL) and added to a stirred solution of pyrrolidine (3 mL) in DCM (20 mL), pre-cooled in an ice-water bath. The mixture was stirred, allowed to warm to r.t., and then

left to stand for 18 h. The mixture was washed with water (20 mL) and adsorbed onto silica. The residue was purified by column chromatography (SiO_2, 20 to 100% EtOAc in heptane) to give the *title compound* (1.68 g, 94%) as a colourless oil. δ_H ($CDCl_3$) 7.61 (s, 1H), 7.44 (s, 1H), 7.32 (s, 1H), 3.64 (t, 2H), 3.41 (t, 2H), 1.87-2.05 (m, 4H). LCMS (ES+) 340 $(M+H)^+$, RT 3.78 minutes.

INTERMEDIATE 13

(3-Bromo-2-methylphenyl)(pyrrolidin-1-yl)methanone

Oxalyl chloride (3 mL) was added to a solution/suspension of 3-bromo-2-methylbenzoic acid (1 g, 4.65 mmol) and DMF (2 drops) in DCM (20 mL) at r.t. The mixture was stirred for 2 h. The mixture was concentrated *in vacuo*, adding DCM (20 mL) to assist removal of oxalyl chloride. The residue was dissolved in DCM (20 mL) and added to a stirred solution of pyrrolidine (3 mL) in DCM (20 mL), pre-cooled in an ice-water bath. The mixture was stirred, allowed to warm to r.t., and then left to stand for 18 h. The mixture was washed with water (20 mL) and adsorbed onto silica. The residue was purified by column chromatography (SiO_2, 20 to 100% EtOAc in heptane) to give the *title compound* (1.17 g, 94%) as a colourless oil. δ_H ($CDCl_3$) 7.55 (d, 1H), 7.16 (d, 1H), 7.08 (t, 1H), 3.66 (t, 2H), 3.12 (t, 2H), 2.36 (s, 3H), 1.83-2.04 (m, 4H). LCMS (ES+) 270 $(M+H)^+$, RT 3.17 minutes.

INTERMEDIATE 14

(4-Bromopyridin-2-yl)(pyrrolidin-1-yl)methanone

HBTU (417 mg, 1.1 mmol) was added to a solution of 4-bromopicolinic acid (202 mg, 1 mmol) and DIPEA (258 mg, 2 mmol) in DMF (2 mL). The mixture was stirred for 5 minutes at r.t. Pyrrolidine (107 mg, 1.5 mmol) was added. The mixture was stirred and left to stand for 15 minutes. The mixture was partitioned between water and EtOAc (30 mL each) and the organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, 10-100% EtOAc in heptane) to give the *title compound* (159 mg, 62%) as a yellow gum. δ_H ($CDCl_3$) 8.40 (d, 1H), 8.04 (d, 1H), 7.52 (dd, 1H), 3.63-3.80 (m, 4H), 1.87-2.01 (m, 4H). LCMS (ES+) 255 $(M+H)^+$, RT 2.47 minutes.

INTERMEDIATE 15

4-Bromo-5-methyl-2-nitrophenylamine

Potassium nitrate (930 mg, 9.21 mmol) was added to a stirred solution of 4-bromo-3-methylacetanilide (2 g, 8.8 mmol) in sulfuric acid (10 mL) at r.t. A mild exotherm was observed. After 1.5 h the mixture was poured onto ice (approximately 100 g) and extracted with EtOAc (100 mL). The organic phase was dried ($MgSO_4$) and the solvent removed *in vacuo* to give an orange-brown solid (2.2 g). 1.6 g of this material was dissolved/suspended in THF (10 mL). Hydrochloric acid (2M, 10 mL) was added, and the mixture heated to 120°C in a sealed tube, under microwave irradiation, for 20 minutes. The mixture was partitioned between EtOAc and saturated sodium hydrogencarbonate solution (100 mL each) and the aqueous phase extracted with EtOAc (50 mL). The combined organic phases were dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was dissolved/suspended in diethyl ether (30 mL) and filtered to give, after air-drying, the *title compound* (400 mg) as an orange solid. δ_H ($CDCl_3$) 8.29 (s, 1H), 6.70 (s, 1H), 6.01 (br, 2H), 2.36 (s, 3H).

INTERMEDIATE 16

4-Bromo-5-fluoro-2-nitrophenylamine

Potassium nitrate (914 mg, 9.05 mmol) was added to a stirred solution of 4-bromo-3-fluoroacetanilide (2 g, 8.6 mmol) in sulfuric acid (10 mL) at r.t. After 1.5 h the mixture was poured onto ice (approximately 100 g) and extracted with EtOAc (100 mL). The organic phase was dried ($MgSO_4$) and the solvent removed *in vacuo* to give a brown solid (2.48 g). 1.9 g of this material was dissolved/suspended in THF (10 mL). Hydrochloric acid (2M, 10 mL) was added, and the mixture heated in a microwave for 20 minutes at 120°C. The mixture was partitioned between EtOAc and sodium hydrogencarbonate solution (100 mL each) and the aqueous phase extracted with EtOAc (50 mL). The combined organic phases were dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified by column chromatography (SiO_2, 10 to 100% EtOAc in heptane) to give an orange-brown solid (1.5 g) which was washed with 9:1 heptane:diethyl ether to

give, after air-drying, the *title compound* (900 mg, 45%) as an orange-yellow solid. δ_H ($CDCl_3$) 8.39 (d, 1H), 6.59 (d, 1H), 6.21 (br, 2H).

INTERMEDIATE 17

6-Bromo-2-methylquinoxaline and 7-bromo-2-methylquinoxaline, 60:40 mixture

Pyruvic aldehyde (2 mL of a 40% solution in water) was added to a solution of 3,4-diaminobromobenzene (500 mg, 2.67 mmol) in ethanol (5 mL) at r.t. After 10 minutes the mixture was partitioned between water (50 mL) and EtOAc (20 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, 10 to 100% EtOAc in heptane) to give the *title compound* (340 mg, 57%; a 1:1 mixture of isomers) as a yellow solid. δ_H ($CDCl_3$) 60% component: 8.74 (s, 1H), 8.20 (d, 1H), 7.94 (d, 1H), 7.81 (dd, 1H), 2.78 (s, 3H); 40% component: 8.74 (s, 1H), 8.25 (d, 1H), 7.89 (d, 1H), 7.79 (dd, 1H), 2.77 (s, 3H). LCMS (ES+) 223 $(M+H)^+$, RT 3.15 minutes (single peak).

INTERMEDIATE 18

6-Bromo-2,3-dimethylquinoxaline

2,3-Butanedione (1 mL) was added to a solution of 3,4-diaminobromobenzene (500 mg, 2.67 mmol) in ethanol (5 mL) at r.t. After 10 minutes the mixture was partitioned between water/brine (1:1, 40 mL) and EtOAc (20 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give the *title compound* (450 mg, 71%) as a brown solid. δ_H ($CDCl_3$) 8.16 (d, 1H), 7.85 (d, 1H), 7.74 (dd, 1H), 2.73 (s, 3H), 2.72 (s, 3H). LCMS (ES+) 239 $(M+H)^+$, RT 3.35 minutes.

INTERMEDIATE 19

7-Bromopyrido[2,3-*b*]pyrazine

2,3-Diamino-5-bromopyridine (2 g, 10.6 mmol) was dissolved in ethanol (25 mL) and glyoxal (5 mL, 40% in water) was added. After standing for 48 h the mixture was concentrated *in vacuo* and the residue triturated with diethyl ether to give, after air-drying,

the *title compound* (2.04 g, 92%) as a pink-brown solid. δ_H (d_6 DMSO) 9.28 (d, 1H), 9.20 (d, 1H), 9.12 (d, 1H), 8.95 (d, 1H). LCMS (ES+) 212 $(M+H)^+$, RT 1.98 minutes.

INTERMEDIATE 20

2-Bromo-6-(pyrrolidin-1-yl)pyridine

A solution/suspension of 2,6-dibromopyridine (1.18 g, 5 mmol), pyrrolidine (391 mg, 5.5 mmol) and triethylamine (505 mg, 5.5 mmol) in ethanol (5 mL) was heated to 150°C in a sealed tube, under microwave irradiation, for 3 h. The mixture was partitioned between water and EtOAc (50 mL each). The organic phase was dried ($MgSO_4$) and the solvent removed *in vacuo* to give the *title compound* (1.06 g, 93%) as a cream solid. δ_H ($CDCl_3$) 7.22 (dd, 1H), 6.64 (d, 1H), 6.23 (d, 1H), 3.38-3.49 (m, 4H), 1.94-2.05 (m, 4H). LCMS (ES+) 227 $(M+H)^+$, RT 4.05 minutes.

INTERMEDIATE 21

6-(2-Chloropyridin-4-yl)quinoxaline

A mixture of 6-bromoquinoxaline (1.07 g, 5.14 mmol), 2-chloropyridine-4-boronic acid (810 mg, 5.14 mmol), 2M aqueous sodium carbonate solution (5.5 mL, 11 mmol) and $Pd(PPh_3)_4$ (178 mg, 0.15 mmol) in DME (11 mL) was heated to 120°C in a sealed tube, under microwave irradiation, for 20 minutes. After cooling, the mixture was partitioned between water and EtOAc (100 mL each). The aqueous phase was extracted with EtOAc/THF (4:1, 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was washed with diethyl ether/THF (9:1, 30 mL) to give the *title compound* (790 mg, 64%) as a brown solid. δ_H ($CDCl_3$) 8.89-8.97 (m, 2H), 8.54 (d, 1H), 8.39 (d, 1H), 8.26 (d, 1H), 8.03 (dd, 1H), 7.72 (s, 1H), 7.60 (dd, 1H). LCMS (ES+) 242 $(M+H)^+$, RT 2.87 minutes.

INTERMEDIATE 22

N-Cyclopentyl-*N*-[3-(quinoxalin-6-yl)benzyl]amine

A mixture of cyclopentylamine (109 mg, 1.28 mmol), silicon-supported cyanoborohydride reagent (660 mg, 0.085 mmol) and *Intermediate 1* (100 mg, 0.42

mmol) in THF (5 mL) was stirred for 18 h at r.t. The mixture was heated to 100°C in a sealed tube, under microwave irradiation, for 1 h. Further cyclopentylamine (109 mg, 1.28 mmol) and silicon-supported cyanoborohydride reagent (660 mg, 0.085 mmol) were added, and the mixture was heated to 100°C in a sealed tube, under microwave irradiation, for 40 minutes. The mixture was filtered, washing with DCM (3 x 10 mL), and the filtrate partitioned between DCM and water (50 mL each). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by preparative HPLC. The column fractions were diluted with saturated sodium hydrogencarbonate solution (30 mL) and the mixture partitioned between water and DCM (50 mL each). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give the *title compound* (77 mg, 29%) as an off-white sticky solid. δ_H ($CDCl_3$) 8.87 (d, 1H), 8.84 (d, 1H), 8.33 (d, 1H), 8.17 (d, 1H), 8.08 (dd, 1H), 7.74 (s, 1H), 7.65 (d, 1H), 7.48 (d, 1H), 7.40 (d, 1H), 3.89 (s, 2H), 3.18 (quintet, 1H), 1.82-1.96 (m, 2H), 1.64-1.80 (m, 2H), 1.48-1.64 (m, 2H), 1.34-1.50 (m, 2H). LCMS (ES+) 304 $(M+H)^+$, RT 1.80 minutes.

INTERMEDIATE 23

N-[3-(Quinoxalin-6-yl)benzyl]-*N*-(tetrahydropyran-4-yl)amine

A mixture of 4-aminotetrahydropyran (173 mg, 1.71 mmol), silicon-supported cyanoborohydride reagent (1.1 g, 1.28 mmol) and *Intermediate 1* (200 mg, 0.85 mmol) in THF (5 mL) was heated to 100°C in a sealed tube, under microwave irradiation, for 1.5 h. The mixture was filtered, washing with DCM (3 x 10 mL), and the filtrate partitioned between DCM (60 mL) and water (40 mL each). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by preparative HPLC. The column fractions were diluted with saturated sodium hydrogencarbonate solution (30 mL) and the mixture partitioned between water and DCM (50 mL each). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give the *title compound* (77 mg, 29%) as an off-white sticky solid. δ_H ($CDCl_3$) 8.88 (d, 1H), 8.84 (d, 1H), 8.33 (d, 1H), 8.18 (d, 1H), 8.07 (dd, 1H), 7.75 (s, 1H), 7.66 (d, 1H), 7.49 (t, 1H), 7.41 (d, 1H), 3.95-4.05 (m, 2H), 3.95 (s, 2H), 3.42 (td, 2H), 2.79 (tt, 1H), 1.84-1.97 (d, 2H), 1.41-1.58 (m, 2H). LCMS (ES+) 320 $(M+H)^+$, RT 1.60 minutes.

INTERMEDIATE 24

N-(1-Methylpiperidin-4-yl)-*N*-[3-(quinoxalin-6-yl)benzyl]amine

A mixture of 4-amino-1-methylpiperidine (195 mg, 1.71 mmol), silicon-supported cyanoborohydride reagent (1.1 g, 1.28 mmol) and *Intermediate 1* (200 mg, 0.85 mmol) in THF (5 mL) was heated to 110°C in a sealed tube, under microwave irradiation, for 1 h. More silicon-supported cyanoborohydride reagent (0.74 g, 0.85 mmol) was added, and the mixture was heated to 110°C in a sealed tube, under microwave irradiation, for a further 1 h. The mixture was filtered, washing with DCM (3 x 10 mL), and the filtrate partitioned between DCM and water (50 mL each). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by preparative HPLC to give the *title compound* (80 mg, 28%) as an off-white solid. δ_H ($CDCl_3$) 8.88 (d, 1H), 8.84 (d, 1H), 8.33 (d, 1H), 8.18 (d, 1H), 8.07 (dd, 1H), 7.75 (s, 1H), 7.65 (d, 1H), 7.48 (t, 1H), 7.41 (d, 1H), 3.93 (s, 2H), 2.76-2.92 (m, 2H), 2.56 (tt, 1H), 2.27 (s, 3H), 1.88-2.10 (m, 4H), 1.41-1.59 (m, 2H). LCMS (ES+) 333 $(M+H)^+$, RT 1.17 minutes.

INTERMEDIATE 25

1-(3-Bromobenzyl)pyrrolidin-2-one

A solution of 2-pyrrolidinone in DMF (3 mL) was added to a suspension of sodium hydride (60% dispersion in mineral oil, 132 mg, 5.5 mmol) in DMF (5 mL) under nitrogen. The mixture was allowed to stir for 4 h at r.t. and then cooled in an ice-water bath. A solution of 3-bromobenzyl bromide in DMF (3 mL) was added, and the mixture stirred, allowed to warm to r.t. and left to stand for 18 h. The mixture was partitioned between water and EtOAc (50 mL each). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*, and adsorbed onto silica. The residue was purified by column chromatography (SiO_2, 20 to 100% EtOAc in heptane) to give the *title compound* (700 mg, 55%) as a pale orange-brown oil. δ_H ($CDCl_3$) 7.36-7.46 (m, 2H), 7.15-7.24 (m, 2H), 4.42 (s, 2H), 3.27 (t, 2H), 2.46 (t, 2H), 2.02 (quintet, 2H).

INTERMEDIATE 26

1-(3-Bromophenylsulfonyl)piperidine

Piperidine (0.11 mL, 1.13 mmol) was added dropwise to an ice-cooled solution of 3-bromobenzene-1-sulfonyl chloride (240 mg, 0.94 mmol) and triethylamine (0.20 mL, 1.41 mmol) in DCM (2 mL). The mixture was stirred for 4 h, diluted with DCM and washed with sat. ammonium chloride solution and sat. aqueous sodium hydrogen-carbonate. The organic phase was passed through a phase separator cartridge and concentrated *in vacuo* to give the *title compound* (239.8 mg, 84%). δ_H ($CDCl_3$) 7.98 (1H, s), 7.78-7.70 (2H, m), 7.44-7.35 (1H, m), 3.26 (4H, t, *J* 6.45 Hz), 1.82-1.75 (4H, m).

INTERMEDIATE 27

4-(3-Bromophenylsulfonyl)morpholine

Prepared by the procedure used for *Intermediate 26* to give the *title compound* (220 mg, 92%) as an off-white solid. δ_H ($CDCl_3$) 7.90 (1H, t, *J* 1.81 Hz), 7.80-7.73 (1H, m), 7.69 (1H, d, *J* 7.87 Hz), 7.45 (1H, t, *J* 7.92 Hz), 3.76 (4H, t, *J* 4.65 Hz), 3.03 (4H, t, *J* 4.56 Hz).

INTERMEDIATE 28

1-(3-Bromophenylsulfonyl)azepane

Prepared by the procedure used for *Intermediate 26* to give the *title compound* (190 mg, 76%) as an off-white solid. δ_H ($CDCl_3$) 7.94 (1H, t, *J* 1.82 Hz), 7.70 (2H, dd, *J* 16.18, 7.92 Hz), 7.38 (1H, t, *J* 7.92 Hz), 3.28 (4H, t, *J* 5.91 Hz), 1.73 (4H, m), 1.62-1.58 (4H, m).

INTERMEDIATE 29

1-(3-Bromophenylsulfonyl)-4-fluoropiperidine

Prepared by the procedure used for *Intermediate 26* to give the *title compound* (180 mg, 60%) as an off-white solid. δ_H ($CDCl_3$) 7.91 (1H, t, *J* 1.83 Hz), 7.75-7.68 (2H,

m), 7.42 (1H, t, *J* 7.92 Hz), 4.86-4.69 (1H, m), 3.44-3.36 (2H, m), 2.95-2.86 (2H, m), 2.01-1.84 (4H, m).

INTERMEDIATE 30

1-(3-Bromophenylsulfonyl)-4,4-difluoropiperidine

Prepared by the procedure used for Intermediate 26 to give the *title compound* (283 mg, 88%) as an off-white solid. δ_H ($CDCl_3$) 7.91 (1H, d, *J* 1.97 Hz), 7.79-7.69 (2H, m), 7.44 (1H, t, *J* 7.93 Hz), 3.27-3.21 (4H, m), 2.15-2.02 (4H, m).

INTERMEDIATE 31

N-{[4-(Quinoxalin-6-yl)pyridin-2-yl]methyl}cyclopropanamine

A mixture of *Intermediate 10* (60 mg, 0.255 mmol), cyclopropylamine (52 µL, 0.76 mmol) and (polystyrylmethyl)trimethylammonium cyanoborohydride (loading: 4.3 mmol/g; 180 mg) in DCM/AcOH (2 mL, 9:1) was stirred at 25°C for 3 h and filtered through a SCX cartridge. Elution of the compound using MeOH (10 mL) followed by 2M NH_3 in MeOH (4 mL) resulted in an orange oil (73 mg), which was purified by preparative HPLC to give the *title compound* (39.8 mg, 55%) as a pale yellow oil. δ_H (CD_3OD) 8.91 (2H, dd, *J* 9.80, 1.87 Hz), 8.62 (1H, d, *J* 5.28 Hz), 8.39 (1H, s), 8.20-8.13 (2H, m), 7.88 (1H, s), 7.73-7.66 (1H, m), 4.04 (2H, s), 2.26-2.19 (1H, m), 0.54-0.42 (4H, m). LCMS (ES+) 277 $(M+H)^+$, RT 2.50 minutes (96.7%).

INTERMEDIATE 32

N-{[4-(Quinoxalin-6-yl)pyridin-2-yl]methyl}cyclopentanamine

Prepared by the procedure used for Intermediate 31 to give the *title compound* (160 mg, 50%) as a pale yellow oil. δ_H (CD_3OD) 8.96 (2H, dd, *J* 9.64, 1.56 Hz), 8.69 (1H, d, *J* 5.21 Hz), 8.49 (1H, s), 8.25 (2H, s), 7.97 (1H, s), 7.84-7.79 (1H, m), 4.14 (2H, s), 2.05-1.97 (2H, m), 1.91 (1H, s), 1.83-1.74 (2H, m), 1.69-1.52 (4H, m).

INTERMEDIATE 33

(3-Bromo-5-nitrophenyl)(pyrrolidin-1-yl)methanone

3-Bromo-5-nitrobenzoic acid (1.60 g, 6.50 mmol) was suspended in thionyl chloride (15 mL) and heated at reflux temperature overnight. The solvent was removed *in vacuo* and the crude re-dissolved in DCM (20 mL). The mixture was cooled to approximately 2°C and treated dropwise with pyrrolidine (97.5 mmol, 8.13 mL). The resulting solution was stirred at room temperature for 1 h and evaporated. The residue was dissolved in DCM (50 mL) and washed with water (x 2), 1M aqueous HCl (x 2), sat. aqueous $NaHCO_3$ (x 2), and brine. The organic layer was dried ($MgSO_4$) and the solvent removed *in vacuo* to give the *title compound* (1.79 g, 92%) as a dark yellow/orange solid. δ_H ($CDCl_3$) 8.43 (1H, t, *J* 1.95 Hz), 8.32 (1H, dd, *J* 2.09, 1.39 Hz), 8.02 (1H, t, *J* 1.60 Hz), 3.68 (2H, t, *J* 6.83 Hz), 3.46 (2H, t, *J* 6.47 Hz), 2.06-1.91 (4H, m). LCMS (ES+) 276 $(M+H)^+$, RT 2.87 minutes (99.1%).

INTERMEDIATE 34

[3-Nitro-5-(quinoxalin-6-yl)phenyl](pyrrolidin-1-yl)methanone

A mixture of *Intermediate 33* (1.69 g, 5.65 mmol), benzopyrazine-6-boronic acid hydrochloride (1.67 g, 7.91 mmol), 2M aqueous sodium carbonate solution (8.48 mL, 16.96 mmol) and $Pd(PPh_3)_4$ (0.57 mmol, 0.65 g) in degassed DME (12 mL) was heated to 120°C in a sealed tube, under microwave irradiation, for 45 minutes. After cooling, the organic phase was adsorbed onto silica and purified by column chromatography (SiO_2, 10-100% EtOAc in petroleum ether) to give the *title compound* (1.0 g, 51%). δ_H ($CDCl_3$) 8.96-8.92 (2H, m), 8.69 (1H, t, *J* 1.93 Hz), 8.47-8.40 (2H, m), 8.30-8.24 (2H, m), 8.10 (1H, dd, *J* 8.75, 2.13 Hz), 3.74 (2H, t, *J* 6.86 Hz), 3.57 (2H, t, *J* 6.50 Hz), 2.11-1.95 (4H, m). LCMS (ES+) 349 $(M+H)^+$, RT 2.72 minutes (97.8%).

INTERMEDIATE 35

[3-Amino-5-(quinoxalin-6-yl)phenyl](pyrrolidin-1-yl)methanone

A solution of *Intermediate 34* (0.76 g, 2.17 mmol) and $SnCl_2$ (1.70 g, 7.60 mmol) in EtOH (25 mL) was heated at reflux temperature for 2.5 h. The solvent was removed *in*

vacuo and the residue dissolved in water (pH adjusted to approximately 8). The aqueous mixture was extracted with chloroform (x 3). The combined organic layers were washed with water (x 2) and brine (x 1), dried ($MgSO_4$) and evaporated to give a yellow powder. This material was triturated with Et_2O to give the *title compound* (0.53 g, 77%). δ_H ($CDCl_3$) 8.89 (2H, ddd, *J* 23.53, 11.46, 1.82 Hz), 8.29-8.22 (1H, m), 8.16 (1H, d, *J* 8.74 Hz), 8.01 (1H, dd, *J* 8.75, 2.05 Hz), 7.29-7.21 (1H, m), 7.08 (1H, t, *J* 1.89 Hz), 6.89 (1H, t, *J* 1.68 Hz), 3.93 (2H, s), 3.67 (2H, t, *J* 6.93 Hz), 3.54-3.45 (2H, m), 2.03-1.85 (4H, m). LCMS (ES+) 319 $(M+H)^+$, RT 2.22 minutes (95.1%).

INTERMEDIATE 36

(Phenyl)[3-(quinoxalin-6-yl)phenyl]methanol

Intermediate 1 (618 mg, 2.64 mmol) and THF (20 mL) were combined under nitrogen at room temperature. PhMgCl (2M in THF) (1.32 mL, 2.64 mmol) was then added dropwise. The mixture was stirred for 4 h, treated with sat. aqueous ammonium chloride solution and extracted with EtOAc. The organic layer was evaporated, adsorbed onto silica and purified by flash chromatography to give the *title compound* as a clear gum (383 mg). δ_H (DMSO-d_6) 9.04-8.98 (2H, m), 8.35 (1H, s), 8.23 (2H, s), 7.96 (1H, s), 7.80-7.75 (1H, m), 7.53-7.49 (4H, m), 7.36 (2H, t, *J* 7.52 Hz), 7.25 (1H, t, *J* 7.33 Hz), 6.04 (1H, d, *J* 4.11 Hz), 5.88 (1H, d, *J* 4.21 Hz).

INTERMEDIATE 37

Phenyl[3-(quinoxalin-6-yl)phenyl]methanone

To a solution of *Example 81* (1.39 g, 4.74 mmol) in THF (20 mL) was added dropwise PhMgCl (2M in THF; 3 mL, 6 mmol) under a nitrogen atmosphere at room temperature. The reaction mixture was stirred for 18 h, quenched with saturated aqueous ammonium chloride solution and extracted with dichloromethane. The combined organic layers were concentrated to dryness and purified by chromatography to give the *title compound* (794 mg, 54%) as a yellow solid. δ_H ($CDCl_3$) 8.89 (1H, d, *J* 1.83 Hz), 8.86 (1H, d, *J* 1.84 Hz), 8.35 (1H, d, *J* 2.06 Hz), 8.23-8.18 (2H, m), 8.08 (1H, dd, *J* 8.75, 2.08 Hz), 7.99 (1H, ddd, *J* 7.75, 1.95, 1.15 Hz), 7.89-7.85 (3H, m), 7.67-7.59 (2H, m), 7.52 (2H, t, *J* 7.62 Hz).

INTERMEDIATE 38

3-(Pyrido[3,4-*b*]pyrazin-7-yl)benzaldehyde

7-Chloropyrido[3,4-*b*]pyrazine (140 mg, 0.85 mmol), 3-formylbenzeneboronic acid (127 mg, 0.85 mmol), potassium phosphate (180 mg, 0.85 mmol), water (2 mL), DME (6 mL) and $Pd(PPh_3)_4$ (100 mg, 0.085 mmol) were combined in a sealed tube and heated under microwave irradiation to 140°C for 30 minutes. The reaction mixture was then partitioned between ethyl acetate and water. The organic layer was dried ($MgSO_4$) and concentrated to dryness to give the *title compound* (155 mg, 77%) as an off-white solid. δ_H (DMSO-d_6) 10.21 (1H, s), 9.69 (1H, s), 9.26 (1H, d, *J* 1.82 Hz), 9.15 (1H, d, *J* 1.83 Hz), 8.93 (1H, s), 8.76 (1H, s), 8.70 (1H, d, *J* 7.80 Hz), 8.07 (1H, d, *J* 7.61 Hz), 7.84 (1H, t, *J* 7.68 Hz).

INTERMEDIATE 39

1-[3-(Quinoxalin-6-yl)phenyl]ethanol

To a solution of *Intermediate 1* (520 mg, 2.22 mmol) in THF (20 mL) was added dropwise MeMgCl (3M in THF; 1 mL, 3.00 mmol) under nitrogen at room temperature. The reaction mixture was stirred for 18 h, quenched with saturated aqueous ammonium chloride solution and extracted with dichloromethane. The combined organic layers were concentrated to dryness and purified by chromatography to give the *title compound* as a clear gum (349 mg, 63%). δ_H ($CDCl_3$) 8.88 (1H, d, *J* 1.84 Hz), 8.85 (1H, d, *J* 1.84 Hz), 8.33 (1H, d, *J* 2.00 Hz), 8.19 (1H, d, *J* 8.73 Hz), 8.07 (1H, dd, *J* 8.75, 2.02 Hz), 7.79 (1H, s), 7.68 (1H, d, *J* 7.74 Hz), 7.57-7.45 (2H, m), 5.07-5.01 (1H, m), 4.83 (1H, d, *J* 5.46 Hz), 1.59 (3H, d, *J* 6.46 Hz).

INTERMEDIATE 40

N-{[4-(Quinoxalin-6-yl)pyridin-2-yl]methyl}cyclobutanamine

To a solution of cyclobutylamine (76 μL, 0.89 mmol) in DCM (2.7 mL) and AcOH (0.3 mL) was added *Intermediate 10* (70 mg, 0.30 mmol). The reaction mixture was stirred for 30 minutes at room temperature. (Polystyrylmethyl)trimethylammonium

cyanoborohydride (4.3 mmol/g; 424.9 mg, 1.83 mmol) was added and the mixture was shaken slowly at room temperature for 22 h. The reaction mixture was filtered and washed thoroughly with dichloromethane. The combined organic layers were dried ($MgSO_4$), concentrated to dryness and purified by preparative HPLC to give the *title compound* (38.7 mg, 44%) as a brown gum. δ_H ($CDCl_3$) 8.92-8.90 (1H, m), 8.90 (1H, d, *J* 2.22 Hz), 8.69 (1H, d, *J* 5.33 Hz), 8.40-8.35 (1H, m), 8.23 (1H, d, *J* 8.76 Hz), 8.07 (1H, dd, *J* 8.69, 2.17 Hz), 7.72 (1H, s), 7.55 (1H, dd, *J* 5.31, 1.56 Hz), 3.99 (2H, s), 3.50-3.38 (1H, m), 2.29-2.16 (2H, m), 1.90-1.77 (2H, m), 1.79-1.59 (2H, m).

INTERMEDIATE 41

(*S*)-2-Methyl-*N*-[3-(quinoxalin-6-yl)benzylidene]propane-2-sulfinamide

Intermediate 1 (650 mg, 2.78 mmol), (*S*)-(-)-2-methyl-2-propanesulfinamide (336 mg, 2.78 mmol), titanium(IV) isopropoxide (2 mL) and THF (40 mL) were combined at room temperature under a nitrogen atmosphere. The reaction mixture was stirred for 3 days, then partitioned between water and dichloromethane. The resulting titanium salts were filtered off through Celite. The filtrate was concentrated to dryness and purified by chromatography (SiO_2, 20-100% EtOAc in petroleum ether) to give the *title compound* (794 mg, 85%) as a clear gum. δ_H (DMSO-d_6) 9.05 (1H, d, *J* 1.85 Hz), 9.01 (1H, d, *J* 1.85 Hz), 8.75 (1H, s), 8.50 (2H, s), 8.34 (1H, dd, *J* 8.78, 2.15 Hz), 8.26 (1H, d, *J* 8.73 Hz), 8.19 (1H, d, *J* 7.82 Hz), 8.09 (1H, d, *J* 7.73 Hz), 7.76 (1H, t, *J* 7.73 Hz), 1.26 (9H, s).

INTERMEDIATE 42

(*R*)-2-Methyl-*N*-[3-(quinoxalin-6-yl)benzylidene]propane-2-sulfinamide

Prepared from *Intermediate 1* (310 mg, 1.32 mmol), (*R*)-(-)-2-methyl-2-propanesulfinamide (160 mg, 1.32 mmol), titanium(IV) isopropoxide (1 mL) and THF (20 mL) by the method of *Intermediate 41* to give the *title compound* (285 mg, 64%) as a clear gum. δ_H (DMSO-d_6) 9.05 (1H, d, *J* 1.85 Hz), 9.01 (1H, d, *J* 1.85 Hz), 8.75 (1H, s), 8.50 (2H, s), 8.34 (1H, dd, *J* 8.78, 2.15 Hz), 8.26 (1H, d, *J* 8.73 Hz), 8.19 (1H, d, *J* 7.82 Hz), 8.09 (1H, d, *J* 7.73 Hz), 7.76 (1H, t, *J* 7.73 Hz), 1.26 (9H, s).

INTERMEDIATE 43

(*S*)-2-Methyl-*N*-{(*R*)-phenyl[3-(quinoxalin-6-yl)phenyl]methyl}propane-2-sulfinamide

To a solution of *Intermediate 41* (790 mg, 2.34 mmol) in dichloromethane (28 mL) was added dropwise PhMgCl (2M in THF; 2.34 mL, 4.69 mmol) under a nitrogen atmosphere at -78°C. The reaction mixture was allowed to warm to room temperature and stirred for 18 h. The reaction mixture was quenched with saturated aqueous ammonium chloride solution and extracted with dichloromethane. The combined organic layers were concentrated to dryness and purified by chromatography (SiO_2, 20-100% EtOAc in petroleum ether) to give the *title compound* (557 mg, 57%) as a clear solid. δ_H ($CDCl_3$) 8.90 (1H, d, *J* 1.84 Hz), 8.87 (1H, d, *J* 1.85 Hz), 8.30 (1H, d, *J* 2.03 Hz), 8.20 (1H, d, *J* 8.74 Hz), 8.05 (1H, dd, *J* 8.75, 2.07 Hz), 7.85 (1H, s), 7.69 (1H, dt, *J* 6.38, 2.16 Hz), 7.54-7.49 (2H, m), 7.50-7.44 (2H, m), 7.38 (2H, t, *J* 7.51 Hz), 7.31 (1H, d, *J* 7.30 Hz), 5.79 (1H, d, *J* 2.31 Hz), 3.80 (1H, d, *J* 2.40 Hz), 1.32 (9H, s).

INTERMEDIATE 44

(*R*)-2-Methyl-*N*-{(*S*)-phenyl[3-(quinoxalin-6-yl)phenyl]methyl}propane-2-sulfinamide

Prepared from *Intermediate 42* (280 mg, 0.83 mmol), DCM (10 mL), PhMgCl (2M in THF; 0.83 mL, 1.66 mmol) by the method of *Intermediate 43* to give the *title compound* (127.6 mg, 37%) as a clear glass. δ_H ($CDCl_3$) 8.90 (1H, d, *J* 1.84 Hz), 8.87 (1H, d, *J* 1.85 Hz), 8.30 (1H, d, *J* 2.03 Hz), 8.20 (1H, d, *J* 8.74 Hz), 8.05 (1H, dd, *J* 8.75, 2.07 Hz), 7.85 (1H, s), 7.69 (1H, dt, *J* 6.38, 2.16 Hz), 7.54-7.49 (2H, m), 7.50-7.44 (2H, m), 7.38 (2H, t, *J* 7.51 Hz), 7.31 (1H, d, *J* 7.30 Hz), 5.79 (1H, d, *J* 2.31 Hz), 3.80 (1H, d, *J* 2.40 Hz), 1.32 (9H, s).

INTERMEDIATE 45

(*S*)-Phenyl[3-(quinoxalin-6-yl)phenyl]methanamine

Intermediate 44 (127 mg, 0.3 mmol), MeOH (2 mL) and conc. HCl (1 mL) were combined and stirred at room temperature for 3.5 h. The reaction was then quenched with a 2M aqueous solution of sodium hydroxide and extracted with dichloromethane. The combined organic layers were dried ($MgSO_4$) and concentrated to dryness to give the *title*

compound (86.9 mg, 93%) as a clear gum. δ_H (DMSO-d_6) 9.02 (1H, d, *J* 1.83 Hz), 8.99 (1H, d, *J* 1.83 Hz), 8.39 (1H, s), 8.26-8.20 (2H, m), 8.05 (1H, s), 7.80-7.76 (1H, m), 7.57-7.49 (4H, m), 7.36 (2H, t, *J* 7.52 Hz), 7.25 (1H, t, *J* 7.33 Hz), 5.35 (1H, s), NH_2 not visible.

EXAMPLE 1

6-[3-(Piperidin-1-ylmethyl)phenyl]quinoxaline

A mixture of 6-bromoquinoxaline (42 mg, 0.2 mmol), 3-(piperidin-1-ylmethyl)-phenylboronic acid pinacol ester hydrochloride (67 mg, 0.21 mmol), 2M aqueous sodium carbonate solution (0.3 mL, 0.6 mmol) and $Pd(PPh_3)_4$ (7 mg, 0.006 mmol) in DME (0.6 mL) was heated to 120°C in a sealed tube, under microwave irradiation, for 20 minutes. After cooling, the mixture was partitioned between saturated ammonium chloride solution and EtOAc (2 mL each), and the organic phase concentrated *in vacuo*. The residue was purified by preparative HPLC to give the *title compound* (34 mg, 56%) as a pale yellow-brown gum. δ_H ($CDCl_3$) 8.88 (d, 1H), 8.85 (d, 1H), 8.33 (d, 1H), 8.19 (d, 1H), 8.08 (dd, 1H), 7.75 (s, 1H), 7.68 (d, 1H), 7.48 (t, 1H), 7.41 (d, 1H), 3.69 (s, 2H), 2.46-2.63 (m, 4H), 1.59-1.72 (m, 4H), 1.40-1.53 (m, 2H). LCMS (ES+) 304 $(M+H)^+$, RT 2.49 minutes.

EXAMPLE 2

6-[3-(Pyrrolidin-1-ylmethyl)phenyl]quinoxaline

Pyrrolidine (53 mg, 0.75 mmol) was added to a solution/suspension of *Intermediate 1* (160 mg, 0.68 mmol) in DCM (5 mL) at r.t. Trimethyl orthoformate (0.5 mL) was added, and the mixture stirred for 30 minutes. Sodium triacetoxyborohydride (174 mg, 0.82 mmol) was added and the mixture stirred for 2 h. The mixture was quenched with saturated ammonium chloride solution (0.1 mL) and concentrated *in vacuo*. The residue was purified by preparative HPLC to give the *title compound* (41 mg, 21%) as a colourless gum. δ_H ($CDCl_3$) 8.88 (d, 1H), 8.85 (d, 1H), 8.33 (d, 1H), 8.18 (d, 1H), 8.08 (dd, 1H), 7.79 (s, 1H), 7.69 (d, 1H), 7.49 (t, 1H), 7.44 (d, 1H), 3.86 (s, 3H), 2.68-2.79 (m, 4H), 1.83-1.91 (m, 4H). LCMS (ES+) 290 $(M+H)^+$, RT 2.21 minutes.

EXAMPLE 3

N-Methyl-*N*-[(*S*)-1-phenylethyl]-*N*-[3-(quinoxalin-6-yl)benzyl]amine

(*S*)-*N*-Methyl-*N*-(1-phenylethyl)amine (32 mg, 0.24 mmol) was added to a solution/suspension of *Intermediate 1* (50 mg, 0.21 mmol) in DCM (3 mL) at r.t. Trimethyl orthoformate (0.2 mL) was added, and the mixture stirred for 30 minutes. Sodium triacetoxyborohydride (54 mg, 0.26 mmol) was added and the mixture stirred for 0.5 h. The mixture was quenched with saturated ammonium chloride solution (0.1 mL) and concentrated *in vacuo*. The residue was purified by preparative HPLC to give the *title compound* (45 mg, 69%) as a beige solid. δ_H ($CDCl_3$) 8.88 (d, 1H), 8.81 (d, 1H), 8.33 (d, 1H), 8.18 (d, 1H), 8.07 (dd, 1H), 7.73 (s, 1H), 7.63 (d, 1H), 7.32-7.50 (m, 6H), 7.22-7.30 (m, 1H), 3.61-3.79 (m, 2H), 3.41 (d, 1H), 2.20 (s, 3H), 1.46 (d, 3H). LCMS (ES+) 354 $(M+H)^+$, RT 4.58 minutes.

EXAMPLE 4

(*S*)-1-[3-(Quinoxalin-6-yl)benzyl]pyrrolidin-3-ol, bis(acetic acid) salt

(*S*)-3-Hydroxypyrrolidine (20 mg, 0.24 mmol) was added to a solution/suspension of *Intermediate 1* (50 mg, 0.21 mmol) in DCM (1 mL) at r.t. Trimethyl orthoformate (0.2 mL) was added, and the mixture stirred for 30 minutes. Sodium triacetoxyborohydride (174 mg, 0.82 mmol) was added and the mixture stirred for 1 h. The mixture was quenched with saturated ammonium chloride solution (0.1 mL) and concentrated *in vacuo*. The residue was purified by preparative HPLC to give the *title compound* (24 mg, 27%) as a pale yellow-brown gum. δ_H ($CDCl_3$) 8.90 (d, 1H), 8.79 (d, 1H), 8.35 (d, 1H), 8.21 (d, 1H), 8.09 (d, 1H), 7.87 (s, 1H), 7.78 (d, 1H), 7.55 (t, 1H), 7.47 (d, 1H), 4.51 (br, 1H), 4.20 (d, 1H), 4.01 (d, 1H), 3.42-3.61 (m, 1H), 3.29 (d, 1H), 2.73-2.98 (m, 2H), 2.24-2.43 (m, 1H), 2.07 (s, 6H), 1.98-2.16 (m, 1H). LCMS (ES+) 306 $(M+H)^+$, RT 2.11 minutes.

EXAMPLE 5

6-{3-[1-(Pyrrolidin-1-yl)ethyl]phenyl}quinoxaline

Pyrrolidine (35 mg, 0.50 mmol) was added to a solution/suspension of *Intermediate 2* (56 mg, 0.23 mmol) in DCM (1 mL) at r.t. Trimethyl orthoformate (0.2 mL) was added, and the mixture stirred for 30 minutes. Sodium triacetoxyborohydride (54 mg, 0.26 mmol) was added and the mixture heated to 100°C in a sealed tube, under microwave irradiation, for 40 minutes. The mixture was quenched with saturated ammonium chloride solution (0.1 mL) and concentrated *in vacuo*. The residue was purified by preparative HPLC to give the *title compound* (8.5 mg, 12%) as a beige solid. δ_H ($CDCl_3$) 8.88 (d, 1H), 8.84 (d, 1H), 8.34 (d, 1H), 8.18 (d, 1H), 8.09 (dd, 1H), 7.77 (s, 1H), 7.65 (d, 1H), 7.39-7.51 (m, 2H), 3.33 (q, 1H), 2.55-2.71 (m, 2H), 2.40-2.55 (m, 2H), 1.73-1.87 (m, 4H), 1.49 (d, 3H). LCMS (ES+) 304 $(M+H)^+$, RT 2.37 minutes.

EXAMPLE 6

6-{3-[1-(Pyrrolidin-1-yl)propyl]phenyl}quinoxaline

Pyrrolidine (71 mg, 1 mmol) was added to a solution of 3-bromopropiophenone (106 mg, 0.5 mmol) in DCM (10 mL) at r.t. Sodium triacetoxyborohydride (328 mg, 1.55 mmol) was added and the mixture stirred for 18 h. The mixture was quenched with water (approximately 50 mL) and extracted with DCM (approximately 50 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in 1,4-dioxane (25 mL), and benzopyrazine-6-boronic acid hydrochloride (100 mg, 0.48 mmol), potassium carbonate (250 mg, 1.8 mmol) and water (5 mL) were added. The mixture was placed under a nitrogen atmosphere, $Pd(PPh_3)_4$ (10 mg, 0.009 mmol) was added, and the mixture heated at 80°C for 18 h. The mixture was partitioned between water and diethyl ether (approximately 50 mL each) and the organic phase dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by preparative HPLC to give the *title compound* (86 mg, 27%) as an orange oil. δ_H ($CDCl_3$) 8.87 (d, 1H), 8.84 (d, 1H), 8.34 (d, 1H), 8.18 (d, 1H), 8.09 (dd, 1H), 7.77 (s, 1H), 7.65 (d, 1H), 7.46 (t, 1H), 7.38 (d, 1H), 3.09 (dd, 1H), 2.54-2.68 (m, 2H), 2.37-2.48 (m, 2H), 1.96-2.11 (m, 1H), 1.68-1.88 (m, 5H), 0.75 (t, 3H). LCMS (ES+) 318 $(M+H)^+$, RT 1.79 minutes.

EXAMPLE 7

6-{3-[(Phenyl)(pyrrolidin-1-yl)methyl]phenyl}quinoxaline

Pyrrolidine (71 mg, 1 mmol) was added to a solution of 3-bromobenzophenone (130 mg, 0.5 mmol) in DCM (10 mL) at r.t. Sodium triacetoxyborohydride (328 mg, 1.55 mmol) was added and the mixture stirred for 18 h. The mixture was refluxed with thionyl chloride (10 mL) for 1 h. The mixture was concentrated *in vacuo*. The residue was dissolved in DCM (10 mL) and pyrrolidine (71 mg, 1 mmol) was added. The mixture was refluxed for 18 h then partitioned between water and DCM (approximately 10 mL each). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The residue (130 mg, 0.41 mmol) was dissolved in 1,4-dioxane (20 mL), and benzopyrazine-6-boronic acid hydrochloride (100 mg, 0.48 mmol), potassium carbonate (140 mg, 1.01 mmol) and water (5 mL) were added. The mixture was placed under a nitrogen atmosphere, $Pd(PPh_3)_4$ (10 mg, 0.009 mmol) was added, and the mixture heated at 80°C for 18 h. The mixture was partitioned between water and diethyl ether (approximately 50 mL each) and the organic phase dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by preparative HPLC to give the *title compound* (85 mg, 58%) as an orange oil. δ_H ($CDCl_3$) 8.87 (d, 1H), 8.85 (d, 1H), 8.31 (d, 1H), 8.15 (d, 1H), 8.04 (dd, 1H), 7.90 (s, 1H), 7.48-7.60 (4H), 7.41 (t, 1H), 7.28 (d, 2H), 7.17 (t, 1H), 4.27 (s, 1H), 2.39-2.58 (m, 2H), 1.72-1.88 (m, 2H). LCMS (ES+) 366 $(M+H)^+$, RT 2.05 minutes.

EXAMPLE 8

6-{3-[1-Methyl-1-(pyrrolidin-1-yl)ethyl]phenyl}quinoxaline

Intermediate 3 (430 mg, 1.69 mmol) was dissolved in THF (5 mL) and the mixture cooled to -10°C under nitrogen. Zirconium tetrachloride (394 mg, 1.69 mmol) was added, and the reaction mixture stirred at around -10°C for 30 minutes. Methylmagnesium bromide (3.4 mL of a 3M solution in diethyl ether, 10.2 mmol) was added dropwise to the stirred mixture whilst maintaining the internal temperature at <0°C. The mixture was allowed to warm to r.t., stirred for 6 h, and left to stand for 5 days before quenching with saturated ammonium chloride solution (5 mL). The mixture was partitioned between water and DCM (50 mL each). The aqueous phase was further extracted with DCM (20 mL), and the combined organic phases dried ($MgSO_4$) and

concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, 10-100% EtOAc in heptane) to give an orange-brown oil (86 mg). 39 mg of this material was dissolved in DME (0.9 mL), and benzopyrazine-6-boronic acid hydrochloride (42 mg, 0.2 mmol), 2M aqueous sodium carbonate solution (0.3 mL, 0.6 mmol) and $Pd(PPh_3)_4$ (7 mg, 0.006 mmol) were added. The mixture was heated to 120°C in a sealed tube, under microwave irradiation, for 20 minutes. After cooling, the mixture was partitioned between saturated ammonium chloride solution and EtOAc (2 mL each), and the organic phase was concentrated *in vacuo*. The residue was purified by preparative HPLC to give the *title compound* (16 mg, 25%) as a pale brown gum. δ_H ($CDCl_3$) 8.88 (d, 1H), 8.86 (d, 1H), 8.34 (d, 1H), 8.20 (d, 1H), 8.11 (dd, 1H), 8.01 (t, 1H), 7.60-7.70 (m, 2H), 7.50 (t, 1H), 2.73-2.83 (m, 4H), 1.74-1.84 (m, 4H), 1.61 (s, 6H). LCMS (ES+) 318 $(M+H)^+$, RT 2.38 minutes.

EXAMPLE 9

(Pyrrolidin-1-yl)[3-(quinoxalin-6-yl)phenyl]methanone

Intermediate 3 (76 mg, 0.3 mmol) was dissolved in DME (0.6 mL), and benzopyrazine-6-boronic acid hydrochloride (63 mg, 0.3 mmol), 2M aqueous sodium carbonate solution (0.45 mL, 0.9 mmol) and $Pd(PPh_3)_4$ (10 mg, 0.009 mmol) were added. The mixture was heated to 120°C in a sealed tube, under microwave irradiation, for 20 minutes. After cooling, the mixture was partitioned between saturated ammonium chloride solution and EtOAc (2 mL each), and the organic phase concentrated *in vacuo*. The residue was purified by preparative HPLC to give the *title compound* (46 mg, 51%) as a colourless gum. δ_H ($CDCl_3$) 8.89 (d, 1H), 8.85 (d, 1H), 8.32 (d, 1H), 8.20 (d, 1H), 8.06 (dd, 1H), 7.92 (s, 1H), 7.81 (dt, 1H), 7.53-7.63 (m, 2H), 3.70 (t, 2H), 3.52 (t, 2H), 1.85-2.07 (m, 4H). LCMS (ES+) 304 $(M+H)^+$, RT 2.86 minutes.

EXAMPLE 10

6-[3-(Pyrrolidine-1-sulfonyl)phenyl]quinoxaline

3-Bromobenzenesulfonyl chloride (255 mg, 1 mmol) was added to a stirred solution of pyrrolidine (1 mL) in DCM (10 mL), pre-cooled in an ice-water bath. The reaction mixture was stirred, and allowed to warm to r.t. After 3 h the mixture was

partitioned between water and DCM (10 mL each), and the aqueous phase further extracted with DCM (20 mL). The combined organic phases were dried ($MgSO_4$) and the solvent removed *in vacuo* to give a pale yellow-brown oil (380 mg). A sample of this material (87 mg, 0.3 mmol) was dissolved in DME (0.9 mL), and benzopyrazine-6-boronic acid hydrochloride (63 mg, 0.3 mmol), 2M aqueous sodium carbonate solution (0.45 mL, 0.9 mmol) and $Pd(PPh_3)_4$ (10 mg, 0.009 mmol) were added. The mixture was heated to 120°C in a sealed tube, under microwave irradiation, for 20 minutes. After cooling, the mixture was partitioned between saturated ammonium chloride solution and EtOAc (2 mL each), and the organic phase concentrated *in vacuo*. The residue was purified by preparative HPLC to give the *title compound* (44 mg, 43%) as a white solid. δ_H ($CDCl_3$) 8.92 (d, 1H), 8.87 (d, 1H), 8.36 (d, 1H), 8.20-8.28 (m, 2H), 8.07 (dd, 1H), 7.99 (d, 1H), 7.91 (d, 1H), 7.70 (t, 1H), 3.28-3.38 (m, 4H), 1.77-1.86 (m, 4H). LCMS (ES+) 381 $(M+MeCN)^+$, RT 3.40 minutes.

EXAMPLE 11

(3-Hydroxyazetidin-1-yl)[3-(quinoxalin-6-yl)phenyl]methanone

3-Bromobenzoyl chloride (66 mg, 0.3 mmol) was added to a stirred solution/ suspension of 3-hydroxyazetidine hydrochloride (33 mg, 0.3 mmol) and *N*,*N*-diisopropyl-ethylamine (0.5 mL) in DCM (3 mL), pre-cooled to -40°C. The reaction mixture was stirred, and allowed to warm to r.t. After 1 h the mixture was washed with water (1 mL). The organic phase was dried ($MgSO_4$) and the solvent was removed *in vacuo*. The residue was dissolved in DME (4 mL), and benzopyrazine-6-boronic acid hydrochloride (63 mg, 0.3 mmol), 2M aqueous sodium carbonate solution (0.33 mL, 0.66 mmol) and $Pd(PPh_3)_4$ (10 mg, 0.009 mmol) were added. The mixture was heated to 120°C in a sealed tube, under microwave irradiation, for 30 minutes. After cooling, the mixture was washed with saturated sodium hydrogencarbonate solution (2 mL). The organic phase was concentrated *in vacuo*, and the residue was purified by preparative HPLC, to give the *title compound* (35 mg, 38%) as a pale yellow-brown gum. δ_H (d_6 DMSO) 9.01 (d, 1H), 8.98 (d, 1H), 8.39 (d, 1H), 8.26 (m, 1H), 8.21 (m, 1H), 8.02-8.09 (m, 2H), 7.60-7.73 (m, 2H), 5.74-5.82 (m, 1H), 4.47-4.61 (m, 2H), 4.24-4.35 (m, 1H), 4.06-4.20 (m, 1H), 3.83 (d, 1H). LCMS (ES+) 306 $(M+H)^+$, RT 2.21 minutes.

EXAMPLE 12

[4-(2,2-Difluoroethyl)piperazin-1-yl][3-(quinoxalin-6-yl)phenyl]methanone

3-Bromobenzoyl chloride (66 mg, 0.3 mmol) was added to a stirred solution/ suspension of 1-(2,2-difluoroethyl)piperazine dihydrochloride (67 mg, 0.3 mmol) and *N*,*N*-diisopropylethylamine (0.5 mL) in DCM (3 mL), pre-cooled to -40°C. The reaction mixture was stirred, and allowed to warm to r.t. After 1 h the mixture was washed with water (1 mL). The organic phase was dried ($MgSO_4$) and the solvent was removed *in vacuo*. The residue was dissolved in DME (4 mL), and benzopyrazine-6-boronic acid hydrochloride (63 mg, 0.3 mmol), 2M aqueous sodium carbonate solution (0.33 mL, 0.66 mmol) and $Pd(PPh_3)_4$ (10 mg, 0.009 mmol) were added. The mixture was heated to 120°C in a sealed tube, under microwave irradiation, for 30 minutes. After cooling, the mixture was washed with saturated sodium hydrogencarbonate solution (2 mL). The organic phase was concentrated *in vacuo*, and the residue was purified by preparative HPLC, to give the *title compound* (28 mg, 24%) as a pale yellow-brown gum. δ_H (d_6 DMSO) 8.90 (d, 1H), 8.87 (d, 1H), 8.32 (d, 1H), 8.21 (d, 1H), 8.05 (dd, 1H), 7.76-7.86 (m, 2H), 7.58 (t, 1H), 7.46 (d, 1H), 5.90 (tt, 1H), 3.42-3.99 (m, 4H), 2.49-2.82 (m, 4H), 2.80 (td, 2H). LCMS (ES+) 383 $(M+H)^+$, RT 2.96 minutes.

EXAMPLE 13

6-{3-[2-(Pyrrolidin-1-yl)ethyl]phenyl}quinoxaline, acetic acid salt

A solution of borane-THF (1M in THF, 1 mL, 1 mmol) was added to a solution of *Intermediate 4* (85 mg, 0.32 mmol) in THF (3 mL). The mixture was heated at 70°C for 1 h, and then, after cooling, quenched with saturated ammonium chloride solution (0.1 mL). The mixture was partitioned between water and EtOAc (20 mL each) and the organic phase dried ($MgSO_4$) and concentrated *in vacuo* to give a pale yellow-brown oil (45 mg). This material was dissolved in DME (0.5 mL), and benzopyrazine-6-boronic acid hydrochloride (37 mg, 0.18 mmol), 2M aqueous sodium carbonate solution (0.26 mL, 0.53 mmol) and $Pd(PPh_3)_4$ (6 mg, 0.005 mmol) were added. The mixture was heated to 120°C in a sealed tube, under microwave irradiation, for 20 minutes. After cooling, the mixture was partitioned between water and EtOAc (2 mL each), and the organic phase concentrated *in vacuo*. The residue was purified by preparative HPLC to give the *title*

compound (7.5 mg, 12%) as a pale yellow-brown gum. δ_H ($CDCl_3$) 8.89 (d, 1H), 8.87 (d, 1H), 8.32 (d, 1H), 8.20 (d, 1H), 8.07 (dd, 2H), 7.59-7.70 (m, 2H), 7.47 (t, 1H), 7.31 (d, 1H), 3.09-3.34 (m, 8H), 1.96-2.12 (m, 4H), 2.05 (s, 3H). LCMS (ES+) 304 $(M+H)^+$, RT 2.32 minutes.

EXAMPLE 14

6-{3-[2-(Pyrrolidin-1-yl)propyl]phenyl}quinoxaline, acetic acid salt

Pyrrolidine (0.2 mL) was added to a solution of *Intermediate 5* (50 mg, 0.19 mmol) and trimethyl orthoformate (0.2 mL) in 1,2-dichloroethane (1 mL) at r.t., and the mixture stirred for 30 minutes. Sodium triacetoxyborohydride (100 mg, 0.47 mmol) was added and the mixture heated to 100°C in a sealed tube, under microwave irradiation, for 10 minutes. The mixture was quenched with saturated ammonium chloride solution (0.5 mL) and concentrated *in vacuo*. The residue was purified by preparative HPLC to give the *title compound* (43 mg, 60%) as a pale cream solid. δ_H ($CDCl_3$) 8.89 (d, 1H), 8.85 (d, 1H), 8.31 (d, 1H), 8.19 (d, 1H), 8.06 (dd, 1H), 7.64 (d, 1H), 7.58 (s, 1H), 7.47 (t, 1H), 7.28 (d, 1H), 3.40 (dd, 1H), 3.02-3.28 (m, 5H), 2.72 (dd, 1H), 2.04 (s, 3H), 1.95-2.03 (m, 4H), 1.19 (d, 3H). LCMS (ES+) 318 $(M+H)^+$, RT 2.32 minutes.

EXAMPLE 15

1-(Pyrrolidin-1-yl)-2-[3-(quinoxalin-6-yl)phenyl]ethanone

A mixture of *Intermediate 4* (53 mg, 0.2 mmol), benzopyrazine-6-boronic acid hydrochloride (42 mg, 0.2 mmol), 2M aqueous sodium carbonate solution (0.3 mL, 0.6 mmol) and $Pd(PPh_3)_4$ (7 mg, 0.006 mmol) in DME (0.6 mL) was heated to 120°C in a sealed tube, under microwave irradiation, for 20 minutes. After cooling, the mixture was partitioned between water and EtOAc (2 mL each), and the organic phase adsorbed onto silica and purified by preparative HPLC to give the *title compound* (19 mg, 30%) as a pale yellow-brown gum. δ_H ($CDCl_3$) 8.88 (d, 1H), 8.85 (d, 1H), 8.31 (d, 1H), 8.17 (d, 1H), 8.07 (dd, 1H), 7.63-7.71 (m, 2H), 7.48 (t, 2H), 7.38 (d, 1H), 3.77 (2, 3H), 3.46-3.57 (m, 4H), 1.81-2.02 (m, 4H). LCMS (ES+) 318 $(M+H)^+$, RT 2.96 minutes.

EXAMPLE 16

6-{3-[2-Methyl-2-(pyrrolidin-1-yl)propyl]phenyl}quinoxaline, acetic acid salt

Example 15 (50 mg, 0.16 mmol) was dissolved in THF (3 mL) and the mixture cooled to -10°C under nitrogen. Zirconium tetrachloride (37 mg, 0.16 mmol) was added, and the reaction mixture stirred at around -10°C for 30 minutes. Methylmagnesium bromide (0.33 mL of a 3M solution in diethyl ether, 1 mmol) was added dropwise, and the mixture was stirred whilst being allowed to warm to r.t. After 3 h the mixture was quenched with saturated ammonium chloride solution (3 mL). The mixture was partitioned between water and EtOAc (30 mL each). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by preparative HPLC to give the *title compound* (2.9 mg, 4%) as a pale brown gum. δ_H ($CDCl_3$) 8.88 (d, 1H), 8.86 (d, 1H), 8.30 (d, 1H), 8.20 (d, 1H), 8.05 (dd, 1H), 7.65 (d, 1H), 7.57 (s, 1H), 7.46 (t, 1H), 7.28 (d, 1H), 3.11-3.23 (m, 4H), 3.06 (s, 2H), 2.06 (s, 3H), 1.91-2.01 (m, 4H), 1.23 (s, 6H). LCMS (ES+) 332 $(M+H)^+$, RT 2.46 minutes.

EXAMPLE 17

2-Methyl-1-(pyrrolidin-1-yl)-2-[3-(quinoxalin-6-yl)phenyl]propan-1-one

A mixture of *Intermediate 9* (89 mg, 0.3 mmol), benzopyrazine-6-boronic acid hydrochloride (63 mg, 0.3 mmol), 2M aqueous sodium carbonate solution (0.3 mL, 0.6 mmol) and $Pd(PPh_3)_4$ (7 mg, 0.006 mmol) in DME (0.9 mL) was heated to 120°C in a sealed tube, under microwave irradiation, for 20 minutes. After cooling, the mixture was partitioned between water and EtOAc (2 mL each), and the organic phase concentrated *in vacuo* and purified by preparative HPLC to give the *title compound* (47 mg, 45%) as a colourless gum. δ_H ($CDCl_3$) 8.89 (d, 1H), 8.86 (d, 1H), 8.30 (d, 1H), 8.19 (d, 1H), 8.04 (dd, 1H), 7.60-7.67 (m, 2H), 7.48 (t, 1H), 7.33 (d, 1H), 3.56 (t, 2H), 2.83 (t, 2H), 1.53-1.80 (m, 4H), 1.63 (s, 6H). LCMS (ES+) 346 $(M+H)^+$, RT 3.41 minutes.

EXAMPLE 18

6-{3-[1,1-Dimethyl-2-(pyrrolidin-1-yl)ethyl]phenyl}quinoxaline, bis(acetic acid) salt

A solution of borane-THF (1M in THF, 2 mL, 2 mmol) was added to a solution of *Intermediate 9* (90 mg, 0.30 mmol) in THF (3 mL) in an ice-water bath. The mixture was heated at 70°C for 2 h, and then, after cooling, quenched with saturated ammonium chloride solution (1 mL). The mixture was partitioned between water and EtOAc (20 mL each) and the organic phase dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in DME (0.9 mL), and benzopyrazine-6-boronic acid hydrochloride (63 mg, 0.3 mmol), 2M aqueous sodium carbonate solution (0.45 mL, 0.9 mmol) and $Pd(PPh_3)_4$ (10 mg, 0.009 mmol) were added. The mixture was heated to 120°C in a sealed tube, under microwave irradiation, for 20 minutes. The organic phase was concentrated *in vacuo*, and the residue was purified by preparative HPLC to give the *title compound* (42 mg, 31%) as a pale yellow-brown gum. δ_H ($CDCl_3$) 8.89 (d, 1H), 8.86 (d, 1H), 8.33 (d, 1H), 8.20 (d, 1H), 8.09 (dd, 1H), 7.80 (s, 1H), 7.57-7.67 (m, 1H), 7.44-7.54 (m, 2H), 3.06 (s, 2H), 2.58-2.69 (m, 4H), 2.05 (s, 6H), 1.69-1.79 (m, 4H), 1.51 (s, 6H). LCMS (ES+) 332 $(M+H)^+$, RT 2.45 minutes.

EXAMPLE 19

6-[4-Fluoro-3-(pyrrolidin-1-ylmethyl)phenyl]quinoxaline

A mixture of 5-bromo-2-fluorobenzaldehyde (61 mg, 0.3 mmol), benzopyrazine-6-boronic acid hydrochloride (63 mg, 0.3 mmol), 2M aqueous sodium carbonate solution (0.45 mL, 0.9 mmol) and $Pd(PPh_3)_4$ (10 mg, 0.009 mmol) in DME (0.9 mL) was heated to 120°C in a sealed tube, under microwave irradiation, for 20 minutes. The mixture was partitioned between water and EtOAc (50 mL each). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in DCM (5 mL). Pyrrolidine (32 mg, 0.45 mmol) and trimethyl orthoformate (0.5 mL) were added, and the mixture was stirred for 30 minutes. Sodium triacetoxyborohydride (64 mg, 0.3 mmol) was added and the mixture stirred for 0.5 h. The mixture was quenched with saturated ammonium chloride solution (0.1 mL) and concentrated *in vacuo*. The residue was purified by preparative HPLC to give the *title compound* (45 mg, 49%) as a pale yellow-brown gum. δ_H ($CDCl_3$) 8.88 (d, 1H), 8.85 (d, 1H), 8.29 (d, 1H), 8.17 (d, 1H), 8.04 (dd,

1H), 7.86 (dd, 1H), 7.61-7.70 (m, 1H), 7.20 (t, 1H), 3.88 (d, 2H), 2.66-2.78 (m, 4H), 1.80-1.91 (m, 4H). LCMS (ES+) 308 $(M+H)^+$, RT 2.32 minutes.

EXAMPLE 20

6-[4-Methoxy-3-(pyrrolidin-1-ylmethyl)phenyl]quinoxaline

A mixture of 5-bromo-2-methoxybenzaldehyde (65 mg, 0.3 mmol), benzopyrazine-6-boronic acid hydrochloride (63 mg, 0.3 mmol), 2M aqueous sodium carbonate solution (0.45 mL, 0.9 mmol) and $Pd(PPh_3)_4$ (10 mg, 0.009 mmol) in DME (0.9 mL) was heated to 120°C in a sealed tube, under microwave irradiation, for 20 minutes. The mixture was partitioned between water and EtOAc (50 mL each). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in DCM (5 mL). Pyrrolidine (32 mg, 0.45 mmol) and trimethyl orthoformate (0.5 mL) were added, and the mixture was stirred for 30 minutes. Sodium triacetoxyborohydride (64 mg, 0.3 mmol) was added and the mixture stirred for 0.5 h. The mixture was quenched with saturated ammonium chloride solution (0.1 mL) and concentrated *in vacuo*. The residue was purified by preparative HPLC to give the *title compound* (28 mg, 49%) as a pale yellow gum. δ_H ($CDCl_3$) 8.86 (d, 1H), 8.82 (d, 1H), 8.28 (d, 1H), 8.15 (d, 1H), 8.08 (dd, 1H), 7.87 (d, 1H), 7.69 (dd, 1H), 7.03 (d, 1H), 3.94 (s, 2H), 3.92 (s, 3H), 2.76-2.87 (m, 4H), 1.82-1.94 (m, 4H). LCMS (ES+) 320 $(M+H)^+$, RT 2.29 minutes.

EXAMPLE 21

6-[2-Methoxy-5-(pyrrolidin-1-ylmethyl)phenyl]quinoxaline

A mixture of 3-iodo-4-methoxybenzaldehyde (79 mg, 0.3 mmol), benzopyrazine-6-boronic acid hydrochloride (63 mg, 0.3 mmol), 2M aqueous sodium carbonate solution (0.45 mL, 0.9 mmol) and $Pd(PPh_3)_4$ (10 mg, 0.009 mmol) in DME (0.9 mL) was heated to 120°C in a sealed tube, under microwave irradiation, for 20 minutes. The mixture was partitioned between water and EtOAc (50 mL each). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in DCM (5 mL). Pyrrolidine (32 mg, 0.45 mmol) and trimethyl orthoformate (0.5 mL) were added, and the mixture was left to stand for 15 minutes. Sodium triacetoxyborohydride (64 mg, 0.3 mmol) was added and the mixture stirred for 18 h. The mixture was quenched with

saturated ammonium chloride solution (0.1 mL) and concentrated *in vacuo*. The residue was purified by preparative HPLC to give the *title compound* (45 mg, 49%) as a pale yellow-brown gum. δ_H ($CDCl_3$) 8.86 (d, 1H), 8.84 (d, 1H), 8.27 (d, 1H), 8.12 (d, 1H), 8.03 (dd, 1H), 7.39-7.51 (m, 2H), 7.02 (d, 1H), 3.87 (s, 3H), 3.82 (s, 2H), 2.71-2.81 (m, 4H), 1.83-1.93 (m, 4H). LCMS (ES+) 320 $(M+H)^+$, RT 2.05 minutes.

EXAMPLE 22

6-[2-Methyl-5-(pyrrolidin-1-ylmethyl)phenyl]quinoxaline

A mixture of 3-bromo-4-methylbenzaldehyde (60 mg, 0.3 mmol), benzopyrazine-6-boronic acid hydrochloride (63 mg, 0.3 mmol), 2M aqueous sodium carbonate solution (0.45 mL, 0.9 mmol) and $Pd(PPh_3)_4$ (10 mg, 0.009 mmol) in DME (0.9 mL) was heated to 120°C in a sealed tube, under microwave irradiation, for 20 minutes. The mixture was partitioned between water and EtOAc (2 mL each). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in DCM (5 mL). Pyrrolidine (32 mg, 0.45 mmol) and trimethyl orthoformate (0.5 mL) were added, and the mixture was stirred for 30 minutes. Sodium triacetoxyborohydride (64 mg, 0.3 mmol) was added and the mixture stirred for 0.5 h. The mixture was quenched with saturated ammonium chloride solution (0.1 mL) and concentrated *in vacuo*. The residue was purified by preparative HPLC to give the *title compound* (46 mg, 51%) as a pale yellow-brown gum. δ_H ($CDCl_3$) 8.89 (d, 1H), 8.87 (d, 1H), 8.15 (d, 1H), 8.07 (d, 1H), 7.80 (dd, 1H), 7.28-7.39 (m, 3H), 3.79 (s, 2H), 2.66-2.78 (m, 4H), 2.33 (s, 3H), 1.79-1.91 (m, 4H). LCMS (ES+) 304 $(M+H)^+$, RT 1.49 minutes.

EXAMPLE 23

6-[6-(Pyrrolidin-1-ylmethyl)pyridin-2-yl]quinoxaline

A mixture of 6-bromo-2-formylpyridine (56 mg, 0.3 mmol), benzopyrazine-6-boronic acid hydrochloride (63 mg, 0.3 mmol), 2M aqueous sodium carbonate solution (0.45 mL, 0.9 mmol) and $Pd(PPh_3)_4$ (10 mg, 0.009 mmol) in DME (0.9 mL) was heated to 120°C in a sealed tube, under microwave irradiation, for 20 minutes. The mixture was partitioned between water and EtOAc (50 mL each). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in DCM (5 mL).

Pyrrolidine (32 mg, 0.45 mmol) and trimethyl orthoformate (0.5 mL) were added, and the mixture was stirred for 30 minutes. Sodium triacetoxyborohydride (64 mg, 0.3 mmol) was added and the mixture stirred for 30 minutes. The mixture was quenched with saturated ammonium chloride solution (0.1 mL) and concentrated *in vacuo*. The residue was purified by preparative HPLC to give the *title compound* (40 mg, 46%) as a colourless gum. δ_H ($CDCl_3$) 8.89 (d, 1H), 8.86 (d, 1H), 8.70 (d, 1H), 8.57 (dd, 1H), 8.21 (d, 1H), 7.78-7.88 (m, 2H), 7.45-7.55 (m, 1H), 4.00 (s, 2H), 2.70-2.87 (m, 4H), 1.80-1.96 (m, 4H). LCMS (ES+) 291 $(M+H)^+$, RT 2.11 minutes.

EXAMPLE 24

6-[5-(Pyrrolidin-1-ylmethyl)pyridin-3-yl]quinoxaline

A mixture of 5-bromo-3-formylpyridine (56 mg, 0.3 mmol), benzopyrazine-6-boronic acid hydrochloride (63 mg, 0.3 mmol), 2M aqueous sodium carbonate solution (0.45 mL, 0.9 mmol) and $Pd(PPh_3)_4$ (10 mg, 0.009 mmol) in DME (0.9 mL) was heated to 120°C in a sealed tube, under microwave irradiation, for 20 minutes. The mixture was partitioned between water and EtOAc (50 mL each). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in DCM (5 mL). Pyrrolidine (32 mg, 0.45 mmol) and trimethyl orthoformate (0.5 mL) were added, and the mixture was stirred for 30 minutes. Sodium triacetoxyborohydride (64 mg, 0.3 mmol) was added and the mixture stirred for 30 minutes. The mixture was quenched with saturated ammonium chloride solution (0.1 mL) and concentrated *in vacuo*. The residue was purified by preparative HPLC to give the *title compound* (2.7 mg, 3%) as a colourless gum. δ_H ($CDCl_3$) 8.93 (d, 1H), 8.91 (d, 1H), 8.89 (d, 1H), 8.62 (d, 1H), 8.36 (d, 1H), 8.23 (d, 1H), 8.12 (t, 1H), 8.07 (dd, 1H), 3.80 (s, 2H), 2.57-2.70 (m, 4H), 1.80-1.91 (m, 4H). LCMS (ES+) 291 $(M+H)^+$, RT 2.09 minutes.

EXAMPLE 25

6-[4-(Pyrrolidin-1-ylmethyl)pyridin-2-yl]quinoxaline

A mixture of 2-bromo-4-formylpyridine (56 mg, 0.3 mmol), benzopyrazine-6-boronic acid hydrochloride (63 mg, 0.3 mmol), 2M aqueous sodium carbonate solution (0.45 mL, 0.9 mmol) and $Pd(PPh_3)_4$ (10 mg, 0.009 mmol) in DME (0.9 mL) was heated to

120°C in a sealed tube, under microwave irradiation, for 20 minutes. The mixture was partitioned between water and EtOAc (50 mL each). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in DCM (5 mL). Pyrrolidine (32 mg, 0.45 mmol) and trimethyl orthoformate (0.5 mL) were added, and the mixture was stirred for 30 minutes. Sodium triacetoxyborohydride (64 mg, 0.3 mmol) was added and the mixture stirred for 30 minutes. The mixture was quenched with saturated ammonium chloride solution (0.1 mL) and concentrated *in vacuo*. The residue was purified by preparative HPLC to give the *title compound* (45 mg, 52%) as a beige solid. δ_H ($CDCl_3$) 8.89 (d, 1H), 8.86 (d, 1H), 8.67-8.74 (m, 2H), 8.57 (dd, 1H), 8.21 (d, 1H), 7.98 (d, 1H), 7.32 (d, 1H), 3.77 (s, 2H), 2.57-2.68 (m, 4H), 1.80-1.91 (m, 4H). LCMS (ES+) 291 $(M+H)^+$, RT 2.27 minutes.

EXAMPLE 26

6-[2-(Pyrrolidin-1-ylmethyl)pyridin-4-yl]quinoxaline, acetic acid salt

Intermediate 10 (60 mg, 0.26 mmol) was dissolved in DCM (2 mL). Pyrrolidine (20 mg, 0.28 mmol) and trimethyl orthoformate (0.4 mL) were added, and the mixture was stirred for 30 minutes. Sodium triacetoxyborohydride (65 mg, 0.31 mmol) was added and the mixture was stirred for 2 h. After quenching with saturated ammonium chloride solution (0.1 mL), the mixture was concentrated *in vacuo*. The residue was purified by preparative HPLC to give the *title compound* (57 mg, 63%) as a pale yellow-brown gum. δ_H ($CDCl_3$) 8.92 (m, 1H), 8.90 (m, 1H), 8.70 (d, 1H), 8.43 (d, 1H), 8.24 (d, 1H), 8.10 (dd, 1H), 7.94 (s, 1H), 7.61 (dd, 1H), 4.08 (s, 2H), 2.80-2.95 (m, 4H), 2.05 (s, 3H), 1.85-1.98 (m, 4H). LCMS (ES+) 291 $(M+H)^+$, RT 1.78 minutes.

EXAMPLE 27

[3-Bromo-5-(quinoxalin-6-yl)phenyl](pyrrolidin-1-yl)methanone, acetic acid salt

Intermediate 11 (1 g, 3 mmol) was dissolved in DME (9 mL), and benzopyrazine-6-boronic acid hydrochloride (631 mg, 3 mmol), 2M aqueous sodium carbonate solution (4.5 mL, 9 mmol) and $Pd(PPh_3)_4$ (104 mg, 0.09 mmol) were added. The mixture was heated to 120°C in a sealed tube, under microwave irradiation, for 20 minutes. After cooling, the mixture was partitioned between water and EtOAc (50 mL each), and the

organic phase concentrated *in vacuo* and purified by column chromatography (SiO_2, 20-100% EtOAc in heptane) to give the *title compound* (370 mg, 28%) as a pale yellow-brown gum. δ_H ($CDCl_3$) 8.90 (d, 1H), 8.88 (d, 1H), 8.30 (d, 1H), 8.21 (d, 1H), 8.01 (dd, 1H), 7.95 (t, 1H), 7.83 (t, 1H), 7.72 (t, 1H), 3.68 (t, 2H), 3.51 (t, 2H), 2.18 (s, 3H), 1.87-2.07 (m, 4H). LCMS (ES+) 384 $(M+H)^+$, RT 3.26 minutes.

EXAMPLE 28

(Pyrrolidin-1-yl)[5-(quinoxalin-6-yl)biphenyl-3-yl]methanone

A mixture of *Example 27* (50 mg, 0.13 mmol), phenylboronic acid (16 mg, 0.13 mmol), 2M aqueous sodium carbonate solution (0.15 mL, 0.29 mmol) and $Pd(PPh_3)_4$ (5 mg, 0.004 mmol) in DME (0.3 mL) was heated to 120°C in a sealed tube, under microwave irradiation, for 20 minutes. After cooling, the mixture was partitioned between water and EtOAc (2 mL each), and the organic phase concentrated *in vacuo* and purified by preparative HPLC to give the *title compound* (40 mg, 81%) as a pale cream solid. δ_H ($CDCl_3$) 8.90 (d, 1H), 8.88 (d, 1H), 8.30 (d, 1H), 8.21 (d, 1H), 8.01 (dd, 1H), 7.95 (t, 1H), 7.83 (t, 1H), 7.72 (t, 1H), 3.68 (t, 2H), 3.51 (t, 2H), 1.87-2.07 (m, 4H). LCMS (ES+) 380 $(M+H)^+$, RT 3.73 minutes.

EXAMPLE 29

[3-(Morpholin-4-yl)-5-(quinoxalin-6-yl)phenyl](pyrrolidin-1-yl)methanone, acetic acid salt

Example 27 (50 mg, 0.13 mmol), sodium *tert*-butoxide (30 mg, 0.31 mmol) and di-μ-bromobis(tri-*tert*-butylphosphine)dipalladium(I) (2 mg, 0.003 mmol) were dissolved/suspended in toluene (2 mL) in a sealed tube. The mixture was degassed by evacuating and purging with nitrogen 3-4 times over approximately 5 minutes. Morpholine (23 mg, 0.26 mmol) was added, and the mixture was heated to 120°C in a sealed tube, under microwave irradiation, for 1 h. The mixture was quenched with saturated ammonium chloride solution (0.1 mL) and concentrated *in vacuo*. The residue was purified by preparative HPLC to give a sample of the *title compound* (26 mg) as a pale yellow-brown gum. δ_H ($CDCl_3$) 8.89 (d, 1H), 8.86 (d, 1H), 8.30 (d, 1H), 8.18 (d, 1H), 8.03 (dd, 1H), 7.35 (t, 1H), 7.29 (t, 1H), 7.11-7.14 (m, 1H), 3.87-3.94 (m, 4H), 3.68

(t, 2H), 3.52 (t, 2H), 3.26-3.33 (m, 4H), 2.10 (s, 3H), 1.85-2.06 (m, 4H). LCMS (ES+) 389 $(M+H)^+$, RT 2.82 minutes.

EXAMPLE 30

(Pyrrolidin-1-yl)[3-(quinoxalin-6-yl)-5-(trifluoromethoxy)phenyl]methanone

A mixture of *Intermediate 12* (169 mg, 0.5 mmol), benzopyrazine-6-boronic acid hydrochloride (105 mg, 0.5 mmol), 2M aqueous sodium carbonate solution (0.75 mL, 1.5 mmol) and $Pd(PPh_3)_4$ (17 mg, 0.015 mmol) in DME (3 mL) was heated to 120°C in a sealed tube, under microwave irradiation, for 20 minutes. The organic phase was adsorbed onto silica and purified by column chromatography (SiO_2, 20-100% EtOAc in heptane) to give the *title compound* (149 mg, 77%) as a pale orange-brown gum. δ_H ($CDCl_3$) 8.91 (d, 1H), 8.82 (d, 1H), 8.32 (d, 1H), 8.22 (d, 1H), 8.03 (dd, 1H), 7.86 (s, 1H), 7.65 (s, 1H), 7.46 (s, 1H), 3.70 (t, 2H), 3.52 (t, 2H), 1.89-2.09 (m, 4H). LCMS (ES+) 388 $(M+H)^+$, RT 3.48 minutes.

EXAMPLE 31

[2-Methyl-3-(quinoxalin-6-yl)phenyl](pyrrolidin-1-yl)methanone

A mixture of *Intermediate 13* (134 mg, 0.5 mmol), benzopyrazine-6-boronic acid hydrochloride (105 mg, 0.5 mmol), 2M aqueous sodium carbonate solution (0.75 mL, 1.5 mmol) and $Pd(PPh_3)_4$ (17 mg, 0.015 mmol) in DME (1.5 mL) was heated to 120°C in a sealed tube, under microwave irradiation, for 20 minutes. The organic phase was adsorbed onto silica and purified by column chromatography (SiO_2, 20-100% EtOAc in heptane and then 0-20% MeOH in EtOAc) to give the *title compound* (146 mg, 92%) as a pale orange-brown gum. δ_H ($CDCl_3$) 8.86-8.93 (m, 2H), 8.16 (d, 1H), 8.05 (d, 1H), 7.76 (dd, 1H), 7.26-7.40 (m, 3H), 3.70 (t, 2H), 3.24 (t, 2H), 2.26 (s, 3H), 1.86-2.06 (m, 4H). LCMS (ES+) 304 $(M+H)^+$, RT 2.83 minutes.

EXAMPLE 32

(Pyrrolidin-1-yl)[4-(quinoxalin-6-yl)pyridin-2-yl]methanone

A mixture of *Intermediate 14* (51 mg, 0.2 mmol), benzopyrazine-6-boronic acid hydrochloride (42 mg, 0.2 mmol), 2M aqueous sodium carbonate solution (0.3 mL, 0.6 mmol) and $Pd(PPh_3)_4$ (7 mg, 0.006 mmol) in DME (0.6 mL) was heated to 120°C in a sealed tube, under microwave irradiation, for 20 minutes. The mixture was partitioned between water and EtOAc (2 mL each). The organic phase was concentrated and purified by preparative HPLC to give a sample of the *title compound* (19 mg, 31%) as a white solid. δ_H ($CDCl_3$) 8.93 (d, 1H), 8.91 (d, 1H), 8.73 (dd, 1H), 8.44 (d, 1H), 8.23-8.27 (m, 2H), 8.11 (dd, 1H), 7.73 (dd, 1H), 3.79-3.89 (m, 2H), 3.69-3.79 (m, 2H), 1.92-2.02 (m, 4H). LCMS (ES+) 305 $(M+H)^+$, RT 2.36 minutes.

EXAMPLE 33

(Pyrrolidin-1-yl)[6-(quinoxalin-6-yl)pyridin-2-yl]methanone

HBTU (167 mg, 0.44 mmol) was added to a solution of 6-bromo-2-pyridinecarboxylic acid (81 mg, 0.4 mmol) and DIPEA (103 mg, 0.8 mmol) in DMF (1 mL). The mixture was stirred for 5 minutes at r.t. Pyrrolidine (43 mg, 0.6 mmol) was added. The mixture was stirred and left to stand for 15 minutes. The mixture was partitioned between water and EtOAc (50 mL each) and the organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in DME (0.9 mL), and benzopyrazine-6-boronic acid hydrochloride (63 mg, 0.3 mmol), 2M aqueous sodium carbonate solution (0.45 mL, 0.9 mmol) and $Pd(PPh_3)_4$ (10 mg, 0.009 mmol) were added. The mixture was heated to 120°C in a sealed tube, under microwave irradiation, for 20 minutes. The organic phase was concentrated and purified by preparative HPLC to give a sample of the *title compound* (39 mg, 32%) as a cream solid. δ_H ($CDCl_3$) 8.91 (d, 1H), 8.84 (d, 1H), 8.73 (d, 1H), 8.53 (dd, 1H), 8.23 (d, 1H), 7.93-8.06 (m, 3H), 3.96-4.04 (m, 2H), 3.72-3.81 (m, 2H), 1.96-2.03 (m, 4H). LCMS (ES+) 305 $(M+H)^+$, RT 2.57 minutes.

EXAMPLE 34

6-Methyl-7-[3-(piperidin-1-ylmethyl)phenyl]quinoxaline

Tin(II) chloride (0.82 g, 4.35 mmol) was added to a solution/suspension of *Intermediate 15* (200 mg, 0.87 mmol) in water (0.16 g, 8.7 mmol), isopropanol (2 mL) and EtOAc (10 mL) at r.t. The mixture was heated for 4 h at 60°C. Glyoxal (0.5 mL, 40% in water) was added, and the mixture was allowed to cool to r.t. The mixture was adsorbed onto silica and purified by column chromatography (SiO_2, 10-100% EtOAc in heptane) to give a yellow-orange gum (51 mg). This material was dissolved in DME (0.7 mL), and 3-(piperidin-1-ylmethyl)phenylboronic acid pinacol ester hydrochloride (77 mg, 0.23 mmol), 2M aqueous sodium carbonate solution (0.35 mL, 0.7 mmol) and $Pd(PPh_3)_4$ (8 mg, 0.007 mmol) were added. The mixture was heated to 120°C in a sealed tube, under microwave irradiation, for 20 minutes. After cooling, the organic phase was concentrated *in vacuo*. The residue was purified by preparative HPLC to give the *title compound* (12 mg, 4% over the three steps) as a pale yellow-brown gum. δ_H ($CDCl_3$) 8.79-8.84 (m, 2H), 7.95-8.01 (m, 2H), 7.26-7.47 (m, 4H), 3.57 (s, 2H), 2.37-2.50 (m, 4H), 2.49 (s, 3H), 1.54-1.66 (m, 4H), 1.39-1.50 (m, 2H). LCMS (ES+) 318 $(M+H)^+$, RT 2.36 minutes.

EXAMPLE 35

6-Fluoro-7-[3-(piperidin-1-ylmethyl)phenyl]quinoxaline

Tin(II) chloride (0.82 g, 4.35 mmol) was added to a solution/suspension of *Intermediate 16* (204 mg, 0.87 mmol) in water (0.16 g, 8.7 mmol), isopropanol (2 mL) and EtOAc (10 mL) at r.t. The mixture was heated for 4 h at 60°C. Glyoxal (0.5 mL, 40% in water) was added, and the mixture was allowed to cool to r.t. The mixture was adsorbed onto silica and purified by column chromatography (SiO_2, 10-100% EtOAc in heptane) to give an orange-brown gum (48 mg). This material was dissolved in DME (0.6 mL), and 3-(piperidin-1-ylmethyl)phenylboronic acid pinacol ester hydrochloride (70 mg, 0.21 mmol), 2M aqueous sodium carbonate solution (0.3 mL, 0.6 mmol) and $Pd(PPh_3)_4$ (8 mg, 0.007 mmol) were added. The mixture was heated to 120°C in a sealed tube, under microwave irradiation, for 20 minutes. After cooling, the organic phase was concentrated *in vacuo*. The residue was purified by preparative HPLC to give the *title*

compound (4 mg, 1.4% over the three steps) as a pale yellow-brown gum. δ_H ($CDCl_3$) 8.85 (m, 2H), 8.21 (d, 1H), 7.84 (d, 1H), 7.64 (s, 1H), 7.37-7.59 (m, 3H), 3.57 (s, 2H), 2.34-2.50 (m, 4H), 1.51-1.70 (m, 4H), 1.39-1.49 (m, 2H). LCMS (ES+) 322 $(M+H)^+$, RT 2.48 minutes.

EXAMPLE 36

5-Fluoro-7-[3-(piperidin-1-ylmethyl)phenyl]quinoxaline

Glyoxal (10 drops of a 40% solution in water) was added to a solution of 5-bromo-2,3-diaminofluorobenzene (82 mg, 0.4 mmol) in ethanol (3 mL). The mixture was stirred and left to stand at r.t. for 1 h. The mixture was partitioned between water and EtOAc (20 mL each), and the organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in DME (1.2 mL), and 3-(piperidin-1-ylmethyl)phenylboronic acid pinacol ester hydrochloride (135 mg, 0.4 mmol), 2M aqueous sodium carbonate solution (0.6 mL, 0.9 mmol) and $Pd(PPh_3)_4$ (14 mg, 0.012 mmol) were added. The mixture was heated to 120°C in a sealed tube, under microwave irradiation, for 20 minutes. The mixture was partitioned between water and EtOAc (2 mL each), and the organic phase was concentrated *in vacuo*. The residue was purified by preparative HPLC to give the *title compound* (23 mg, 18% over the two steps) as a pale yellow-brown gum. δ_H ($CDCl_3$) 8.94 (d, 1H), 8.89 (d, 1H), 8.17 (s, 1H), 7.80 (d, 1H), 7.72 (s, 1H), 7.64 (d, 1H), 7.48 (t, 1H), 7.43 (d, 1H), 3.64 (s, 2H), 2.40-2.60 (m, 4H), 1.55-1.70 (m, 4H), 1.39-1.54 (m, 2H). LCMS (ES+) 322 $(M+H)^+$, RT 2.25 minutes.

EXAMPLE 37

5-Methyl-7-[3-(piperidin-1-ylmethyl)phenyl]quinoxaline

Glyoxal (10 drops of a 40% solution in water) was added to a solution of 5-bromo-2,3-diaminomethylbenzene (80 mg, 0.4 mmol) in ethanol (3 mL). The mixture was stirred and left to stand at r.t. for 1 h. The mixture was partitioned between water and EtOAc (20 mL each), and the organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in DME (1.2 mL), and 3-(piperidin-1-ylmethyl)phenylboronic acid pinacol ester hydrochloride (135 mg, 0.4 mmol), 2M aqueous sodium carbonate solution (0.6 mL, 0.9 mmol) and $Pd(PPh_3)_4$ (14 mg, 0.012 mmol) were added.

The mixture was heated to 120°C in a sealed tube, under microwave irradiation, for 20 minutes. The mixture was partitioned between water and EtOAc (2 mL each), and the organic phase was concentrated *in vacuo*. The residue was purified by preparative HPLC to give the *title compound* (5 mg, 4% over the two steps) as a pale yellow-brown gum. δ_H ($CDCl_3$) 8.87 (d, 1H), 8.85 (d, 1H), 8.17 (s, 1H), 7.93 (s, 1H), 7.72 (s, 1H), 7.65 (d, 1H), 7.46 (t, 1H), 7.39 (d, 1H), 3.58 (s, 2H), 2.88 (s, 3H), 2.34-2.52 (m, 4H), 1.51-1.68 (m, 4H), 1.39-1.51 (m, 2H). LCMS (ES+) 318 $(M+H)^+$, RT 2.43 minutes.

EXAMPLE 38

2-Methyl-6-[3-(piperidin-1-ylmethyl)phenyl]quinoxaline and 2-methyl-6-[3-(piperidin-1-ylmethyl)phenyl]quinoxaline, acetic acid salts, 60:40 mixture

6-Bromo-2-methylquinoxaline and 7-bromo-2-methylquinoxaline (1:1 mixture) (*Intermediate 17*) (46 mg, 2.07 mmol), 3-(piperidin-1-ylmethyl)phenylboronic acid pinacol ester hydrochloride (70 mg, 2.07 mmol), 2M aqueous sodium carbonate solution (0.3 mL, 0.6 mmol) and $Pd(PPh_3)_4$ (7 mg, 0.006 mmol) in DME (0.6 mL) were heated to 120°C in a sealed tube, under microwave irradiation, for 20 minutes. The mixture was partitioned between water and EtOAc (2 mL each), and the organic phase was concentrated *in vacuo*. The residue was purified by preparative HPLC to give the *title compound* (47 mg, 60%) as a pale pink gum. δ_H ($CDCl_3$) 60% component: 8.74 (s, 1H), 8.24 (d, 1H), 8.14 (d, 1H), 8.03 (dd, 1H), 7.75 (s, 1H), 7.69 (d, 2H), 7.49 (t, 2H), 7.41 (d, 2H), 3.79 (m, 2H), 2.80 (s, 3H), 2.57-2.69 (m, 4H), 2.07 (s, 3H), 1.63-1.76 (m, 4H), 1.41-1.56 (m, 2H); 40% component: 8.78 (s, 1H), 8.28 (d, 1H), 8.08 (d, 1H), 8.00 (dd, 1H), 7.75 (s, 1H), 7.69 (d, 2H), 7.49 (t, 2H), 7.41 (d, 2H), 3.79 (m, 2H), 2.80 (s, 3H), 2.57-2.69 (m, 4H), 2.07 (s, 3H), 1.63-1.76 (m, 4H), 1.41-1.56 (m, 2H). LCMS (ES+) 318 $(M+H)^+$, RT 1.48 minutes (single peak).

EXAMPLE 39

2,3-Dimethyl-6-[3-(piperidin-1-ylmethyl)phenyl]quinoxaline

Intermediate 18 (49 mg, 2.07 mmol), 3-(piperidin-1-ylmethyl)phenylboronic acid pinacol ester hydrochloride (70 mg, 2.07 mmol), 2M aqueous sodium carbonate solution (0.3 mL, 0.6 mmol) and $Pd(PPh_3)_4$ (7 mg, 0.006 mmol) in DME (0.6 mL) were heated to

120°C in a sealed tube, under microwave irradiation, for 20 minutes. The mixture was partitioned between water and EtOAc (2 mL each), and the organic phase was concentrated *in vacuo*. The residue was purified by preparative HPLC to give the *title compound* (34 mg, 50%) as a pale yellow gum. δ_H ($CDCl_3$) 8.22 (d, 1H), 8.04 (d, 1H), 7.97 (dd, 1H), 7.72 (s, 1H), 7.64 (d, 1H), 7.44 (t, 1H), 7.37 (d, 1H), 3.57 (s, 2H), 2.76 (s, 3H), 2.37-2.49 (m, 4H), 1.55-1.65 (m, 4H), 1.40-1.50 (m, 2H). LCMS (ES+) 332 $(M+H)^+$, RT 2.63 minutes.

EXAMPLE 40

6-[3-(Piperidin-1-ylmethyl)phenyl]pyrido[2,3-*b*]pyrazine

Tin(II) chloride (9.45 g, 50 mmol) was added to a solution/suspension of 2-amino-6-chloro-3-nitropyridine (1.74 g, 10 mmol) in water (1.8 g, 100 mmol), isopropanol (5 mL) and EtOAc (40 mL) at r.t. The mixture was heated for 1 h at 60°C. Sodium borohydride (190 mg, 5 mmol) was added cautiously and the mixture heated for 3 h at 60°C. After cooling, the mixture was diluted with EtOAc (100 mL) and washed with a mixture of water (100 mL) and saturated sodium hydrogencarbonate solution (50 mL). The aqueous phase was extracted with EtOAc (100 mL), and the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in ethanol (10 mL) and glyoxal (2 mL, 40% in water) was added. After standing for 18 h the mixture was filtered and air-dried to give a brown solid (200 mg). A sample of this material (70 mg, 0.21 mmol) was dissolved in DME (0.6 mL), and 3-(piperidin-1-ylmethyl)phenylboronic acid pinacol ester hydrochloride (70 mg, 0.21 mmol), 2M aqueous sodium carbonate solution (0.3 mL, 0.6 mmol) and $Pd(PPh_3)_4$ (7 mg, 0.006 mmol) were added. The mixture was heated to 120°C in a sealed tube, under microwave irradiation, for 20 minutes. After cooling, the organic phase was concentrated *in vacuo*. The residue was purified by preparative HPLC to give the *title compound* (14 mg, 1.3% over the three steps) as a pale yellow-brown gum. δ_H ($CDCl_3$) 9.08 (d, 1H), 8.91 (d, 1H), 8.52 (d, 1H), 8.26-8.31 (m, 2H), 8.16-8.22 (m, 1H), 7.46-7.56 (m, 2H), 3.63 (s, 2H), 2.40-2.52 (m, 4H), 1.52-1.69 (m, 4H), 1.39-1.52 (m, 2H). LCMS (ES+) 305 $(M+H)^+$, RT 1.90 minutes.

EXAMPLE 41

7-[3-(Piperidin-1-ylmethyl)phenyl]pyrido[3,4-*b*]pyrazine

4,5-Diamino-2-chloropyridine (35 mg, 0.24 mmol) was dissolved in ethanol (1 mL) and glyoxal (0.5 mL, 40% in water) was added. After standing for 18 h the mixture was partitioned between water and EtOAc (20 mL each). The organic phase was washed with water, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in DME (0.7 mL), and 3-(piperidin-1-ylmethyl)phenylboronic acid pinacol ester hydrochloride (81 mg, 0.24 mmol), 2M aqueous sodium carbonate solution (0.35 mL, 0.7 mmol) and $Pd(PPh_3)_4$ (8 mg, 0.007 mmol) were added. The mixture was heated to 120°C in a sealed tube, under microwave irradiation, for 20 minutes. After cooling, the mixture was partitioned between water and EtOAc (2 mL each). The organic phase was concentrated *in vacuo* and the residue was purified by preparative HPLC to give the *title compound* (53 mg, 64%) as a pale yellow gum. δ_H ($CDCl_3$) 9.63 (d, 1H), 9.03 (d, 1H), 8.92 (d, 1H), 8.37 (d, 1H), 8.17 (s, 1H), 8.08-8.14 (m, 1H), 7.44-7.57 (m, 2H), 3.74 (s, 2H), 2.50-2.65 (m, 4H), 1.59-1.73 (m, 4H), 1.40-1.54 (m, 2H). LCMS (ES+) 305 $(M+H)^+$, RT 1.89 minutes.

EXAMPLE 42

7-[3-(Piperidin-1-ylmethyl)phenyl]pyrido[2,3-*b*]pyrazine, bis(acetic acid) salt

Intermediate 19 (41 mg, 0.21 mmol), 3-(piperidin-1-ylmethyl)phenylboronic acid pinacol ester hydrochloride (70 mg, 0.21 mmol), 2M aqueous sodium carbonate solution (0.3 mL, 0.6 mmol) and $Pd(PPh_3)_4$ (7 mg, 0.006 mmol) in DME (0.6 mL) were heated to 120°C in a sealed tube, under microwave irradiation, for 20 minutes. After cooling, the organic phase was concentrated *in vacuo* and the residue was purified by preparative HPLC to give the *title compound* (68 mg, 76%) as a beige solid. δ_H ($CDCl_3$) 9.49 (d, 1H), 9.08 (d, 1H), 8.99 (d, 1H), 8.65 (d, 1H), 7.82 (s, 1H), 7.73 (d, 1H), 7.55 (t, 1H), 7.49 (d, 1H), 3.84 (s, 2H), 2.59-2.75 (m, 4H), 2.09 (s, 6H), 1.65-1.79 (m, 4H), 1.43-1.60 (m, 2H). LCMS (ES+) 305 $(M+H)^+$, RT 2.02 minutes.

EXAMPLE 43

6-[6-(Pyrrolidin-1-yl)pyridin-2-yl]quinoxaline

Intermediate 20 (57 mg, 0.25 mmol), benzopyrazine-6-boronic acid hydrochloride (53 mg, 0.25 mmol), 2M aqueous sodium carbonate solution (0.3 mL, 0.6 mmol) and $Pd(PPh_3)_4$ (9 mg, 0.008 mmol) in DME (0.6 mL) were heated to 120°C in a sealed tube, under microwave irradiation, for 20 minutes. After cooling, the mixture was partitioned between water and EtOAc (2 mL each). The organic phase was concentrated *in vacuo* and the residue was purified by preparative HPLC to give the *title compound* (37 mg, 54%) as a yellow solid. δ_H ($CDCl_3$) 8.87 (d, 1H), 8.84 (d, 1H), 8.78 (d, 1H), 8.57 (dd, 1H), 8.17 (d, 1H), 7.48 (t, 1H), 7.22 (d, 1H), 6.42 (d, 1H), 3.53-3.68 (m, 4H), 1.98-2.13 (m, 4H). LCMS (ES+) 277 $(M+H)^+$, RT 4.23 minutes.

EXAMPLE 44

N-Cyclohexyl-*N*-[6-(quinoxalin-6-yl)pyridin-2-yl]amine

A solution of 2,6-dibromopyridine (237 mg, 1 mmol), cyclohexylamine (158 mg, 1.6 mmol) and triethylamine (121 mg, 1.2 mmol) in NMP (1 mL) was heated to 150°C in a sealed tube, under microwave irradiation, for 220 minutes. The mixture was partitioned between water and EtOAc (20 mL each). The organic phase was dried ($MgSO_4$) and the solvent removed *in vacuo* to give a brown oil (560 mg). 25% of this material was dissolved in DME (0.6 mL), and benzopyrazine-6-boronic acid hydrochloride (53 mg, 0.25 mmol), 2M aqueous sodium carbonate solution (0.3 mL, 0.6 mmol) and $Pd(PPh_3)_4$ (9 mg, 0.008 mmol) were added. The mixture was heated to 120°C in a sealed tube, under microwave irradiation, for 20 minutes. After cooling, the mixture was partitioned between water and EtOAc (2 mL each). The organic phase was concentrated *in vacuo* and the residue was purified by preparative HPLC to give the *title compound* (42 mg, 55%) as a yellow gum. δ_H ($CDCl_3$) 8.88 (d, 1H), 8.85 (d, 1H), 8.66 (d, 1H), 8.50 (dd, 1H), 8.16 (d, 1H), 7.55 (t, 1H), 7.21 (d, 1H), 6.42 (d, 1H), 4.62 (br, 1H), 3.71 (br, 1H), 2.06-2.20 (m, 2H), 1.62-1.87 (m, 3H), 1.37-1.56 (m, 2H), 1.17-1.37 (m, 3H). LCMS (ES+) 305 $(M+H)^+$, RT 4.43 minutes.

EXAMPLE 45

N-Cyclohexyl-*N*-methyl-*N*-[6-(quinoxalin-6-yl)pyridin-2-yl]amine

A solution of 2,6-dibromopyridine (237 mg, 1 mmol), *N*-methylcyclohexylamine (181 mg, 1.6 mmol) and triethylamine (121 mg, 1.2 mmol) in NMP (1 mL) was heated to 150°C in a sealed tube, under microwave irradiation, for 220 minutes. The mixture was partitioned between water and EtOAc (20 mL each). The organic phase was dried ($MgSO_4$) and the solvent removed *in vacuo* to give a brown oil (440 mg). 25% of this material was dissolved in DME (0.6 mL), and benzopyrazine-6-boronic acid hydrochloride (53 mg, 0.25 mmol), 2M aqueous sodium carbonate solution (0.3 mL, 0.6 mmol) and $Pd(PPh_3)_4$ (9 mg, 0.008 mmol) were added. The mixture was heated to 120°C in a sealed tube, under microwave irradiation, for 20 minutes. After cooling, the mixture was partitioned between water and EtOAc (2 mL each). The organic phase was concentrated *in vacuo* and the residue was purified by preparative HPLC to give the *title compound* (52 mg, 65%) as a yellow gum. δ_H ($CDCl_3$) 8.88 (d, 1H), 8.85 (d, 1H), 8.73 (d, 1H), 8.56 (dd, 1H), 8.16 (d, 1H), 7.49 (t, 1H), 7.22 (d, 1H), 6.56 (d, 1H), 4.46 (br, 1H), 3.04 (s, 3H), 1.80-1.94 (m, 4H), 1.68-1.80 (m, 1H), 1.40-1.65 (m, 4H), 1.10-1.28 (m, 1H).

EXAMPLE 46

6-[2-(Pyrrolidin-1-yl)pyridin-4-yl]quinoxaline

Intermediate 21 (70 mg, 0.29 mmol), sodium *tert*-pentoxide (77 mg, 0.7 mmol) and di-μ-bromobis(tri-*tert*-butylphosphine)dipalladium(I) (5 mg, 0.006 mmol) in toluene (2 mL) were placed in a sealed tube and degassed by evacuating and purging with nitrogen 3-4 times over approximately 5 minutes. Pyrrolidine (23 mg, 0.32 mmol) was added, and the mixture was heated to 120°C in a sealed tube, under microwave irradiation, for 1 h. After cooling, the mixture was partitioned between water and EtOAc (2 mL each). The organic phase was concentrated *in vacuo* and the residue was purified by preparative HPLC to give the *title compound* (3.7 mg, 5%) as a yellow gum. δ_H ($CDCl_3$) 8.90 (d, 1H), 8.88 (d, 1H), 8.37 (d, 1H), 8.29 (d, 1H), 8.20 (d, 1H), 8.06 (dd, 1H), 6.89 (dd, 1H), 6.68 (d, 1H), 3.51-3.61 (m, 4H), 2.00-2.12 (m, 4H). LCMS (ES+) 277 $(M+H)^+$, RT 3.14 minutes.

EXAMPLE 47

N-Cyclohexyl-*N*-[4-(quinoxalin-6-yl)pyridin-2-yl]amine

Intermediate 21 (70 mg, 0.29 mmol), sodium *tert*-butoxide (67 mg, 0.7 mmol) and di-μ-bromobis(tri-*tert*-butylphosphine)dipalladium(I) (5 mg, 0.006 mmol) in toluene (2 mL) were placed in a sealed tube and degassed by evacuating and purging with nitrogen 3-4 times over approximately 5 minutes. Cyclohexylamine (32 mg, 0.32 mmol) was added, and the mixture was heated to 120°C in a sealed tube, under microwave irradiation, for 1 h. After cooling, the mixture was partitioned between water and EtOAc (2 mL each). The organic phase was concentrated *in vacuo* and the residue was purified by preparative HPLC to give the *title compound* (2.8 mg, 3%) as a pale yellow-brown gum. δ_H ($CDCl_3$) 8.91 (d, 1H), 8.89 (d, 1H), 8.35 (d, 1H), 8.21 (d, 1H), 8.13 (d, 1H), 8.02 (dd, 1H), 6.90 (dd, 1H), 6.71 (s, 1H), 5.47 (br, 1H), 3.59 (br, 1H), 2.03-2.16 (m, 2H), 1.73-1.87 (m, 2H), 1.60-1.74 (m, 1H), 1.21-1.53 (m, 5H). LCMS (ES+) 305 $(M+H)^+$, RT 3.74 minutes.

EXAMPLE 48

N-Cyclohexyl-*N*-methyl-*N*-[4-(quinoxalin-6-yl)pyridin-2-yl]amine

A solution of 4-bromo-2-chloropyridine (385 mg, 2 mmol), *N*-methyl-cyclohexylamine (249 mg, 2.2 mmol) and triethylamine (242 mg, 2.4 mmol) in NMP (2 mL) was heated to 150°C in a sealed tube, under microwave irradiation, for 2 h. Half the mixture was purified by preparative HPLC to give a pale yellow-brown gum (17 mg). This material was dissolved in DME (0.2 mL), and benzopyrazine-6-boronic acid hydrochloride (13 mg, 0.06 mmol), 2M aqueous sodium carbonate solution (0.1 mL, 0.2 mmol) and $Pd(PPh_3)_4$ (2 mg, 0.002 mmol) were added. The mixture was heated to 120°C in a sealed tube, under microwave irradiation, for 20 minutes. After cooling, the mixture was partitioned between water and EtOAc (2 mL each). The organic phase was concentrated *in vacuo* and the residue was purified by preparative HPLC to give the *title compound* (18 mg, 6%) as a yellow gum. δ_H ($CDCl_3$) 8.90 (d, 1H), 8.87 (d, 1H), 8.36 (d, 1H), 8.29 (d, 1H), 8.20 (d, 1H), 8.05 (dd, 1H), 6.88 (dd, 1H), 6.79 (s, 1H), 4.48 (m, 1H), 2.98 (s, 3H), 1.65-1.94 (m, 5H), 1.39-1.62 (m, 4H) 1.08-1.28 (m, 1H). LCMS (ES+) 319 $(M+H)^+$, RT 4.51 minutes.

EXAMPLE 49

N-Cyclohexyl-*N*-[3-(quinoxalin-6-yl)benzyl]acetamide

Cyclohexylamine (558 mg, 6.41 mmol) was added to a solution of *Intermediate 1* (300 mg, 1.28 mmol) in DCM (5 mL) and THF (5 mL) at r.t. Trimethyl orthoformate (1 mL) was added, and the mixture left to stand for 30 minutes. Sodium triacetoxy-borohydride (544 mg, 2.56 mmol) was added and the mixture stirred for 18 h. The mixture was quenched with saturated ammonium chloride solution (1 mL) and concentrated *in vacuo*. The residue was partitioned between water and EtOAc (50 mL each). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. Half the residue was dissolved in DCM (3 mL). Triethylamine (0.1 mL) was added, followed by acetyl chloride (0.1 mL). After standing for 18 h, the mixture was concentrated *in vacuo* and the residue was purified by preparative HPLC to give the *title compound* (8 mg, 3%) as a pale brown gum. δ_H ($CDCl_3$) rotamers observed, 50:50; 8.81-8.93 (m, 2H), 8.29 (s, 1H), 8.19 (t, 1H), 8.00-8.08 (m, 1H), 7.66 (d, 0.5H), 7.56-7.63 (m, 1.5H), 7.51 (t, 0.5H), 7.44 (t, 0.5H), 7.30 (d, 1H), 4.68 (s, 1H), 4.61 (s, 1H), 3.68 (tt, 1H), 2.29 (s, 1.5H), 2.09 (s, 1.5H), 1.56-2.01 (m, 5H), 1.20-1.54 (m, 4H), 0.95-1.18 (m, 1H). LCMS (ES+) 360 $(M+H)^+$, RT 3.71 minutes.

EXAMPLE 50

N-Cyclohexyl-*N*-[3-(quinoxalin-6-yl)benzyl]benzamide

Cyclohexylamine (558 mg, 6.41 mmol) was added to a solution of *Intermediate 1* (300 mg, 1.28 mmol) in DCM (5 mL) and THF (5 mL) at r.t. Trimethyl orthoformate (1 mL) was added, and the mixture left to stand for 30 minutes. Sodium triacetoxy-borohydride (544 mg, 2.56 mmol) was added and the mixture stirred for 18 h. The mixture was quenched with saturated ammonium chloride solution (1 mL) and concentrated *in vacuo*. The residue was partitioned between water and EtOAc (50 mL each). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. Half the residue was dissolved in DCM (3 mL) and triethylamine (0.1 mL) added, followed by benzoyl chloride (0.1 mL). After standing for 18 h, the mixture was concentrated *in vacuo* and the residue was purified by preparative HPLC to give the *title compound* (11 mg, 4%) as a

cream solid. δ_H ($CDCl_3$) 8.87 (d, 1H), 8.83 (d, 1H), 8.30 (s, 1H), 8.18 (t, 1H), 8.04 (d, 1H), 7.30-7.75 (m, 9H), 4.75 (s, 2H), 3.20 (tt, 1H), 1.64-1.88 (m, 4H), 1.46-1.63 (m, 4H), 0.94-1.20 (m, 2H). LCMS (ES+) 442 $(M+H)^+$, RT 4.43 minutes.

EXAMPLE 51

N-Cyclopentyl-*N*-[3-(quinoxalin-6-yl)benzyl]acetamide

Intermediate 22 (40 mg, 0.013 mmol) was dissolved in DCM (5 mL) and triethylamine (40 mg, 0.039 mmol) was added. Acetyl chloride (20 mg, 0.026 mmol) was added, and the mixture was stirred at r.t. After 2 h the mixture was partitioned between water and DCM (50 mL each). The organic phase was washed with saturated sodium hydrogencarbonate solution (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by preparative HPLC to give the *title compound* (22 mg, 15%) as an off-white solid. δ_H ($CDCl_3$) rotamers observed, 50:50; 8.82-8.91 (m, 2H), 8.29 (s, 1H), 8.19 (t, 1H), 8.03 (d, 1H), 7.67 (d, 0.5H), 7.55-7.63 (m, 1.5H), 7.52 (m, 0.5H), 7.45 (t, 0.5H), 7.24-7.32 (m, 1H), 4.99 (quintet, 0.5H), 4.64 (s, 1H), 4.56 (s, 1H), 4.26 (quintet, 0.5H), 2.30 (s, 1H), 2.06 (s, 1H), 1.80-1.99 (m, 2H), 1.37-1.79 (m, 6H). LCMS (ES+) 346 $(M+H)^+$, RT 3.40 minutes.

EXAMPLE 52

N-[3-(Quinoxalin-6-yl)benzyl]-*N*-(tetrahydropyran-4-yl)acetamide

Intermediate 23 (70 mg, 0.22 mmol) was dissolved in DCM (5 mL) and triethylamine (66 mg, 0.66 mmol) was added. Acetyl chloride (34 mg, 0.44 mmol) was added, and the mixture was stirred at r.t. After 4 h the mixture was partitioned between water and DCM (50 mL each). The organic phase was washed with saturated sodium hydrogencarbonate solution (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by preparative HPLC to give the *title compound* (31 mg, 39%) as an off-white solid. δ_H (d_6 DMSO) rotamers observed, 50:50; 8.98 (d, 2H), 8.94 (m, 1H), 8.32 (d, 1H), 8.14-8.22 (m, 2H), 7.79 (d, 0.5H), 7.67-7.75 (m, 1.5H), 7.55 (t, 0.5H), 7.46 (t, 0.5H), 7.32 (d, 0.5H), 7.28 (d, 0.5H), 4.69 (s, 1H), 4.60 (s, 1H), 4.57 (tt, 0.5H), 4.02 (tt, 0.5H), 3.78-3.88 (m, 2H), 3.26-3.40 (m, 2H), 2.25 (s, 1.5H), 2.00 (s, 1.5H), 1.58-1.77 (m, 2H), 1.57 (d, 1H), 1.48 (d, 1H). LCMS (ES+) 362 $(M+H)^+$, RT 2.67 minutes.

EXAMPLE 53

N-(Pyridin-2-yl)-*N*-[3-(quinoxalin-6-yl)benzyl]-*N*-(tetrahydropyran-4-yl)amine

Intermediate 23 (50 mg, 0.16 mmol), 2-chloropyridine (27 mg, 0.24 mmol), sodium *tert*-butoxide (30 mg, 0.31 mmol) and [1,1'-bis(di-*tert*-butylphosphino)ferrocene]-palladium(II) dichloride (5 mg, 0.007 mmol) in toluene (3 mL) was heated to 120°C in a sealed tube, under microwave irradiation, for 1 h. More [1,1'-bis(di-*tert*-butylphosphino)-ferrocene]palladium(II) dichloride (5 mg, 0.007 mmol) was added, and the mixture heated to 140°C in a sealed tube, under microwave irradiation, for 3 h. The mixture was partitioned between water and EtOAc (50 mL each). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by preparative HPLC. The column fractions were partitioned between saturated sodium hydrogencarbonate solution and DCM (100 mL each). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give the *title compound* (11 mg, 17%) as an off-white solid. δ_H ($CDCl_3$) 8.87 (d, 1H), 8.84 (d, 1H), 8.26 (d, 1H), 8.21 (dd, 1H), 8.16 (d, 1H), 8.00 (dd, 1H), 7.58-7.68 (m, 2H), 7.47 (t, 1H), 7.39 (t, 1H), 7.32 (d, 1H), 6.59 (dd, 1H), 6.39 (d, 1H), 5.05 (tt, 1H), 4.70 (s, 2H), 4.04 (d, 2H), 3.53-3.68 (m, 2H), 1.72-1.95 (m, 4H). LCMS (ES+) 397 $(M+H)^+$, RT 3.93 minutes.

EXAMPLE 54

N-(1-Methylpiperidin-4-yl)-*N*-[3-(quinoxalin-6-yl)benzyl]acetamide

Intermediate 24 (35 mg, 0.11 mmol) was dissolved in DCM (5 mL) and triethylamine (32 mg, 0.32 mmol) was added. Acetyl chloride (16 mg, 0.21 mmol) was added, and the mixture was stirred at r.t. After 2 days the mixture was partitioned between water and DCM (30 mL each). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by preparative HPLC. The resulting residue was dissolved in DCM (30 mL) and MP-carbonate resin (1 g) was added. The mixture was stirred for 10 minutes and then filtered. The filtrate was concentrated *in vacuo* to give the *title compound* (10 mg, 24%) as an off-white solid. δ_H ($CDCl_3$) rotamers observed, approximately 70:30; 8.83-8.92 (m, 2H), 8.28 (d, 1H), 8.19 (t, 1H), 7.98-8.07 (m, 1H), 7.39-7.71 (m, 3H), 7.23-7.32 (m, 1H), 4.70 (s, 0.6H), ~4.66 (br, 0.7H),

4.64 (s, 1.4H), 3.70 (tt, 0.3H), 2.80-2.96 (m, 2H), 2.29 (s, 0.9H), 2.26 (s, 2.1H), 1.79-2.15 (m, 4H), 2.12 (s, 3H), 1.60-1.77 (m, 2H). LCMS (ES+) 375 $(M+H)^+$, RT 1.64 minutes.

EXAMPLE 55

N-[4-(Quinoxalin-6-yl)pyridin-2-ylmethyl]-*N*-(tetrahydropyran-4-yl)acetamide

4-Aminotetrahydropyran (28 mg, 0.28 mmol) was added to a solution of *Intermediate 10* (60 mg, 0.26 mmol) in DCM (2 mL). Acetic acid (2 drops) was added and the mixture was left to stand for 30 minutes. Sodium triacetoxyborohydride (191 mg, 0.9 mmol) was added and the mixture was stirred at r.t. for 2 h. The mixture was quenched with saturated ammonium chloride solution (0.1 mL) and washed with water (2 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in DCM (5 mL). Triethylamine (0.1 mL) was added, followed by acetyl chloride (0.1 mL). The mixture was stirred and left to stand. After 30 minutes the mixture was washed with water (2 mL) and concentrated *in vacuo*. The residue was purified by preparative HPLC to give the *title compound* (5.7 mg, 6%) as a cream solid. δ_H ($CDCl_3$) rotamers observed, approximately 60:40; 8.89-8.96 (m, 2H), 8.72 (d, 0.6H), 8.65 (d, 0.4H), 8.33-8.39 (m, 1H), 8.21-8.29 (m, 1H), 7.98-8.07 (m, 1H), 7.50-7.63 (m, 2H), 4.84-4.98 (m, 0.6H), 4.81 (s, 0.8H), 4.73 (s, 1.2H), 3.90-4.08 (m, 2H), 3.38-3.58 (m, 2.4H), 2.33 (s, 1.2H), 2.15 (s, 1.8H), 1.84-2.01 (m, 1H), 1.60-1.75 (m, 3H). LCMS (ES+) 363 $(M+H)^+$, RT 2.24 minutes.

EXAMPLE 56

6-[3-(Pyrrolidin-1-yl)phenyl]quinoxaline

A mixture of 3-(pyrrolidin-1-yl)bromobenzene (68 mg, 0.3 mmol), benzopyrazine-6-boronic acid hydrochloride (63 mg, 0.3 mmol), 2M aqueous sodium carbonate solution (0.45 mL, 0.9 mmol) and $Pd(PPh_3)_4$ (10 mg, 0.009 mmol) in DME (0.9 mL) was heated to 120°C in a sealed tube, under microwave irradiation, for 20 minutes. After cooling, the mixture was partitioned between water and EtOAc (2 mL each). The organic phase was concentrated *in vacuo* and the residue was purified by preparative HPLC to give the *title compound* (6.5 mg, 8%) as a yellow-brown solid. δ_H ($CDCl_3$) 8.87 (d, 1H), 8.83 (d, 1H), 8.34 (d, 1H), 8.16 (d, 1H), 8.09 (dd, 1H), 7.36 (t, 1H), 7.04 (d, 1H),

6.91 (t, 1H), 6.66 (d, 1H), 3.33-3.44 (m, 4H), 2.00-2.11 (m, 4H). LCMS (ES+) 276 $(M+H)^+$, RT 4.41 minutes.

EXAMPLE 57

1-[3-(Quinoxalin-6-yl)benzyl]pyrrolidin-2-one

Intermediate 25 (51 mg, 0.2 mmol), benzopyrazine-6-boronic acid hydrochloride (42 mg, 0.2 mmol), 2M aqueous sodium carbonate solution (0.3 mL, 0.6 mmol) and $Pd(PPh_3)_4$ (7 mg, 0.006 mmol) in DME (0.6 mL) were heated to 120°C in a sealed tube, under microwave irradiation, for 20 minutes. After cooling, the mixture was partitioned between water and EtOAc (2 mL each). The organic phase was concentrated *in vacuo* and the residue was purified by preparative HPLC to give the *title compound* (32 mg, 53%) as a colourless gum. δ_H ($CDCl_3$) 8.89 (d, 1H), 8.86 (d, 1H), 8.31 (d, 1H), 8.19 (d, 1H), 8.05 (dd, 1H), 7.69 (d, 1H), 7.63 (s, 1H), 7.50 (t, 1H), 7.34 (d, 1H), 4.57 (s, 2H), 3.35 (t, 2H), 2.49 (t, 2H), 2.04 (quintet, 2H). LCMS (ES+) 304 $(M+H)^+$, RT 2.82 minutes.

EXAMPLE 58

Cyclopentanecarboxylic acid {1-[3-(quinoxalin-6-yl)phenyl]cyclopropyl}amide

6-Quinoxalineboronic acid (348 mg, 2.0 mmol) was dissolved in DME/water (9:1, 10 mL), and 1-(3-bromophenyl)cyclopropylamine hydrochloride (500 mg, 2.0 mmol), cesium carbonate (1.95 g, 6.0 mmol) and $Pd(PPh_3)_4$ (116 mg, 0.1 mmol) were added. The mixture was heated to 120°C in a sealed tube, under microwave irradiation, for 20 minutes. After cooling, the mixture was partitioned between DCM and water (20 mL each), and the organic phase concentrated *in vacuo*. The residue was purified by reverse-phase column chromatography to give 1-[3-(quinoxalin-6-yl)phenyl]cyclopropylamine (100 mg, 20 %). LCMS (ES+) 262.3 $(M+H)^+$, RT 1.67 minutes. A sample of this material (100 mg, 0.4 mmol) was dissolved in DCM (5 mL). *N,N*-Diisopropylethylamine (0.15 mL, 0.8 mmol) was added, followed by cyclopentylcarbonyl chloride (0.3 mL, 2.2 mmol). The mixture was stirred at room temperature for 18 h and then concentrated *in vacuo*. The residue was partitioned between DCM and saturated sodium hydrogen-carbonate solution (5 mL of each). The organic phase was concentrated *in vacuo* and the

residue purified by preparative HPLC to give the *title compound* as a white solid (5 mg, 4%). δ_H ($CDCl_3$) 8.89 (d, 1H), 8.84 (d, 1H), 0.30 (s, 1H), 8.15 (d, 1H), 8.02 (dd, 1H), 7.58 (m, 2H), 7.44 (dd, 1H), 7.32 (dd, 1H), 6.13 (br s, 1H), 2.55 (m, 1H), 1.50-1.95 (m, 8H), 1.35 (m, 4H). LCMS (ES+) 358.3 $(M+H)^+$, RT 3.30 minutes.

EXAMPLE 59

trans-(±)-2-[3-(Quinoxalin-6-yl)phenyl]cyclopropanecarboxylic acid

DMAP (220 mg, 1.8 mmol) was added to a solution of 3-bromocinnamic acid (2.00 g, 8.8 mmol) and di-*tert*-butyl dicarbonate (2.31 g, 10.6 mmol) in THF (7 mL) at 0°C. The solution was allowed to warm to room temperature and then stirred for 3 days. The mixture was partitioned between EtOAc (30 mL) and 1M hydrochloric acid (10 mL). The organic phase was washed with saturated sodium hydrogencarbonate solution (20 mL) and concentrated *in vacuo*. The residue was dissolved in DCM (10 mL) and cooled to -78°C under nitrogen. A solution of trimethylsulfonium iodide (2.31 g, 10.5 mmol) in DMSO (10 mL) was added, followed by sodium hydride (422 mg, 11.4 mmol). The solution was warmed to 50°C and stirred for 18 h. The mixture was partitioned between EtOAc (30 mL) and water (30 mL), and the organic phase concentrated *in vacuo*. The residue was purified by column chromatography to give 2-(3-bromophenyl)cyclopropane-carboxylic acid *tert*-butyl ester as a yellow oil (2.04 g, 78% over 2 steps). A sample of this material (440 mg, 1.48 mmol) and 6-pinacolatoboranylquinoxaline (380 mg, 1.48 mmol) was dissolved in DME/water (9:1, 7 mL), and cesium carbonate (975 mg, 3.0 mmol) and $Pd(PPh_3)_4$ (80 mg, 0.07 mmol) were added. The mixture was heated to 120°C in a sealed tube, under microwave irradiation, for 20 minutes. After cooling, the mixture was passed through a silica plug and concentrated *in vacuo*. The residue was dissolved in DCM (3 mL) and TFA (2.5 mL) added. The mixture was stirred at room temperature for 4 h. The mixture was concentrated *in vacuo* and the residue partitioned between DCM (10 mL) and 2M sodium hydroxide solution (5 mL). The aqueous phase was neutralized to pH 7 with 2M hydrochloric acid, and extracted with EtOAc (10 mL). The organic phase was concentrated *in vacuo* to give the title compound as a brown solid (75% purity, 200 mg). A portion of this material was purified by preparative HPLC to yield the *title compound* (5 mg). δ_H (CD_3OD) 8.92 (d, 1H), 8.89 (d, 1H), 8.30 (s, 1H), 8.17 (s, 2H),

7.53 (dd, 1H), 7.50 (d, 1H), 7.48 (dd, 1H), 7.22 (d, 1H), 2.60 (m, 1H), 1.95 (m, 1H), 1.63 (m, 1H), 1.48 (m, 1H). LCMS (ES+) 291.3 $(M+H)^+$, RT 2.99 minutes.

EXAMPLE 60

trans-(±)-2-[3-(Quinoxalin-6-yl)phenyl]cyclopropanecarboxylic acid cyclopentylamide

Example 59 (140 mg, 0.48 mmol) was dissolved in thionyl chloride (3 mL). The mixture was heated to 70°C for 1 h and then concentrated *in vacuo*. A portion of the crude material (0.12 mmol) was dissolved in DCM (1 mL) and added to a stirred solution of cyclopentylamine (150 µL, 2.6 mmol) in DCM (2 mL). After stirring at room temperature for 2 h the mixture was partitioned between DCM (5 mL) and saturated sodium hydrogencarbonate solution (5 mL). The organic phase was concentrated *in vacuo* and purified by preparative HPLC to give the *title compound* as a white solid (8 mg, 19%). δ_H ($CDCl_3$) 8.89 (d, 1H), 8.85 (d, 1H), 8.27 (d, 1H), 8.19 (d, 1H), 8.03 (dd, 1H), 7.57 (dd, 1H), 7.39-7.49 (m, 2H), 7.17 (d, 1H), 5.68 (br d, 1H) 4.20-4.32 (m, 1H), 2.59 (m, 1H), 1.95-2.08 (m, 2H), 1.55-1.68 (m, 7H), 1.33-1.47 (m, 2H), 1.31 (m, 1H). LCMS (ES+) 358.3 $(M+H)^+$, RT 3.52 minutes.

EXAMPLE 61

trans-(±)-2-[3-(Quinoxalin-6-yl)phenyl]cyclopropanecarboxylic acid [(*R*)-3-hydroxy-pyrrolidin-1-yl]amide

Prepared in an analogous manner to *Example 60* from (*R*)-3-hydroxypyrrolidine (59 mg, 0.48 mmol) to give the *title compound* as a white solid (5 mg, 12%). δ_H ($CDCl_3$) 8.89 (d, 1H), 8.86 (d, 1H), 8.30 (d, 1H), 8.19 (d, 1H), 8.05 (dd, 1H), 7.57 (d, 1H), 7.39-7.50 (m, 2H), 7.20 (d, 1H), 4.55 (m, 1H), 3.55-3.89 (m, 4H), 2.60-2.72 (m, 2H), 2.50 (br, 1H), 1.90-2.12 (m, 2H), 1.70 (m, 1H), 1.38 (m, 1H). LCMS (ES+) 360.3 $(M+H)^+$, RT 2.60 minutes.

EXAMPLE 62

2,5-Dimethyl-5-[3-(quinoxalin-6-yl)phenyl]tetrahydrofuran-2-ol

6-Bromoquinoxaline (3.14 g, 15 mmol) was dissolved in DME/water (9:1, 500 mL), and 3-acetylphenylboronic acid (2.5 g, 15 mmol), cesium carbonate (9.75 g, 30 mmol) and $Pd(PPh_3)_4$ (870 mg, 0.75 mmol) were added. The mixture was heated to 110°C for 18 h. After cooling, the mixture was partitioned between EtOAc and water (100 mL each), and the organic phase concentrated *in vacuo*. The residue was triturated with diethyl ether (50 mL) to give 1-[3-(quinoxalin-6-yl)phenyl]ethanone (3.8 g, >95%). LCMS (ES+) 249.2 $(M+H)^+$, RT 3.04 minutes. A sample of this material (500 mg, 2 mmol) was dissolved in THF (4 mL), and cooled to 0°C. But-1-en-4-ylmagnesium bromide (0.5M in THF, 4 mL, 2 mmol) was added and the mixture allowed to warm to room temperature. After stirring for 2 h, water (2 mL) was added. The organic phase was passed though a silica plug and concentrated *in vacuo*. The residue was dissolved in DCM (3 mL). *N*-Bromosuccinimide (146 mg, 0.9 mmol) was added and the mixture stirred at room temperature for 18 h. The mixture was partitioned between DCM (5 mL) and saturated sodium hydrogencarbonate solution (5 mL). The organic phase was passed through a silica plug and the filtrate concentrated *in vacuo*. The residue was dissolved in MeOH (3 mL). Sodium methoxide (200 mg) was added and the mixture was stirred at 60°C for 3 days. The mixture was neutralized to pH 7.0 with 1M hydrochloric acid and then concentrated *in vacuo*. The residue was purified by preparative HPLC to isolate the *title compound* (5 mg, 2:1 mixture of *cis*:*trans* isomers). δ_H ($CDCl_3$) 8.89 (d, 1H), 8.86 (d, 1H), 8.32 (m, 1H), 8.20 (m, 1H), 8.08 (m, 1H), 7.84 (m, 1H), 7.62 (m, 1H), 7.50 (m, 2H), 2.10-2.58 (m, 4H), 2.11 (s, 3H), 1.56-1.72 (m, 4H). LCMS (ES+) 321.3 $(M+H)^+$, RT 2.93 minutes.

EXAMPLE 63

6-{3-[5-(Methoxymethyl)-2-methyltetrahydrofuran-2-yl]phenyl}quinoxaline

Isolated from *Example 62* as an additional preparative HPLC fraction (3 mg, 7:3 mixture of *trans*:*cis* isomers). δ_H ($CDCl_3$) 8.88 (d, 1H), 8.84 (d, 1H), 8.32 (m, 1H), 8.18 (d, 1H), 8.08 (m, 1H), 7.80-7.90 (m, 1H), 7.61 (m, 1H), 7.42-7.53 (m, 2H), 4.24-4.46 (m,

1H), 3.40-3.58 (m, 5H), 2.02-2.38 (m, 3H), 1.64-1.95 (m, 2H), 1.60 (d, 3H). LCMS (ES+) 335.3 $(M+H)^+$, RT 3.79 minutes.

EXAMPLE 64

6-[3-(Piperidin-1-ylsulfonyl)phenyl]quinoxaline

A mixture of *Intermediate 26* (100 mg, 0.329 mmol), benzopyrazine-6-boronic acid hydrochloride (69 mg, 0.329 mmol), 2M aqueous sodium carbonate solution (0.5 mL, 0.986 mmol) and $Pd(PPh_3)_4$ (11.4 mg, 0.009 mmol) in DME (1.0 mL) was heated to 120°C in a sealed tube, under microwave irradiation, for 20 minutes. After cooling, the mixture was partitioned between water and EtOAc (5 mL each), and the organic phase concentrated *in vacuo*. The residue was purified by flash silica column chromatography eluting with a gradient of 0-50% EtOAc in isohexane to give the *title compound* (88.9 mg, 76%) as an off-white solid. δ_H ($CDCl_3$) 8.90 (2H, d, *J* 7.49 Hz), 8.35 (1H, d, *J* 2.04 Hz), 8.24 (1H, d, *J* 8.74 Hz), 8.13 (1H, s), 8.06 (1H, dd, *J* 8.75, 2.09 Hz), 7.98 (1H, dd, *J* 7.79, 1.57 Hz), 7.83 (1H, d, *J* 7.87 Hz), 7.70 (1H, t, *J* 7.78 Hz), 3.10-3.04 (4H, m), 1.72-1.64 (4H, m), 1.49-1.41 (2H, m). LCMS (ES+) 354 $(M+H)^+$, RT 3.90 minutes (97.4%).

EXAMPLE 65

4-[3-(Quinoxalin-6-yl)phenylsulfonyl]morpholine

A mixture of *Intermediate 27* (106.7 mg, 0.35 mmol), benzopyrazine-6-boronic acid hydrochloride (81 mg, 0.385 mmol), 2M aqueous sodium carbonate solution (0.52 mL, 1.05 mmol) and $Pd(PPh_3)_4$ (12.1 mg, 0.009 mmol) in DME (1.0 mL) was heated to 120°C in a sealed tube, under microwave irradiation, for 20 minutes. After cooling, the mixture was partitioned between water and EtOAc (5 mL each), and the organic phase concentrated *in vacuo*. The residue was purified by preparative HPLC to give the *title compound* (71.5 mg, 57%) as an off-white solid. δ_H ($CDCl_3$) 8.91 (2H, dd, *J* 7.81, 1.83 Hz), 8.35 (1H, d, *J* 2.09 Hz), 8.25 (1H, d, *J* 8.74 Hz), 8.13 (1H, t, *J* 1.81 Hz), 8.06-7.99 (2H, m), 7.83 (1H, dt, *J* 7.85, 1.39 Hz), 7.73 (1H, t, *J* 7.77 Hz), 3.78 (4H, t, *J* 4.65 Hz), 3.09 (4H, t, *J* 4.59 Hz). LCMS (ES+) 356 $(M+H)^+$, RT 3.06 minutes.

EXAMPLE 66

6-[3-(Azepan-1-ylsulfonyl)phenyl]quinoxaline

Prepared from *Intermediate 28* by the procedure used for *Example 65*. This yielded a purple solid which was recrystallized from isopropanol to give the *title compound* (38.1 mg, 29%) as a grey solid. δ_H ($CDCl_3$) 8.92-8.86 (2H, m), 8.34 (1H, d, *J* 2.11 Hz), 8.26-8.16 (2H, m), 8.06 (1H, dd, *J* 8.69, 2.17 Hz), 7.94 (1H, d, *J* 7.77 Hz), 7.86 (1H, d, *J* 7.82 Hz), 7.67 (1H, t, *J* 7.77 Hz), 3.38-3.32 (4H, m), 1.81-1.75 (4H, m), 1.65-1.55 (4H, m). LCMS (ES+) 368 $(M+H)^+$, RT 3.79 minutes (98.3%).

EXAMPLE 67

6-[3-(4-Fluoropiperidin-1-ylsulfonyl)phenylquinoxaline

Prepared from *Intermediate 29* by the procedure used for *Example 64*. The residue was purified by flash silica column chromatography eluting with a gradient of 0-60% EtOAc in isohexane. The resultant solid was passed down a SCX Isolute to remove triphenylphosphine oxide to give the *title compound* (34 mg, 56%) as a pale yellow solid (81.4 mg, 50%). δ_H ($CDCl_3$) 8.92-8.88 (2H, m), 8.35 (1H, d, *J* 2.09 Hz), 8.24 (1H, d, *J* 8.73 Hz), 8.14 (1H, t, *J* 1.81 Hz), 8.06-7.97 (2H, m), 7.84 (1H, dt, *J* 7.86, 1.36 Hz), 7.71 (1H, t, *J* 7.78 Hz), 4.87-4.69 (1H, m), 3.50-3.42 (2H, m), 3.00-2.91 (2H, m), 2.04-1.87 (4H, m). LCMS (ES+) 372 $(M+H)^+$, RT 3.39 minutes (97.5%).

EXAMPLE 68

6-[3-(4,4-Difluoropiperidin-1-ylsulfonyl)phenyl]quinoxaline

Prepared from *Intermediate 30* by the procedure used for *Example 64*. The residue was purified by flash silica column chromatography eluting with a gradient of 0-60% EtOAc in isohexane to give the *title compound* (130 mg, 77%) as an off-white solid. δ_H ($CDCl_3$) 8.93-8.89 (2H, m), 8.35 (1H, d, *J* 2.09 Hz), 8.25 (1H, d, *J* 8.73 Hz), 8.14 (1H, t, *J* 1.82 Hz), 8.01 (2H, dt, *J* 7.77, 1.41 Hz), 7.84 (1H, dt, *J* 7.87, 1.39 Hz), 7.72 (1H, t, *J* 7.79 Hz), 3.29 (4H, t, *J* 5.65 Hz), 2.18-2.05 (4H, m). LCMS (ES+) 390 $(M+H)^+$, RT 3.20 minutes (99.8%).

EXAMPLE 69

1-[4-(Quinoxalin-6-yl)pyridin-2-yl]piperidine-4-carboxamide

A mixture of *Intermediate 21* (60 mg, 0.248 mmol) and piperidine-4-carboxamide (381 mg, 2.97 mmol) in DMSO (1.5 mL) was stirred at 80°C for approximately 48 h and cooled to 25°C. Purification of the crude material by HPLC gave the *title compound* (42 mg, 51%). δ_H ($CDCl_3$) 8.89 (2H, dd, *J* 7.35, 1.83 Hz), 8.36-8.30 (2H, m), 8.21 (1H, d, *J* 8.73 Hz), 8.03 (1H, dd, *J* 8.73, 2.05 Hz), 7.00-6.95 (2H, m), 5.49 (1H, s), 5.35 (1H, s), 4.48 (2H, d, *J* 13.25 Hz), 3.05-2.96 (2H, m), 2.46 (1H, tt, *J* 11.61, 3.84 Hz), 2.03 (2H, d, *J* 12.81 Hz), 1.83 (2H, qd, *J* 12.34, 4.00 Hz). LCMS (ES+) 334 $(M+H)^+$, RT 2.16 minutes (96.8%).

EXAMPLE 70

6-[2-(Piperidin-1-yl)pyridin-4-yl]quinoxaline

A mixture of *Intermediate 21* (75 mg, 0.30 mmol) and piperidine (184 μL, 1.86 mmol) in DMSO (1.5 mL) was stirred at 80°C for approximately 48 h and cooled to 25°C. Purification of the crude material by HPLC gave the *title compound* (44.6 mg, 44%) as a yellow gum. δ_H ($CDCl_3$) 8.90-8.87 (2H, m), 8.37-8.29 (2H, m), 8.20 (1H, d, *J* 8.73 Hz), 8.04 (1H, dd, *J* 8.74, 2.05 Hz), 6.97-6.89 (2H, m), 3.60-3.68 (4H, m), 1.63-1.73 (6H, m). LCMS (ES+) 291 $(M+H)^+$, RT 3.39 minutes (97%).

EXAMPLE 71

N-Cyclopropyl-*N*-{[4-(quinoxalin-6-yl)pyridin-2-yl]methyl}acetamide

A solution of *Intermediate 31* (39.2 mg, 0.142 mmol) in DCM (2 mL) was treated with Et_3N (24 μL, 0.17 mmol) and acetyl chloride (11 μL, 0.16 mmol) and stirred for 2 h at 25°C. The mixture was diluted with DCM, washed with H_2O, dried ($MgSO_4$) and evaporated. Purification by preparative HPLC gave the *title compound* (30 mg, 75%) as an off-white solid. δ_H ($CDCl_3$) 8.90 (2H, dd, *J* 6.97, 1.79 Hz), 8.66 (1H, d, *J* 5.14 Hz), 8.36 (1H, d, *J* 2.05 Hz), 8.23 (1H, d, *J* 8.73 Hz), 8.03 (1H, dd, *J* 8.73, 2.08 Hz), 7.57-7.50 (2H, m), 4.83 (2H, s), 2.89-2.85 (1H, m), 2.34 (3H, s), 0.92-0.85 (4H, m). LCMS (ES+) 319 $(M+H)^+$, RT 2.17 minutes (99.4%).

EXAMPLE 72

N-Cyclopentyl-*N*-{[4-(quinoxalin-6-yl)pyridin-2-yl]methyl}acetamide

Prepared from *Intermediate 32* by the procedure used for *Example 71*. Preparative HPLC purification yielded a pale brown gum, which was freeze-dried to give the *title compound* (38 mg, 69%) as a pale brown solid. δ_H ($CDCl_3$) (mixture of rotamers at r.t.) 8.94-8.88 (2H, m), 8.72 (0.40H, d, *J* 5.05 Hz), 8.65 (0.6H, d, *J* 5.18 Hz), 8.35 (1H, d, *J* 1.99 Hz), 8.24 (1H, dd, *J* 13.89, 8.70 Hz), 8.02 (1H, t, *J* 8.55 Hz), 7.60-7.54 (1H, m), 7.50 (1H, d, *J* 5.27 Hz), 5.10-4.97 (0.4H, m), 4.74 (1H, s), 4.67 (1H, s), 4.33-4.22 (0.6H, m) 2.31 (1.8H, s), 2.08 (1.2H, s), 1.97-1.80 (2H, m), 1.77-1.39 (6H, m). LCMS (ES+) 347 $(M+H)^+$, RT 2.54 minutes (98.2%).

EXAMPLE 73

N-Cyclopentyl-*N*-{[4-(quinoxalin-6-yl)pyridin-2-yl]methyl}isobutyramide

Prepared from *Intermediate 32* by the procedure used for *Example 72*, using isobutyryl chloride instead of acetyl chloride. Purification by preparative HPLC gave the *title compound* as a pale brown glass (47 mg, 82%). δ_H ($CDCl_3$) (mixture of rotamers at r.t.) 8.90 (2H, dd, *J* 8.48, 6.55 Hz), 8.71 (0.4H, d, *J* 5.10 Hz), 8.64 (0.6H, d, *J* 5.11 Hz), 8.33 (1H, t, *J* 2.45 Hz), 8.22 (1H, dd, *J* 13.50, 8.74 Hz), 8.01-7.96 (1H, m), 7.59-7.45 (2H, m), 5.08-4.97 (0.4H, m), 4.72 (1.2H, s), 4.68 (0.8H, m), 4.43 (0.6H, m,), 3.10-3.02 (0.6H, m), 2.61-2.54 (0.4H, m), 1.95-1.81 (2H, m), 1.78-1.52 (5H, m), 1.49-1.38 (1H, m), 1.24 (1.8H, d, *J* 6.71 Hz), 1.10 (1.2H, d, *J* 6.62 Hz). LCMS (ES+) 375 $(M+H)^+$, RT 2.95 minutes (99.5%).

EXAMPLE 74

N-Cyclopentyl-*N*-{[4-(quinoxalin-6-yl)pyridin-2-yl]methyl}methanesulfonamide

A solution of *Intermediate 32* (53.6 mg, 0.176 mmol) in DCM (2 mL) was treated with Et_3N (29 μL, 0.21 mmol) and methylsulfonyl chloride (15 μL, 0.19 mmol) and stirred for 2 h at 25°C. The mixture was diluted with DCM, washed with H_2O, dried ($MgSO_4$) and evaporated. Purification by preparative HPLC gave the *title compound* (17

mg, 30%) as a pale brown solid. δ_H ($CDCl_3$) 8.91 (2H, dd, *J* 7.11, 1.80 Hz), 8.64 (1H, d, *J* 5.17 Hz), 8.40 (1H, d, *J* 2.04 Hz), 8.24 (1H, d, *J* 8.73 Hz), 8.07 (1H, dd, *J* 8.74, 2.08 Hz), 7.96 (1H, s), 7.57 (1H, dd, *J* 5.17, 1.75 Hz), 4.57 (2H, s), 4.42-4.32 (1H, m), 2.99 (3H, s), 1.93-1.85 (2H, m), 1.80-1.61 (2H, m), 1.60-1.48 (4H, m). LCMS (ES+) 383 $(M+H)^+$, RT 2.78 minutes (98.0%).

EXAMPLE 75

N-[3-(Pyrrolidine-1-carbonyl)-5-(quinoxalin-6-yl)phenyl]acetamide

A solution of *Intermediate 35* (80 mg, 0.25 mmol) in DCM (3 mL) was treated with DIPEA (0.11 mL, 0.63 mmol) followed by acetyl chloride (0.027 mL, 0.38 mmol) and stirred for 5 h. The mixture was diluted with DCM (10 mL) and washed with water (x 3). The organic layer was separated, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography (SiO_2, 0-50% EtOAc in petroleum ether) to give the *title compound* (66 mg, 73%) as a white solid. δ_H ($CDCl_3$) 8.87-8.83 (2H, m), 8.26 (1H, d, *J* 2.01 Hz), 8.12 (2H, t, *J* 12.86 Hz), 8.00 (2H, dd, *J* 8.46, 2.10 Hz), 7.74 (1H, s), 7.62 (1H, s), 3.68 (2H, t, *J* 6.90 Hz), 3.54 (2H, t, *J* 6.56 Hz), 2.23 (3H, s), 2.04-1.87 (4H, m). LCMS (ES+) 361 $(M+H)^+$, RT 2.44 minutes (98.2%).

EXAMPLE 76

Ethyl 2-{(phenyl)[3-(quinoxalin-6-yl)phenyl]methoxy}acetate

Intermediate 36 (117 mg, 0.344 mmol), DMF (2 mL), NaH (60% in oil) (14 mg, 0.344 mmol) and ethyl bromoacetate (38 µL, 0.344 mmol) were combined under nitrogen at room temperature and stirred for 16 h. The mixture was diluted with DMSO (2 mL) and purified by preparative HPLC to give the *title compound* as a clear gum (56.3 mg). δ_H (DMSO-d_6) 9.01 (2H, dd, *J* 13.54, 1.89 Hz), 8.37 (1H, s), 8.23 (2H, s), 7.97 (1H, s), 7.85 (1H, d, *J* 7.59 Hz), 7.60-7.45 (4H, m), 7.41 (2H, t, *J* 7.39 Hz), 7.32 (1H, t, *J* 7.15 Hz), 5.78 (1H, s), 4.21-4.13 (4H, m), 1.22 (3H, t, *J* 7.04 Hz). LCMS (ES+) 399 $(M+H)^+$, RT 4.06 minutes (96.0%).

EXAMPLE 77

6-{3-[(Ethoxy)(phenyl)methyl]phenyl}quinoxaline

Prepared by the procedure used for *Example 76*, using *Intermediate 36* (117 mg, 0.344 mmol), DMF (2 mL), NaH (60% in oil) (14 mg, 0.344 mmol) and ethyl iodide (27 μL, 0.344 mmol). This method gave the *title compound* as a brown gum (71.9 mg). δ_H (DMSO-d_6) 9.01 (2H, dd, *J* 13.66, 1.83 Hz), 8.35 (1H, s), 8.22 (2H, s), 7.93 (1H, s), 7.81 (1H, d, *J* 7.56 Hz), 7.59-7.47 (4H, m), 7.38 (2H, t, *J* 7.52 Hz), 7.28 (1H, t, *J* 7.32 Hz), 5.63 (1H, s), 3.54 (2H, q, *J* 7.02 Hz), 1.25 (3H, t, *J* 6.98 Hz). LCMS (ES+) 341 $(M+H)^+$, RT 4.33 minutes (98.3%).

EXAMPLE 78

2-{(Phenyl)[3-(quinoxalin-6-yl)phenyl]methoxy}acetamide

Prepared by the procedure used for *Example 76*, using *Intermediate 36* (130 mg, 0.416 mmol), DMF (2 mL), NaH (60% in oil) (16.6 mg, 0.416 mmol) and 2-bromo-acetamide (57.5 mg, 0.416 mmol). This procedure gave the *title compound* as a light brown solid (20.3 mg). δ_H (DMSO-d_6) 9.01 (2H, dd, *J* 14.03, 1.83 Hz), 8.40 (1H, d, *J* 1.82 Hz), 8.28-8.22 (2H, m), 8.05 (1H, s), 7.85-7.82 (1H, m), 7.60-7.53 (4H, m), 7.43-7.27 (5H, m), 5.71 (1H, s), 3.89 (2H, s). LCMS (ES+) 370 $(M+H)^+$, RT 3.11 minutes (92.7%).

EXAMPLE 79

[3-(Quinoxalin-6-yl)phenyl]methanamine, formic acid salt

6-Bromoquinoxaline (100 mg, 0.48 mmol), 3-(aminomethyl)phenylboronic acid hydrochloride (89 mg, 0.48 mmol), potassium phosphate (100 mg, 0.48 mmol), water (2 mL), DME (6 mL) and $Pd(PPh_3)_4$ (55 mg, 0.048 mmol) were combined in a sealed tube and heated under microwave irradiation to 140°C for 1 h. After cooling, the mixture was filtered through Celite. The filtrate was then concentrated to dryness and purified by preparative HPLC to give the *title compound* (17.7 mg, 16%) as a tan solid. δ_H (DMSO-d_6) 9.00 (1H, d, *J* 1.86 Hz), 8.96 (1H, d, *J* 1.86 Hz), 8.39 (1H, d, *J* 1.96 Hz), 8.34 (1H, s,

HCOOH), 8.24 (1H, dd, *J* 8.78, 2.03 Hz), 8.22-8.18 (1H, m), 7.97 (1H, t, *J* 1.69 Hz), 7.82 (1H, dt, *J* 7.62, 1.47 Hz), 7.53 (1H, t, *J* 7.60 Hz), 7.47 (1H, d, *J* 7.63 Hz), 3.97 (2H, s), 2 NH not visible. LCMS (ES+) 236 $(M+H)^+$, RT 2.09 minutes (*Method 1*).

EXAMPLE 80

N-[3-(Quinoxalin-6-yl)benzyl]acetamide

Prepared from 6-bromoquinoxaline (100 mg, 0.48 mmol), 3-(acetamidomethyl)-phenylboronic acid (92 mg, 0.48 mmol), potassium phosphate (100 mg, 0.48 mmol), water (2 mL), DME (6 mL) and $Pd(PPh_3)_4$ (55 mg, 0.048 mmol) by the method of *Example 79* to give the *title compound* (63.4 mg, 48%) as an off-white solid. δ_H ($CDCl_3$) 8.88 (1H, d, *J* 1.86 Hz), 8.85 (1H, d, *J* 1.88 Hz), 8.30 (1H, d, *J* 2.06 Hz), 8.19 (1H, d, *J* 8.72 Hz), 8.04 (1H, dd, *J* 8.73, 2.10 Hz), 7.71-7.65 (2H, m), 7.50 (1H, t, *J* 7.80 Hz), 7.37 (1H, d, *J* 7.61 Hz), 5.82 (1H, s), 4.56 (2H, d, *J* 5.81 Hz), 2.07 (3H, s). LCMS (ES+) 278 $(M+H)^+$, RT 2.52 minutes (*Method 2*).

EXAMPLE 81

N-Methoxy-*N*-methyl-3-(quinoxalin-6-yl)benzamide

Prepared from 6-bromoquinoxaline (100 mg, 0.48 mmol), 3-(*N*-methoxy-*N*-methylcarbamoyl)phenylboronic acid (100 mg, 0.48 mmol), potassium phosphate (100 mg, 0.48 mmol), water (2 mL), DME (6 mL) and $Pd(PPh_3)_4$ (55 mg, 0.048 mmol) by the method of *Example 79* to give the *title compound* (30 mg, 21%) as an off-white gum. δ_H (DMSO-d_6) 9.01 (2H, d, *J* 12.66 Hz), 8.41 (1H, s), 8.25 (2H, s), 8.12-8.02 (2H, m), 7.74-7.64 (2H, m), 3.67 (3H, s), 3.36 (3H, s). LCMS (ES+) 294 $(M+H)^+$, RT 2.80 minutes (*Method 2*).

EXAMPLE 82

6-(2-Methoxypyridin-4-yl)quinoxaline

Prepared from 6-bromoquinoxaline (100 mg, 0.48 mmol), 2-methoxypyridine-4-boronic acid (65 mg, 0.48 mmol), potassium phosphate (100 mg, 0.48 mmol), water (2 mL), DME (6 mL) and $Pd(PPh_3)_4$ (55 mg, 0.048 mmol) by the method of *Example 79* to

give the *title compound* (61.8 mg, 54%) as a white solid. δ_H ($CDCl_3$) 8.91 (1H, d, *J* 1.84 Hz), 8.89 (1H, d, *J* 1.85 Hz), 8.37 (1H, d, *J* 2.07 Hz), 8.31 (1H, dd, *J* 5.36, 0.72 Hz), 8.22 (1H, d, *J* 8.75 Hz), 8.04 (1H, dd, *J* 8.74, 2.07 Hz), 7.26 (1H, masked by $CHCl_3$), 7.11 (1H, dd, *J* 1.60, 0.73 Hz), 4.03 (3H, s). LCMS (ES+) 238 $(M+H)^+$, RT 2.7 minutes (*Method 1*).

EXAMPLE 83

N-Cyclopropyl-3-(quinoxalin-6-yl)benzamide

Prepared from 6-bromoquinoxaline (100 mg, 0.48 mmol), 3-(cyclopropylamino-carbonyl)phenylboronic acid (100 mg, 0.48 mmol), potassium phosphate (100 mg, 0.48 mmol), water (2 mL), DME (6 mL) and $Pd(PPh_3)_4$ (55 mg, 0.048 mmol) by the method of *Example 79* to give the *title compound* (62.9 mg, 45%) as a white solid. δ_H (DMSO-d_6) 9.04 (1H, d, *J* 1.82 Hz), 9.01 (1H, d, *J* 1.82 Hz), 8.67 (1H, d, *J* 4.08 Hz), 8.51 (1H, d, *J* 2.01 Hz), 8.36-8.30 (2H, m), 8.26 (1H, d, *J* 8.75 Hz), 8.09 (1H, d, *J* 7.81 Hz), 7.95 (1H, d, *J* 7.78 Hz), 7.70-7.63 (1H, m), 2.97-2.88 (1H, m), 0.81-0.70 (2H, m), 0.70-0.62 (2H, m). LCMS (ES+) 290 $(M+H)^+$, RT 14.4 minutes (*Method 7*).

EXAMPLE 84

N-[3-(Pyrido[3,4-*b*]pyrazin-7-yl)benzyl]acetamide

Prepared from 7-chloropyrido[3,4-*b*]pyrazine (100 mg, 0.60 mmol), 3-(acetamido-methyl)phenylboronic acid (115 mg, 0.60 mmol), potassium phosphate (125 mg, 0.60 mmol), water (2 mL), DME (6 mL) and $Pd(PPh_3)_4$ (68 mg, 0.06 mmol) by the method of *Example 79* to give the *title compound* (31.6 mg, 19%) as an off-white solid. δ_H (DMSO-d_6) 9.64 (1H, d, *J* 0.82 Hz), 9.23 (1H, d, *J* 1.80 Hz), 9.11 (1H, d, *J* 1.80 Hz), 8.58 (1H, d, *J* 0.86 Hz), 8.48 (1H, t, *J* 5.87 Hz), 8.27 (1H, t, *J* 1.69 Hz), 8.22 (1H, dt, *J* 7.80, 1.37 Hz), 7.55 (1H, t, *J* 7.67 Hz), 7.42 (1H, dt, *J* 7.56, 1.27 Hz), 4.42 (2H, d, *J* 5.95 Hz), 1.94 (3H, s). LCMS (ES+) 279 $(M+H)^+$, RT 3.21 minutes (*Method 2*).

EXAMPLE 85

4-(Quinoxalin-6-yl)pyridin-2-amine

Quinoxaline-6-boronic acid hydrochloride (100 mg, 0.48 mmol), 4-bromo-pyridine-2-amine (83 mg, 0.48 mmol), potassium phosphate (100 mg, 0.48 mmol), water (2 mL), DME (6 mL) and $Pd(PPh_3)_4$ (55 mg, 0.048 mmol) were combined in a sealed tube and heated under microwave irradiation to 140°C for 1 h. After cooling, the mixture was filtered through Celite. The filtrate was then concentrated to dryness and purified by preparative HPLC to give the *title compound* (18.5 mg, 17%) as a yellow solid. δ_H (DMSO-d_6) 8.97 (1H, d, *J* 1.85 Hz), 8.92 (1H, d, *J* 1.86 Hz), 8.54 (1H, d, *J* 2.58 Hz), 8.27 (1H, d, *J* 2.03 Hz), 8.20 (1H, dd, *J* 8.86, 2.12 Hz), 8.14 (1H, d, *J* 8.75 Hz), 8.00 (1H, dd, *J* 8.65, 2.64 Hz), 6.63 (1H, d, *J* 8.65 Hz), 6.31 (2H, s). LCMS (ES+) 223 $(M+H)^+$, RT 12.31 minutes (*Method 7*).

EXAMPLE 86

4-(Quinoxalin-6-yl)pyridin-2-ol

Prepared from quinoxaline-6-boronic acid hydrochloride (100 mg, 0.48 mmol), 4-bromo-2-hydroxypyridine (84 mg, 0.48 mmol), potassium phosphate (100 mg, 0.48 mmol), water (2 mL), DME (6 mL) and $Pd(PPh_3)_4$ (55 mg, 0.048 mmol) by the method of *Example 85* to give the *title compound* (14.1 mg, 13%) as a white solid. δ_H (DMSO-d_6) 9.06 (1H, d, *J* 1.85 Hz), 9.04 (1H, d, *J* 1.84 Hz), 8.44 (1H, s), 8.23 (2H, s), 7.57 (1H, d, *J* 6.82 Hz), 6.86 (1H, d, *J* 1.81 Hz), 6.76 (1H, dd, *J* 6.82, 1.94 Hz), NH not visible. LCMS (ES+) 224 $(M+H)^+$, RT 11.15 minutes (*Method 4*).

EXAMPLE 87

4-(Quinoxalin-6-yl)picolinic acid

Prepared from quinoxaline-6-boronic acid hydrochloride (100 mg, 0.48 mmol), 4-iodopicolinic acid (118 mg, 0.48 mmol), potassium phosphate (100 mg, 0.48 mmol), water (2 mL), DME (6 mL) and $Pd(PPh_3)_4$ (55 mg, 0.048 mmol) by the method of *Example 85* to give the *title compound* (4.1 mg, 3%) as an off-white solid. δ_H (DMSO-d_6) 9.07 (1H, d, *J* 1.83 Hz), 9.04 (1H, d, *J* 1.82 Hz), 8.70 (1H, d, *J* 5.35 Hz), 8.52 (1H, d, *J*

1.97 Hz), 8.38 (1H, s), 8.33 (1H, dd, *J* 8.83, 2.05 Hz), 8.28 (1H, d, *J* 8.74 Hz), 7.94 (1H, d, *J* 5.09 Hz), OH not visible. LCMS (ES+) 252 $(M+H)^+$, RT 9.95 minutes (*Method 7*).

EXAMPLE 88

Methyl 3-(quinoxalin-6-yl)benzoate

Prepared from quinoxaline-6-boronic acid hydrochloride (681 mg, 3.25 mmol), methyl 3-bromobenzoate (698 mg, 3.25 mmol), potassium phosphate (500 mg, 3.25 mmol), water (3 mL), DME (12 mL) and $Pd(PPh_3)_4$ (366 mg, 0.32 mmol) by the method of *Example 85* to give the *title compound* (354 mg, 41%) as an off-white solid. δ_H ($CDCl_3$) 8.90 (1H, d, *J* 1.83 Hz), 8.87 (1H, d, *J* 1.85 Hz), 8.46 (1H, t, *J* 1.79 Hz), 8.37 (1H, d, *J* 2.06 Hz), 8.22 (1H, d, *J* 8.73 Hz), 8.14-8.08 (2H, m), 7.97-7.94 (1H, m), 7.61 (1H, t, *J* 7.76 Hz), 3.98 (3H, s). LCMS (ES+) 265 $(M+H)^+$, RT 15.25 minutes (*Method 4*).

EXAMPLE 89

N-Phenyl-3-(quinoxalin-6-yl)aniline

Prepared from quinoxaline-6-boronic acid hydrochloride (100 mg, 0.48 mmol), *N*-(3-bromophenyl)aniline (118 mg, 0.48 mmol), potassium phosphate (100 mg, 0.48 mmol), water (2 mL), DME (6 mL) and $Pd(PPh_3)_4$ (55 mg, 0.048 mmol) by the method of *Example 85* to give the *title compound* (60.3 mg, 42%) as a yellow solid. δ_H ($CDCl_3$) 8.87 (1H, d, *J* 1.86 Hz), 8.84 (1H, d, *J* 1.87 Hz), 8.29 (1H, d, *J* 2.04 Hz), 8.17 (1H, d, *J* 8.73 Hz), 8.03 (1H, dd, *J* 8.74, 2.08 Hz), 7.45 (1H, t, *J* 2.00 Hz), 7.41 (1H, t, *J* 7.83 Hz), 7.37-7.26 (3H, m), 7.17-7.10 (3H, m), 7.02-6.96 (1H, m), 5.85 (1H, s). LCMS (ES+) 298 $(M+H)^+$, RT 20.49 minutes (*Method 7*).

EXAMPLE 90

2-[3-(Quinoxalin-6-yl)phenyl]propan-2-ol

To a solution of *Example 88* (340 mg, 1.29 mmol) in THF (10 mL) was added dropwise MeMgCl (3M in THF; 1.3 mL, 3.9 mmol) under nitrogen at room temperature. The reaction mixture was stirred for 18 h, quenched with saturated aqueous ammonium

chloride solution and extracted with dichloromethane. The combined organic layer was concentrated to dryness and purified by chromatography (SiO_2, 20-100% EtOAc in petroleum ether) to give a yellow gum (166 mg). Half of this material was then further purified by preparative HPLC to give the *title compound* (46.9 mg, 28%) as an off-white solid. δ_H ($CDCl_3$) 8.88 (1H, d, *J* 1.85 Hz), 8.85 (1H, d, *J* 1.84 Hz), 8.34 (1H, d, *J* 2.03 Hz), 8.19 (1H, d, *J* 8.74 Hz), 8.08 (1H, dd, *J* 8.75, 2.06 Hz), 7.92 (1H, t, *J* 1.87 Hz), 7.65 (1H, dt, *J* 7.53, 1.50 Hz), 7.58 (1H, dt, *J* 7.87, 1.50 Hz), 7.50 (1H, t, *J* 7.65 Hz), 1.82 (1H, s), 1.68 (6H, s). LCMS (ES+) 265 $(M+H)^+$, RT 2.64 minutes (*Method 1*).

EXAMPLE 91

1-Phenyl-1-[3-(quinoxalin-6-yl)phenyl]ethanol

Prepared from *Intermediate 37* (390 mg, 1.26 mmol), THF (10 mL) and MeMgCl (3M in THF; 1 mL, 3.00 mmol) by the method of *Example 90* to give the *title compound* (132.4 mg, 32%) as a yellow gum. δ_H (DMSO-d_6) 8.99-8.98 (1H, m), 9.00-8.92 (1H, m), 8.31 (1H, s), 8.23-8.15 (2H, m), 7.97 (1H, d, *J* 2.74 Hz), 7.73 (1H, d, *J* 7.45 Hz), 7.58-7.46 (4H, m), 7.38-7.30 (2H, m), 7.23 (1H, t, *J* 7.27 Hz), 5.68 (1H, s), 1.98 (3H, s). LCMS (ES+) 327 $(M+H)^+$, RT 3.17 minutes (*Method 1*).

EXAMPLE 92

Cyclopropyl[3-(quinoxalin-6-yl)phenyl]methanol

Prepared from *Intermediate 1* (620 mg, 2.65 mmol), THF (20 mL) and cyclopropylmagnesium bromide (0.5M in THF; 10 mL, 5.00 mmol) by the method of *Example 90* to give the *title compound* (32.8 mg, 4%) as an off-white solid. δ_H (DMSO-d_6) 9.03 (1H, d, *J* 1.83 Hz), 8.99 (1H, d, *J* 1.84 Hz), 8.38 (1H, s), 8.29-8.21 (2H, m), 7.92 (1H, s), 7.80 (1H, dt, *J* 6.52, 2.13 Hz), 7.58-7.50 (2H, m), 5.32 (1H, d, *J* 4.49 Hz), 4.14 (1H, dd, *J* 7.42, 3.79 Hz), 1.22-1.12 (1H, m), 0.56-0.41 (4H, m). LCMS (ES+) 277 $(M+H)^+$, RT 14.0 minutes (*Method 4*).

EXAMPLE 93

Phenyl[3-(pyrido[3,4-*b*]pyrazin-7-yl)phenyl]methanol

Prepared from *Intermediate 38* (390 mg, 1.66 mmol), THF (10 mL), PhMgCl (2M in THF; 1 mL, 2.00 mmol) by the method of *Example 90* to give the *title compound* (22.8 mg, 4%) as a light brown solid. δ_H ($CDCl_3$) 9.62 (1H, s), 9.01 (1H, d, *J* 1.76 Hz), 8.91 (1H, d, *J* 1.76 Hz), 8.33 (1H, s), 8.27 (1H, s), 8.12-8.07 (1H, m), 7.55-7.48 (2H, m), 7.46 (2H, d, *J* 7.65 Hz), 7.40-7.32 (2H, m), 7.29 (1H, d, *J* 7.41 Hz), 5.99 (1H, s), 2.35 (1H, s). LCMS (ES+) 314 $(M+H)^+$, RT 3.19 minutes (*Method 2*).

EXAMPLE 94

6-[3-(2-Ethoxyprop-2-yl)phenyl]quinoxaline

Example 90 (80 mg, 0.30 mmol), DMF (1 mL), NaH (12 mg, 0.30 mmol; 60% in mineral oil) and ethyl iodide (24 μL, 0.30 mmol) were combined under a nitrogen atmosphere at room temperature. The reaction mixture was stirred for 18 h then diluted with DMSO and purified by preparative HPLC to give the *title compound* (6.9 mg, 8%) as a light brown gum. δ_H ($CDCl_3$) 8.88 (1H, d, *J* 1.85 Hz), 8.85 (1H, d, *J* 1.85 Hz), 8.33 (1H, d, *J* 2.04 Hz), 8.19 (1H, d, *J* 8.74 Hz), 8.08 (1H, dd, *J* 8.75, 2.06 Hz), 7.83 (1H, s), 7.67-7.63 (1H, m), 7.51-7.48 (2H, m), 3.31 (2H, q, *J* 6.99 Hz), 1.62 (6H, s), 1.21 (3H, t, *J* 6.99 Hz). LCMS (ES+) 294 $(M+H)^+$, RT 2.80 minutes (*Method 2*).

EXAMPLE 95

Phenyl[3-(quinoxalin-6-yl)phenyl]methanone *O*-ethyl oxime

Prepared from *Example 125* (80 mg, 0.25 mmol), ethyl iodide (20 μL, 0.25 mmol), NaH (10 mg, 0.25 mmol; 60% in mineral oil) and DMF (2 mL) by the method of *Example 94* to give the *title compound* (43.5 mg, 49%) as a tan solid. δ_H (DMSO-d_6) 9.02 (1H, d, *J* 2.26 Hz), 8.99 (1H, d, *J* 8.65 Hz), 8.40-8.23 (1H, m), 8.26-8.14 (2H, m), 8.01 (1H, dd, *J* 17.54, 7.88 Hz), 7.85 (1H, d, *J* 11.97 Hz), 7.66 (1H, dt, *J* 34.57, 7.83 Hz), 7.58-7.40 (6H, m), 4.24 (2H, q, *J* 7.14 Hz), 1.29 (3H, t, *J* 7.12 Hz). LCMS (ES+) 354 $(M+H)^+$, RT 21.4 minutes (*Method 4*).

EXAMPLE 96

Phenyl[3-(quinoxalin-6-yl)phenyl]methanone *O*-(pyridin-3-ylmethyl) oxime

Prepared from *Example 125* (80 mg, 0.25 mmol), 3-picolyl chloride hydrochloride (41 mg, 0.25 mmol), NaH (10 mg, 0.25 mmol; 60% in mineral oil) and DMF (2 mL) by the method of *Example 94* to give the *title compound* (57.2 mg, 55%) as a tan solid. δ_H (DMSO-d_6) 9.07-8.99 (1H, m), 9.00 (1H, d, *J* 1.96 Hz), 8.65 (1H, s), 8.56 (1H, d, *J* 4.78 Hz), 8.39 (1H, s), 8.25-8.13 (2H, m), 8.02 (1H, dd, *J* 15.88, 7.83 Hz), 7.90-7.82 (2H, m), 7.66 (1H, dt, *J* 35.41, 7.80 Hz), 7.58-7.40 (7H, m), 5.31 (2H, d, *J* 3.55 Hz). LCMS (ES+) 417 $(M+H)^+$, RT 3.18 minutes (*Method 2*).

EXAMPLE 97

6-{3-[Cyclopropyl(ethoxy)methyl]phenyl}quinoxaline

Prepared from *Example 92* (90 mg, 0.33 mmol), ethyl iodide (26 μL, 0.33 mmol), NaH (13 mg, 0.33 mmol; 60% in mineral oil) and DMF (2 mL) by the method of *Example 94* to give the *title compound* (31 mg, 31%) as a tan gum. δ_H ($CDCl_3$) 8.88 (1H, d, *J* 1.87 Hz), 8.85 (1H, d, *J* 1.88 Hz), 8.34 (1H, d, *J* 2.06 Hz), 8.19 (1H, d, *J* 8.73 Hz), 8.08 (1H, dd, *J* 8.73, 2.09 Hz), 7.74 (1H, t, *J* 1.79 Hz), 7.68 (1H, dt, *J* 7.65, 1.51 Hz), 7.51 (1H, t, *J* 7.61 Hz), 7.42 (1H, dt, *J* 6.59, 1.46 Hz), 3.75 (1H, d, *J* 7.93 Hz), 3.47 (2H, q, *J* 7.00 Hz), 1.26-1.19 (4H, m), 0.73-0.65 (1H, m), 0.56-0.46 (2H, m), 0.38-0.30 (1H, m). LCMS (ES+) 305 $(M+H)^+$, RT 19.88 minutes (*Method 4*).

EXAMPLE 98

6-{3-[Cyclopropyl(pyridin-3-ylmethoxy)methyl]phenyl}quinoxaline

Prepared from *Example 92* (90 mg, 0.33 mmol), 3-picolyl chloride hydrochloride (53 mg, 0.33 mmol), NaH (13 mg, 0.33 mmol; 60% in mineral oil) and DMF (2 mL) by the method of *Example 94* to give the *title compound* (12.5 mg, 10%) as a clear gum. δ_H (DMSO-d_6) 9.04 (1H, d, *J* 1.87 Hz), 9.00 (1H, d, *J* 1.87 Hz), 8.57 (1H, d, *J* 2.16 Hz), 8.53 (1H, dd, *J* 4.83, 1.65 Hz), 8.41 (1H, d, *J* 1.95 Hz), 8.28 (1H, dd, *J* 8.86, 2.06 Hz), 8.24 (1H, d, *J* 8.69 Hz), 7.92 (1H, s), 7.88 (1H, d, *J* 7.71 Hz), 7.79 (1H, dt, *J* 7.70, 2.13 Hz), 7.61 (1H, t, *J* 7.57 Hz), 7.55 (1H, d, *J* 7.53 Hz), 7.42 (1H, dd, *J* 7.82, 4.76 Hz), 4.53 (2H,

s), 3.99 (1H, d, *J* 8.02 Hz), 1.33-1.24 (1H, m), 0.69-0.62 (1H, m), 0.58-0.40 (3H, m). LCMS (ES+) 368 $(M+H)^+$, RT 18.56 minutes (*Method 7*).

EXAMPLE 99

3-({Cyclopropyl[3-(quinoxalin-6-yl)phenyl]methoxy}methyl)-5-methylisoxazole

Prepared from *Example 92* (90 mg, 0.33 mmol), 3-(bromomethyl)-5-methyl-isoxazole (50 μL, 0.33 mmol), NaH (13 mg, 0.33 mmol; 60% in mineral oil) and DMF (2 mL) by the method of *Example 94* to give the *title compound* (53.4 mg, 44%) as a tan gum. δ_H ($CDCl_3$) 8.88 (1H, d, *J* 1.85 Hz), 8.85 (1H, d, *J* 1.86 Hz), 8.33 (1H, d, *J* 2.05 Hz), 8.19 (1H, d, *J* 8.73 Hz), 8.08 (1H, dd, *J* 8.74, 2.07 Hz), 7.74 (1H, t, *J* 0.93 Hz), 7.71 (1H, dt, *J* 7.69, 1.50 Hz), 7.53 (1H, t, *J* 7.62 Hz), 7.43 (1H, dt, *J* 6.60, 1.43 Hz), 6.08 (1H, d, *J* 1.05 Hz), 4.58 (1H, d, *J* 12.72 Hz), 4.49 (1H, d, *J* 12.72 Hz), 3.84 (1H, d, *J* 7.95 Hz), 2.42 (3H, d, *J* 0.89 Hz), 1.30-1.21 (1H, m), 0.75-0.67 (1H, m), 0.55-0.46 (2H, m), 0.36-0.30 (1H, m). LCMS (ES+) 372 $(M+H)^+$, RT 18.81 minutes (*Method 4*).

EXAMPLE 100

2-{Cyclopropyl[3-(quinoxalin-6-yl)phenyl]methoxy}acetamide

Prepared from *Example 92* (90 mg, 0.33 mmol), 2-bromoacetamide (45 mg, 0.33 mmol), NaH (13 mg, 0.33 mmol; 60% in mineral oil) and DMF (2 mL) by the method of *Example 94* to give the *title compound* (9.2 mg, 8%) as a tan solid. δ_H (DMSO-d_6) 8.85 (1H, d, *J* 1.85 Hz), 8.82 (1H, d, *J* 1.86 Hz), 8.25 (1H, d, *J* 2.03 Hz), 8.11 (1H, dd, *J* 8.80, 2.09 Hz), 8.06 (1H, d, *J* 8.74 Hz), 7.78 (1H, t, *J* 1.67 Hz), 7.70 (1H, dt, *J* 7.59, 1.54 Hz), 7.41 (1H, t, *J* 7.56 Hz), 7.35 (1H, d, *J* 7.63 Hz), 7.12 (1H, s), 7.04 (1H, s), 3.76 (1H, d, *J* 8.19 Hz), 3.69-3.59 (2H, m), 1.12-1.09 (1H, m), 0.46-0.43 (2H, m), 0.28-0.22 (2H, m). LCMS (ES+) 334 $(M+H)^+$, RT 19.1 minutes (*Method 4*).

EXAMPLE 101

7-{3-[Ethoxy(phenyl)methyl]phenyl}pyrido[3,4-*b*]pyrazine

Prepared from *Example 93* (100 mg, 0.32 mmol), ethyl iodide (26 μL, 0.32 mmol), NaH (12 mg, 0.32 mmol; 60% in mineral oil) and DMF (2 mL) by the method of

Example 94 to give the *title compound* (19.5 mg, 18%) as a brown solid. δ_H ($CDCl_3$) 9.62 (1H, s), 9.01 (1H, d, *J* 1.77 Hz), 8.91 (1H, d, *J* 1.78 Hz), 8.33 (1H, s), 8.21 (1H, s), 8.09 (1H, dt, *J* 6.85, 1.99 Hz), 7.54-7.39 (4H, m), 7.34 (3H, t, *J* 7.58 Hz), 5.50 (1H, s), 3.59 (2H, q, *J* 7.00 Hz), 1.31 (3H, t, *J* 6.99 Hz). LCMS (ES+) 342 $(M+H)^+$, 17.51 minutes (*Method 4*).

EXAMPLE 102

7-{3-[Phenyl(pyridin-3-ylmethoxy)methyl]phenyl}pyrido[3,4-*b*]pyrazine formic acid salt

Prepared from *Example 93* (100 mg, 0.32 mmol), 3-picolyl chloride hydrochloride (0.32 mmol), NaH (12 mg, 0.32 mmol; 60% in mineral oil) and DMF (2 mL) by the method of *Example 94* to give the *title compound* (15.7 mg, 12%) as a brown solid. δ_H (DMSO-d_6) 9.63 (1H, s, HCOOH), 9.23 (1H, d, *J* 1.79 Hz), 9.11 (1H, d, *J* 1.79 Hz), 8.63 (1H, d, *J* 2.14 Hz), 8.59 (1H, s), 8.56 (1H, dd, *J* 4.85, 1.64 Hz), 8.43 (1H, s), 8.25 (1H, dt, *J* 6.79, 1.96 Hz), 7.86 (1H, dt, *J* 7.93, 1.99 Hz), 7.63-7.52 (4H, m), 7.47-7.37 (4H, m), 7.31 (1H, t, *J* 7.29 Hz), 5.80 (1H, s), 4.64 (2H, s). LCMS (ES+) 405 $(M+H)^+$, 2.69 minutes (*Method 2*).

EXAMPLE 103

6-[3-(1-Ethoxyethyl)phenyl]quinoxaline

Prepared from *Intermediate 39* (110 mg, 0.44 mmol), ethyl iodide (40 μL, 0.44 mmol), NaH (18 mg, 0.44 mmol; 60% in mineral oil) and DMF (2 mL) by the method of *Example 94* to give the *title compound* (57.3 mg, 47%) as a clear gum. δ_H ($CDCl_3$) 8.89 (1H, d, *J* 1.85 Hz), 8.85 (1H, d, *J* 1.85 Hz), 8.34 (1H, d, *J* 2.04 Hz), 8.19 (1H, d, *J* 8.73 Hz), 8.08 (1H, dd, *J* 8.74, 2.06 Hz), 7.73 (1H, t, *J* 1.77 Hz), 7.68 (1H, dt, *J* 7.67, 1.48 Hz), 7.51 (1H, t, *J* 7.63 Hz), 7.40 (1H, dt, *J* 6.76, 1.37 Hz), 4.52 (1H, q, *J* 6.48 Hz), 3.44 (2H, q, *J* 7.02 Hz), 1.52 (3H, d, *J* 6.48 Hz), 1.23 (3H, t, *J* 7.01 Hz). LCMS (ES+) 279 $(M+H)^+$, 3.42 minutes (*Method 1*).

EXAMPLE 104

2-{*N*-Cyclopentyl-*N*-[3-(quinoxalin-6-yl)benzyl]amino}acetamide

3-Iodobenzyl bromide (126 mg, 0.42 mmol), 2-(cyclopentylamino)acetamide (60 mg, 0.42 mmol), potassium phosphate (100 mg, 0.47 mmol) and DME (6 mL) were combined in a sealed tube and heated under microwave irradiation to 140°C for 1 h. Quinoxaline-6-boronic acid hydrochloride (89 mg, 0.42 mmol), water (2 mL) and $Pd(PPh_3)_4$ (48 mg, 0.042 mmol) were added to the sealed tube and the reaction was heated under microwave irradiation to 140°C for an extra hour. After cooling, the mixture was filtered through Celite. The filtrate was then concentrated to dryness and purified by preparative HPLC to give the *title compound* (28.2 mg, 19%) as an off-white solid. δ_H (DMSO-d_6) 9.03 (1H, d, *J* 1.85 Hz), 8.99 (1H, d, *J* 1.85 Hz), 8.41 (1H, d, *J* 2.02 Hz), 8.28 (1H, dd, *J* 8.78, 2.09 Hz), 8.22 (1H, d, *J* 8.73 Hz), 7.95 (1H, s), 7.82 (1H, dt, *J* 6.57, 2.11 Hz), 7.57-7.48 (2H, m), 7.28 (1H, d, *J* 3.51 Hz), 7.10 (1H, d, *J* 3.45 Hz), 3.81 (2H, s), 3.22-3.14 (1H, m), 3.01 (2H, s), 1.83 (2H, s), 1.66 (2H, s), 1.51 (4H, s). LCMS (ES+) 361 $(M+H)^+$, 10.94 minutes (*Method 4*).

EXAMPLE 105

2-{*N*-Cyclohexyl-*N*-[3-(quinoxalin-6-yl)benzyl]amino}ethanol

Prepared from 3-iodobenzyl bromide (126 mg, 0.42 mmol), *N*-cyclohexylethanolamine (60.1 mg, 0.42 mmol), potassium phosphate (100 mg, 0.47 mmol) and DME (6 mL), then quinoxaline-6-boronic acid hydrochloride (89 mg, 0.42 mmol), water (2 mL) and $Pd(PPh_3)_4$ (48 mg, 0.042 mmol), by the method of *Example 104* to give the *title compound* (32.8 mg, 22%) as a tan solid. δ_H (DMSO-d_6) 9.02 (1H, d, *J* 1.86 Hz), 8.99 (1H, d, *J* 1.87 Hz), 8.36 (1H, s), 8.27-8.20 (2H, m), 7.90 (1H, s), 7.77 (1H, d, *J* 7.50 Hz), 7.55-7.43 (2H, m), 3.79 (2H, s), 3.40 (2H, t, *J* 6.86 Hz), 2.63 (2H, t, *J* 6.83 Hz), 1.85 (2H, d, *J* 11.41 Hz), 1.77 (2H, d, *J* 11.41 Hz), 1.60 (1H, d, *J* 11.60 Hz), 1.38-1.01 (6H, m), OH not visible. LCMS (ES+) 362 $(M+H)^+$, 4.43 minutes.

EXAMPLE 106

(*R*)-*N*-{1-[3-(Quinoxalin-6-yl)benzyl]pyrrolidin-3-yl}acetamide formic acid salt

Prepared from 3-iodobenzyl bromide (126 mg, 0.42 mmol), (3*R*)-(+)-3-acetamidopyrrolidine (54 mg, 0.42 mmol), potassium phosphate (100 mg, 0.47 mmol) and DME (6 mL), then quinoxaline-6-boronic acid hydrochloride (89 mg, 0.42 mmol), water (2 mL) and $Pd(PPh_3)_4$ (48 mg, 0.042 mmol), by the method of *Example 104* to give the *title compound* (36.2 mg, 25%) as a tan solid. δ_H (DMSO-d_6) 9.03 (1H, d, *J* 1.84 Hz), 8.99 (1H, d, *J* 1.85 Hz), 8.38 (1H, d, *J* 1.87 Hz), 8.26 (1H, dd, *J* 8.75, 1.98 Hz), 8.24 (1H, d, *J* 7.09 Hz), 8.20 (1H, s, HCOOH), 8.04 (1H, d, *J* 6.99 Hz), 7.85 (1H, s), 7.82 (1H, dt, *J* 7.69, 1.47 Hz), 7.54 (1H, t, *J* 7.59 Hz), 7.45 (1H, d, *J* 7.58 Hz), 4.21-4.15 (1H, m), 3.73 (2H, dd, *J* 16.94, 13.32 Hz), 2.76-2.65 (2H, m), 2.51-2.44 (1H, m), 2.39 (1H, dd, *J* 9.49, 4.78 Hz), 2.19-2.08 (1H, m), 1.80 (3H, s), 1.65-1.55 (1H, m). LCMS (ES+) 347 $(M+H)^+$, 14.01 minutes (*Method 6*).

EXAMPLE 107

2-Methoxy-*N*-methyl-*N*-[3-(quinoxalin-6-yl)benzyl]ethanamine

Prepared from 3-iodobenzyl bromide (126 mg, 0.42 mmol), *N*-(2-methoxyethyl)-*N*-methylamine (37.4 mg, 0.42 mmol), potassium phosphate (100 mg, 0.47 mmol) and DME (6 mL), then quinoxaline-6-boronic acid hydrochloride (89 mg, 0.42 mmol), water (2 mL) and $Pd(PPh_3)_4$ (48 mg, 0.042 mmol), by the method of *Example 104* to give the *title compound* (50.1 mg, 39%) as a clear gum. δ_H (DMSO-d_6) 9.03 (1H, d, *J* 1.86 Hz), 8.99 (1H, d, *J* 1.86 Hz), 8.38 (1H, d, *J* 1.86 Hz), 8.30-8.19 (2H, m), 7.86 (1H, s), 7.82 (1H, d, *J* 7.74 Hz), 7.54 (1H, t, *J* 7.60 Hz), 7.43 (1H, d, *J* 7.56 Hz), 3.66 (2H, s), 3.52 (2H, t, *J* 5.87 Hz), 3.29 (3H, s), 2.61 (2H, t, *J* 5.86 Hz), 2.26 (3H, s). LCMS (ES+) 308 $(M+H)^+$, 2.51 minutes (*Method 3*).

EXAMPLE 108

2-{*N*-Ethyl-*N*-[3-(quinoxalin-6-yl)benzyl]amino}ethanol

Prepared from 3-iodobenzyl bromide (126 mg, 0.42 mmol), 2-(ethylamino)ethanol (37.4 mg, 0.42 mmol), potassium phosphate (100 mg, 0.47 mmol) and DME (6 mL), then

quinoxaline-6-boronic acid hydrochloride (89 mg, 0.42 mmol), water (2 mL) and $Pd(PPh_3)_4$ (48 mg, 0.042 mmol), by the method of *Example 104* to give the *title compound* (39.7 mg, 31%) as a pale yellow gum. δ_H (DMSO-d_6) 9.03 (1H, d, *J* 1.86 Hz), 8.99 (1H, d, *J* 1.87 Hz), 8.38 (1H, d, *J* 1.86 Hz), 8.29-8.19 (2H, m), 7.89 (1H, s), 7.80 (1H, d, *J* 7.65 Hz), 7.53 (1H, t, *J* 7.58 Hz), 7.46 (1H, d, *J* 7.57 Hz), 4.42 (1H, s), 3.75 (2H, s), 3.54 (2H, t, *J* 6.41 Hz), 2.63-2.56 (4H, m), 1.06 (3H, t, *J* 7.05 Hz). LCMS (ES+) 308 $(M+H)^+$, 2.44 minutes (*Method 3*).

EXAMPLE 109

6-[3-(Isoindolin-2-ylmethyl)phenyl]quinoxaline

3-(Bromomethyl)phenylboronic acid (215 mg, 1.00 mmol), isoindoline (119 mg, 1.00 mmol), potassium phosphate (200 mg, 1.00 mmol) and DME (7 mL) were combined in a sealed tube and heated under microwave irradiation to 140°C for 1 h. 6-Bromoquinoxaline (209 mg, 1.00 mmol), water (2 mL) and $Pd(PPh_3)_4$ (115 mg, 0.10 mmol) were added to the reaction mixture, which was heated under microwave irradiation to 140°C for a further 1 h. After cooling, the mixture was filtered through Celite. The filtrate was concentrated to dryness and purified by preparative HPLC to give the *title compound* (50.1 mg, 15%) as a brown solid. δ_H (DMSO-d_6) 9.02 (1H, d, *J* 1.85 Hz), 8.99 (1H, d, *J* 1.86 Hz), 8.40 (1H, d, *J* 2.01 Hz), 8.32-8.21 (2H, m), 7.93 (1H, s), 7.85 (1H, dt, *J* 7.61, 1.57 Hz), 7.58 (1H, t, *J* 7.55 Hz), 7.52 (1H, d, *J* 7.63 Hz), 7.28-7.19 (4H, m), 4.04 (2H, s), 3.95 (4H, s). LCMS (ES+) 338 $(M+H)^+$, 3.85 minutes (*Method 1*).

EXAMPLE 110

N-[3-(Quinoxalin-6-yl)benzyl]-2,3-dihydro-1*H*-inden-1-amine

Prepared from 3-(bromomethyl)phenylboronic acid (107 mg, 0.50 mmol), 1-aminoindane (0.50 mmol), potassium phosphate (100 mg, 0.50 mmol) and DME (4.5 mL), then 6-bromoquinoxaline (104 mg, 0.50 mmol), water (1 mL) and $Pd(PPh_3)_4$ (50 mg, 0.05 mmol), by the method of *Example 109* to give the *title compound* (15.7 mg, 9%) as a brown solid. δ_H (DMSO-d_6) 9.03 (1H, d, *J* 1.85 Hz), 8.99 (1H, d, *J* 1.86 Hz), 8.41 (1H, d, *J* 1.99 Hz), 8.31-8.21 (3H, m), 7.99 (1H, s), 7.84-7.76 (1H, m), 7.54 (2H, d, *J* 4.62 Hz), 7.46 (1H, dd, *J* 5.73, 3.55 Hz), 7.27-7.19 (3H, m), 4.28-4.22 (1H, m), 3.96 (2H, m),

3.03-2.94 (1H, m), 2.83-2.71 (1H, m), 2.41-2.32 (1H, m), 1.88 (1H, dd, *J* 12.73, 7.13 Hz). LCMS (ES+) 352 $(M+H)^+$, 3.78 minutes (*Method 1*).

EXAMPLE 111

7-[3-(Pyrrolidin-1-ylmethyl)phenyl]pyrido[3,4-*b*]pyrazine

A mixture of 3-(bromomethyl)phenylboronic acid (150 mg, 0.69 mmol), pyrrolidine (70 μL, 0.84 mmol) and potassium phosphate (440 mg, 2.10 mmol) in DME (3 mL) was heated at 80°C in a sealed reaction tube for 16 h. The reaction mixture was cooled to room temperature. 7-Chloropyrido[3,4-*b*]pyrazine (110 mg, 0.69 mmol), $Pd(PPh_3)_4$ (40 mg, 0.035 mmol) and water (0.5 mL) were then added. The resulting mixture was purged with nitrogen for 5 minutes, sealed and heated at 85°C for 16 h. After cooling to room temperature, the mixture was diluted with ethyl acetate (5 mL) and filtered through Celite. The filtrate was concentrated to dryness and purified by preparative HPLC to give the *title compound* (12.0 mg, 6%) as a pale brown solid. δ_H ($CDCl_3$) 9.62 (1H, s), 9.02 (1H, d, *J* 1.78 Hz), 8.91 (1H, d, *J* 1.78 Hz), 8.37 (1H, s), 8.22 (1H, s), 8.13 (1H, dt, *J* 6.69, 2.04 Hz), 7.58-7.48 (2H, m), 3.96 (2H, s), 2.70-2.84 (4H, m), 2.03-1.79 (4H, m). LCMS (ES+) 291 $(M+H)^+$, 9.83 minutes (*Method 5*).

EXAMPLE 112

N-[3-(Pyrido[3,4-*b*]pyrazin-7-yl)benzyl]cyclopropanamine

Prepared from 3-(bromomethyl)phenylboronic acid (150 mg, 0.69 mmol), cyclopropylamine (58 μL, 0.84 mmol) and potassium phosphate (440 mg, 2.10 mmol) in DME (3 mL), then 7-chloropyrido[3,4-*b*]pyrazine (110 mg, 0.69 mmol), $Pd(PPh_3)_4$ (40 mg, 0.035 mmol) and water (0.5 mL), by the method of *Example 111* to give the *title compound* (4.3 mg, 2%) as a pale brown solid. δ_H ($CDCl_3$) 9.63 (1H, s), 9.02 (1H, d, *J* 1.79 Hz), 8.92 (1H, d, *J* 1.78 Hz), 8.36 (1H, s), 8.19 (1H, s), 8.07 (1H, dt, *J* 7.61, 1.55 Hz), 7.55-7.41 (2H, m), 4.00 (2H, s), 2.66 (1H, br s), 2.27-2.20 (1H, m), 0.52-0.47 (4H, m). LCMS (ES+) 277 $(M+H)^+$, 17.13 minutes (*Method 6*).

EXAMPLE 113

N-[3-(Pyrido[4,3-*b*]pyrazin-7-yl)benzyl]cyclopentanamine formic acid salt

Prepared from 3-(bromomethyl)phenylboronic acid (150 mg, 0.69 mmol), cyclopentylamine (83 μL, 0.84 mmol) and potassium phosphate (440 mg, 2.10 mmol) in DME (3 mL), then 7-chloropyrido[3,4-*b*]pyrazine (110 mg, 0.69 mmol), $Pd(PPh_3)_4$ (40 mg, 0.035 mmol) and water (0.5 mL), by the method of *Example 111* to give the *title compound* (14.4 mg, 7%) as a pale brown gum. δ_H ($CDCl_3$) 9.56 (1H, d, *J* 0.87 Hz), 8.99 (1H, d, *J* 1.78 Hz), 8.89 (1H, d, *J* 1.78 Hz), 8.60 (1H, s, HCOOH), 8.31 (1H, d, *J* 0.89 Hz), 8.26-8.19 (1H, m), 8.08 (1H, dt, *J* 7.04, 1.89 Hz), 7.53-7.45 (2H, m), 4.43 (1H, br s), 3.95 (2H, s), 3.24 (1H, p, *J* 6.98 Hz), 1.96-1.86 (2H, m), 1.74-1.67 (2H, m), 1.62-1.46 (4H, m). LCMS (ES+) 305 $(M+H)^+$, 2.57 minutes (*Method 3*).

EXAMPLE 114

N-[3-(Pyrido[4,3-*b*]pyrazin-7-yl)benzyl]cyclohexanamine formic acid salt

Prepared from 3-(bromomethyl)phenylboronic acid (150 mg, 0.69 mmol), cyclohexylamine (96 μL, 0.84 mmol) and potassium phosphate (440 mg, 2.10 mmol) in DME (3 mL), then 7-chloropyrido[3,4-*b*]pyrazine (110 mg, 0.69 mmol), $Pd(PPh_3)_4$ (40 mg, 0.035 mmol) and water (0.5 mL), by the method of *Example 111* to give the *title compound* (20 mg, 9%) as a pale brown gum. δ_H ($CDCl_3$) 9.56 (1H, d, *J* 0.86 Hz), 8.99 (1H, d, *J* 1.78 Hz), 8.89 (1H, d, *J* 1.77 Hz), 8.60 (1H, s, HCOOH), 8.31 (1H, d, *J* 0.90 Hz), 8.26 (1H, t, *J* 1.74 Hz), 8.11-8.05 (1H, m), 7.55-7.42 (2H, m), 6.07 (1H, s), 3.99 (2H, s), 2.77-2.67 (1H, m), 2.07-1.96 (2H, m), 1.79-1.68 (2H, m), 1.40-1.12 (6H, m). LCMS (ES+) 319 $(M+H)^+$, 3.18 minutes (*Method 1*).

EXAMPLE 115

4-{[4-(Quinoxalin-6-yl)pyridin-2-yl]methyl}piperazin-2-one

To a solution of piperazin-2-one (63.9 mg, 0.64 mmol) in DCM (1.8 mL) and AcOH (0.2 mL) was added *Intermediate 10* (50 mg, 0.21 mmol). The reaction mixture was stirred for 30 minutes at room temperature. (Polystyrylmethyl)trimethylammonium cyanoborohydride (4.3 mmol/g; 127 mg, 0.42 mmol) was added and the mixture was

shaken slowly at room temperature for 22 h. The reaction mixture was filtered and washed thoroughly with dichloromethane. The combined organic layers were dried ($MgSO_4$), concentrated to dryness and purified by preparative HPLC to give the *title compound* (29.9 mg, 43%) as a brown gum. δ_H ($CDCl_3$) 8.92 (1H, d, *J* 1.85 Hz), 8.91 (1H, d, *J* 1.84 Hz), 8.72 (1H, dd, *J* 5.17, 0.77 Hz), 8.41 (1H, d, *J* 2.07 Hz), 8.25 (1H, d, *J* 8.74 Hz), 8.08 (1H, dd, *J* 8.74, 2.09 Hz), 7.82 (1H, d, *J* 1.75 Hz), 7.60 (1H, dd, *J* 5.18, 1.85 Hz), 6.16 (1H, s), 3.87 (2H, s), 3.46-3.41 (2H, m), 3.29 (2H, s), 2.85-2.79 (2H, m). LCMS (ES+) 320 $(M+H)^+$, 11.4 minutes (*Method 7*).

EXAMPLE 116

(1*R*,4*R*)-4-{[4-(Quinoxalin-6-yl)pyridin-2-yl]methylamino}cyclohexanol

Prepared from *Intermediate 10* (60 mg, 0.25 mmol), *trans*-4-aminocyclohexanol (88.1 mg, 0.76 mmol), DCM (2.7 mL), AcOH (0.3 mL) and (polystyrylmethyl)trimethylammonium cyanoborohydride (152 mg, 0.51 mmol) by the method of *Example 115* to give the *title compound* (72.5 mg, 84%) as a pale orange solid. δ_H (DMSO-d_6) 9.08 (1H, d, *J* 1.41 Hz), 9.05 (1H, d, *J* 2.02 Hz), 8.70 (1H, d, *J* 5.32 Hz), 8.58 (1H, s), 8.38-8.23 (3H, m), 8.05 (1H, s), 7.87 (1H, d, *J* 5.33 Hz), 4.05 (2H, m), 3.41 (1H, m), 2.56 (1H, masked by DMSO), 2.06-1.89 (2H, m), 1.89-1.80 (2H, m), 1.30-1.08 (4H, m), OH not visible. LCMS (ES+) 335 $(M+H)^+$, 9.48 minutes (*Method 4*).

EXAMPLE 117

(1*R*,2*S*)-2-{[4-(Quinoxalin-6-yl)pyridin-2-yl]methylamino}cyclopentanecarboxamide

Prepared from *Intermediate 10* (60 mg, 0.25 mmol), *cis*-2-aminocyclopentanecarboxamide (98 mg, 0.76 mmol), DCM (2.7 mL), AcOH (0.3 mL) and (polystyrylmethyl)trimethylammonium cyanoborohydride (152 mg, 0.51 mmol) by the method of *Example 115* to give the *title compound* (55.6 mg, 62%) as a pale orange solid. δ_H (DMSO-d_6) 9.07 (1H, d, *J* 1.84 Hz), 9.05 (1H, d, *J* 1.83 Hz), 8.68 (1H, d, *J* 5.19 Hz), 8.57 (1H, d, *J* 1.98 Hz), 8.34 (1H, dd, *J* 8.80, 2.06 Hz), 8.29 (1H, d, *J* 8.73 Hz), 7.99 (1H, s), 7.85 (1H, dd, *J* 5.20, 1.84 Hz), 7.52 (1H, s), 6.87 (1H, s), 4.05-3.92 (2H, m), 3.31-3.27 (1H, m), 2.74 (1H, q, *J* 7.24 Hz), 1.96-1.87 (1H, m), 1.80-1.70 (4H, m), 1.57-1.48 (1H, m). LCMS (ES+) 348 $(M+H)^+$, 2.07 minutes (*Method 1*).

EXAMPLE 118

(1*R*,2*S*)-2-{[4-(Quinoxalin-6-yl)pyridin-2-yl]methylamino}cyclohexanecarboxamide

Prepared from *Intermediate 10* (60 mg, 0.25 mmol), *cis*-2-aminocyclohexanecarboxamide (108.7 mg, 0.76 mmol), DCM (2.7 mL), AcOH (0.3 mL) and (polystyrylmethyl)trimethylammonium cyanoborohydride (152 mg, 0.51 mmol) by the method of *Example 115* to give the *title compound* (70.0 mg, 76%) as a pale orange solid. δ_H (DMSO-d_6 + D_2O) 9.05 (1H, d, *J* 1.86 Hz), 9.02 (1H, d, *J* 1.85 Hz), 8.69 (1H, d, *J* 5.23 Hz), 8.55 (1H, d, *J* 1.95 Hz), 8.33 (1H, dd, *J* 8.85, 2.10 Hz), 8.31-8.26 (1H, m), 8.00 (1H, s), 7.86 (1H, dd, *J* 5.22, 1.83 Hz), 4.16-3.95 (2H, m), 3.09-3.05 (1H, m), 2.60-2.56 (1H, m), 2.01-1.90 (1H, m), 1.95-1.75 (1H, m), 1.71-1.64 (1H, m), 1.58-1.37 (3H, m), 1.37-1.31 (2H, m). LCMS (ES+) 362 $(M+H)^+$, 2.26 minutes (*Method 1*).

EXAMPLE 119

N-Cyclobutyl-*N*-{[4-(quinoxalin-6-yl)pyridin-2-yl]methyl}acetamide

To a solution of *Intermediate 40* (35 mg, 0.12 mmol) in DCM (2 mL) and Et_3N (20 μL, 0.14 mmol) was added dropwise acetyl chloride (9.4 μL, 0.13 mmol) at 0°C under nitrogen. The reaction mixture was then allowed to warm up to room temperature and stirred for 3 h. The mixture was partitioned between saturated aqueous sodium hydrogencarbonate solution and dichloromethane. The combined organic layers were dried ($MgSO_4$), concentrated to dryness and purified by preparative HPLC to give the *title compound* (26.1 mg, 65%) as an opaque white gum. δ_H ($CDCl_3$) (mixture of rotamers) 8.94-8.88 (2H, m), 8.72 (0.33H, d, *J* 5.26 Hz), 8.66 (0.67H, d, *J* 5.16 Hz), 8.34 (1H, s), 8.26-8.17 (1H, m), 8.05-7.97 (1H, m), 7.62-7.44 (2H, m), 5.15-5.07 (0.33H, m), 4.91 (1.2H, s), 4.80 (0.8H, s), 4.46-4.36 (0.67H, m), 2.28-2.14 (5.25H, m), 2.14-1.95 (1.75H, m), 1.73-1.56 (2H, m). LCMS (ES+) 333 $(M+H)^+$, 2.4 minutes (*Method 1*).

EXAMPLE 120

Methyl *N*-cyclopentyl-*N*-[3-(quinoxalin-6-yl)benzyl]carbamate

Prepared from *Intermediate 22* (50 mg, 0.16 mmol), triethylamine (30 μL, 0.21 mmol) and methyl chloroformate (15.2 μL, 0.20 mmol) in DCM (1 mL) by the method of *Example 119* to give the *title compound* (33.3 mg, 55%) as a pale yellow gum. δ_H ($CDCl_3$) 8.88 (1H, d, *J* 1.86 Hz), 8.85 (1H, d, *J* 1.86 Hz), 8.30 (1H, d, *J* 2.05 Hz), 8.18 (1H, d, *J* 8.73 Hz), 8.04 (1H, dd, *J* 8.74, 2.07 Hz), 7.65-7.56 (2H, m), 7.47 (1H, t, *J* 7.66 Hz), 7.29 (1H, d, *J* 7.75 Hz), 4.54 (2H, s), 4.51-4.30 (1H, m), 3.73 (3H, s), 1.96-1.73 (2H, m), 1.77-1.55 (2H, m), 1.61-1.50 (4H, m). LCMS (ES+) 362 $(M+H)^+$, 20.82 minutes (*Method 7*).

EXAMPLE 121

tert-Butyl 3-(quinoxalin-6-yl)benzylcarbamate

6-Bromoquinoxaline (500 mg, 2.39 mmol), 3-(aminomethyl)phenylboronic acid hydrochloride (445 mg, 2.39 mmol), potassium phosphate (1000 mg, 4.78 mmol), water (3 mL), DME (13 mL) and $Pd(PPh_3)_4$ (277 mg, 0.24 mmol) were combined in a sealed tube and heated under microwave irradiation to 140°C for 1 h. Di-*tert*-butyl dicarbonate (545 mg, 2.50 mmol) was then added and the reaction mixture stirred at room temperature for 18 h. The organic layer was concentrated to dryness and purified by chromatography (SiO_2, 20-100% EtOAc in petroleum ether) to give a yellow gum (232 mg). A sample (30 mg) was further purified by preparative HPLC to give the *title compound* (21.6 mg) as a clear solid. δ_H ($CDCl_3$) 8.88 (1H, d, *J* 1.85 Hz), 8.85 (1H, d, *J* 1.86 Hz), 8.31 (1H, d, *J* 2.05 Hz), 8.18 (1H, d, *J* 8.73 Hz), 8.05 (1H, dd, *J* 8.74, 2.08 Hz), 7.67 (2H, d, *J* 6.92 Hz), 7.49 (1H, t, *J* 7.84 Hz), 7.37 (1H, d, *J* 7.61 Hz), 4.93 (1H, s), 4.44 (2H, d, *J* 5.95 Hz), 1.48 (9H, s). LCMS (ES+) 336 $(M+H)^+$, RT 3.58 minutes (*Method 2*).

EXAMPLE 122

1-[3-(Quinoxalin-6-yl)benzyl]pyrrolidine-2,5-dione

Example 79 (84 mg, 0.30 mmol), succinic anhydride (30 mg, 0.30 mmol) and acetic acid (2 mL) were combined in a sealed tube. The reaction was heated to 80°C for

18 h. More succinic anhydride (30 mg, 0.30 mmol) was added and the reaction was heated to 90°C for 20 h. The reaction mixture was then concentrated to dryness and purified by preparative HPLC to give the *title compound* (48.8 mg, 51%) as an off-white solid. δ_H ($CDCl_3$) 8.88 (1H, d, *J* 1.83 Hz), 8.85 (1H, d, *J* 1.86 Hz), 8.30 (1H, d, *J* 2.04 Hz), 8.18 (1H, d, *J* 8.74 Hz), 8.04 (1H, dd, *J* 8.73, 2.08 Hz), 7.79 (1H, s), 7.71-7.67 (1H, m), 7.49-7.44 (2H, m), 4.77 (2H, s), 2.75 (4H, s). LCMS (ES+) 318 $(M+H)^+$, RT 14.82 minutes (*Method 4*).

EXAMPLE 123

1-Ethyl-3-[3-(quinoxalin-6-yl)benzyl]urea

Example 79 (84 mg, 0.30 mmol), ethyl isocyanate (24 μL, 0.30 mmol) and dichloromethane (10 mL) were combined and stirred at room temperature for 18 h. More ethyl isocyanate (100 μL, 1.25 mmol) and triethylamine (1 mL) were added and the reaction was stirred at room temperature for a further 24 h. The reaction mixture was then concentrated to dryness and purified by preparative HPLC to give the *title compound* (43.6 mg, 47%) as an off-white solid. δ_H ($CDCl_3$) 8.88 (1H, d, *J* 1.83 Hz), 8.85 (1H, d, *J* 1.86 Hz), 8.30 (1H, d, *J* 2.04 Hz), 8.17 (1H, d, *J* 8.74 Hz), 8.04 (1H, dd, *J* 8.74, 2.07 Hz), 7.69 (1H, s), 7.66 (1H, d, *J* 7.88 Hz), 7.49 (1H, t, *J* 7.63 Hz), 7.39 (1H, d, *J* 7.62 Hz), 4.67 (1H, s), 4.51 (2H, d, *J* 5.83 Hz), 4.30 (1H, s), 3.29-3.21 (2H, m), 1.15 (3H, t, *J* 7.21 Hz). LCMS (ES+) 307 $(M+H)^+$, RT 2.64 minutes (*Method 2*).

EXAMPLE 124

6-[3-(1-Phenylethyl)phenyl]quinoxaline

Example 91 (200 mg, 0.60 mmol), dichloromethane (30 mL), TFA (3 mL) and triethylsilane (0.29 mL, 1.80 mmol) were combined at room temperature and stirred for 18 h. The reaction mixture was then concentrated to dryness and purified by preparative HPLC to give the *title compound* (109 mg, 59%) as a clear gum. δ_H ($CDCl_3$) 8.82-8.80 (1H, m), 8.79 (1H, d, *J* 1.93 Hz), 8.27 (1H, d, *J* 2.06 Hz), 8.13 (1H, d, *J* 8.73 Hz), 7.99 (1H, dd, *J* 8.78, 1.56 Hz), 7.61 (1H, s), 7.56 (1H, d, *J* 8.31 Hz), 7.41 (1H, t, *J* 7.61 Hz), 7.26 (5H, masked by $CHCl_3$), 7.21-7.13 (1H, m), 4.25 (1H, q, *J* 7.12 Hz), 1.72 (3H, d, *J* 7.19 Hz). LCMS (ES+) 311 $(M+H)^+$, RT 4.35 minutes (*Method 2*).

EXAMPLE 125

Phenyl[3-(quinoxalin-6-yl)phenyl]methanone oxime

Intermediate 37 (390 mg, 1.26 mmol), hydroxylamine hydrochloride (175 mg, 2.52 mmol), NaOAc.$3H_2O$ (514 mg, 3.78 mmol) and ethanol (10 mL) were combined and stirred as a suspension for 18 h. THF (10 mL) was then added to improve solubility and the reaction mixture was stirred for a further 12 days. The reaction mixture was then concentrated to dryness onto silica and purified by chromatography (SiO_2, 40-100% EtOAc in petroleum ether) to give an off-white solid (284 mg). A sample (50 mg) of this material was further purified by preparative HPLC to give the *title compound* (27 mg) as a white solid. δ_H (DMSO-d_6) 11.30 (1H, d, *J* 6.20 Hz), 8.82-8.77 (2H, m), 8.16-7.89 (3H, m), 7.78 (1H, dd, *J* 25.10, 7.74 Hz), 7.65 (1H, d, *J* 17.54 Hz), 7.45 (1H, dt, *J* 38.10, 7.69 Hz), 7.36-7.27 (3H, m), 7.26-7.20 (3H, m). LCMS (ES+) 326 $(M+H)^+$, RT 3.13 minutes (*Method 1*).

EXAMPLE 126

N-(2,3-Dihydro-1*H*-inden-1-yl)-*N*-[3-(quinoxalin-6-yl)benzyl]acetamide

Example 110 (175 mg, 0.50 mmol), DME (3.5 mL), triethylamine (0.4 mL) and acetyl chloride (0.14 mL, 2.00 mmol) were combined at room temperature under a nitrogen atmosphere. The reaction mixture was stirred for 35 minutes, then concentrated to dryness and purified by preparative HPLC to give the *title compound* (11.9 mg, 6%) as a pale yellow solid. δ_H (DMSO-d_6) (mixture of rotamers) 9.02 (1H, d, *J* 1.92 Hz), 8.99 (1H, d, *J* 2.57 Hz), 8.34 (0.5H, d, *J* 1.85 Hz), 8.29 (0.5H, d, *J* 1.99 Hz), 8.25-8.14 (2H, m), 7.82 (0.5H, d, *J* 7.73 Hz), 7.73 (0.5H, d, *J* 7.82 Hz), 7.67-7.41 (2H, m), 7.34-7.15 (5H, m), 6.21 (0.5H, t, *J* 8.17 Hz), 5.69 (0.5H, t, *J* 7.83 Hz), 4.80-4.72 (1H, m), 4.32 (0.5H, d, *J* 18.20 Hz), 4.05 (0.5H, d, *J* 16.03 Hz), 2.92-2.77 (2H, m), 2.49-2.41 (0.5H, m), 2.36 (1.5H, s), 2.34-2.30 (0.5H, m), 2.10 (1.5H, s), 1.95-1.83 (1H, m). LCMS (ES+) 394 $(M+H)^+$, 19.56 minutes (*Method 6*).

EXAMPLE 127

6-[3-(1*H*-Pyrazol-1-yl)phenyl]quinoxaline

6-Bromoquinoxaline (100 mg, 0.48 mmol), 3-(1*H*-pyrazol-1-yl)phenylboronic acid (108 mg, 0.57 mmol), Na_2CO_3 (0.15 g, 1.44 mmol), $Pd(PPh_3)_4$ (55 mg, 0.048 mmol), water (2 mL) and DME (6 mL) were combined in a sealed tube and heated under microwave irradiation to 120°C for 1 h. The reaction mixture was concentrated to dryness and purified by preparative HPLC to give the *title compound* (62.1 mg, 47%) as a pale yellow solid. δ_H ($CDCl_3$) 8.89 (1H, d, *J* 1.84 Hz), 8.86 (1H, d, *J* 1.84 Hz), 8.38 (1H, d, *J* 2.05 Hz), 8.20 (1H, d, *J* 8.74 Hz), 8.15-8.09 (2H, m), 8.03 (1H, d, *J* 2.51 Hz), 7.78 (1H, d, *J* 1.76 Hz), 7.75 (1H, ddd, *J* 8.00, 2.25, 1.14 Hz), 7.69-7.66 (1H, m), 7.63-7.55 (1H, m), 6.52 (1H, dd, *J* 2.50, 1.78 Hz). LCMS (ES+) 273 $(M+H)^+$, 15.14 minutes (*Method 4*).

EXAMPLE 128

6-[2-(Methylthio)pyridin-4-yl]quinoxaline

To a suspension of sodium thiomethoxide (31.9 mg, 0.45 mmol) in THF (1 mL) was added a solution of *Intermediate 21* (100 mg, 0.41 mmol) in THF (4 mL). The resulting yellow mixture was heated at 75°C for 18 h. After cooling to room temperature, the reaction mixture was poured onto water (20 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic layers was dried ($MgSO_4$), concentrated to dryness and purified by chromatography (SiO_2, 10-50% EtOAc in isohexane) to give the *title compound* (73.0 mg, 69%) as a yellow solid. δ_H ($CDCl_3$) 8.91 (1H, d, *J* 1.83 Hz), 8.89 (1H, d, *J* 1.83 Hz), 8.58 (1H, d, *J* 5.24 Hz), 8.36 (1H, d, *J* 2.05 Hz), 8.23 (1H, d, *J* 8.74 Hz), 8.03 (1H, dd, *J* 8.74, 2.09 Hz), 7.55 (1H, s), 7.35 (1H, dd, *J* 5.25, 1.68 Hz), 2.65 (3H, s). LCMS (ES+) 254 $(M+H)^+$, 3.16 minutes (*Method 2*).

EXAMPLE 129

6-[2-(Cyclopentylthio)pyridin-4-yl]quinoxaline

To a suspension of NaH (36.4 mg, 0.54 mmol) in THF (3 mL) was added dropwise cyclopentyl mercaptan (49 μL, 0.45 mmol). After 20 minutes at 30°C, a

solution of *Intermediate 21* (100 mg, 0.41 mmol) in THF (7 mL) was added. The reaction mixture was heated at 75°C for 18 h. After being cooled to room temperature, the mixture was poured onto water and extracted with dichloromethane. The combined organic layers were dried ($MgSO_4$), concentrated to dryness and purified by chromatography (SiO_2, 0-50% EtOAc in isohexane) to give the *title compound* (68.4 mg, 53%) as a pale yellow solid. δ_H ($CDCl_3$) 8.91 (1H, d, *J* 1.83 Hz), 8.89 (1H, d, *J* 1.84 Hz), 8.56 (1H, d, *J* 5.23 Hz), 8.35 (1H, d, *J* 2.05 Hz), 8.22 (1H, d, *J* 8.74 Hz), 8.02 (1H, dd, *J* 8.74, 2.08 Hz), 7.52 (1H, s), 7.33 (1H, dd, *J* 5.22, 1.70 Hz), 4.17-4.09 (1H, m), 2.29-2.21 (2H, m), 1.84-1.76 (2H, m), 1.74-1.66 (4H, m). LCMS (ES+) 308 $(M+H)^+$, 4.22 minutes (*Method 2*).

EXAMPLE 130

6-[2-(Cyclopentylsulfonyl)pyridin-4-yl]quinoxaline

To a solution of *Example 129* (49 mg, 0.16 mmol) in DCM (4 mL) was added dropwise a solution of mCPBA (120 mg, 0.35 mmol) in DCM (4 mL) previously dried with $MgSO_4$. The reaction mixture was stirred for 30 minutes, quenched with a saturated solution of sodium metabisulphite and extracted with dichloromethane. The combined organic layers was dried ($MgSO_4$), concentrated to dryness and purified by preparative HPLC to give the *title compound* (45.2 mg, 83%) as a white solid. δ_H ($CDCl_3$) 8.95 (1H, d, *J* 1.83 Hz), 8.94 (1H, d, *J* 1.88 Hz), 8.88 (1H, dd, *J* 5.00, 0.75 Hz), 8.49-8.46 (2H, m), 8.29 (1H, d, *J* 8.74 Hz), 8.10 (1H, dd, *J* 8.75, 2.15 Hz), 7.90 (1H, dd, *J* 5.01, 1.83 Hz), 4.20-4.11 (1H, m), 2.22-2.12 (2H, m), 2.03-1.92 (2H, m), 1.90-1.81 (2H, m), 1.73-1.65 (2H, m). LCMS (ES+) 340 $(M+H)^+$, 3.10 minutes (*Method 2*).

EXAMPLE 131

N-Cyclopentyl-*N*-[4-(quinoxalin-6-yl)pyridin-2-yl]acetamide

To a solution of *Intermediate 21* (350 mg, 1.45 mmol) in dry DMSO (10 mL) was added cyclopentylamine (171 µL, 1.70 mmol). The reaction mixture was heated at 120°C in a sealed tube for 18 h. The mixture was cooled to room temperature and concentrated to dryness to give a brown gum (240 mg). To a solution of the crude material (120 mg, 0.41 mmol) in DCM (2 mL) and Et_3N (75 µL, 0.54 mmol) was added dropwise acetyl chloride (35 µL, 0.50 mmol) at 0°C under nitrogen. The reaction mixture was then

allowed to warm up to room temperature and stirred for 18 h. The mixture was partitioned between saturated aqueous sodium hydrogencarbonate solution and dichloromethane. The combined organic layers were dried ($MgSO_4$), concentrated to dryness and purified by preparative HPLC to give the *title compound* (10.1 mg, 11%) as an orange gum. δ_H ($CDCl_3$) 8.94 (1H, d, *J* 1.80 Hz), 8.93 (1H, d, *J* 1.82 Hz), 8.73 (1H, d, *J* 5.19 Hz), 8.40 (1H, d, *J* 2.06 Hz), 8.28 (1H, d, *J* 8.74 Hz), 8.05 (1H, dd, *J* 8.75, 2.10 Hz), 7.69 (1H, dd, *J* 5.19, 1.68 Hz), 7.52 (1H, d, *J* 1.57 Hz), 4.98-4.86 (1H, m), 2.05-1.97 (2H, m), 1.90 (3H, s), 1.60-1.40 (6H, m). LCMS (ES+) 333 $(M+H)^+$, 2.89 minutes (*Method 2*).

EXAMPLE 132

6-[3-(Azetidin-1-ylsulfonyl)phenyl]quinoxaline

Quinoxaline-6-boronic acid hydrochloride (100 mg, 0.47 mmol), 1-(3-bromo-benzenesulfonyl)azetidine (119 mg, 0.43 mmol), sodium carbonate (137 mg, 1.30 mmol), water (0.65 mL), DME (1 mL) and $Pd(PPh_3)_4$ (16.5 mg, 0.013 mmol) were combined in a sealed tube, degassed and heated under microwave irradiation to 120°C for 30 minutes. The mixture was partitioned between water and EtOAc. The combined organic layers were dried ($MgSO_4$), concentrated to dryness and purified by chromatography (SiO_2, 0-60% EtOAc in isohexane) to give the *title compound* (20.3 mg, 14%) as an off-white solid. δ_H ($CDCl_3$) 8.91 (1H, d, *J* 1.99 Hz), 8.89 (1H, d, *J* 1.99 Hz), 8.38 (1H, d, *J* 2.17 Hz), 8.28-8.20 (2H, m), 8.08 (1H, dd, *J* 8.75, 2.25 Hz), 8.04 (1H, d, *J* 7.86 Hz), 7.92 (1H, d, *J* 7.82 Hz), 7.75 (1H, t, *J* 7.77 Hz), 3.87 (4H, t, *J* 7.59 Hz), 2.14 (2H, p, *J* 7.60 Hz). LCMS (ES+) 326 $(M+H)^+$, 3.1 minutes (*Method 2*).

EXAMPLE 133

1-{[4-(Quinoxalin-6-yl)pyridin-2-yl]methyl}pyrrolidin-2-one

To a suspension of *Intermediate 10* (100 mg, 0.42 mmol) in methanol (4 mL) at 0°C was added $NaBH_4$ (16.1 mg, 0.42 mmol) in two portions. The resulting precipitate was stirred for 1 h, then quenched with ice water and concentrated to dryness. The residue was partitioned between water and EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated to dryness to give an orange solid (49.7 mg). To a

solution of the crude alcohol (48 mg, 0.20 mmol) in DCM (2 mL) and Et_3N (37 μL, 0.26 mmol) was added dropwise methanesulfonyl chloride (19 μL, 0.24 mmol) at 0°C under nitrogen. The reaction mixture was then allowed to warm up to room temperature and stirred for 18 h. The mixture was partitioned between saturated aqueous sodium hydrogencarbonate solution and dichloromethane. The combined organic layers were dried ($MgSO_4$) and concentrated to dryness to give the crude mesylate as an orange gum (65 mg). To a solution of 2-pyrrolidinone (18.7 mg, 0.22 mmol) in DMF (1 mL) was added NaH (16 mg, 0.24 mmol; 60% in oil). After 30 minutes at 35°C, the reaction mixture was cooled to 0°C and a solution of the crude mesylate (60 mg, 0.20 mmol) in DMF (1 mL) was added dropwise. The reaction mixture was quenched with water, concentrated to dryness and purified by preparative HPLC to give the *title compound* (12.6 mg, 20%) as a white solid. δ_H ($CDCl_3$) 8.92 (1H, d, *J* 1.89 Hz), 8.90 (1H, d, *J* 1.91 Hz), 8.69 (1H, d, *J* 5.15 Hz), 8.38 (1H, d, *J* 2.09 Hz), 8.24 (1H, d, *J* 8.72 Hz), 8.05 (1H, dd, *J* 8.67, 2.14 Hz), 7.63 (1H, d, *J* 1.64 Hz), 7.58 (1H, dd, *J* 5.19, 1.83 Hz), 4.71 (2H, s), 3.49 (2H, t, *J* 7.04 Hz), 2.49 (2H, t, *J* 8.09 Hz), 2.08 (2H, p, *J* 7.53 Hz). LCMS (ES+) 305 $(M+H)^+$, 12.4 minutes (*Method 7*).

EXAMPLE 134

1-Cyclopentyl-3-ethyl-1-[3-(quinoxalin-6-yl)benzyl]urea

To a solution of *Intermediate 22* (50 mg, 0.16 mmol) in DCM (1 mL) was added ethyl isocyanate (15.6 μL, 0.20 mmol) at 0°C. The reaction mixture was stirred for 3 h at room temperature. The mixture was partitioned between water and dichloromethane. The combined organic layers were dried ($MgSO_4$), concentrated to dryness and purified by preparative HPLC to give the *title compound* (29.5 mg, 47%) as a yellow solid. δ_H ($CDCl_3$) 8.89 (1H, d, *J* 1.85 Hz), 8.86 (1H, d, *J* 1.85 Hz), 8.29 (1H, d, *J* 2.05 Hz), 8.19 (1H, d, *J* 8.73 Hz), 8.03 (1H, dd, *J* 8.74, 2.08 Hz), 7.68-7.61 (2H, m), 7.51 (1H, t, *J* 7.63 Hz), 7.34 (1H, d, *J* 7.67 Hz), 4.77-4.68 (1H, m), 4.46 (2H, s), 4.22 (1H, t, *J* 5.39 Hz), 3.23 (2H, qd, *J* 7.21, 5.40 Hz), 1.99-1.90 (2H, m), 1.70-1.55 (4H, m), 1.53-1.41 (2H, m), 1.02 (3H, t, *J* 7.19 Hz). LCMS (ES+) 375 $(M+H)^+$, 3.48 minutes (*Method 2*).

EXAMPLE 135

(*R*)-Phenyl[3-(quinoxalin-6-yl)phenyl]methanamine formic acid salt

Intermediate 43 (557 mg, 1.34 mmol), MeOH (6 mL) and conc. HCl (3 mL) were combined and stirred at room temperature for 3.5 h. The reaction was then quenched with a 2M solution of sodium hydroxide and extracted with dichloromethane. The combined organic layers were dried ($MgSO_4$) and concentrated to dryness to give a clear gum (400 mg). A sample (80 mg) of the crude product was further purified by preparative HPLC to give the *title compound* (55.3 mg) as a clear gum. δ_H (DMSO-d_6) 9.02 (1H, d, *J* 1.83 Hz), 8.99 (1H, d, *J* 1.83 Hz), 8.39 (1H, s), 8.28-8.25 (1H, m, HCOOH), 8.26-8.20 (2H, m), 8.05 (1H, s), 7.80-7.76 (1H, m), 7.57-7.49 (4H, m), 7.36 (2H, t, *J* 7.52 Hz), 7.25 (1H, t, *J* 7.33 Hz), 5.35 (1H, s), NH_2 not visible. LCMS (ES+) 312 $(M+H)^+$, 2.04 minutes (*Method 2*).

EXAMPLE 136

(*R*)-*N*,*N*-Dimethyl-1-phenyl-1-[3-(quinoxalin-6-yl)phenyl]methanamine

Example 135 (80 mg, 0.26 mmol), formic acid (3 mL) and formaldehyde (1.5 mL, 37% aq) were combined in a sealed tube and heated to 80°C for 18 h. The reaction mixture was then concentrated to dryness and purified by preparative HPLC to give the *title compound* (46.7 mg, 53%) as a brown gum. δ_H (DMSO-d_6) 9.01 (1H, d, *J* 1.86 Hz), 8.97 (1H, d, *J* 1.85 Hz), 8.33 (1H, d, *J* 1.81 Hz), 8.22-8.20 (2H, m), 7.97 (1H, t, *J* 1.86 Hz), 7.74 (1H, dt, *J* 7.55, 1.64 Hz), 7.59-7.48 (4H, m), 7.35 (2H, t, *J* 7.52 Hz), 7.23 (1H, tt, *J* 7.36, 1.65 Hz), 4.36 (1H, s), 2.24 (6H, s). LCMS (ES+) 340 $(M+H)^+$, 2.1 minutes (*Method 2*).

EXAMPLE 137

(*S*)-*N*,*N*-Dimethyl-1-phenyl-1-[3-(quinoxalin-6-yl)phenyl]methanamine

Prepared from *Intermediate 45* (80 mg, 0.26 mmol), formic acid (3 mL) and formaldehyde (1.5 mL, 37% aq) by the method of *Example 136* to give the *title compound* (52.4 mg, 59%) as a beige solid. δ_H (DMSO-d_6) 9.00 (1H, d, *J* 4.86 Hz), 8.97 (1H, d, *J* 5.15 Hz), 8.33 (1H, s), 8.24-8.17 (2H, m), 7.97 (1H, s), 7.74 (1H, d, *J* 7.75 Hz), 7.60-7.48

(4H, m), 7.35 (2H, t, *J* 7.53 Hz), 7.23 (1H, t, *J* 7.31 Hz), 4.36 (1H, s), 2.24 (6H, s). LCMS (ES+) 340 $(M+H)^+$, 2.08 minutes (*Method 2*).

EXAMPLE 138

(*R*)-*N*-{Phenyl[3-(quinoxalin-6-yl)phenyl]methyl}acetamide

Example 135 (80 mg, 0.26 mmol), dichloromethane (2 mL), triethylamine (140 μL, 1.00 mmol) and acetyl chloride (35 μL, 0.5 mmol) were combined and stirred at room temperature for 18 h. The reaction mixture was then concentrated to dryness and purified by preparative HPLC to give the *title compound* (57.3 mg, 62%) as an off-white solid. δ_H (DMSO-d_6) 9.00 (1H, d, *J* 1.90 Hz), 8.97 (1H, d, *J* 1.96 Hz), 8.72 (1H, d, *J* 8.70 Hz), 8.36 (1H, s), 8.27-8.16 (2H, m), 7.88 (1H, s), 7.81 (1H, d, *J* 7.68 Hz), 7.55 (1H, t, *J* 7.62 Hz), 7.46-7.34 (4H, m), 7.29 (1H, t, *J* 6.70 Hz), 6.31 (1H, d, *J* 8.60 Hz), 3.23 (1H, d, *J* 4.48 Hz), 2.02 (3H, s). LCMS (ES+) 354 $(M+H)^+$, 3.12 minutes (*Method 2*).

EXAMPLE 139

(*R*)-6-{3-[Phenyl(pyrrolidin-1-yl)methyl]phenyl}quinoxaline

Example 135 (80 mg, 0.26 mmol), DME (5 mL), potassium carbonate (200 mg, 0.26 mmol) and 1,4-dibromobutane (31 μL, 0.26 mmol) were combined in a sealed tube and heated to 80°C for 18 h. Additional 1,4-dibromobutane (120 μL) was then added and heating to 80°C was continued for 4 days. The mixture was filtered. The filtrate was concentrated to dryness and purified by preparative HPLC to give the *title compound* (25.4 mg, 33%) as a clear solid. δ_H ($CDCl_3$) 8.83 (1H, d, *J* 1.87 Hz), 8.80 (1H, d, *J* 1.92 Hz), 8.31 (1H, d, *J* 2.02 Hz), 8.17 (1H, d, *J* 8.65 Hz), 8.10 (1H, s), 8.01 (1H, s), 7.63 (3H, m), 7.49-7.41 (1H, m), 7.36-7.28 (2H, m), 7.26 (1H, masked by $CHCl_3$), 7.23 (1H, s), 4.54 (1H, s), 2.75 (4H, s), 1.94 (4H, s). LCMS (ES+) 295 $(M+H)^+$, 2.17 minutes (*Method 2*).

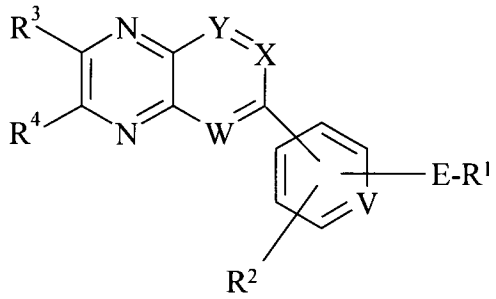
EXAMPLE 140

(*R*)-1-Ethyl-3-{phenyl[3-(quinoxalin-6-yl)phenyl]methyl}urea

Example 135 (80 mg, 0.26 mmol), dichloromethane (5 mL) and ethyl isocyanate (20 μL, 0.26 mmol) were combined and stirred at room temperature for 4 h. The reaction mixture was then concentrated to dryness and purified by preparative HPLC to give the *title compound* (39.2 mg, 45%) as an off-white solid. δ_H (DMSO-d_6) 9.03 (1H, d, *J* 1.86 Hz), 8.99 (1H, d, *J* 1.86 Hz), 8.36 (1H, s), 8.25-8.19 (2H, m), 7.85 (1H, s), 7.80 (1H, d, *J* 7.73 Hz), 7.54 (1H, t, *J* 7.66 Hz), 7.42-7.34 (4H, m), 7.29-7.24 (1H, m), 7.02 (1H, d, *J* 8.59 Hz), 6.08 (1H, d, *J* 8.56 Hz), 5.92 (1H, t, *J* 5.57 Hz), 3.12-3.03 (2H, m), 1.56 (1H, masked by H_2O), 1.04 (3H, t, *J* 7.12 Hz). LCMS (ES+) 338 $(M+H)^+$, 2.88 minutes (*Method 1*).

Claims:

1. A compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof:



(I)

wherein

V represents N or CH;

W represents N or C-R^5;

X represents N or C-R^6; and

Y represents N or C-R^7; provided that no more than one of W, X and Y represents N at any one time;

E represents a covalent bond, -O-, -N(R^8)-, -C(O)-, -C(=N-OR^9)-, -C(O)N(R^8)-, -N(R^8)C(O)-, -S-, -S(O)-, -S$(O)_2$-, -S$(O)_2$N(R^8)- or -N(R^8)S$(O)_2$-; or E represents an optionally substituted straight-chained or branched alkylene chain containing 1 to 5 carbon atoms; or E represents an optionally substituted straight-chained or branched heteroalkylene chain containing 1 to 5 carbon atoms and one or more heteroatoms independently selected from O, S and -N(R^8)-;

R^1 represents -OR^9, -N$R^c R^d$, -N(R^8)(OR^9), -NR^dCOR^a, -CO_2R^b, -N$R^d CO_2R^b$, -CON$R^c R^d$, -NHCON$R^c R^d$ or -SR^e; or R^1 represents C_{3-7} cycloalkyl, aryl, C_{3-7} heterocycloalkyl or heteroaryl, any of which groups may be optionally substituted by one or more substituents;

R^2 represents hydrogen, halogen, cyano, trifluoromethyl, difluoromethoxy, trifluoromethoxy, -N$R^c R^d$, -COR^a, -CO_2R^b, -CON$R^c R^d$ or -NR^dCOR^a; or R^2 represents C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, 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;

R^3 and R^4 independently represent hydrogen or C_{1-6} alkyl;

R^5, R^6 and R^7 independently represent hydrogen, halogen or C_{1-6} alkyl;

R^8 represents hydrogen, trifluoromethyl, $-COR^a$, $-CO_2R^b$, $-CONR^cR^d$ or $-SO_2R^e$; or R^8 represents 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;

R^9 represents hydrogen; or C_{1-6} alkyl, aryl(C_{1-6})alkyl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents;

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

R^b represents hydrogen; or optionally substituted C_{1-6} alkyl;

R^c represents hydrogen; or C_{1-6} alkyl, aryl, aryl(C_{1-6})alkyl, heteroaryl, heteroaryl(C_{1-6})alkyl or (aryl)(heteroaryl)(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents;

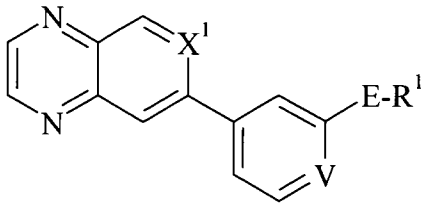
R^d represents hydrogen or C_{1-6} alkyl; and

R^e represents C_{1-6} alkyl.

2. A compound as claimed in claim 1 wherein R^2 represents hydrogen, halogen, trifluoromethoxy, $-NR^cR^d$ or $-NR^dCOR^a$; or R^2 represents C_{1-6} alkyl, C_{1-6} alkoxy, aryl or C_{3-7} heterocycloalkyl, any of which groups may be optionally substituted by one or more substituents; and

R^a, R^c and R^d are as defined in claim 1.

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



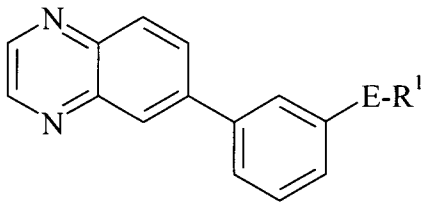
(IIA)

wherein

X^1 represents N or C-R^6; and

V, E, R^1 and R^6 are as defined in claim 1.

4. A compound as claimed in claim 3 represented by formula (IIB), or a pharmaceutically acceptable salt or solvate thereof:

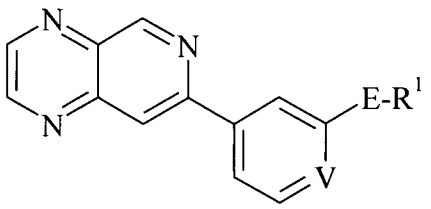


(IIB)

wherein

E and R^1 are as defined in claim 1.

5. A compound as claimed in claim 3 represented by formula (IIC), or a pharmaceutically acceptable salt or solvate thereof:



(IIC)

wherein

V, E and R^1 are as defined in claim 1.

6. A compound as claimed in any one of the preceding claims wherein E represents a covalent bond, -N(R^8)-, -C(O)-, -C(=N-OR^9)-, -C(O)N(R^8)-, -S-, -S(O)$_2$- or -S(O)$_2$N(R^8)-; or E represents an optionally substituted straight-chained or branched alkylene chain containing 1 to 5 carbon atoms; or E represents an optionally substituted straight-chained or branched heteroalkylene chain containing 1 to 5 carbon atoms and one or more heteroatoms independently selected from O, S and -N(R^8)-; and

R^8 and R^9 are as defined in claim 1.

7. A compound as claimed in any one of the preceding claims wherein R^1 represents -OR^9, -N$R^c$$R^d$, -N$R^d$C(O)$R^a$, -C(O)O$R^b$, -N$R^d$C(O)O$R^b$, -NHC(O)N$R^c$$R^d$ or -SR^e; or R^1 represents C_{3-7} cycloalkyl, aryl, C_{3-7} heterocycloalkyl or heteroaryl, any of which groups may be optionally substituted by one or more substituents; and

R^9, R^a, R^b, R^c, R^d and R^e are as defined in claim 1.

8. A compound as claimed in claim 7 wherein R^1 represents C_{3-7} cycloalkyl, aryl, C_{3-7} heterocycloalkyl or heteroaryl, any of which groups may be optionally substituted by one or more substituents.

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

10. A compound of formula (I) as defined in claim 1, or a pharmaceutically acceptable salt or solvate thereof, for use in therapy.

11. A compound of formula (I) as defined in claim 1, 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.

12. A pharmaceutical composition comprising a compound of formula (I) as defined in claim 1, or a pharmaceutically acceptable salt or solvate thereof, in association with a pharmaceutically acceptable carrier.

13. The use of a compound of formula (I) as defined in claim 1, 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.

14. 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 a pharmaceutically acceptable salt or solvate thereof.