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(72) **Inventeurs/Inventors:**
BENTLEY, JONATHAN MARK, GB;
BROOKINGS, DANIEL CHRISTOPHER, GB;
BROWN, JULIEN ALISTAIR, GB;
CAIN, THOMAS PAUL, GB;
CHOVATIA, PRAFUL TULSHI, GB;
FOLEY, ANNE MARIE, GB;

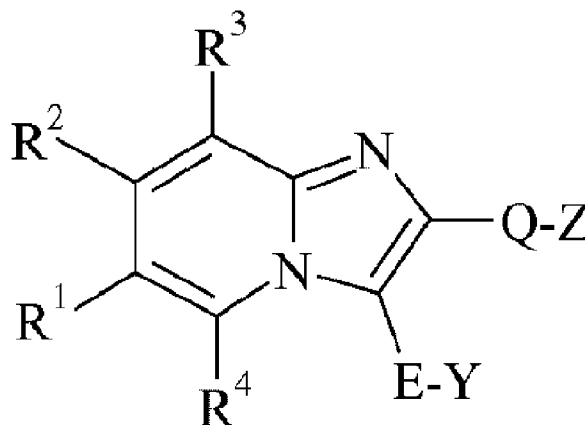
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(73) **Propriétaire/Owner:**
UCB BIOPHARMA SRL, BE

(74) **Agent:** ROBIC

(54) **Titre :** DERIVES D'IMIDAZOPYRIDINE UTILISABLES EN TANT QUE MODULATEURS DE L'ACTIVITE TNF

(54) **Title:** IMIDAZOPYRIDINE DERIVATIVES AS MODULATORS OF TNF ACTIVITY



(I)

(57) **Abrégé/Abstract:**

A series of imidazo[1,2-a]pyridine derivatives of formula (I), being potent modulators of human TNF α activity, are accordingly of benefit in the treatment and/or prevention of various human ailments, including autoimmune and inflammatory disorders;

(72) **Inventeurs(suite)/Inventors(continued):** GALLIMORE, ELLEN OLIVIA, GB; GLEAVE, LAURA JANE, GB; HEIFETZ, ALEXANDER, GB; HORSLEY, HELEN TRACEY, GB; HUTCHINGS, MARTIN CLIVE, GB; JACKSON, VICTORIA ELIZABETH, GB; JOHNSON, JAMES ANDREW, GB; JOHNSTONE, CRAIG, GB; KROEPLIEN, BORIS, GB; LECOMTE, FABIEN CLAUDE, GB; LEIGH, DEBORAH, GB; LOWE, MARTIN ALEXANDER, GB; MADDEN, JAMES, GB; PORTER, JOHN ROBERT, GB; QUINCEY, JOANNA RACHEL, GB; REED, LAURA CLAIRE, GB; REUBERSON, JAMES THOMAS, GB; RICHARDSON, ANTHONY JOHN, GB; RICHARDSON, SARAH EMILY, GB; SELBY, MATTHEW DUNCAN, GB; SHAW, MICHAEL ALAN, GB; ZHU, ZHAONING, GB

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neurological and neurodegenerative disorders; pain and nociceptive disorders; cardiovascular disorders; metabolic disorders; ocular disorders; and oncological disorders.

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(71) Applicant: UCB PHARMA S.A. [BE/BE]; 60 Allée de la Recherche, B-1070 Brussels (BE).

(72) Inventors: **BENTLEY, Jonathan Mark**; c/o Evotec (UK) Ltd, 114 Innovation Drive, Milton Park, Abingdon Oxfordshire OX14 4RZ (GB). **BROOKINGS, Daniel Christopher**; c/o IPD, UCB Celltech, 208 Bath Road, Slough Berkshire SL1 3WE (GB). **BROWN, Julien Alistair**; c/o IPD, UCB Celltech, 208 Bath Road, Slough Berkshire SL1 3WE (GB). **CAIN, Thomas Paul**; c/o Evotec (UK) Ltd, 114 Innovation Drive, Milton Park, Abingdon Oxfordshire OX14 4RZ (GB). **CHOVATIA, Praful Tulshi**; c/o Evotec (UK) Ltd, 114 Innovation Drive, Milton Park, Abingdon Oxfordshire OX14 4RZ (GB). **FOLEY, Anne Marie**; c/o IPD, UCB Celltech, 208 Bath Road, Slough Berkshire SL1 3WE (GB). **GALLIMORE, Ellen Olivia**; c/o IPD, UCB Celltech, 208 Bath Road, Slough Berkshire SL1 3WE (GB). **GLEAVE, Laura Jane**; c/o Evotec (UK) Ltd, 114 Innovation Drive, Milton Park, Abingdon Oxfordshire OX14 4RZ (GB). **HEIFETZ, Alexander**; c/o Evotec (UK) Ltd, 114 Innovation Drive, Milton Park, Abingdon Oxfordshire OX14 4RZ (GB). **HORSLEY, Helen Tracey**; c/o IPD, UCB Celltech, 208 Bath Road, Slough Berkshire SL1 3WE (GB). **HUTCHINGS, Martin Clive**; c/o IPD, UCB Celltech, 208 Bath Road, Slough Berkshire SL1 3WE (GB). **JACKSON, Victoria Elizabeth**; c/o IPD, UCB Celltech, 208 Bath Road, Slough Berkshire SL1 3WE (GB).

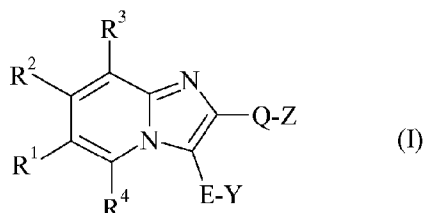
(GB). **JOHNSON, James Andrew**; c/o IPD, UCB Celltech, 208 Bath Road, Slough Berkshire SL1 3WE (GB). **JOHNSTONE, Craig**; c/o Evotec (UK) Ltd, 114 Innovation Drive, Milton Park, Abingdon Oxfordshire OX14 4RZ (GB). **KROEPLIEN, Boris**; c/o IPD, UCB Celltech, 208 Bath Road, Slough Berkshire SL1 3WE (GB). **LECOMTE, Fabien Claude**; c/o IPD, UCB Celltech, 208 Bath Road, Slough Berkshire SL1 3WE (GB). **LEIGH, Deborah**; c/o Evotec (UK) Ltd, 114 Innovation Drive, Milton Park, Abingdon Oxfordshire OX14 4RZ (GB). **LOWE, Martin Alexander**; c/o IPD, UCB Celltech, 208 Bath Road, Slough Berkshire SL1 3WE (GB). **MADDEN, James**; c/o Evotec (UK) Ltd, 114 Innovation Drive, Milton Park, Abingdon Oxfordshire OX14 4RZ (GB). **PORTER, John Robert**; c/o IPD, UCB Celltech, 208 Bath Road, Slough Berkshire SL1 3WE (GB). **QUINCEY, Joanna Rachel**; c/o IPD, UCB Celltech, 208 Bath Road, Slough Berkshire SL1 3WE (GB). **REED, Laura Claire**; c/o Evotec (UK) Ltd, 114 Innovation Drive, Milton Park, Abingdon Oxfordshire OX14 4RZ (GB). **REUBERSON, James Thomas**; c/o IPD, UCB Celltech, 208 Bath Road, Slough Berkshire SL1 3WE (GB). **RICHARDSON, Anthony John**; c/o Evotec (UK) Ltd, 114 Innovation Drive, Milton Park, Abingdon Oxfordshire OX14 4RZ (GB). **RICHARDSON, Sarah Emily**; c/o Evotec (UK) Ltd, 114 Innovation Drive, Milton Park, Abingdon Oxfordshire OX14 4RZ (GB). **SELBY, Matthew Duncan**; c/o IPD, UCB Celltech, 208 Bath Road, Slough Berkshire SL1 3WE (GB). **SHAW, Michael Alan**; c/o IPD, UCB Celltech, 208 Bath Road, Slough Berkshire SL1 3WE (GB). **ZHU, Zhaoning**; c/o IPD, UCB Celltech, 208 Bath Road, Slough Berkshire SL1 3WE (GB).

(74) Agent: **THOMPSON, John**; UCB Celltech, 208 Bath Road, Slough Berkshire SL1 3WE (GB).

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(54) Title: IMIDAZOPYRIDINE DERIVATIVES AS MODULATORS OF TNF ACTIVITY



(57) Abstract: A series of imidazo[1,2-a]pyridine derivatives of formula (I), being potent modulators of human TNF α activity, are accordingly of benefit in the treatment and/or prevention of various human ailments, including autoimmune and inflammatory disorders; neurological and neurodegenerative disorders; pain and nociceptive disorders; cardiovascular disorders; metabolic disorders; ocular disorders; and oncological disorders.



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JUMBO APPLICATIONS / PATENTS

**THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE
THAN ONE VOLUME.**

THIS IS VOLUME __1__ OF __2__

NOTE: For additional volumes please contact the Canadian Patent Office.

IMIDAZOPYRIDINE DERIVATIVES AS MODULATORS OF TNF ACTIVITY

The present invention relates to a class of fused imidazole derivatives, and to their
5 use in therapy. More particularly, this invention is concerned with pharmacologically
active substituted imidazo[1,2-*a*]pyridine derivatives. These compounds are modulators of
the signalling of TNF α , and are accordingly of benefit as pharmaceutical agents, especially
in the treatment of adverse inflammatory and autoimmune disorders, neurological and
neurodegenerative disorders, pain and nociceptive disorders, cardiovascular disorders,
10 metabolic disorders, ocular disorders, and oncological disorders.

TNF α is the prototypical member of the Tumour Necrosis Factor (TNF)
superfamily of proteins that share a primary function of regulating cell survival and cell
death. One structural feature common to all known members of the TNF superfamily is
the formation of trimeric complexes that bind to, and activate, specific TNF superfamily
15 receptors. By way of example, TNF α exists in soluble and transmembrane forms and
signals through two receptors, known as TNFR1 and TNFR2, with distinct functional
endpoints.

Various products capable of modulating TNF α activity are already commercially
available. All are approved for the treatment of inflammatory and autoimmune disorders
20 such as rheumatoid arthritis and Crohn's disease. All currently approved products are
macromolecular and act by inhibiting the binding of human TNF α to its receptor. Typical
macromolecular TNF α inhibitors include anti-TNF α antibodies; and soluble TNF α
receptor fusion proteins. Examples of commercially available anti-TNF α antibodies
include fully human antibodies such as adalimumab (Humira®) and golimumab
25 (Simponi®), chimeric antibodies such as infliximab (Remicade®), and pegylated Fab'
fragments such as certulizumab pegol (Cimzia®). An example of a commercially
available soluble TNF α receptor fusion protein is etanercept (Enbrel®).

TNF superfamily members, including TNF α itself, are implicated in a variety of
physiological and pathological functions that are believed to play a part in a range of
30 conditions of significant medical importance (see, for example, M.G. Tansey & D.E.
Szymkowski, *Drug Discovery Today*, 2009, **14**, 1082-1088; and F.S. Carneiro *et al.*, *J.
Sexual Medicine*, 2010, **7**, 3823-3834).

The compounds in accordance with the present invention, being potent modulators of human TNF α activity, are therefore beneficial in the treatment and/or prevention of various human ailments. These include autoimmune and inflammatory disorders; neurological and neurodegenerative disorders; pain and nociceptive disorders;

5 cardiovascular disorders; metabolic disorders; ocular disorders; and oncological disorders.

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, in one embodiment, the compounds of this invention may be useful as radioligands in assays for detecting

10 pharmacologically active compounds. In an alternative embodiment, certain compounds of this invention may be useful for coupling to a fluorophore to provide fluorescent conjugates that can be utilised in assays (e.g. a fluorescence polarisation assay) for detecting pharmacologically active compounds.

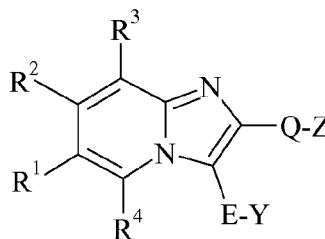
The compounds in accordance with the present invention potentially neutralise the

15 activity of TNF α in a commercially available HEK-293 derived reporter cell line known as HEK-Blue™ CD40L. This cell line is a stable transfectant expressing SEAP (secreted alkaline phosphatase) under the control of the IFN β minimal promoter fused to five NF- κ B binding sites. Secretion of SEAP by these cells is stimulated in a concentration-dependent manner by TNF α . When tested in the HEK-293 bioassay, the compounds of the present

20 invention exhibit an IC₅₀ value of 50 μ M or less, generally of 20 μ M or less, usually of 5 μ M or less, typically of 1 μ M 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* IC₅₀ figure denotes a *more active* compound).

The present invention provides a compound of formula (I) or an *N*-oxide thereof,

25 or a pharmaceutically acceptable salt or solvate thereof, or a glucuronide derivative thereof, or a co-crystal thereof:



(I)

wherein

E represents a covalent bond; or E represents -O-, -S-, -S(O)-, -S(O)₂- or -N(R⁵)-; or E represents an optionally substituted straight or branched C₁₋₄ alkylene chain;

5 Q represents a covalent bond; or Q represents -O-, -S-, -S(O)-, -S(O)₂-, -N(R⁶)-, -C(O)N(R⁶)-, -N(R⁶)C(O)-, -S(O)₂N(R⁶)- or -N(R⁶)S(O)₂-; or Q represents an optionally substituted straight or branched C₁₋₆ alkylene chain optionally comprising one, two or three heteroatom-containing linkages independently selected from -O-, -S-, -S(O)-, -S(O)₂-, -N(R⁶)-, -C(O)N(R⁶)-, -N(R⁶)C(O)-, -S(O)₂N(R⁶)- and -N(R⁶)S(O)₂-;

10 Y represents C₃₋₇ cycloalkyl, aryl, C₃₋₇ heterocycloalkyl or heteroaryl, any of which groups may be optionally substituted by one or more substituents;

Z represents hydrogen, halogen or trifluoromethyl; or Z represents C₁₋₆ alkyl, C₃₋₇ cycloalkyl, aryl, C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkenyl or heteroaryl, any of which groups may be optionally substituted by one or more substituents; or Z represents
15 -Z¹-Z² or -Z¹-C(O)-Z², either of which moieties may be optionally substituted by one or more substituents;

Z¹ represents a divalent radical derived from an aryl, C₃₋₇ heterocycloalkyl or heteroaryl group;

Z² represents aryl, C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkenyl or heteroaryl;

20 R¹, R², R³ and R⁴ independently represent hydrogen, halogen, cyano, nitro, hydroxy, trifluoromethyl, trifluoromethoxy, -OR^a, -SR^a, -SOR^a, -SO₂R^a, -SF₅, -NR^bR^c, -NR^cCOR^d, -NR^cCO₂R^d, -NHCONR^bR^c, -NR^cSO₂R^e, -N(SO₂R^e)₂, -NHSO₂NR^bR^c, -COR^d, -CO₂R^d, -CONR^bR^c, -CON(OR^a)R^b or -SO₂NR^bR^c; or C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇ cycloalkyl, C₄₋₇ cycloalkenyl, C₃₋₇ cycloalkyl(C₁₋₆)alkyl, aryl,
25 aryl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkyl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkenyl, C₄₋₉ heterobicycloalkyl, heteroaryl, heteroaryl(C₁₋₆)alkyl, (C₃₋₇)heterocycloalkyl(C₁₋₆)alkyl-aryl-, heteroaryl(C₃₋₇)heterocycloalkyl-, (C₃₋₇)cycloalkyl-heteroaryl-, (C₃₋₇)cycloalkyl(C₁₋₆)alkyl-heteroaryl-, (C₄₋₇)cycloalkenyl-heteroaryl-, (C₄₋₉)bicycloalkyl-heteroaryl-, (C₃₋₇)heterocycloalkyl-heteroaryl-,
30 (C₃₋₇)heterocycloalkyl(C₁₋₆)alkyl-heteroaryl-, (C₃₋₇)heterocycloalkenyl-heteroaryl-, (C₄₋₉)heterobicycloalkyl-heteroaryl- or (C₄₋₉)spiroheterocycloalkyl-heteroaryl-, any of which groups may be optionally substituted by one or more substituents;

R⁵ and R⁶ independently represent hydrogen or C₁₋₆ alkyl;

R^a represents C₁₋₆ alkyl, aryl, aryl(C₁₋₆)alkyl, heteroaryl or heteroaryl(C₁₋₆)alkyl, any of which groups may be optionally substituted by one or more substituents;

R^b and R^c independently represent hydrogen or trifluoromethyl; or C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl(C₁₋₆)alkyl, aryl, aryl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkyl(C₁₋₆)alkyl, heteroaryl or heteroaryl(C₁₋₆)alkyl, any of which groups may be optionally substituted by one or more substituents; or

R^b and R^c, when taken together with the nitrogen atom to which they are both attached, represent azetidin-1-yl, pyrrolidin-1-yl, oxazolidin-3-yl, isoxazolidin-2-yl, thiazolidin-3-yl, isothiazolidin-2-yl, piperidin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, piperazin-1-yl, homopiperidin-1-yl, homomorpholin-4-yl or homopiperazin-1-yl, any of which groups may be optionally substituted by one or more substituents;

R^d represents hydrogen; or C₁₋₆ alkyl, C₃₋₇ cycloalkyl, aryl, C₃₋₇ heterocycloalkyl or heteroaryl, any of which groups may be optionally substituted by one or more substituents; and

R^e represents C₁₋₆ alkyl, aryl or heteroaryl, any of which groups may be optionally substituted by one or more substituents.

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

R¹, R², R³ and R⁴ independently represent hydrogen, halogen, cyano, nitro, hydroxy, trifluoromethyl, trifluoromethoxy, -OR^a, -SR^a, -SOR^a, -SO₂R^a, -SF₅, -NR^bR^c, -NR^cCOR^d, -NR^cCO₂R^d, -NHCONR^bR^c, -NR^cSO₂R^e, -N(SO₂R^e)₂, -NHSO₂NR^bR^c, -COR^d, -CO₂R^d, -CONR^bR^c, -CON(OR^a)R^b or -SO₂NR^bR^c; or C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇ cycloalkyl, C₄₋₇ cycloalkenyl, C₃₋₇ cycloalkyl(C₁₋₆)alkyl, aryl, aryl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkyl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkenyl, C₄₋₉ heterobicycloalkyl, heteroaryl, heteroaryl(C₁₋₆)alkyl, (C₃₋₇)heterocycloalkyl(C₁₋₆)alkyl-aryl-, heteroaryl-(C₃₋₇)heterocycloalkyl-, (C₃₋₇)cycloalkyl-heteroaryl-, (C₄₋₇)cycloalkenyl-heteroaryl-, (C₃₋₇)heterocycloalkyl-heteroaryl-, (C₃₋₇)heterocycloalkyl(C₁₋₆)alkyl-heteroaryl-, (C₃₋₇)heterocycloalkenyl-heteroaryl-, (C₄₋₉)heterobicycloalkyl-heteroaryl- or (C₄₋₉)spiroheterocycloalkyl-heteroaryl-, any of which groups may be optionally substituted by one or more substituents; and

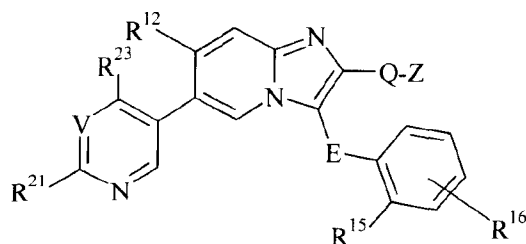
E, Q, Y, Z, R^a, R^b, R^c, R^d and R^e are as defined above.

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

- R^1 , R^2 , R^3 and R^4 independently represent hydrogen, halogen, cyano, nitro,
 5 hydroxy, trifluoromethyl, trifluoromethoxy, $-OR^a$, $-SR^a$, $-SOR^a$, $-SO_2R^a$, $-SF_5$, $-NR^bR^c$,
 $-NR^cCOR^d$, $-NR^cCO_2R^d$, $-NHCONR^bR^c$, $-NR^cSO_2R^e$, $-N(SO_2R^e)_2$, $-NHSO_2NR^bR^c$,
 $-COR^d$, $-CO_2R^d$, $-CONR^bR^c$, $-CON(OR^a)R^b$ or $-SO_2NR^bR^c$; or C_{1-6} alkyl, C_{2-6} alkenyl,
 C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl, 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, C_{3-7}
 10 heterocycloalkenyl, C_{4-9} heterobicycloalkyl, heteroaryl, heteroaryl(C_{1-6})alkyl,
 (C_{3-7}) heterocycloalkyl(C_{1-6})alkyl-aryl-, heteroaryl(C_{3-7})heterocycloalkyl-,
 (C_{4-7}) cycloalkenyl-heteroaryl-, (C_{3-7}) heterocycloalkyl-heteroaryl-, (C_{3-7}) heterocycloalkyl-
 (C_{1-6}) alkyl-heteroaryl-, (C_{3-7}) heterocycloalkenyl-heteroaryl-, (C_{4-9}) heterobicycloalkyl-
 heteroaryl- or (C_{4-9}) spiroheterocycloalkyl-heteroaryl-, any of which groups may be
 15 optionally substituted by one or more substituents; and

E, Q, Y, Z, R^a , R^b , R^c , R^d and R^e are as defined above.

According to one example, the compound is of formula (IIB) or an *N*-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof, or a co-crystal thereof:



20

(IIB)

wherein

- E represents $-N(R^5)-$, $-CH_2-$, $-CH(OH)-$, $-CH(OCH_3)-$, $-CH(OCH_2CO_2H)-$,
 $-CH(NH_2)-$, $-CH(NHCOCH_3)-$, $-CH(CO_2H)-$, $-CH(CO_2benzyl)-$, $-CH(CH_3)-$ or
 25 $-C(CH_3)(OH)-$;

Q represents $-CH_2-$, $-CH(CN)-$, $-CH(OH)-$, $-CH(OCH_3)-$, $-CH_2O-$, $-CH_2N(R^6)-$ or
 $-CH_2OCH_2-$;

Z represents hydrogen, fluoro, trifluoromethyl, methyl, ethyl, *n*-propyl, isopropyl, isobutyl, *tert*-butyl, cyclopropyl, cyclopentyl, cyclohexyl, oxocyclohexyl, phenyl, bromophenyl, cyanophenyl, nitrophenyl, methoxyphenyl, difluoromethoxyphenyl, trifluoromethoxyphenyl, methylenedioxyphenyl, methylsulfonylphenyl, dimethylaminophenyl, acetylaminophenyl, methylsulfonylaminophenyl, carboxyphenyl, aminocarbonylphenyl, methylaminocarbonylphenyl, dimethylaminocarbonylphenyl, aminocarbonylamino-phenyl, tetrahydrofuranyl, oxopyrrolidiny, dimethylaminopyrrolidiny, *tert*-butoxycarbonylpyrrolidiny, indoliny, tetrahydropyrany, piperidiny, ethylpiperidiny, *tert*-butoxycarbonylpiperidiny, aminocarbonylpiperidiny, 2-oxo-3,4-dihydroquinoliny, morpholiny, azocany, oxothiazoliny, fury, hydroxymethylfury, thieny, methylpyrazolyl, dimethylpyrazolyl, 4,5,6,7-tetrahydroindazolyl, benzoxazolyl, methylisoxazolyl, dimethylisoxazolyl, methylthiazolyl, aminothiazolyl, benzothiazolyl, methylbenzothiazolyl, aminobenzothiazolyl, imidazolyl, methylimidazolyl, methylbenzimidazolyl, dimethyl[1,2,4]triazolo[1,5-*a*]pyrimidiny, dimethylaminoethyltetrazolyl, pyridiny, fluoropyridiny, chloropyridiny, cyanopyridiny, methylpyridiny, (cyano)-(methyl)pyridiny, trifluoromethylpyridiny, oxopyridiny, methoxypyridiny, dimethylaminomethylpyridiny, acetylaminopyridiny, carboxypyridiny, methoxycarbonylpyridiny, aminocarbonylpyridiny, (aminocarbonyl)(fluoro)pyridiny, methylaminocarbonylpyridiny, dimethylaminocarbonylpyridiny, hydrazinocarbonylpyridiny, quinoliny, isoquinoliny, (methyl)(oxo)phthalaziny, pyrimidiny, pyraziny, oxopyrrolidinylphenyl, dioxopyrrolidinylphenyl, (hydroxy)(oxo)pyrrolidinylphenyl, (amino)(oxo)pyrrolidinylphenyl, (oxo)oxazolidinylphenyl, oxoimidazolidinylphenyl, imidazolinyphenyl, methylthiazolylphenyl, formylthiazolylphenyl, imidazolylphenyl, tetrazolylphenyl, phenylpyrrolidinyl, hydroxyphenylpiperaziny, (methyl)(phenyl)-pyrazolyl, oxoimidazolidinylthiazolyl, hydroxyphenyltriazolyl, morpholinytetrazolyl, oxopyrrolidinylpyridiny, (oxo)oxazolidinylpyridiny, oxoimidazolidinylpyridiny, pyridinythiazolyl, pyridinytetrazolyl, morpholiny carbonylphenyl or methylsulfonylpyridiny;

V represents C-R²² or N;

R⁵ and R⁶ independently represent hydrogen or C₁₋₆ alkyl;

R¹² represents hydrogen, fluoro, chloro, trifluoromethyl, methyl or ethoxycarbonylethyl;

R¹⁵ and R¹⁶ independently represent hydrogen, halogen, cyano, nitro, C₁₋₆ alkyl, trifluoromethyl, hydroxy, C₁₋₆ alkoxy, difluoromethoxy, trifluoromethoxy, C₁₋₆ alkylthio, C₁₋₆ alkylsulfinyl, C₁₋₆ alkylsulfonyl, amino, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino, phenylamino, C₂₋₆ alkylcarbonylamino, C₁₋₆ alkylsulfonylamino, formyl, C₂₋₆ alkylcarbonyl, C₃₋₆ cycloalkylcarbonyl, C₃₋₆ heterocycloalkylcarbonyl, carboxy, C₂₋₆ alkoxy carbonyl, aminocarbonyl, C₁₋₆ alkylaminocarbonyl, di(C₁₋₆)alkylaminocarbonyl, aminosulfonyl, C₁₋₆ alkylaminosulfonyl or di(C₁₋₆)alkylaminosulfonyl;

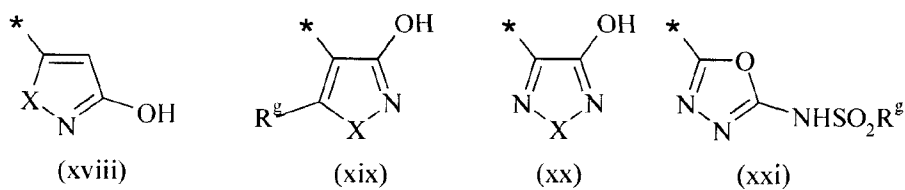
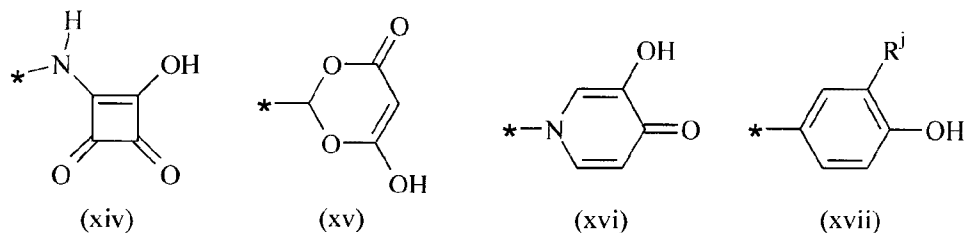
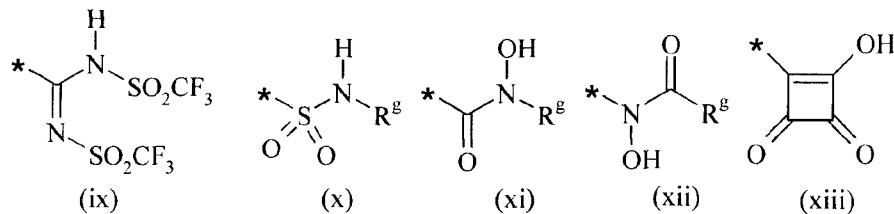
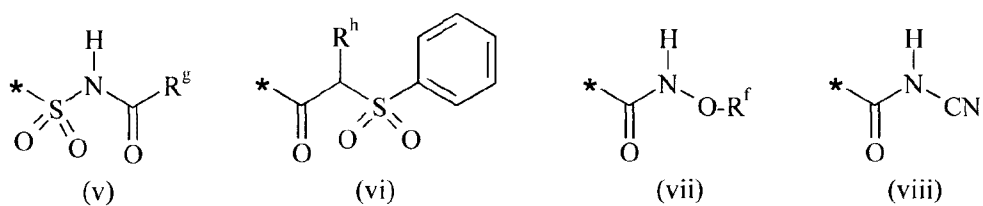
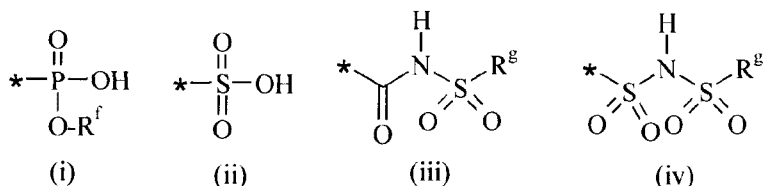
R²¹ represents hydrogen, halogen, halo(C₁₋₆)alkyl, cyano, C₁₋₆ alkyl, trifluoromethyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, hydroxy, hydroxy(C₁₋₆)alkyl, C₁₋₆ alkoxy, (C₁₋₆)alkoxy-
 10 (C₁₋₆)alkyl, difluoromethoxy, trifluoromethoxy, trifluoroethoxy, carboxy(C₃₋₇)cycloalkyl-
 oxy, C₁₋₆ alkylthio, C₁₋₆ alkylsulphonyl, (C₁₋₆)alkylsulphonyl(C₁₋₆)alkyl, amino, amino-
 (C₁₋₆)alkyl, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino, (C₁₋₆)alkoxy(C₁₋₆)alkylamino, *N*-(C₁₋₆)-
 alkyl]-*N*-[hydroxy(C₁₋₆)alkyl]amino, C₂₋₆ alkylcarbonylamino, (C₂₋₆)alkylcarbonylamino-
 (C₁₋₆)alkyl, C₂₋₆ alkoxy carbonylamino, *N*-(C₁₋₆)alkyl]-*N*-[carboxy(C₁₋₆)alkyl]amino,
 15 carboxy(C₃₋₇)cycloalkylamino, carboxy(C₃₋₇)cycloalkyl(C₁₋₆)alkylamino, C₁₋₆ alkyl-
 sulphonylamino, C₁₋₆ alkylsulphonylamino(C₁₋₆)alkyl, formyl, C₂₋₆ alkylcarbonyl,
 (C₂₋₆)alkylcarbonyloxy(C₁₋₆)alkyl, carboxy, carboxy(C₁₋₆)alkyl, C₂₋₆ alkoxy carbonyl,
 morpholinyl(C₁₋₆)alkoxy carbonyl, C₂₋₆ alkoxy carbonyl(C₁₋₆)alkyl, C₂₋₆ alkoxy carbonyl-
 methylidenyl, aminocarbonyl, C₁₋₆ alkylaminocarbonyl, di(C₁₋₆)alkylaminocarbonyl,
 20 aminosulphonyl, C₁₋₆ alkylaminosulphonyl or di(C₁₋₆)alkylaminosulphonyl; or R²¹
 represents (C₃₋₇)cycloalkyl, (C₃₋₇)cycloalkyl(C₁₋₆)alkyl, (C₄₋₇)cycloalkenyl,
 (C₄₋₉)bicycloalkyl, (C₃₋₇)heterocycloalkyl, (C₃₋₇)heterocycloalkenyl,
 (C₄₋₉)heterobicycloalkyl or (C₄₋₉)spiroheterocycloalkyl, any of which groups may be
 optionally substituted by one or more substituents independently selected from the group
 25 consisting of halogen, cyano, cyano(C₁₋₆)alkyl, C₁₋₆ alkyl, trifluoromethyl, trifluoroethyl,
 C₂₋₆ alkenyl, hydroxy, C₁₋₆ alkoxy, difluoromethoxy, trifluoromethoxy, trifluoroethoxy, C₁₋₆
 alkylthio, C₁₋₆ alkylsulphonyl, (C₁₋₆)alkyl-sulphonyl(C₁₋₆)alkyl, oxo, amino, C₁₋₆
 alkylamino, di(C₁₋₆)alkylamino, C₂₋₆ alkylcarbonyl-amino, C₂₋₆ alkoxy carbonylamino, C₁₋₆
 alkylsulphonylamino, formyl, C₂₋₆ alkylcarbonyl, carboxy, carboxy(C₁₋₆)alkyl, C₂₋₆
 30 alkoxy carbonyl, C₂₋₆ alkoxy carbonyl(C₁₋₆)alkyl, a carboxylic acid isostere or prodrug
 moiety Ω as defined below, aminocarbonyl, C₁₋₆ alkyl-aminocarbonyl, di(C₁₋₆)
 alkylaminocarbonyl, aminosulphonyl, di(C₁₋₆)alkylamino-sulphonyl, -(C₁₋₆)alkyl- Ω ,
 halo(C₁₋₆)alkyl, nitro(C₁₋₆)alkyl, hydroxy(C₁₋₆)alkyl,

(C₂₋₆)alkylcarbonylamino(C₁₋₆)alkyl, morpholinyl(C₁₋₆)alkoxycarbonyl, C₂₋₆ alkoxy-carbonylmethylenyl and C₁₋₆ alkoxyaminocarbonyl;

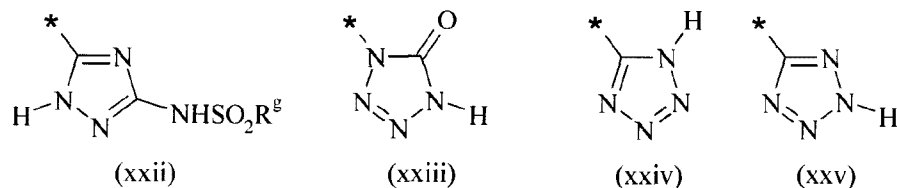
R²² represents hydrogen, halogen or C₁₋₆ alkyl; and

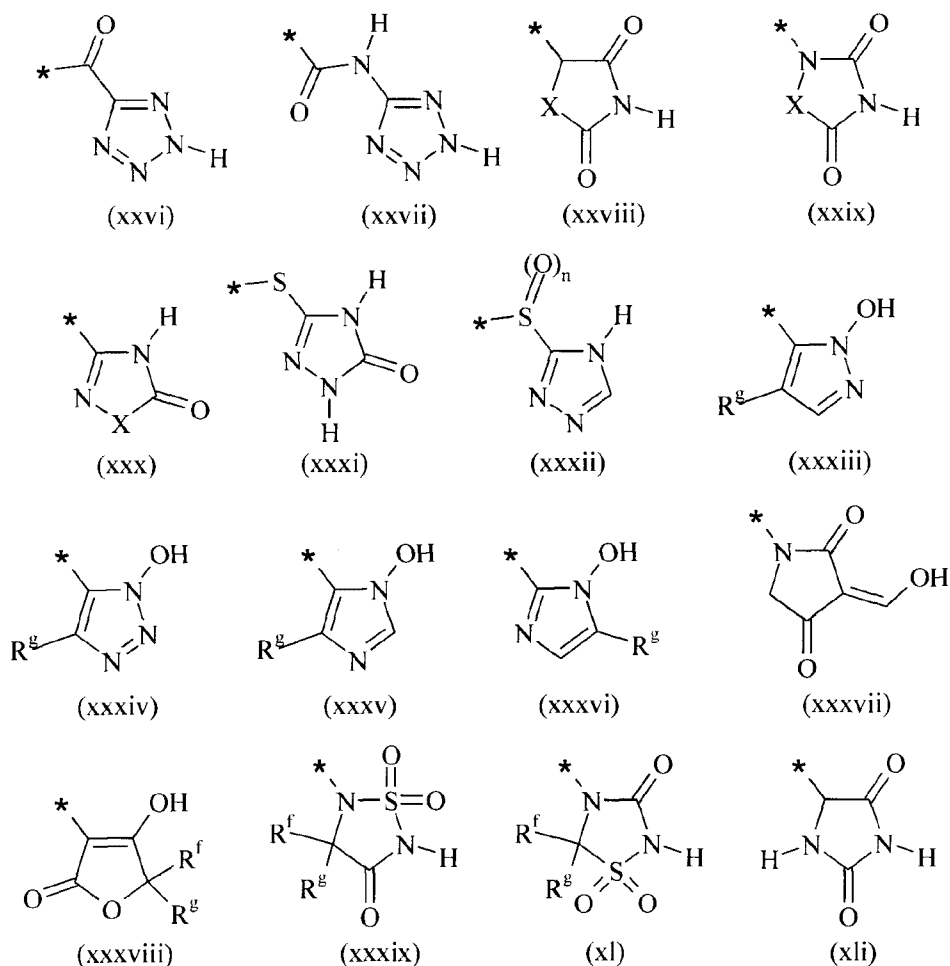
R²³ represents hydrogen, C₁₋₆ alkyl, trifluoromethyl or C₁₋₆ alkoxy;

5 where Ω represents one of the following groups (i)-(xli):



10





5 wherein

the asterisk (*) represents the site of attachment to the remainder of the molecule;

n is zero, 1 or 2;

X represents oxygen or sulphur;

R^f represents hydrogen, C₁₋₆ alkyl or -CH₂CH(OH)CH₂OH;

10 R^g represents C₁₋₆ alkyl, trifluoromethyl, -CH₂CH₂F, -CH₂CHF₂, -CH₂CF₃ or -CF₂CF₃;

R^h represents hydrogen, cyano or -CO₂R^d, in which R^d is hydrogen, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, aryl, C₃₋₇ heterocycloalkyl or heteroaryl any of which groups may be optionally substituted by one or more substituents selected from the group consisting of halogen, C₁₋₆

15 alkyl, C₁₋₆ alkoxy, oxo, C₂₋₆ alkylcarbonyloxy and di(C₁₋₆)alkylamino; and

R^j represents hydrogen or halogen.

The present invention also provides a compound of formula (I) as defined above or an *N*-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof, or a glucuronide derivative thereof, or a co-crystal thereof, for use in the treatment and/or prevention of disorders for which the administration of a modulator of TNF α function is indicated. For example, the compound is of formula (IIB).

In another aspect, the present invention provides a compound of formula (I) as defined above or an *N*-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof, or a glucuronide derivative thereof, or a co-crystal thereof, for use in the treatment and/or prevention of an inflammatory or autoimmune disorder, a neurological or neurodegenerative disorder, pain or a nociceptive disorder, a cardiovascular disorder, a metabolic disorder, an ocular disorder, or an oncological disorder. For example, the compound is of formula (IIB).

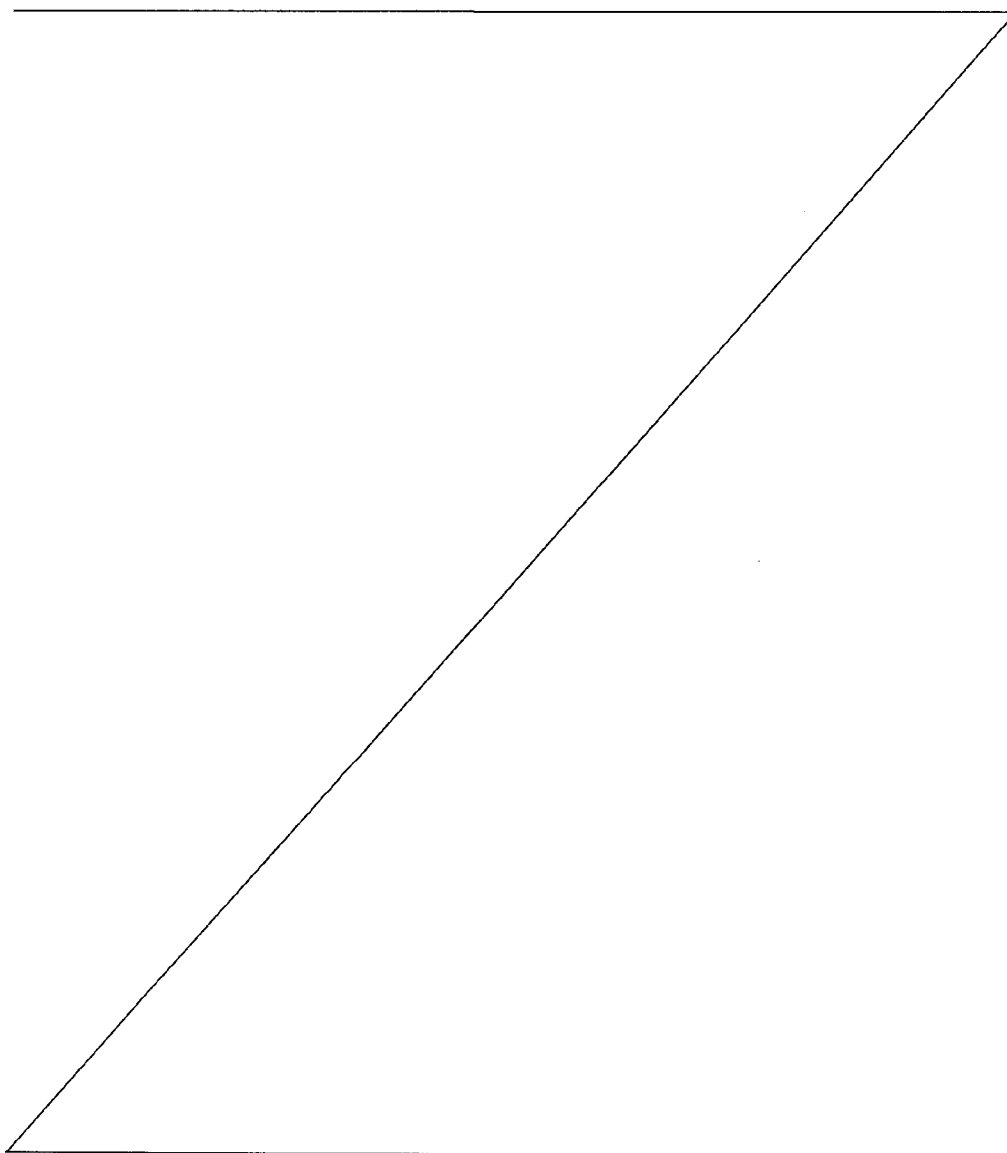
The invention also further provides the use of a compound of formula (IIB) as defined herein or an *N*-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof, or a co-crystal thereof, in the treatment and/or prevention of disorders for which the administration of a modulator of TNF α function is indicated.

In a further aspect, the invention provides the use of a compound of formula (IIB) as defined herein or an *N*-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof, or a co-crystal thereof, in the treatment and/or prevention of an inflammatory or autoimmune disorder, a neurological or neurodegenerative disorder, pain or a nociceptive disorder, a cardiovascular disorder, a metabolic disorder, an ocular disorder, or an oncological disorder.

In yet another aspect, the invention provides the use of a compound of formula (IIB) as defined herein or an *N*-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof, or a co-crystal thereof, in the manufacture of a medicament for the treatment and/or prevention of disorders for which the administration of a modulator of TNF α function is indicated.

In another aspect, the invention provides the use of a compound of formula (IIB) as defined herein or an *N*-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof, or a co-crystal thereof, in the manufacture of a medicament for the treatment and/or prevention of an inflammatory or autoimmune disorder, a neurological or neurodegenerative disorder, pain or a nociceptive disorder, a cardiovascular disorder, a metabolic disorder, an ocular disorder, or an oncological disorder.

The present invention also provides a method for the treatment and/or prevention of disorders for which the administration of a modulator of TNF α function is indicated which comprises administering to a patient in need of such treatment an effective amount of a compound of formula (I) as defined above or an *N*-oxide thereof, or a
5 pharmaceutically acceptable salt or solvate thereof, or a glucuronide derivative thereof, or a co-crystal thereof.



In another aspect, the present invention provides a method for the treatment and/or prevention of an inflammatory or autoimmune disorder, a neurological or neuro-degenerative disorder, pain or a nociceptive disorder, a cardiovascular disorder, a metabolic disorder, an ocular disorder, or an oncological disorder, which comprises
5 administering to a patient in need of such treatment an effective amount of a compound of formula (I) as defined above or an *N*-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof, or a glucuronide derivative thereof, or a co-crystal thereof.

Where any of the groups in the compounds of formula (I) above is stated to be optionally substituted, this group may be unsubstituted, or substituted by one or more
10 substituents. Typically, such groups will be unsubstituted, or substituted by one or two substituents.

For use in medicine, the salts of the compounds of formula (I) will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds of use in the invention or of their pharmaceutically acceptable salts.
15 Suitable pharmaceutically acceptable salts of the compounds of use in this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound of use in 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.
20 Furthermore, where the compounds of use in 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; ammonium salts; and salts formed with suitable organic ligands, e.g. quaternary ammonium salts, and meglumine salts.

25 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.
30 Alternatively, the solvates of the compounds of formula (I) may be formed with water, in which case they will be hydrates.

The present invention also includes co-crystals within its scope. The technical term "co-crystal" is used to describe the situation where neutral molecular components are

present within a crystalline compound in a definite stoichiometric ratio. The preparation of pharmaceutical co-crystals enables modifications to be made to the crystalline form of an active pharmaceutical ingredient, which in turn can alter its physicochemical properties without compromising its intended biological activity (see *Pharmaceutical Salts and Co-crystals*, ed. J. Wouters & L. Quere, RSC Publishing, 2012). Typical examples of co-crystal formers, which may be present in the co-crystal alongside the active pharmaceutical ingredient, include *L*-ascorbic acid, citric acid, glutaric acid, urea and nicotinamide.

The present invention includes within its scope prodrugs of the compounds of formula (I) above. In general, such prodrugs will be functional derivatives of the compounds of formula (I) which are readily convertible *in vivo* into the required compound of formula (I). Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in *Design of Prodrugs*, ed. H. Bundgaard, Elsevier, 1985.

Suitable alkyl groups which may be present on the compounds of use in the invention include straight-chained and branched C₁₋₆ alkyl groups, for example C₁₋₄ 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 “C₁₋₆ alkoxy”, “C₁₋₆ alkylthio”, “C₁₋₆ alkylsulphonyl” and “C₁₋₆ alkylamino” are to be construed accordingly.

The expression “C₁₋₄ alkylene chain” refers to a divalent straight or branched alkylene chain containing 1 to 4 carbon atoms. Typical examples include methylene, ethylene, methylenemethylene, ethylenemethylene and dimethylenemethylene.

Suitable C₂₋₆ alkenyl groups include vinyl and allyl.

Suitable C₂₋₆ alkynyl groups include ethynyl, propargyl and butynyl.

Suitable C₃₋₇ cycloalkyl groups, which may comprise benzo-fused analogues thereof, include cyclopropyl, cyclobutyl, benzocyclobutenyl, cyclopentyl, indanyl, cyclohexyl and cycloheptyl.

Suitable C₄₋₇ cycloalkenyl groups include cyclobutenyl, cyclopentenyl, cyclohexenyl and cycloheptenyl.

Typical bicycloalkyl groups include bicyclo[3.1.0]hexanyl, bicyclo[4.1.0]heptanyl and bicyclo[2.2.2]octanyl.

Suitable aryl groups include phenyl and naphthyl, preferably phenyl.

Suitable aryl(C₁₋₆)alkyl groups include benzyl, phenylethyl, phenylpropyl and naphthylmethyl.

The term “C₃₋₇ heterocycloalkyl” as used herein refers to saturated monocyclic rings containing 3 to 7 carbon atoms and at least one heteroatom selected from oxygen, sulphur and nitrogen, and may comprise benzo-fused analogues thereof. Suitable heterocycloalkyl groups include azetidiny, tetrahydrofuranyl, dihydrobenzofuranyl, pyrrolidinyl, indolinyl, oxazolidinyl, thiazolidinyl, imidazolidinyl, tetrahydropyranyl, chromanyl, tetrahydrothiopyranyl, piperidinyl, 1,2,3,4-tetrahydroquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, piperazinyl, 1,2,3,4-tetrahydroquinoxalinyl, homopiperazinyl, morpholinyl, benzoxazinyl, thiomorpholinyl, diazepanyl, thiadiazepanyl and azocanyl. Additional values include oxetanyl, dihydrobenzothienyl, isoindolinyl, isothiazolidinyl, hexahydro-[1,2,5]thiadiazolo[2,3-*a*]pyrazinyl, azepanyl and oxazepanyl.

The term “C₃₋₇ heterocycloalkenyl” as used herein refers to monounsaturated or polyunsaturated monocyclic rings containing 3 to 7 carbon atoms and at least one heteroatom selected from oxygen, sulphur and nitrogen, and may comprise benzo-fused analogues thereof. Suitable heterocycloalkenyl groups include thiazolinyl, imidazolinyl, dihydropyranyl, dihydrothiopyranyl and 1,2,3,6-tetrahydropyridinyl.

Typical heterobicycloalkyl groups include 3-azabicyclo[3.1.0]hexanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, quinuclidinyl, 2-oxa-5-azabicyclo[2.2.2]octanyl, 8-azabicyclo[3.2.1]octanyl, 3,8-diazabicyclo[3.2.1]octanyl and 3,9-diazabicyclo[4.2.1]nonanyl. Additional values include 6-azabicyclo[3.2.0]heptanyl, 3-azabicyclo[3.1.1]heptanyl, 3-azabicyclo[4.1.0]heptanyl, 2-oxabicyclo[2.2.2]octanyl, 3-azabicyclo[3.2.1]octanyl, 3-oxa-8-azabicyclo[3.2.1]octanyl, 3,6-diazabicyclo[3.2.2]nonanyl and 3-oxa-7-azabicyclo[3.3.1]nonanyl.

Suitable spiroheterocycloalkyl groups include 2-azaspiro[3.3]heptanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 2-oxa-6-azaspiro[3.4]octanyl, 2-oxa-6-azaspiro[3.5]nonanyl and 2-oxa-7-azaspiro[3.5]nonanyl. Additional values include 5-azaspiro[2.3]hexanyl, 5-azaspiro[2.4]heptanyl, 7-oxa-2-azaspiro[3.5]nonanyl and 2,4,8-triazaspiro[4.5]decanyl.

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, pyrazolo[3,4-*d*]pyrimidinyl, indazolyl, 4,5,6,7-tetrahydroindazolyl, oxazolyl, benzoxazolyl, isoxazolyl, thiazolyl, benzothiazolyl,

isothiazolyl, imidazolyl, benzimidazolyl, imidazo[1,2-*a*]pyridinyl, imidazo[4,5-*b*]pyridinyl, purinyl, imidazo[1,2-*a*]pyrimidinyl, imidazo[1,2-*a*]pyrazinyl, oxadiazolyl, thiadiazolyl, triazolyl, [1,2,4]triazolo[1,5-*a*]pyrimidinyl, benzotriazolyl, tetrazolyl, pyridinyl, quinolinyl, isoquinolinyl, naphthyridinyl, pyridazinyl, cinnolinyl, phthalazinyl, pyrimidinyl, quinazolinyl, pyrazinyl, quinoxalinyl, pteridinyl, triazinyl and chromenyl groups. Additional values include thieno[2,3-*c*]pyrazolyl, thieno[3,4-*b*][1,4]dioxinyl, pyrrolo[3,4-*b*]pyridinyl and imidazo[2,1-*b*]thiazolyl.

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

Where the compounds of formula (I) have one or more asymmetric centres, they may accordingly exist as enantiomers. Where the compounds of use in the invention possess two or more asymmetric centres, they may additionally exist as diastereomers. The invention is to be understood to extend to the use of 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 ($\text{CH}_2\text{C}=\text{O}$) $\leftrightarrow$ enol ($\text{CH}=\text{CHOH}$) tautomers or amide ($\text{NHC}=\text{O}$) $\leftrightarrow$ hydroxyimine ($\text{N}=\text{COH}$) tautomers. Formula (I) and the formulae depicted hereinafter are intended to represent all individual tautomers and all possible mixtures thereof, unless stated or shown otherwise.

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

In one aspect, the present invention provides a compound of formula (I) as depicted above or an *N*-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof, or a glucuronide derivative thereof, or a co-crystal thereof, wherein

Q represents -O-, -S-, -S(O)-, -S(O)₂-, -N(R⁶)-, -C(O)N(R⁶)-, -N(R⁶)C(O)-, -S(O)₂N(R⁶)- or -N(R⁶)S(O)₂-; or Q represents an optionally substituted straight or branched C₁₋₆ alkylene chain optionally comprising one, two or three heteroatom-

containing linkages independently selected from -O-, -S-, -S(O)-, -S(O)₂-, -N(R⁶)-, -C(O)N(R⁶)-, -N(R⁶)C(O)-, -S(O)₂N(R⁶)- and -N(R⁶)S(O)₂;

Z represents C₃₋₇ cycloalkyl, aryl, C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkenyl or heteroaryl, any of which groups may be optionally substituted by one or more substituents; or Z represents -Z¹-Z² or -Z¹-C(O)-Z², either of which moieties may be optionally substituted by one or more substituents; and

E, Y, R¹, R², R³, R⁴, R⁶, Z¹ and Z² are as defined above.

In another aspect, the present invention provides a compound of formula (I) as depicted above or an *N*-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof, or a glucuronide derivative thereof, or a co-crystal thereof, wherein

R¹ represents halogen or cyano; or C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇ cycloalkyl, C₄₋₇ cycloalkenyl, C₃₋₇ cycloalkyl(C₁₋₆)alkyl, aryl, aryl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkyl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkenyl, C₄₋₉ heterobicycloalkyl, heteroaryl, heteroaryl(C₁₋₆)alkyl, (C₃₋₇)heterocycloalkyl(C₁₋₆)alkyl-aryl-, heteroaryl(C₃₋₇)heterocycloalkyl-, (C₃₋₇)cycloalkyl-heteroaryl-, (C₃₋₇)cycloalkyl-(C₁₋₆)alkyl-heteroaryl-, (C₄₋₇)cycloalkenyl-heteroaryl-, (C₄₋₉)bicycloalkyl-heteroaryl-, (C₃₋₇)heterocycloalkyl-heteroaryl-, (C₃₋₇)heterocycloalkyl(C₁₋₆)alkyl-heteroaryl-, (C₃₋₇)heterocycloalkenyl-heteroaryl-, (C₄₋₉)heterobicycloalkyl-heteroaryl- or (C₄₋₉)spiroheterocycloalkyl-heteroaryl-, any of which groups may be optionally substituted by one or more substituents; and

E, Q, Y, Z, R², R³ and R⁴ are as defined above.

In another aspect, the present invention provides a compound of formula (I) as depicted above or an *N*-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof, or a co-crystal thereof, wherein

R¹ represents halogen or cyano; or C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇ cycloalkyl, C₄₋₇ cycloalkenyl, C₃₋₇ cycloalkyl(C₁₋₆)alkyl, aryl, aryl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkyl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkenyl, C₄₋₉ heterobicycloalkyl, heteroaryl, heteroaryl(C₁₋₆)alkyl, (C₃₋₇)heterocycloalkyl(C₁₋₆)alkyl-aryl-, heteroaryl(C₃₋₇)heterocycloalkyl-, (C₃₋₇)cycloalkyl-heteroaryl-, (C₄₋₇)cycloalkenyl-heteroaryl-, (C₃₋₇)heterocycloalkyl-heteroaryl-, (C₃₋₇)heterocycloalkyl(C₁₋₆)alkyl-heteroaryl-, (C₃₋₇)heterocycloalkenyl-heteroaryl-, (C₄₋₉)heterobicycloalkyl-heteroaryl- or (C₄₋₉)spiroheterocycloalkyl-heteroaryl-, any of which groups may be optionally substituted by one or more substituents; and

E, Q, Y, Z, R², R³ and R⁴ are as defined above.

In another aspect, the present invention provides a compound of formula (I) as depicted above or an *N*-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof, or a co-crystal thereof, wherein

- 5 R¹ represents halogen or cyano; or C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇ cycloalkyl, C₄₋₇ cycloalkenyl, C₃₋₇ cycloalkyl(C₁₋₆)alkyl, aryl, aryl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkyl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkenyl, C₄₋₉ heterobicycloalkyl, heteroaryl, heteroaryl(C₁₋₆)alkyl, (C₃₋₇)heterocycloalkyl(C₁₋₆)alkyl-aryl-, heteroaryl(C₃₋₇)heterocycloalkyl-, (C₄₋₇)cycloalkenyl-heteroaryl-,
 10 (C₃₋₇)heterocycloalkyl-heteroaryl-, (C₃₋₇)heterocycloalkyl(C₁₋₆)alkyl-heteroaryl-, (C₃₋₇)heterocycloalkenyl-heteroaryl-, (C₄₋₉)heterobicycloalkyl-heteroaryl- or (C₄₋₉)spiroheterocycloalkyl-heteroaryl-, any of which groups may be optionally substituted by one or more substituents; and

E, Q, Y, Z, R², R³ and R⁴ are as defined above.

- 15 Where the compounds in accordance with the invention comprise an optionally substituted straight or branched alkylene chain, typical values thereof include methylene (-CH₂-), (methyl)methylene, ethylene (-CH₂CH₂-), (ethyl)methylene, (dimethyl)methylene, (methyl)ethylene, propylene (-CH₂CH₂CH₂-), (propyl)methylene and (dimethyl)ethylene, any of which chains may be optionally substituted by one or more
 20 substituents. Suitably, such chains are unsubstituted, monosubstituted or disubstituted. Typically, such chains are unsubstituted or monosubstituted. In one embodiment, such chains are unsubstituted. In another embodiment, such chains are monosubstituted. In a further embodiment, such chains are disubstituted.

- Examples of typical substituents on the alkylene chain which may be present in a
 25 compound in accordance with the invention include halogen, trifluoromethyl, oxo, hydroxy, C₁₋₆ alkoxy, trifluoromethoxy, amino, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino, carboxy, tetrazolyl, aminocarbonyl, C₁₋₆ alkylaminocarbonyl and di(C₁₋₆)alkylaminocarbonyl. Additional examples include cyano, carboxy(C₁₋₆)alkoxy, C₂₋₆ alkylcarbonylamino and benzyloxycarbonyl.

- 30 Examples of suitable substituents on the alkylene chain which may be present in a compound in accordance with the invention include halogen, trifluoromethyl, hydroxy, C₁₋₆ alkoxy, amino, carboxy and tetrazolyl. Additional examples include cyano, carboxy-(C₁₋₆)alkoxy, C₂₋₆ alkylcarbonylamino and benzyloxycarbonyl.

Specific examples of suitable substituents on the alkylene chain which may be present in a compound in accordance with the invention include fluoro, trifluoromethyl, hydroxy, methoxy, amino, carboxy and tetrazolyl. Additional examples include cyano, carboxymethoxy, acetylamino and benzyloxycarbonyl.

5 In a first embodiment, E represents a covalent bond, whereby the integer Y is attached directly to the imidazo[1,2-*a*]pyridine nucleus.

In a second embodiment, E represents -O-, -S-, -S(O)-, -S(O)₂- or -N(R⁵)-. In a first aspect of that embodiment, E represents -O-. In a second aspect of that embodiment, E represents -S-. In a third aspect of that embodiment, E represents -S(O)-. In a fourth
10 aspect of that embodiment, E represents -S(O)₂-. In a fifth aspect of that embodiment, E represents -N(R⁵)-.

In a third embodiment, E represents an optionally substituted straight or branched C₁₋₄ alkylene chain. In a first aspect of that embodiment, E represents an optionally substituted methylene (-CH₂-) linkage. In a second aspect of that embodiment, E
15 represents an optionally substituted (methyl)methylene linkage. In a third aspect of that embodiment, E represents an optionally substituted (ethyl)methylene linkage.

Generally, E represents a covalent bond; or E represents -N(R⁵)-; or E represents an optionally substituted straight or branched C₁₋₄ alkylene chain.

Typically, E represents -N(R⁵)-; or E represents an optionally substituted straight
20 or branched C₁₋₄ alkylene chain.

Suitably, E represents a covalent bond; or E represents -N(R⁵)-; or E represents methylene (-CH₂-), (methyl)methylene or (ethyl)methylene, any of which groups may be optionally substituted by one or more substituents.

Generally, E represents -N(R⁵)-; or E represents methylene (-CH₂-) or
25 (ethyl)methylene, either of which groups may be optionally substituted by one or more substituents.

Appositely, E represents -N(R⁵)-, or optionally substituted methylene.

Selected examples of typical substituents on the linkage represented by E include halogen, trifluoromethyl, hydroxy, C₁₋₆ alkoxy, trifluoromethoxy, amino, C₁₋₆ alkylamino,
30 di(C₁₋₆)alkylamino, carboxy and tetrazolyl. Additional examples include carboxy(C₁₋₆)-alkoxy, C₂₋₆ alkylcarbonylamino and benzyloxycarbonyl.

Selected examples of suitable substituents on the linkage represented by E include hydroxy, C₁₋₆ alkoxy, carboxy(C₁₋₆)alkoxy, amino, C₂₋₆ alkylcarbonylamino, carboxy and benzyloxycarbonyl.

Specific examples of typical substituents on the linkage represented by E include
 5 fluoro, trifluoromethyl, hydroxy, methoxy, trifluoromethoxy, amino, methylamino, dimethylamino, carboxy and tetrazolyl. Additional examples include carboxymethoxy, acetylamino and benzyloxycarbonyl.

Specific examples of suitable substituents on the linkage represented by E include hydroxy, methoxy, carboxymethoxy, amino, acetylamino, carboxy and benzyloxy-
 10 carbonyl.

A particular example of a typical substituent on E is hydroxy.

Typical values of E include -N(R⁵)-, -CH₂-, -CH(OH)-, -CH(CH₃)- and -CH(CH₂CH₃)-; or E may represent a covalent bond.

Selected values of E include -N(R⁵)-, -CH₂-, -CH(OH)-, -CH(OCH₃)-,
 15 -CH(OCH₂CO₂H)-, -CH(NH₂)-, -CH(NHCOCH₃)-, -CH(CO₂H)-, -CH(CO₂benzyl)-, -CH(CH₃)- and -C(CH₃)(OH)-.

Suitable values of E include -N(R⁵)-, -CH₂- and -CH(OH)-. In one embodiment, E represents -N(R⁵)-. In another embodiment, E represents -CH₂-. In a further embodiment, E represents -CH(OH)-.

20 In another embodiment, E represents -CH(OCH₃)-.

In another embodiment, E represents -CH(NH₂)-.

In an additional embodiment, E represents -CH(CH₃)-. In a particular aspect of that embodiment, the -CH(CH₃)- linkage represented by E is in the (*S*) stereochemical configuration.

25 In a further embodiment, E represents -C(CH₃)(OH)-.

In a first embodiment, Q represents a covalent bond, whereby the integer Z is attached directly to the imidazo[1,2-*a*]pyridine nucleus.

In a second embodiment, Q represents -O-, -S-, -S(O)-, -S(O)₂-, -N(R⁶)-, -C(O)N(R⁶)-, -N(R⁶)C(O)-, -S(O)₂N(R⁶)- or -N(R⁶)S(O)₂-. In a first aspect of that
 30 embodiment, Q represents -O-. In a second aspect of that embodiment, Q represents -S-. In a third aspect of that embodiment, Q represents -S(O)-. In a fourth aspect of that embodiment, Q represents -S(O)₂-. In a fifth aspect of that embodiment, Q represents -N(R⁶)-. In a sixth aspect of that embodiment, Q represents -C(O)N(R⁶)-. In a seventh

aspect of that embodiment, Q represents $-N(R^6)C(O)-$. In an eighth aspect of that embodiment, Q represents $-S(O)_2N(R^6)-$. In a ninth aspect of that embodiment, Q represents $-N(R^6)S(O)_2-$.

- In a third embodiment, Q represents an optionally substituted straight or branched
- 5 C_{1-6} alkylene chain optionally comprising one, two or three heteroatom-containing linkages independently selected from $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-N(R^6)-$, $-C(O)N(R^6)-$, $-N(R^6)C(O)-$, $-S(O)_2N(R^6)-$ and $-N(R^6)S(O)_2-$. In a first aspect of that embodiment, Q represents an optionally substituted straight or branched C_{1-6} alkylene chain. In a second aspect of that embodiment, Q represents an optionally substituted straight or branched
- 10 C_{1-6} alkylene chain comprising one heteroatom-containing linkage independently selected from $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-N(R^6)-$, $-C(O)N(R^6)-$, $-N(R^6)C(O)-$, $-S(O)_2N(R^6)-$ and $-N(R^6)S(O)_2-$. In a third aspect of that embodiment, Q represents an optionally substituted straight or branched C_{1-6} alkylene chain comprising two heteroatom-containing linkages independently selected from $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-N(R^6)-$,
- 15 $-C(O)N(R^6)-$, $-N(R^6)C(O)-$, $-S(O)_2N(R^6)-$ and $-N(R^6)S(O)_2-$. In a fourth aspect of that embodiment, Q represents an optionally substituted straight or branched C_{1-6} alkylene chain comprising three heteroatom-containing linkages independently selected from $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-N(R^6)-$, $-C(O)N(R^6)-$, $-N(R^6)C(O)-$, $-S(O)_2N(R^6)-$ and $-N(R^6)S(O)_2-$. In a fifth aspect of that embodiment, Q represents an optionally substituted straight or
- 20 branched C_{1-6} alkylene chain comprising one, two or three heteroatom-containing linkages independently selected from $-O-$, $-S-$, $-N(R^6)-$, $-C(O)N(R^6)-$ and $-N(R^6)C(O)-$.

- Typically, Q represents a covalent bond; or Q represents $-S(O)-$ or $-S(O)_2-$; or Q represents an optionally substituted straight or branched C_{1-6} alkylene chain optionally comprising one or two heteroatom-containing linkages selected from $-O-$, $-S-$, $-N(R^6)-$,
- 25 $-C(O)N(R^6)-$, and $-N(R^6)C(O)-$.

Selected examples of typical substituents on the linkage represented by Q include halogen, trifluoromethyl, hydroxy, C_{1-6} alkoxy and amino. An additional example is cyano.

- Selected examples of suitable substituents on the linkage represented by Q include
- 30 cyano, hydroxy and C_{1-6} alkoxy.

Specific examples of typical substituents on the linkage represented by Q include fluoro, trifluoromethyl, hydroxy, methoxy and amino. An additional example is cyano.

Specific examples of suitable substituents on the linkage represented by Q include cyano, hydroxy and methoxy.

Suitably, Q represents a covalent bond; or Q represents -S(O)- or -S(O)₂-; or Q represents -CH₂-, -CH(F)-, -CF₂-, -CH(CH₃)-, -CH(OH)-, -CH(OCH₃)-, -CH(NH₂)-,
 5 -CH₂CH₂-, -CH(OH)CH₂-, -CH(OH)CF₂-, -CH(OCH₃)CH₂-, -CH₂O-, -CH(CH₃)O-,
 -C(CH₃)₂O-, -CH(CH₂CH₃)O-, -CH(CF₃)O-, -CH₂S-, -CH₂N(R⁶)-, -CH₂CH₂CH₂-,
 -CH(OH)CH₂CH₂-, -CH(OCH₃)CH₂CH₂-, -CH₂CH₂O-, -CH₂OCH₂-, -CH₂OCH(F)-,
 -CH₂OCF₂-, -CH₂OCH(CH₃)-, -CH(CH₃)OCH₂-, -CH₂OC(CH₃)₂-, -C(CH₃)₂OCH₂-,
 -CH₂SCH₂-, -CH₂CH₂N(R⁶)-, -CH₂N(R⁶)CH₂-, -CH₂CH₂OCH₂-, -CH₂CH₂N(R⁶)C(O)-,
 10 -CH₂OCH₂CH₂-, -CH₂OCH₂CF₂-, -CH₂OCH₂CH(CH₃)-, -CH₂OCH(CH₃)CH₂-,
 -CH₂OC(CH₃)₂CH₂-, -CH₂OCH₂CH(CH₃)CH₂-, -CH₂OCH₂CH₂O-,
 -CH₂OCH₂C(O)N(R⁶)- or -CH₂OCH₂CH₂OCH₂-. Additional values include -N(R⁵)-,
 -CH(CN)-, -CH(CH₂OH)-, -CH₂S(O)-, -CH₂S(O)₂-, -CH₂S(O)CH₂-, -CH₂S(O)₂CH₂- and
 -CH₂N(R⁵)C(O)-.

15 Appositely, Q represents a covalent bond; or Q represents -CH₂-, -CH(CN)-,
 -CH(OH)-, -CH(OCH₃)-, -CH₂O-, -CH₂N(R⁶)- or -CH₂OCH₂-.

Particular values of Q include -CH₂-, -CH(OH)-, -CH₂O-, -CH₂S- and
 -CH₂OCH₂-. In a first embodiment, Q represents -CH₂-. In a second embodiment, Q
 represents -CH(OH)-. In a third embodiment, Q represents -CH₂O-. In a fourth
 20 embodiment, Q represents -CH₂S-. In a fifth embodiment, Q represents -CH₂OCH₂-.

Generally, Y represents C₃₋₇ cycloalkyl, aryl or heteroaryl, any of which groups may be optionally substituted by one or more substituents.

Typically, Y represents aryl or heteroaryl, either of which groups may be optionally substituted by one or more substituents.

25 In a first embodiment, Y represents optionally substituted C₃₋₇ cycloalkyl. In one aspect of that embodiment, Y represents unsubstituted C₃₋₇ cycloalkyl. In another aspect of that embodiment, Y represents monosubstituted C₃₋₇ cycloalkyl. In a further aspect of that embodiment, Y represents disubstituted C₃₋₇ cycloalkyl.

In a second embodiment, Y represents optionally substituted aryl. In one aspect of
 30 that embodiment, Y represents unsubstituted aryl. In another aspect of that embodiment, Y represents monosubstituted aryl. In a further aspect of that embodiment, Y represents disubstituted aryl.

In a third embodiment, Y represents optionally substituted C₃₋₇ heterocycloalkyl. In one aspect of that embodiment, Y represents unsubstituted C₃₋₇ heterocycloalkyl. In another aspect of that embodiment, Y represents monosubstituted C₃₋₇ heterocycloalkyl. In a further aspect of that embodiment, Y represents disubstituted C₃₋₇ heterocycloalkyl.

5 In a fourth embodiment, Y represents optionally substituted heteroaryl. In one aspect of that embodiment, Y represents unsubstituted heteroaryl. In another aspect of that embodiment, Y represents monosubstituted heteroaryl. In a further aspect of that embodiment, Y represents disubstituted heteroaryl.

Suitably, Y represents benzocyclobutenyl, phenyl, thienyl, thiazolyl or pyridinyl, any of which groups may be optionally substituted by one or more substituents.

Appropriately, Y represents phenyl, thienyl or thiazolyl, any of which groups may be optionally substituted by one or more substituents.

Appositely, Y represents phenyl, which may be optionally substituted by one or more substituents.

15 Examples of optional substituents which may be present on the moiety Y include one, two or three substituents independently selected from halogen, cyano, nitro, C₁₋₆ alkyl, trifluoromethyl, hydroxy, C₁₋₆ alkoxy, difluoromethoxy, trifluoromethoxy, C₁₋₆ alkylthio, C₁₋₆ alkylsulfinyl, C₁₋₆ alkylsulfonyl, amino, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino, arylamino, C₂₋₆ alkylcarbonylamino, C₁₋₆ alkylsulfonylamino, formyl, C₂₋₆ alkylcarbonyl, C₃₋₆ cycloalkylcarbonyl, C₃₋₆ heterocycloalkylcarbonyl, carboxy, C₂₋₆ alkoxy carbonyl, aminocarbonyl, C₁₋₆ alkylaminocarbonyl, di(C₁₋₆)alkylaminocarbonyl, aminosulfonyl, C₁₋₆ alkylaminosulfonyl and di(C₁₋₆)alkylaminosulfonyl. An additional example is (C₁₋₆)alkylsulfonyloxy.

25 Selected examples of optional substituents on the moiety Y include halogen, C₁₋₆ alkyl, difluoromethoxy and (C₁₋₆)alkylsulfonyloxy.

Typical examples of optional substituents on the moiety Y include halogen, C₁₋₆ alkyl and difluoromethoxy.

30 Examples of particular substituents on the moiety Y include fluoro, chloro, bromo, cyano, nitro, methyl, isopropyl, trifluoromethyl, hydroxy, methoxy, difluoromethoxy, trifluoromethoxy, methylthio, methylsulfinyl, methylsulfonyl, amino, methylamino, *tert*-butylamino, dimethylamino, phenylamino, acetilamino, methylsulfonylamino, formyl, acetyl, cyclopropylcarbonyl, azetidiny carbonyl, pyrrolidinylcarbonyl, piperidinylcarbonyl, piperazinylcarbonyl, morpholinylcarbonyl, carboxy, methoxycarbonyl,

aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, aminosulfonyl, methylaminosulfonyl and dimethylaminosulfonyl. An additional example is methylsulfonyloxy.

Selected examples of particular substituents on the moiety Y include fluoro,
 5 chloro, methyl, difluoromethoxy and methylsulfonyloxy.

Typical examples of particular substituents on the moiety Y include chloro, methyl and difluoromethoxy.

Typical values of Y include benzocyclobutenyl, phenyl, fluorophenyl (including 2-fluorophenyl, 3-fluorophenyl and 4-fluorophenyl), chlorophenyl (including 2-chloro-phenyl, 3-chlorophenyl and 4-chlorophenyl), difluorophenyl (including 2,6-difluorophenyl), (chloro)(fluoro)phenyl (including 5-chloro-2-fluorophenyl and 2-chloro-5-fluorophenyl), dichlorophenyl (including 2,5-dichlorophenyl and 2,6-dichlorophenyl), methylphenyl (including 4-methylphenyl), dimethylphenyl (including 2,5-dimethylphenyl and 2,6-dimethylphenyl), (trifluoromethyl)phenyl [including 2-(trifluoromethyl)phenyl],
 10 (chloro)(trifluoromethyl)phenyl [including 5-chloro-2-(trifluoromethyl)phenyl], (methyl)-(trifluoromethyl)phenyl [including 2-methyl-5-(trifluoromethyl)phenyl], bis(trifluoromethyl)phenyl [including 2,5-bis(trifluoromethyl)phenyl], methoxyphenyl (including 2-methoxyphenyl), (difluoromethoxy)phenyl [including 2-(difluoromethoxy)phenyl and 3-(difluoromethoxy)phenyl], (difluoromethoxy)(fluoro)phenyl [including 2-(difluoro-
 20 methoxy)-5-fluorophenyl and 5-(difluoromethoxy)-2-fluorophenyl], (chloro)(difluoromethoxy)phenyl [including 5-chloro-2-(difluoromethoxy)phenyl and 6-chloro-2-(difluoromethoxy)phenyl], (trifluoromethoxy)phenyl [including 2-(trifluoromethoxy)-phenyl], (amino)(chloro)phenyl (including 5-amino-2-chlorophenyl), methylthienyl (including 3-methylthien-2-yl), methylthiazolyl (including 2-methyl-1,3-thiazol-4-yl),
 25 (chloro)(methyl)thiazolyl (including 5-chloro-2-methyl-1,3-thiazol-4-yl), dimethylthiazolyl (including 2,4-dimethyl-1,3-thiazol-5-yl) and pyridinyl (including pyridin-3-yl and pyridin-4-yl). An additional value is methylsulfonyloxyphenyl.

Selected values of Y include dichlorophenyl, dimethylphenyl, (difluoromethoxy)-phenyl, (difluoromethoxy)(fluoro)phenyl, methylsulfonyloxyphenyl, methylthienyl and
 30 dimethylthiazolyl.

Suitable values of Y include dichlorophenyl, dimethylphenyl, (difluoromethoxy)-phenyl, methylthienyl and dimethylthiazolyl.

In one embodiment, Y represents 2,5-dichlorophenyl.

In another embodiment, Y represents 2,5-dimethylphenyl.

In a particular embodiment, Y represents 2-(difluoromethoxy)phenyl.

In another embodiment, Y represents (difluoromethoxy)(fluoro)phenyl.

In another embodiment, Y represents 3-methylthien-2-yl.

5 In another embodiment, Y represents 2,4-dimethyl-1,3-thiazol-5-yl.

In one embodiment, Z represents hydrogen.

In another embodiment, Z is other than hydrogen.

In a selected embodiment, Z represents hydrogen; or Z represents C₁₋₆ alkyl, C₃₋₇ cycloalkyl, aryl, C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkenyl or heteroaryl, any of
10 which groups may be optionally substituted by one or more substituents; or Z represents -Z¹-Z² or -Z¹-C(O)-Z², either of which moieties may be optionally substituted by one or more substituents.

In a further embodiment, Z represents C₁₋₆ alkyl, C₃₋₇ cycloalkyl, aryl, C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkenyl or heteroaryl, any of which groups may be
15 optionally substituted by one or more substituents; or Z represents -Z¹-Z² or -Z¹-C(O)-Z², either of which moieties may be optionally substituted by one or more substituents.

Suitably, Z represents hydrogen; or Z represents C₁₋₆ alkyl, aryl or heteroaryl, any of which groups may be optionally substituted by one or more substituents; or Z
20 represents -Z¹-Z², which moiety may be optionally substituted by one or more substituents.

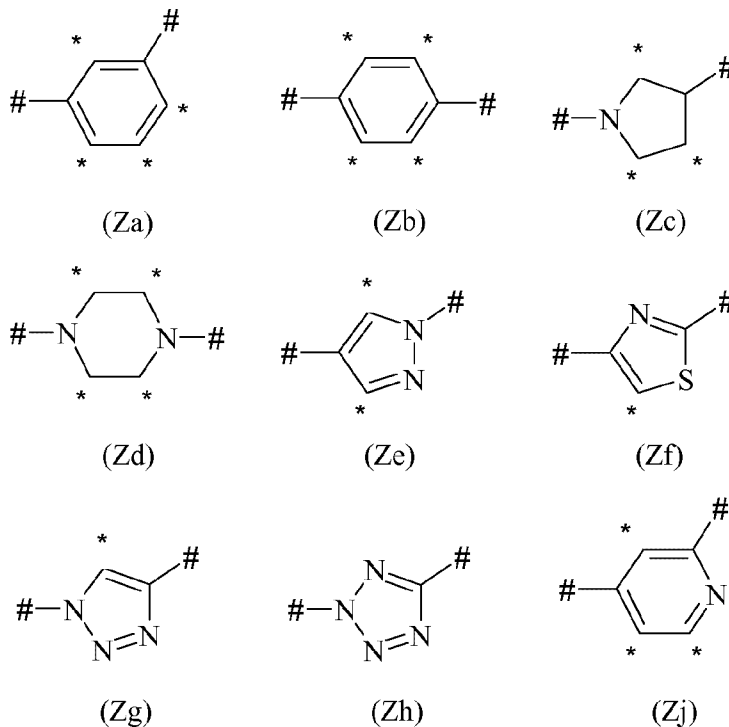
Typically, Z represents hydrogen, fluoro or trifluoromethyl; or Z represents methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, tetrahydrofuranyl, pyrrolidinyl, indolyl, tetrahydropyranyl, piperidinyl, 1,2,3,4-tetrahydroquinolyl, morpholinyl, azocanyl,
25 thiazolyl, furyl, thienyl, pyrazolyl, 4,5,6,7-tetrahydroindazolyl, benzoxazolyl, isoxazolyl, thiazolyl, benzothiazolyl, imidazolyl, benzimidazolyl, [1,2,4]triazolo[1,5-*a*]-pyrimidinyl, tetrazolyl, pyridinyl, quinolyl, isoquinolyl, phthalazinyl, pyrimidinyl or pyrazinyl, any of which groups may be optionally substituted by one or more substituents; or Z represents -Z¹-Z² or -Z¹-C(O)-Z², either of which moieties may be optionally
30 substituted by one or more substituents.

Appositely, Z represents hydrogen; or Z represents methyl, phenyl or pyridinyl, any of which groups may be optionally substituted by one or more substituents; or Z

represents $-Z^1-Z^2$, which moiety may be optionally substituted by one or more substituents.

The moiety Z^1 represents a divalent radical derived from an aryl, C_{3-7} heterocyclo-alkyl or heteroaryl group, any of which groups may be optionally substituted by one or
 5 more substituents. Typically, the moiety Z^1 represents a divalent radical derived from a phenyl, pyrrolidinyl, piperazinyl, pyrazolyl, thiazolyl, triazolyl, tetrazolyl or pyridinyl group, any of which groups may be optionally substituted by one or more substituents. Typical values of the moiety Z^1 include the groups of formula (Za), (Zb), (Zc), (Zd), (Ze), (Zf), (Zg), (Zh) and (Zj):

10



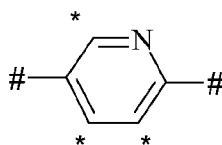
15 wherein

the symbols # represent the points of attachment of the moiety Z^1 to the remainder of the molecule; and

the asterisks (*) represent the site of attachment of optional substituents.

Additional values of the moiety Z^1 include the group of formula (Zk):

20



(Zk)

wherein

and * are as defined above.

- 5 Particular values of the moiety Z^1 include the groups of formula (Za), (Zc), (Ze), (Zf), (Zg), (Zh) and (Zj) as depicted above.

The moiety Z^2 represents aryl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkenyl or heteroaryl, any of which groups may be optionally substituted by one or more substituents. Typically, Z^2 represents phenyl, pyrrolidinyl, oxazolidinyl, imidazolidinyl, morpholinyl, imidazolinyl, thiazolyl, imidazolyl, tetrazolyl or pyridinyl, any of which groups may be optionally substituted by one or more substituents.

10

Examples of optional substituents which may be present on the moiety Z, Z^1 or Z^2 include one, two or three substituents independently selected from halogen, cyano, nitro, C_{1-6} alkyl, trifluoromethyl, oxo, hydroxy, hydroxy(C_{1-6})alkyl, C_{1-6} alkoxy, difluoro-methoxy, trifluoromethoxy, C_{1-3} alkylenedioxy, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, di(C_{1-6})alkylamino(C_{1-6})alkyl, C_{2-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, formyl, C_{2-6} alkylcarbonyl, carboxy, C_{2-6} alkoxy carbonyl, aminocarbonyl, C_{1-6} alkylaminocarbonyl, di(C_{1-6})alkylamino-carbonyl, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6})alkylaminosulfonyl, aminocarbonylamino and hydrazinocarbonyl.

15

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Typical examples of optional substituents on the moiety Z, Z^1 or Z^2 include halogen, cyano, nitro, C_{1-6} alkyl, trifluoromethyl, oxo, hydroxy, hydroxy(C_{1-6})alkyl, C_{1-6} alkoxy, difluoromethoxy, trifluoromethoxy, C_{1-3} alkylenedioxy, C_{1-6} alkylsulfonyl, amino, di(C_{1-6})alkylamino, di(C_{1-6})alkylamino(C_{1-6})alkyl, C_{2-6} alkylcarbonylamino, C_{1-6} alkyl-sulfonylamino, formyl, carboxy, C_{2-6} alkoxy carbonyl, aminocarbonyl, C_{1-6} alkylamino-carbonyl, di(C_{1-6})alkylaminocarbonyl, aminocarbonylamino and hydrazinocarbonyl.

25

Selected examples of optional substituents on the moiety Z, Z^1 or Z^2 include oxo and C_{1-6} alkylsulfonyl.

Examples of particular substituents on the moiety Z, Z^1 or Z^2 include fluoro, chloro, bromo, cyano, nitro, methyl, ethyl, isopropyl, trifluoromethyl, oxo, hydroxy,

30

hydroxymethyl, methoxy, difluoromethoxy, trifluoromethoxy, methylenedioxy, methylthio, methylsulfinyl, methylsulfonyl, amino, methylamino, *tert*-butylamino, dimethylamino, dimethylaminomethyl, dimethylaminoethyl, acetylamino, methylsulfonyl-amino, formyl, acetyl, carboxy, methoxycarbonyl, *tert*-butoxycarbonyl, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, aminosulfonyl, methylaminosulfonyl, dimethylaminosulfonyl, aminocarbonylamino and hydrazinocarbonyl.

Typical examples of particular substituents on the moiety Z, Z¹ or Z² include fluoro, chloro, bromo, cyano, nitro, methyl, ethyl, trifluoromethyl, oxo, hydroxy, hydroxymethyl, methoxy, difluoromethoxy, trifluoromethoxy, methylenedioxy, methylsulfonyl, amino, dimethylamino, dimethylaminomethyl, dimethylaminoethyl, acetylamino, methylsulfonylamino, formyl, carboxy, methoxycarbonyl, *tert*-butoxycarbonyl, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, aminocarbonylamino and hydrazinocarbonyl.

Selected examples of optional substituents on the moiety Z, Z¹ or Z² include oxo and methylsulfonyl.

Typical values of Z² include phenyl, hydroxyphenyl, oxopyrrolidinyl, dioxo-pyrrolidinyl, (hydroxy)(oxo)pyrrolidinyl, (amino)(oxo)pyrrolidinyl, (oxo)oxazolidinyl, oxoimidazolidinyl, morpholinyl, imidazolyl, methylthiazolyl, formylthiazolyl, imidazolyl, tetrazolyl and pyridinyl.

Selected values of Z² include oxopyrrolidinyl and (oxo)oxazolidinyl. In one embodiment, Z² represents oxopyrrolidinyl. In another embodiment, Z² represents (oxo)oxazolidinyl.

Typical values of Z include hydrogen, fluoro, trifluoromethyl, methyl, ethyl, *n*-propyl, isopropyl, isobutyl, *tert*-butyl, cyclopropyl, cyclopentyl, cyclohexyl, oxo-cyclohexyl, phenyl, bromophenyl, cyanophenyl, nitrophenyl, methoxyphenyl, difluoromethoxyphenyl, trifluoromethoxyphenyl, methylenedioxyphenyl, methylsulfonylphenyl, dimethylaminophenyl, acetylamino-phenyl, methylsulfonylamino-phenyl, carboxyphenyl, aminocarbonylphenyl, methylaminocarbonylphenyl, dimethylaminocarbonylphenyl, aminocarbonylamino-phenyl, tetrahydrofuranyl, oxopyrrolidinyl, dimethylamino-pyrrolidinyl, *tert*-butoxycarbonylpyrrolidinyl, indolinyl, tetrahydropyranyl, piperidinyl, ethylpiperidinyl, *tert*-butoxycarbonylpiperidinyl, aminocarbonylpiperidinyl, 2-oxo-3,4-dihydroquinolinyl, morpholinyl, azocanyl, oxothiazolinyl, furyl, hydroxymethylfuryl, thienyl, methylpyrazolyl, dimethylpyrazolyl, 4,5,6,7-tetrahydroindazolyl, benzoxazolyl,

methylisoxazolyl, dimethylisoxazolyl, methylthiazolyl, aminothiazolyl, benzothiazolyl, methylbenzothiazolyl, aminobenzothiazolyl, imidazolyl, methylimidazolyl, methylbenzimidazolyl, dimethyl[1,2,4]triazolo[1,5-*a*]pyrimidinyl, dimethylaminoethyltetrazolyl, pyridinyl, fluoropyridinyl, chloropyridinyl, cyanopyridinyl, methylpyridinyl, (cyano)-
 5 (methyl)pyridinyl, trifluoromethylpyridinyl, oxopyridinyl, methoxypyridinyl, dimethylaminomethylpyridinyl, acetylaminopyridinyl, carboxypyridinyl, methoxycarbonylpyridinyl, aminocarbonylpyridinyl, (aminocarbonyl)(fluoro)pyridinyl, methylaminocarbonylpyridinyl, dimethylaminocarbonylpyridinyl, hydrazinocarbonylpyridinyl, quinolinyl, isoquinolinyl, (methyl)(oxo)phthalazinyl, pyrimidinyl, pyrazinyl,
 10 oxopyrrolidinylphenyl, dioxopyrrolidinylphenyl, (hydroxy)(oxo)pyrrolidinylphenyl, (amino)(oxo)pyrrolidinylphenyl, (oxo)oxazolidinylphenyl, oxoimidazolidinylphenyl, imidazolinylphenyl, methylthiazolylphenyl, formylthiazolylphenyl, imidazolylphenyl, tetrazolylphenyl, phenylpyrrolidinyl, hydroxyphenylpiperazinyl, (methyl)(phenyl)pyrazolyl, oxoimidazolidinylthiazolyl, hydroxyphenyltriazolyl, morpholinyltetrazolyl,
 15 oxopyrrolidinylpyridinyl, (oxo)oxazolidinylpyridinyl, oxoimidazolidinylpyridinyl, pyridinylthiazolyl, pyridinyltetrazolyl and morpholinylcarbonylphenyl. Additionally, Z may represent methylsulfonylpyridinyl.

Particular values of Z include hydrogen, methyl, methylsulfonylphenyl, pyridinyl, oxopyrrolidinylphenyl, (hydroxy)(oxo)pyrrolidinylphenyl and (oxo)oxazolidinylphenyl.
 20 Additionally, Z may represent methylsulfonylpyridinyl. In a first embodiment, Z represents hydrogen. In a second embodiment, Z represents methyl. In a third embodiment, Z represents methylsulfonylphenyl. In one aspect of that embodiment, Z represents 3-(methylsulfonyl)phenyl. In another aspect of that embodiment, Z represents 4-(methylsulfonyl)phenyl. In a fourth embodiment, Z represents pyridinyl. In one aspect
 25 of that embodiment, Z represents pyridin-4-yl. In a fifth embodiment, Z represents oxopyrrolidinylphenyl. In one aspect of that embodiment, Z represents 3-(2-oxopyrrolidin-1-yl)phenyl. In a sixth embodiment, Z represents (hydroxy)(oxo)pyrrolidinylphenyl. In one aspect of that embodiment, Z represents 3-(3-hydroxy-2-oxopyrrolidin-1-yl)phenyl. In another aspect of that embodiment, Z represents 3-(4-hydroxy-2-oxo-
 30 pyrrolidin-1-yl)phenyl. In a seventh embodiment, Z represents (oxo)oxazolidinylphenyl. In one aspect of that embodiment, Z represents 3-(2-oxo-oxazolidinyl-3-yl)phenyl. In an eighth embodiment, Z represents methylsulfonylpyridinyl.

In general, R^1 , R^2 , R^3 and R^4 independently represent hydrogen, halogen, cyano, nitro, hydroxy, trifluoromethyl, trifluoromethoxy, $-OR^a$, $-SR^a$, $-SOR^a$, $-SO_2R^a$, $-SF_5$, $-NR^bR^c$, $-NR^cCOR^d$, $-NR^cCO_2R^d$, $-NHCONR^bR^c$, $-NR^cSO_2R^c$, $-N(SO_2R^c)_2$, $-NHSO_2NR^bR^c$, $-COR^d$, $-CO_2R^d$, $-CONR^bR^c$, $-CON(OR^a)R^b$ or $-SO_2NR^bR^c$; or C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl, 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, C_{3-7} heterocycloalkenyl, C_{4-9} heterobicycloalkyl, heteroaryl, heteroaryl(C_{1-6})alkyl, (C_{3-7})heterocycloalkyl(C_{1-6})alkyl-aryl-, heteroaryl(C_{3-7})heterocycloalkyl-, (C_{3-7})cycloalkyl-heteroaryl-, (C_{4-7})cycloalkenyl-heteroaryl-, (C_{3-7})heterocycloalkyl-heteroaryl-, (C_{3-7})heterocycloalkyl(C_{1-6})alkyl-heteroaryl-, (C_{3-7})heterocycloalkenyl-heteroaryl-, (C_{4-9})heterobicycloalkyl-heteroaryl- or (C_{4-9})spiroheterocycloalkyl-heteroaryl-, any of which groups may be optionally substituted by one or more substituents.

Generally, R^1 , R^2 , R^3 and R^4 independently represent hydrogen, halogen, cyano, nitro, hydroxy, trifluoromethyl, trifluoromethoxy, $-OR^a$, $-SR^a$, $-SOR^a$, $-SO_2R^a$, $-SF_5$, $-NR^bR^c$, $-NR^cCOR^d$, $-NR^cCO_2R^d$, $-NHCONR^bR^c$, $-NR^cSO_2R^c$, $-N(SO_2R^c)_2$, $-NHSO_2NR^bR^c$, $-COR^d$, $-CO_2R^d$, $-CONR^bR^c$, $-CON(OR^a)R^b$ or $-SO_2NR^bR^c$; or C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl, 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, C_{3-7} heterocycloalkenyl, C_{4-9} heterobicycloalkyl, heteroaryl, heteroaryl(C_{1-6})alkyl, (C_{3-7})heterocycloalkyl(C_{1-6})alkyl-aryl-, heteroaryl(C_{3-7})heterocycloalkyl-, (C_{4-7})cycloalkenyl-heteroaryl-, (C_{3-7})heterocycloalkyl-heteroaryl-, (C_{3-7})heterocycloalkyl- (C_{1-6})alkyl-heteroaryl-, (C_{3-7})heterocycloalkenyl-heteroaryl-, (C_{4-9})heterobicycloalkyl-heteroaryl- or (C_{4-9})spiroheterocycloalkyl-heteroaryl-, any of which groups may be optionally substituted by one or more substituents.

Suitably, R^1 , R^2 , R^3 and R^4 independently represent hydrogen, halogen, cyano, trifluoromethyl or $-CO_2R^d$; or C_{1-6} alkyl, C_{2-6} alkynyl, aryl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkenyl, heteroaryl, (C_{3-7})cycloalkyl-heteroaryl-, (C_{4-7})cycloalkenyl-heteroaryl-, (C_{3-7})heterocycloalkyl-heteroaryl-, (C_{4-9})heterobicycloalkyl-heteroaryl- or (C_{4-9})spiroheterocycloalkyl-heteroaryl-, any of which groups may be optionally substituted by one or more substituents. Additionally, R^1 , R^2 , R^3 and R^4 may independently represent (C_{3-7})cycloalkyl(C_{1-6})alkyl-heteroaryl- or (C_{4-9})bicycloalkyl-

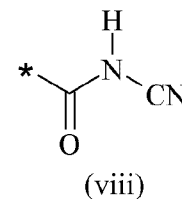
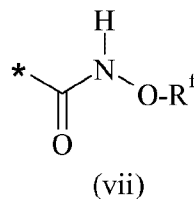
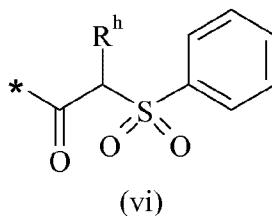
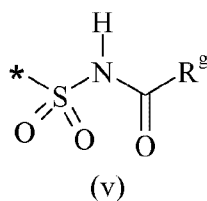
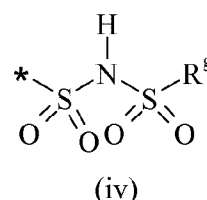
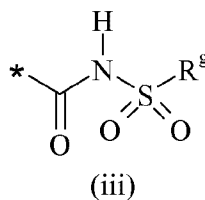
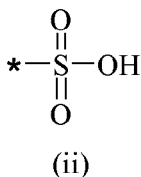
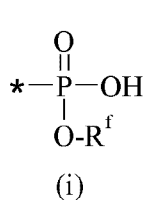
heteroaryl-, either of which groups may be optionally substituted by one or more substituents.

Typically, R¹, R², R³ and R⁴ independently represent hydrogen, halogen, cyano, trifluoromethyl or -CO₂R^d, or C₁₋₆ alkyl, aryl, C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkenyl, heteroaryl, (C₃₋₇)heterocycloalkyl(C₁₋₆)alkyl-aryl-, heteroaryl-(C₃₋₇)heterocycloalkyl-, (C₄₋₇)cycloalkenyl-heteroaryl-, (C₃₋₇)heterocycloalkyl-heteroaryl-, (C₃₋₇)heterocycloalkyl(C₁₋₆)alkyl-heteroaryl-, (C₃₋₇)heterocycloalkenyl-heteroaryl-, (C₄₋₉)heterobicycloalkyl-heteroaryl- or (C₄₋₉)spiroheterocycloalkyl-heteroaryl-, any of which groups may be optionally substituted by one or more substituents.

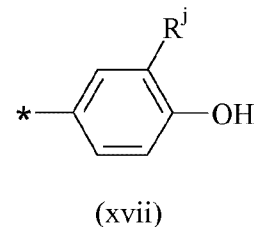
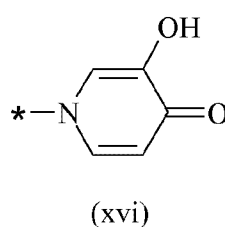
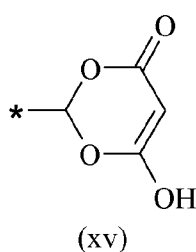
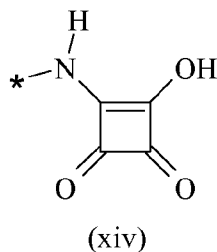
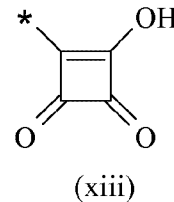
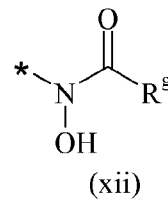
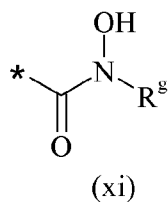
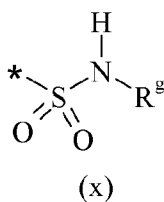
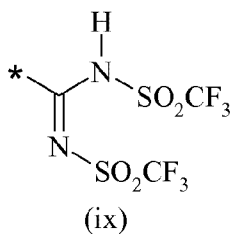
- Examples of optional substituents which may be present on R¹, R², R³ or R⁴ include one, two or three substituents independently selected from halogen, cyano, cyano(C₁₋₆)alkyl, nitro, C₁₋₆ alkyl, trifluoromethyl, trifluoroethyl, C₂₋₆ alkenyl, hydroxy, C₁₋₆ alkoxy, difluoromethoxy, trifluoromethoxy, trifluoroethoxy, C₁₋₃ alkylenedioxy, C₁₋₆ alkoxy(C₁₋₆)alkyl, C₁₋₆ alkylthio, C₁₋₆ alkylsulphonyl, (C₁₋₆)alkylsulphonyl(C₁₋₆)alkyl, oxo, amino, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino, (C₁₋₆)alkoxy(C₁₋₆)alkylamino, *N*-[(C₁₋₆)alkyl]-*N*-[hydroxy(C₁₋₆)alkyl]amino, C₂₋₆ alkylcarbonylamino, C₂₋₆ alkoxycarbonylamino, C₁₋₆ alkylaminocarbonylamino, C₁₋₆ alkylsulphonylamino, formyl, C₂₋₆ alkylcarbonyl, carboxy, carboxy(C₁₋₆)alkyl, C₂₋₆ alkoxycarbonyl, C₂₋₆ alkoxycarbonyl(C₁₋₆)alkyl, a carboxylic acid isostere or prodrug moiety Ω , aminocarbonyl, C₁₋₆ alkylaminocarbonyl, di(C₁₋₆)alkyl-aminocarbonyl, aminosulphonyl and di(C₁₋₆)alkylaminosulphonyl. Additional examples include bis[(C₁₋₆)alkylsulphonyl]amino, *N*-[(C₁₋₆)alkyl]-*N*-[carboxy(C₁₋₆)alkyl]amino, carboxy(C₃₋₇)cycloalkylamino, carboxy(C₃₋₇)cycloalkyl(C₁₋₆)alkylamino and -(C₁₋₆)alkyl- Ω , in which Ω is as defined herein. Additional examples include halo(C₁₋₆)-alkyl, nitro(C₁₋₆)alkyl, difluoromethyl, difluoroethyl, hydroxy(C₁₋₆)alkyl, carboxy(C₃₋₇)-cycloalkyloxy, C₁₋₆ alkylsulphinyl, amino(C₁₋₆)alkyl, hydroxy(C₁₋₆)alkylamino, C₁₋₆ alkoxyamino, [(C₁₋₆)alkoxy](hydroxy)(C₁₋₆)alkylamino, [(C₁₋₆)alkylthio](hydroxy)(C₁₋₆)alkylamino, di(C₁₋₆)alkylamino(C₁₋₆)alkylamino, *N*-[di(C₁₋₆)alkylamino(C₁₋₆)alkyl]-*N*-[hydroxy(C₁₋₆)alkyl]amino, hydroxy(C₁₋₆)alkyl(C₃₋₇)cycloalkylamino, (hydroxy)[(C₃₋₇)cycloalkyl(C₁₋₆)alkyl]amino, (C₃₋₇)heterocycloalkyl(C₁₋₆)alkylamino, oxo(C₃₋₇)-heterocycloalkyl(C₁₋₆)alkylamino, (C₁₋₆)alkylheteroarylamino, heteroaryl(C₁₋₆)alkylamino, (C₁₋₆)alkylheteroaryl(C₁₋₆)alkylamino, *N*-[(C₁₋₆)alkyl]-*N*-[(C₂₋₆)alkylcarbonyl]amino, (C₂₋₆)alkylcarbonylamino(C₁₋₆)alkyl, C₃₋₆ alkenylcarbonylamino, bis[(C₃₋₆)alkenylcarbonyl]amino, *N*-[(C₁₋₆)alkyl]-*N*-[(C₃₋₇)cycloalkylcarbonyl]amino, C₂₋₆ alkoxycarbonyl-

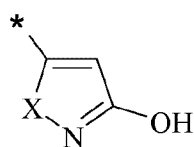
(C₁₋₆)alkylamino, *N*-[(C₁₋₆)alkyl]-*N*-[(C₁₋₆)alkylsulphonyl]amino, (C₃₋₇)cycloalkylcarbonyl, phenylcarbonyl, (C₂₋₆)alkylcarbonyloxy(C₁₋₆)alkyl, morpholinyl(C₁₋₆)alkoxycarbonyl, C₂₋₆alkoxycarbonylmethylidenyl, hydroxy(C₁₋₆)alkylaminocarbonyl, aminocarbonyl(C₁₋₆)alkyl and C₁₋₆alkoxyaminocarbonyl.

- 5 By the expression “carboxylic acid isostere or prodrug moiety” is meant any functional group, structurally distinct from a carboxylic acid moiety, that will be recognised by a biological system as being similar to, and thus capable of mimicking, a carboxylic acid moiety, or will be readily convertible by a biological system *in vivo* into a carboxylic acid moiety. A synopsis of some common carboxylic acid isosteres is
- 10 presented by N.A. Meanwell in *J. Med. Chem.*, 2011, **54**, 2529-2591 (cf. in particular Figures 25 and 26). Typical examples of suitable carboxylic acid isostere or prodrug moieties represented by Ω include the functional groups of formula (i) to (xli):

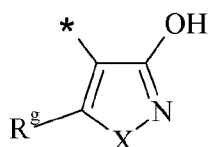


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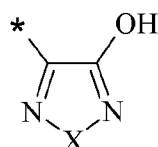




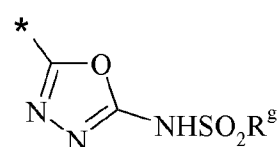
(xviii)



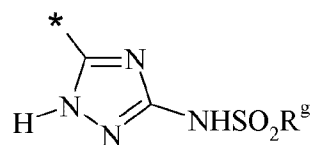
(xix)



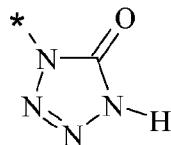
(xx)



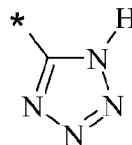
(xxi)



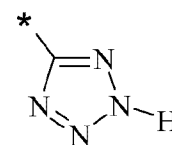
(xxii)



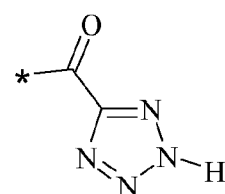
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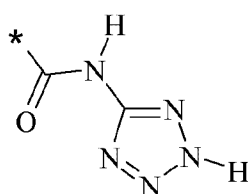
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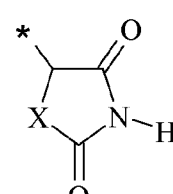
(xxv)



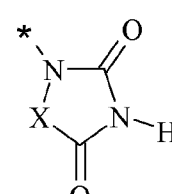
(xxvi)



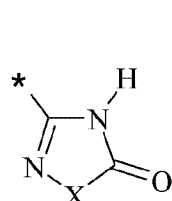
(xxvii)



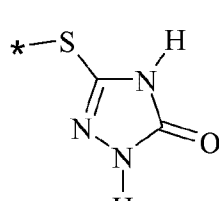
(xxviii)



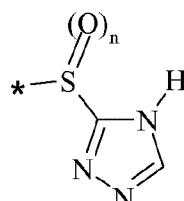
(xxix)



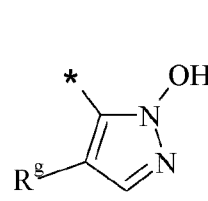
(xxx)



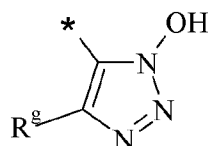
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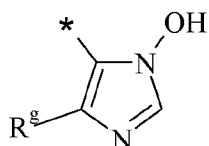
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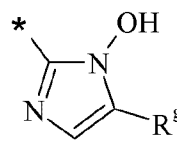
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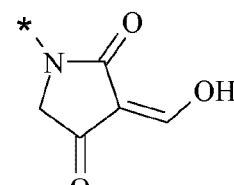
(xxxiv)



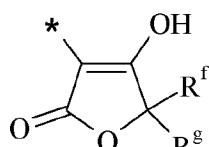
(xxxv)



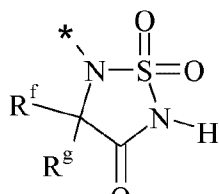
(xxxvi)



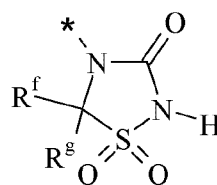
(xxxvii)



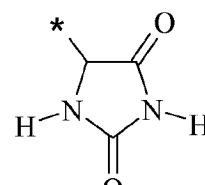
(xxxviii)



(xxxix)



(xl)



(xli)

wherein

the asterisk (*) represents the site of attachment to the remainder of the molecule;

n is zero, 1 or 2;

X represents oxygen or sulphur;

R^f represents hydrogen, C₁₋₆ alkyl or -CH₂CH(OH)CH₂OH;

R^g represents C₁₋₆ alkyl, trifluoromethyl, -CH₂CH₂F, -CH₂CHF₂, -CH₂CF₃ or -CF₂CF₃;

5 R^h represents hydrogen, cyano or -CO₂R^d, in which R^d is as defined above; and
R^j represents hydrogen or halogen.

In one embodiment, n is zero. In another embodiment, n is 1. In a further embodiment, n is 2.

10 In one embodiment, X represents oxygen. In another embodiment, X represents sulphur.

In one embodiment, R^f represents hydrogen. In another embodiment, R^f represents C₁₋₆ alkyl, especially methyl. In a further embodiment, R^f is -CH₂CH(OH)CH₂OH.

In one embodiment, R^g represents C₁₋₆ alkyl, especially methyl. In another embodiment, R^g represents trifluoromethyl, -CH₂CH₂F, -CH₂CHF₂, -CH₂CF₃ or -CF₂CF₃.

15 In a first aspect of that embodiment, R^g represents trifluoromethyl. In a second aspect of that embodiment, R^g represents -CH₂CH₂F. In a third aspect of that embodiment, R^g represents -CH₂CHF₂. In a fourth aspect of that embodiment, R^g represents -CH₂CF₃. In a fifth aspect of that embodiment, R^g represents -CF₂CF₃.

In one embodiment, R^h is hydrogen. In another embodiment, R^h represents cyano.

20 In a further embodiment, R^h represents -CO₂R^d, especially methoxycarbonyl.

In one embodiment, R^j represents hydrogen. In another embodiment, R^j represents halogen, especially chloro.

In a selected embodiment, Ω represents tetrazolyl, especially a C-linked tetrazolyl moiety of formula (xxiv) or (xxv) as depicted above, in particular a group of formula

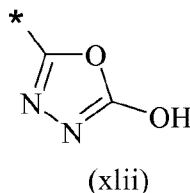
25 (xxiv) as depicted above.

In another embodiment, Ω represents C₁₋₆ alkylsulphonylaminocarbonyl, i.e. a moiety of formula (iii) as depicted above wherein R^g represents C₁₋₆ alkyl.

In another embodiment, Ω represents C₁₋₆ alkylaminosulphonyl, i.e. a moiety of formula (x) as depicted above wherein R^g represents C₁₋₆ alkyl.

30 In a further embodiment, Ω represents (C₁₋₆)alkylcarbonylaminosulphonyl, i.e. a moiety of formula (v) as depicted above wherein R^g represents C₁₋₆ alkyl.

Additional examples of suitable carboxylic acid isostere or prodrug moieties represented by Ω include the functional group of formula (xlii):



wherein

- 5 the asterisk (*) represents the site of attachment to the remainder of the molecule.
- Suitable examples of optional substituents which may be present on R¹, R², R³ or R⁴ include one, two or three substituents independently selected from C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkylsulphonyl, oxo, amino, C₁₋₆ alkylsulphonylamino, bis[(C₁₋₆)alkylsulphonyl]amino, *N*-[(C₁₋₆)alkyl]-*N*-[carboxy(C₁₋₆)alkyl]amino, carboxy(C₃₋₇)cycloalkyl-
- 10 amino, carboxy(C₃₋₇)cycloalkyl(C₁₋₆)alkylamino, C₂₋₆ alkylcarbonyl, carboxy, carboxy-(C₁₋₆)alkyl, C₂₋₆ alkoxycarbonyl, C₂₋₆ alkoxycarbonyl(C₁₋₆)alkyl, a carboxylic acid isostere or prodrug moiety Ω as defined herein, -(C₁₋₆)alkyl- Ω , and aminosulphonyl. Additional examples include halogen, halo(C₁₋₆)alkyl, cyano, nitro(C₁₋₆)alkyl, trifluoromethyl, hydroxy(C₁₋₆)alkyl, carboxy(C₃₋₇)cycloalkyloxy, C₁₋₆ alkylthio, amino(C₁₋₆)alkyl, C₁₋₆
- 15 alkylamino, (C₂₋₆)alkylcarbonylamino(C₁₋₆)alkyl, *N*-[(C₁₋₆)alkyl]-*N*-[(C₁₋₆)alkylsulphonyl]-amino, formyl, (C₂₋₆)alkylcarbonyloxy(C₁₋₆)alkyl, morpholinyl(C₁₋₆)alkoxycarbonyl, C₂₋₆ alkoxycarbonylmethylidenyl and C₁₋₆ alkoxyaminocarbonyl.

- Typical examples of optional substituents which may be present on R¹, R², R³ or R⁴ include one, two or three substituents independently selected from C₁₋₆ alkyl, hydroxy,
- 20 C₁₋₆ alkoxy, oxo, amino, C₁₋₆ alkylsulphonylamino, carboxy and C₂₋₆ alkoxycarbonyl.

- Examples of particular substituents on R¹, R², R³ or R⁴ include fluoro, chloro, bromo, cyano, cyanoethyl, nitro, methyl, ethyl, *tert*-butyl, trifluoromethyl, trifluoroethyl, ethenyl, hydroxy, methoxy, isopropoxy, difluoromethoxy, trifluoromethoxy, trifluoroethoxy, methylenedioxy, ethylenedioxy, methoxymethyl, methylthio, methylsulphonyl,
- 25 methylsulphonylethyl, oxo, amino, methylamino, dimethylamino, methoxyethylamino, *N*-(hydroxyethyl)-*N*-(methyl)amino, acetylamino, methoxycarbonylamino, ethoxycarbonylamino, ethylaminocarbonylamino, butylaminocarbonylamino, methylsulphonylamino, formyl, acetyl, carboxy, carboxymethyl, carboxyethyl, methoxycarbonyl, ethoxycarbonyl, *tert*-butoxycarbonyl, ethoxycarbonylmethyl, ethoxycarbonylethyl, tetrazolyl, amino-
- 30 carbonyl, methylaminocarbonyl, dimethylaminocarbonyl, methylsulphonylaminocarbonyl,

aminosulphonyl, methylaminosulphonyl and dimethylaminosulphonyl. Additional examples include bis(methylsulphonyl)amino, *N*-(carboxyethyl)-*N*-(methyl)amino, carboxycyclopentylamino, carboxycyclopropylmethylamino, methoxycarbonylmethyl, tetrazolylmethyl and acetylaminosulphonyl. Additional examples include fluoromethyl, 5 fluoroisopropyl, nitromethyl, isopropyl, isobutyl, difluoromethyl, difluoroethyl, hydroxymethyl, hydroxyisopropyl, methoxyethyl, carboxycyclobutyl, methylsulphinyl, aminomethyl, aminoisopropyl, ethylamino, hydroxyethylamino, hydroxypropylamino, (hydroxy)(methyl)propylamino, (hydroxy)(methoxy)(methyl)propylamino, (hydroxy)-(methylthio)butylamino, dimethylaminoethylamino, (dimethylamino)(methyl)propyl- 10 amino, *N*-(dimethylaminoethyl)-*N*-(hydroxyethyl)amino, hydroxymethylcyclopentylamino, hydroxycyclobutylmethylamino, (cyclopropyl)(hydroxy)propylamino, morpholinylethylamino, oxopyrrolidinylmethylamino, ethyloxadiazolylamino, methylthiadiazolylamino, thiazolylmethylamino, thiazolylethylamino, pyrimidinylmethylamino, methylpyrazolylmethylamino, *N*-acetyl-*N*-methylamino, *N*-isopropylcarbonyl-*N*- 15 methylamino, acetylaminomethyl, ethenylcarbonylamino, bis(ethenylcarbonyl)amino, *N*-cyclopropylcarbonyl-*N*-methylamino, *N*-(carboxymethyl)-*N*-methylamino, *tert*-butoxycarbonylamino, methoxycarbonylethylamino, *N*-methyl-*N*-(methylsulphonyl)amino, isopropylcarbonyl, cyclobutylcarbonyl, phenylcarbonyl, acetoxisopropyl, *n*-butoxycarbonyl, morpholinylethoxycarbonyl, ethoxycarbonylmethylidenyl, hydroxyoxadiazolyl, 20 hydroxyethylaminocarbonyl and methoxyaminocarbonyl.

Suitable examples of particular substituents on R¹, R², R³ or R⁴ include methyl, hydroxy, methoxy, methylsulphonyl, oxo, amino, methylsulphonylamino, bis(methylsulphonyl)amino, *N*-(carboxyethyl)-*N*-(methyl)amino, carboxycyclopentylamino, carboxycyclopropylmethylamino, acetyl, carboxy, carboxyethyl, methoxycarbonyl, 25 ethoxycarbonyl, *tert*-butoxycarbonyl, methoxycarbonylmethyl, ethoxycarbonylethyl, tetrazolyl, tetrazolylmethyl, aminosulphonyl and acetylaminosulphonyl. Additional examples include fluoro, chloro, fluoromethyl, fluoroisopropyl, cyano, nitromethyl, ethyl, isopropyl, trifluoromethyl, hydroxymethyl, hydroxyisopropyl, carboxycyclobutyl, methylthio, aminomethyl, aminoisopropyl, methylamino, acetylaminomethyl, *N*-methyl-*N*- 30 (methylsulphonyl)amino, formyl, acetoxisopropyl, carboxymethyl, *n*-butoxycarbonyl, ethoxycarbonylmethyl, morpholinylethoxycarbonyl, ethoxycarbonylmethylidenyl, hydroxyoxadiazolyl, methoxyaminocarbonyl and methylsulphonylaminocarbonyl.

Typical examples of particular substituents on R¹, R², R³ or R⁴ include methyl, hydroxy, methoxy, oxo, amino, methylsulphonylamino, carboxy, methoxycarbonyl and *tert*-butoxycarbonyl.

Typically, R¹ represents hydrogen, halogen, cyano or -CO₂R^d; or C₁₋₆ alkyl, aryl, C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkenyl, heteroaryl, (C₃₋₇)heterocycloalkyl-(C₁₋₆)alkyl-aryl-, heteroaryl(C₃₋₇)heterocycloalkyl-, (C₄₋₇)cycloalkenyl-heteroaryl-, (C₃₋₇)heterocycloalkyl-heteroaryl-, (C₃₋₇)heterocycloalkyl(C₁₋₆)alkyl-heteroaryl-, (C₃₋₇)heterocycloalkenyl-heteroaryl-, (C₄₋₉)heterobicycloalkyl-heteroaryl- or (C₄₋₉)spiroheterocycloalkyl-heteroaryl-, any of which groups may be optionally substituted by one or more substituents. Additionally, R¹ may represent C₂₋₆ alkynyl or (C₃₋₇)cycloalkyl-heteroaryl-, either of which groups may be optionally substituted by one or more substituents. Additionally, R¹ may represent (C₃₋₇)cycloalkyl(C₁₋₆)alkyl-heteroaryl- or (C₄₋₉)bicycloalkyl-heteroaryl-, either of which groups may be optionally substituted by one or more substituents.

Suitably, R¹ represents halogen, cyano or -CO₂R^d; or C₁₋₆ alkyl, aryl, C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkenyl, heteroaryl, (C₃₋₇)heterocycloalkyl(C₁₋₆)alkyl-aryl-, heteroaryl(C₃₋₇)heterocycloalkyl-, (C₄₋₇)cycloalkenyl-heteroaryl-, (C₃₋₇)heterocycloalkyl-heteroaryl-, (C₃₋₇)heterocycloalkyl(C₁₋₆)alkyl-heteroaryl-, (C₃₋₇)heterocycloalkenyl-heteroaryl-, (C₄₋₉)heterobicycloalkyl-heteroaryl- or (C₄₋₉)spiroheterocycloalkyl-heteroaryl-, any of which groups may be optionally substituted by one or more substituents. Additionally, R¹ may represent C₂₋₆ alkynyl or (C₃₋₇)cycloalkyl-heteroaryl-, either of which groups may be optionally substituted by one or more substituents. Additionally, R¹ may represent (C₃₋₇)cycloalkyl(C₁₋₆)alkyl-heteroaryl- or (C₄₋₉)bicycloalkyl-heteroaryl-, either of which groups may be optionally substituted by one or more substituents.

Generally, R¹ represents halogen or cyano; or C₁₋₆ alkyl, aryl, C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkenyl, heteroaryl, (C₃₋₇)heterocycloalkyl(C₁₋₆)alkyl-aryl-, heteroaryl(C₃₋₇)heterocycloalkyl-, (C₄₋₇)cycloalkenyl-heteroaryl-, (C₃₋₇)heterocycloalkyl-heteroaryl-, (C₃₋₇)heterocycloalkyl(C₁₋₆)alkyl-heteroaryl-, (C₃₋₇)heterocycloalkenyl-heteroaryl-, (C₄₋₉)heterobicycloalkyl-heteroaryl- or (C₄₋₉)spiroheterocycloalkyl-heteroaryl-, any of which groups may be optionally substituted by one or more substituents. Additionally, R¹ may represent C₂₋₆ alkynyl or (C₃₋₇)cycloalkyl-heteroaryl-, either of which groups may be optionally substituted by one

or more substituents. Additionally, R^1 may represent (C₃₋₇)cycloalkyl(C₁₋₆)alkyl-heteroaryl- or (C₄₋₉)bicycloalkyl-heteroaryl-, either of which groups may be optionally substituted by one or more substituents.

More generally, R^1 represents halogen or cyano; or C₁₋₆ alkyl, aryl, C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkenyl, heteroaryl, (C₃₋₇)heterocycloalkyl(C₁₋₆)alkyl-aryl-, heteroaryl(C₃₋₇)heterocycloalkyl-, (C₃₋₇)heterocycloalkyl-heteroaryl-, (C₃₋₇)heterocycloalkyl(C₁₋₆)alkyl-heteroaryl-, (C₄₋₉)heterobicycloalkyl-heteroaryl- or (C₄₋₉)spiroheterocycloalkyl-heteroaryl-, any of which groups may be optionally substituted by one or more substituents. Additionally, R^1 may represent C₂₋₆ alkynyl, (C₃₋₇)cycloalkyl-heteroaryl- or (C₄₋₇)cycloalkenyl-heteroaryl-, any of which groups may be optionally substituted by one or more substituents. Additionally, R^1 may represent (C₃₋₇)cycloalkyl(C₁₋₆)alkyl-heteroaryl- or (C₄₋₉)bicycloalkyl-heteroaryl-, either of which groups may be optionally substituted by one or more substituents.

Still more generally, R^1 represents C₁₋₆ alkyl, C₂₋₆ alkynyl, aryl, C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkenyl, heteroaryl, (C₃₋₇)cycloalkyl-heteroaryl-, (C₄₋₇)cycloalkenyl-heteroaryl-, (C₃₋₇)heterocycloalkyl-heteroaryl-, (C₄₋₉)heterobicycloalkyl-heteroaryl- or (C₄₋₉)spiroheterocycloalkyl-heteroaryl-, any of which groups may be optionally substituted by one or more substituents. Additionally, R^1 may represent (C₃₋₇)cycloalkyl(C₁₋₆)alkyl-heteroaryl- or (C₄₋₉)bicycloalkyl-heteroaryl-, either of which groups may be optionally substituted by one or more substituents.

Even more generally, R^1 represents C₁₋₆ alkyl, C₃₋₇ heterocycloalkenyl, heteroaryl, (C₃₋₇)heterocycloalkyl-heteroaryl- or (C₄₋₉)heterobicycloalkyl-heteroaryl-, any of which groups may be optionally substituted by one or more substituents.

In a first embodiment, R^1 represents hydrogen.

In a second embodiment, R^1 represents halogen. In one aspect of that embodiment, R^1 represents bromo.

In a third embodiment, R^1 represents cyano.

In a fourth embodiment, R^1 represents -CO₂R^d.

In a fifth embodiment, R^1 represents optionally substituted C₁₋₆ alkyl. In one aspect of that embodiment, R^1 represents optionally substituted ethyl.

In a sixth embodiment, R^1 represents optionally substituted C₂₋₆ alkynyl. In one aspect of that embodiment, R^1 represents optionally substituted butynyl.

In a seventh embodiment, R¹ represents optionally substituted aryl. In one aspect of that embodiment, R¹ represents optionally substituted phenyl.

In an eighth embodiment, R¹ represents optionally substituted C₃₋₇ heterocycloalkyl.

5 In a ninth embodiment, R¹ represents optionally substituted C₃₋₇ heterocycloalkenyl.

In a tenth embodiment, R¹ represents optionally substituted heteroaryl. In selected aspects of that embodiment, R¹ represents benzofuryl, thienyl, indolyl, pyrazolyl, indazolyl, isoxazolyl, imidazolyl, pyridinyl, quinolinyl, pyridazinyl, pyrimidinyl or
10 pyrazinyl, any of which groups may be optionally substituted by one or more substituents. In a further aspect, R¹ represents optionally substituted thiazolyl.

In an eleventh embodiment, R¹ represents optionally substituted (C₃₋₇)-heterocycloalkyl(C₁₋₆)alkyl-aryl-. In a first aspect of that embodiment, R¹ represents optionally substituted pyrrolidinylmethylphenyl-. In a second aspect of that embodiment,
15 R¹ represents optionally substituted piperazinylmethylphenyl-.

In a twelfth embodiment, R¹ represents optionally substituted heteroaryl(C₃₋₇)-heterocycloalkyl-. In one aspect of that embodiment, R¹ represents optionally substituted pyridinylpiperazinyl-.

In a thirteenth embodiment, R¹ represents optionally substituted (C₃₋₇)cycloalkyl-heteroaryl-. In a first aspect of that embodiment, R¹ represents optionally substituted
20 cyclohexylpyrazolyl-. In a second aspect of that embodiment, R¹ represents optionally substituted cyclohexylpyridinyl-. In a third aspect of that embodiment, R¹ represents optionally substituted cyclopropylpyrimidinyl-. In a fourth aspect of that embodiment, R¹ represents optionally substituted cyclobutylpyrimidinyl-. In a fifth aspect of that
25 embodiment, R¹ represents optionally substituted cyclopentylpyrimidinyl-. In a sixth aspect of that embodiment, R¹ represents optionally substituted cyclohexylpyrimidinyl-. In a seventh aspect of that embodiment, R¹ represents optionally substituted cyclohexylpyrazinyl-.

In a fourteenth embodiment, R¹ represents optionally substituted (C₄₋₇)-cycloalkenyl-heteroaryl-.
30

In a fifteenth embodiment, R¹ represents optionally substituted (C₃₋₇)-heterocycloalkyl-heteroaryl-. In a first aspect of that embodiment, R¹ represents optionally substituted pyrrolidinylpyridinyl-. In a second aspect of that embodiment, R¹

represents optionally substituted tetrahydropyranylpyridinyl-. In a third aspect of that embodiment, R¹ represents optionally substituted piperidinylpyridinyl-. In a fourth aspect of that embodiment, R¹ represents optionally substituted piperazinylpyridinyl-. In a fifth aspect of that embodiment, R¹ represents optionally substituted morpholinylpyridinyl-. In a sixth aspect of that embodiment, R¹ represents optionally substituted thiomorpholinylpyridinyl-. In a seventh aspect of that embodiment, R¹ represents optionally substituted diazepanylpyridinyl-. In an eighth aspect of that embodiment, R¹ represents optionally substituted oxetanylpyrimidinyl-. In a ninth aspect of that embodiment, R¹ represents optionally substituted azetidinympyrimidinyl-. In a tenth aspect of that embodiment, R¹ represents optionally substituted tetrahydrofuranylpurimidinyl-. In an eleventh aspect of that embodiment, R¹ represents optionally substituted pyrrolidinylpyrimidinyl-. In a twelfth aspect of that embodiment, R¹ represents optionally substituted tetrahydropyranylpurimidinyl-. In a thirteenth aspect of that embodiment, R¹ represents optionally substituted piperidinylpyrimidinyl-. In a fourteenth aspect of that embodiment, R¹ represents optionally substituted piperazinylpyrimidinyl-. In a fifteenth aspect of that embodiment, R¹ represents optionally substituted morpholinylpyrimidinyl-. In a sixteenth aspect of that embodiment, R¹ represents optionally substituted thiomorpholinylpyrimidinyl-. In a seventeenth aspect of that embodiment, R¹ represents optionally substituted azepanylpyrimidinyl-. In an eighteenth aspect of that embodiment, R¹ represents optionally substituted oxazepanylpyrimidinyl-. In a nineteenth aspect of that embodiment, R¹ represents optionally substituted diazepanylpyrimidinyl-. In a twentieth aspect of that embodiment, R¹ represents optionally substituted thiadiazepanylpyrimidinyl-. In a twenty-first aspect of that embodiment, R¹ represents optionally substituted piperidinylpyrazinyl-.

25 In a sixteenth embodiment, R¹ represents optionally substituted (C₃₋₇)-heterocycloalkyl(C₁₋₆)alkyl-heteroaryl-. In a first aspect of that embodiment, R¹ represents optionally substituted morpholinylmethylthienyl-. In a second aspect of that embodiment, R¹ represents optionally substituted morpholinylethylpyrazolyl-.

30 In a seventeenth embodiment, R¹ represents optionally substituted (C₃₋₇)-heterocycloalkenyl-heteroaryl-.

In an eighteenth embodiment, R¹ represents optionally substituted (C₄₋₉)-heterobicycloalkyl-heteroaryl-.

In a nineteenth embodiment, R¹ represents optionally substituted (C₄₋₉)-spiroheterocycloalkyl-heteroaryl-.

In a twentieth embodiment, R¹ represents optionally substituted (C₃₋₇)cycloalkyl-(C₁₋₆)alkyl-heteroaryl-. In one aspect of that embodiment, R¹ represents optionally substituted cyclohexylmethylpyrimidinyl-.

In a twenty-first embodiment, R¹ represents optionally substituted (C₄₋₉)-bicycloalkyl-heteroaryl-.

Appositely, R¹ represents hydrogen, bromo, cyano or -CO₂R^d; or ethyl, phenyl, piperidinyl, piperazinyl, morpholinyl, 1,2,3,6-tetrahydropyridinyl, benzofuryl, thienyl, indolyl, pyrazolyl, indazolyl, isoxazolyl, imidazolyl, pyridinyl, quinolinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrrolidinylmethylphenyl, piperazinylmethylphenyl, pyridinyl-piperazinyl, pyrrolidinylpyridinyl, piperidinylpyridinyl, piperazinylpyridinyl, morpholinylpyridinyl, thiomorpholinylpyridinyl, diazepanylpyridinyl, pyrrolidinyl-pyrimidinyl, piperidinylpyrimidinyl, piperazinylpyrimidinyl, morpholinylpyrimidinyl, thiomorpholinylpyrimidinyl, diazepanylpyrimidinyl, thiadiazepanylpyrimidinyl, morpholinylmethylthienyl, morpholinylethylpyrazolyl, 2-oxa-5-azabicyclo[2.2.1]-heptanylpyrimidinyl, 2-oxa-6-azaspiro[3.3]heptanylpyrimidinyl, 2-oxa-6-azaspiro[3.4]-octanylpyrimidinyl, 2-oxa-6-azaspiro[3.5]nonanylpyrimidinyl or 2-oxa-7-azaspiro[3.5]-nonanylpyrimidinyl, any of which groups may be optionally substituted by one or more substituents. Additionally, R¹ may represent butynyl, cyclohexylpyrimidinyl, cyclohexenylpyrimidinyl, azetidinympyrimidinyl, 3-azabicyclo[3.1.0]hexanylpyrimidinyl or 2-azaspiro[3.3]heptanylpyrimidinyl, any of which groups may be optionally substituted by one or more substituents. Additionally, R¹ may represent pyrrolidinyl, thiazolyl, cyclohexylpyrazolyl, cyclohexylpyridinyl, cyclopropylpyrimidinyl, cyclobutyl-pyrimidinyl, cyclopentylpyrimidinyl, cyclohexylpyrazinyl, cyclohexylmethylpyrimidinyl, cyclohexenylpyridinyl, bicyclo[3.1.0]hexanylpyridinyl, bicyclo[3.1.0]hexanyl-pyrimidinyl, bicyclo[4.1.0]heptanylpyrimidinyl, bicyclo[2.2.2]octanylpyrimidinyl, tetrahydropyranylpyridinyl, oxetanylpyrimidinyl, tetrahydrofuranylpyrimidinyl, tetrahydropyranylpyrimidinyl, hexahydro-[1,2,5]thiadiazolo[2,3-*a*]pyrazinylpyrimidinyl, azepanylpyrimidinyl, oxazepanylpyrimidinyl, piperidinylpyrazinyl, 3-azabicyclo[3.1.0]-hexanylpyridinyl, 3-azabicyclo[3.1.0]hexanylpyridazinyl, 3-azabicyclo[3.1.1]heptanyl-pyrimidinyl, 3-azabicyclo[4.1.0]heptanylpyrimidinyl, 2-oxabicyclo[2.2.2]octanyl-pyrimidinyl, 3-azabicyclo[3.2.1]octanylpyrimidinyl, 8-azabicyclo[3.2.1]octanyl-

pyrimidinyl, 3-oxa-8-azabicyclo[3.2.1]octanylpyrimidinyl, 3,6-diazabicyclo[3.2.2]-nonanylpyrimidinyl, 3-oxa-7-azabicyclo[3.3.1]nonanylpyrimidinyl, 5-azaspiro[2.3]-hexanylpyrimidinyl, 5-azaspiro[2.4]heptanylpyrimidinyl or 2,4,8-triazaspiro[4.5]decanylpyrimidinyl, any of which groups may be optionally substituted by one or more
 5 substituents.

Appropriately, R¹ represents ethyl, butynyl, phenyl, morpholinyl, 1,2,3,6-tetrahydropyridinyl, pyrazolyl, pyridinyl, pyrimidinyl, cyclohexylpyrimidinyl, cyclohexenylpyrimidinyl, piperazinylpyridinyl, morpholinylpyridinyl, azetidiny-pyrimidinyl, pyrrolidinylpyrimidinyl, piperidinylpyrimidinyl, piperazinylpyrimidinyl,
 10 morpholinylpyrimidinyl, thiomorpholinylpyrimidinyl, diazepanylpyrimidinyl, thiadiazepanylpyrimidinyl, 3-azabicyclo[3.1.0]hexanylpyrimidinyl, 2-oxa-5-azabicyclo[2.2.1]heptanylpyrimidinyl or 2-azaspiro[3.3]heptanylpyrimidinyl, any of which groups may be optionally substituted by one or more substituents. Additionally, R¹ may represent pyrrolidinyl, piperidinyl, isoxazolyl, thiazolyl, imidazolyl, cyclohexylpyrazolyl,
 15 cyclohexylpyridinyl, cyclopropylpyrimidinyl, cyclobutylpyrimidinyl, cyclopentylpyrimidinyl, cyclohexylpyrazinyl, cyclohexylmethylpyrimidinyl, cyclohexenylpyridinyl, bicyclo[3.1.0]hexanylpyridinyl, bicyclo[3.1.0]hexanylpyrimidinyl, bicyclo[4.1.0]-heptanylpyrimidinyl, bicyclo[2.2.2]octanylpyrimidinyl, tetrahydropyranylpyridinyl, piperidinylpyridinyl, oxetanylpyrimidinyl, tetrahydrofuranylpyrimidinyl,
 20 tetrahydropyranylpyrimidinyl, hexahydro-[1,2,5]thiadiazolo[2,3-*a*]pyrazinylpyrimidinyl, azepanylpyrimidinyl, oxazepanylpyrimidinyl, piperidinylpyrazinyl, 3-azabicyclo[3.1.0]-hexanylpyridinyl, 3-azabicyclo[3.1.0]hexanylpyridazinyl, 3-azabicyclo[3.1.1]heptanylpyrimidinyl, 3-azabicyclo[4.1.0]heptanylpyrimidinyl, 2-oxabicyclo[2.2.2]octanylpyrimidinyl, 3-azabicyclo[3.2.1]octanylpyrimidinyl, 8-azabicyclo[3.2.1]octanylpyrimidinyl, 3-oxa-8-azabicyclo[3.2.1]octanylpyrimidinyl, 3,6-diazabicyclo[3.2.2]-nonanylpyrimidinyl, 3-oxa-7-azabicyclo[3.3.1]nonanylpyrimidinyl, 5-azaspiro[2.3]-hexanylpyrimidinyl, 5-azaspiro[2.4]heptanylpyrimidinyl or 2,4,8-triazaspiro[4.5]decanylpyrimidinyl, any of which groups may be optionally substituted by one or more
 25 substituents.

Illustratively, R¹ represents ethyl, 1,2,3,6-tetrahydropyridinyl, pyrazolyl, pyridinyl, piperazinylpyridinyl, morpholinylpyridinyl, piperidinylpyrimidinyl, piperazinylpyrimidinyl, morpholinylpyrimidinyl, thiomorpholinylpyrimidinyl, diazepanylpyrimidinyl, thiadiazepanylpyrimidinyl or 2-oxa-5-azabicyclo[2.2.1]heptanyl-

pyrimidinyl, any of which groups may be optionally substituted by one or more substituents.

Typical examples of optional substituents on R¹ include one, two or three substituents independently selected from halogen, cyano, cyano(C₁₋₆)alkyl, C₁₋₆ alkyl, trifluoromethyl, trifluoroethyl, C₂₋₆ alkenyl, hydroxy, C₁₋₆ alkoxy, trifluoroethoxy, C₁₋₆ alkylsulphonyl, (C₁₋₆)alkylsulphonyl(C₁₋₆)alkyl, oxo, amino, di(C₁₋₆)alkylamino, (C₁₋₆)alkoxy(C₁₋₆)alkylamino, *N*-[(C₁₋₆)alkyl]-*N*-[hydroxy(C₁₋₆)alkyl]amino, C₁₋₆ alkylsulphonylamino, C₂₋₆ alkylcarbonyl, carboxy, carboxy(C₁₋₆)alkyl, C₂₋₆ alkoxy-carbonyl, C₂₋₆ alkoxy-carbonyl(C₁₋₆)alkyl, a carboxylic acid isostere or prodrug moiety Ω as defined herein, and aminocarbonyl. Additional examples include bis[(C₁₋₆)alkylsulphonyl]amino, *N*-[(C₁₋₆)alkyl]-*N*-[carboxy(C₁₋₆)alkyl]amino, carboxy(C₃₋₇)cycloalkylamino, carboxy(C₃₋₇)cycloalkyl(C₁₋₆)alkylamino, -(C₁₋₆)alkyl- Ω , in which Ω is as defined herein, and aminosulphonyl. Additional examples include halo(C₁₋₆)alkyl, nitro(C₁₋₆)alkyl, hydroxy(C₁₋₆)alkyl, carboxy(C₃₋₇)cycloalkyloxy, C₁₋₆ alkylthio, amino(C₁₋₆)alkyl, C₁₋₆ alkylamino, (C₂₋₆)alkylcarbonylamino(C₁₋₆)alkyl, *N*-[(C₁₋₆)alkyl]-*N*-[(C₁₋₆)alkylsulphonyl]amino, formyl, (C₂₋₆)alkylcarbonyloxy(C₁₋₆)alkyl, morpholinyl(C₁₋₆)alkoxy-carbonyl, C₂₋₆ alkoxy-carbonylmethylidenyl and C₁₋₆ alkoxyaminocarbonyl.

Particular examples of optional substituents on R¹ include one, two or three substituents independently selected from C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkylsulphonyl, oxo, amino, *N*-[(C₁₋₆)alkyl]-*N*-[carboxy(C₁₋₆)alkyl]amino, carboxy-(C₃₋₇)cycloalkylamino, carboxy(C₃₋₇)cycloalkyl(C₁₋₆)alkylamino, C₁₋₆ alkylsulphonylamino, bis[(C₁₋₆)alkylsulphonyl]amino, C₂₋₆ alkylcarbonyl, carboxy, carboxy(C₁₋₆)alkyl, C₂₋₆ alkoxy-carbonyl, C₂₋₆ alkoxy-carbonyl(C₁₋₆)alkyl, a carboxylic acid isostere or prodrug moiety Ω as defined herein, -(C₁₋₆)alkyl- Ω , and aminosulphonyl. Additional examples include halogen, halo(C₁₋₆)alkyl, cyano, nitro(C₁₋₆)alkyl, trifluoromethyl, hydroxy(C₁₋₆)alkyl, carboxy(C₃₋₇)cycloalkyloxy, C₁₋₆ alkylthio, amino(C₁₋₆)alkyl, C₁₋₆ alkylamino, (C₂₋₆)alkylcarbonylamino(C₁₋₆)alkyl, *N*-[(C₁₋₆)alkyl]-*N*-[(C₁₋₆)alkylsulphonyl]amino, formyl, (C₂₋₆)alkylcarbonyloxy(C₁₋₆)alkyl, morpholinyl(C₁₋₆)alkoxy-carbonyl, C₂₋₆ alkoxy-carbonylmethylidenyl and C₁₋₆ alkoxyaminocarbonyl.

Suitable examples of optional substituents on R¹ include one, two or three substituents independently selected from C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, oxo, amino, C₁₋₆ alkylsulphonylamino, carboxy and C₂₋₆ alkoxy-carbonyl.

Typical examples of particular substituents on R¹ include one, two or three substituents independently selected from fluoro, chloro, cyano, cyanoethyl, methyl, trifluoromethyl, trifluoroethyl, ethenyl, hydroxy, methoxy, isopropoxy, trifluoroethoxy, methylsulphonyl, methylsulphonylethyl, oxo, amino, dimethylamino, methoxyethylamino, *N*-(hydroxyethyl)-*N*-(methyl)amino, methylsulphonylamino, acetyl, carboxy, carboxy-
 5 methyl, carboxyethyl, methoxycarbonyl, ethoxycarbonyl, *tert*-butoxycarbonyl, ethoxycarbonylmethyl, ethoxycarbonylethyl, tetrazolyl, aminocarbonyl and methylsulphonylaminocarbonyl. Additional examples include bis(methylsulphonyl)amino, *N*-(carboxyethyl)-*N*-(ethyl)amino, carboxycyclopentylamino, carboxycyclopropylmethylamino, methoxycarbonylmethyl, tetrazolylmethyl, aminosulphonyl and acetylaminosulphonyl.
 10 Additional examples include fluoromethyl, fluoroisopropyl, nitromethyl, ethyl, isopropyl, hydroxymethyl, hydroxyisopropyl, carboxycyclobutyl, methylthio, aminomethyl, aminoisopropyl, methylamino, acetylaminomethyl, *N*-methyl-*N*-(methylsulphonyl)amino, formyl, acetoxymethyl, *n*-butoxycarbonyl, morpholinylethoxycarbonyl, ethoxycarbonylmethylidenyl, hydroxyoxadiazolyl and methoxyaminocarbonyl.
 15

Representative examples of particular substituents on R¹ include one, two or three substituents independently selected from methyl, hydroxy, methoxy, methylsulphonyl, oxo, amino, methylsulphonylamino, bis(methylsulphonyl)amino, *N*-(carboxyethyl)-*N*-(ethyl)amino, carboxycyclopentylamino, carboxycyclopropylmethylamino, acetyl, carboxy, carboxyethyl, methoxycarbonyl, ethoxycarbonyl, *tert*-butoxycarbonyl, methoxycarbonylmethyl, ethoxycarbonylethyl, tetrazolyl, tetrazolylmethyl, aminosulphonyl and acetylaminosulphonyl. Additional examples include fluoro, chloro, fluoromethyl, fluoroisopropyl, cyano, nitromethyl, ethyl, isopropyl, trifluoromethyl, hydroxymethyl, hydroxyisopropyl, carboxycyclobutyl, methylthio, aminomethyl, aminoisopropyl, methylamino, acetylaminomethyl, *N*-methyl-*N*-(methylsulphonyl)amino, formyl, acetoxymethyl, carboxymethyl, *n*-butoxycarbonyl, morpholinylethoxycarbonyl, ethoxycarbonylmethylidenyl, hydroxyoxadiazolyl, methoxyaminocarbonyl and methylsulphonylaminocarbonyl.
 20
 25

Suitable examples of particular substituents on R¹ include one, two or three substituents independently selected from methyl, hydroxy, methoxy, oxo, amino, methylsulphonylamino, carboxy, methoxycarbonyl and *tert*-butoxycarbonyl.
 30

In a particular embodiment, R¹ is substituted by hydroxy(C₁₋₆)alkyl. In one aspect of that embodiment, R¹ is substituted by hydroxyisopropyl, especially 2-hydroxyprop-2-yl.

Selected values of R¹ include hydrogen, bromo, cyano, -CO₂R^d, methoxycarbonyl-ethyl, ethoxycarbonyl-ethyl, chlorophenyl, hydroxyphenyl, acetylphenyl, aminocarbonyl-phenyl, oxopiperidinyl, methylsulphonylpiperazinyl, morpholinyl, *tert*-butoxycarbonyl-1,2,3,6-tetrahydropyridinyl, benzofuryl, thienyl, indolyl, pyrazolyl, methylpyrazolyl, dimethylpyrazolyl, methylindazolyl, dimethylisoxazolyl, methylimidazolyl, pyridinyl, fluoropyridinyl, cyanopyridinyl, methylpyridinyl, (cyano)(methyl)pyridinyl, dimethylpyridinyl, trifluoromethylpyridinyl, ethenylpyridinyl, methoxypyridinyl, (methoxy)-(methyl)pyridinyl, isopropoxypyridinyl, trifluoroethoxypyridinyl, (methyl)(trifluoroethoxy)pyridinyl, oxopyridinyl, (methyl)(oxo)pyridinyl, (dimethyl)(oxo)pyridinyl, aminopyridinyl, dimethylaminopyridinyl, methoxyethylaminopyridinyl, *N*-(hydroxyethyl)-*N*-(methyl)aminopyridinyl, methylsulphonylaminopyridinyl, carboxypyridinyl, quinolinyl, hydroxypyridazinyl, pyrimidinyl, methoxypyrimidinyl, oxopyrimidinyl, aminopyrimidinyl, dimethylaminopyrimidinyl, methoxyethylaminopyrimidinyl, hydroxypyrazinyl, pyrrolidinylmethylphenyl, piperazinylmethylphenyl, pyridinylpiperazinyl, pyrrolidinylpyridinyl, hydroxypyrrolidinylpyridinyl, piperidinylpyridinyl, acetyl piperidinylpyridinyl, piperazinylpyridinyl, (methyl)(piperazinyl)pyridinyl, cyanoethylpiperazinylpyridinyl, trifluoroethylpiperazinylpyridinyl, methylsulphonylpiperazinylpyridinyl, methylsulphonyl-ethylpiperazinylpyridinyl, oxopiperazinylpyridinyl, acetyl piperazinylpyridinyl, (*tert*-butoxycarbonylpiperazinyl)-(methyl)pyridinyl, carboxymethylpiperazinylpyridinyl, carboxyethylpiperazinylpyridinyl, ethoxycarbonylmethylpiperazinylpyridinyl, ethoxycarbonyl-ethylpiperazinylpyridinyl, morpholinylpyridinyl, thiomorpholinylpyridinyl, oxothiomorpholinylpyridinyl, dioxothiomorpholinylpyridinyl, oxodiazepanylpyridinyl, hydroxypyrrolidinylpyrimidinyl, carboxypiperidinylpyrimidinyl, piperazinylpyrimidinyl, methylsulphonylpiperazinylpyrimidinyl, oxopiperazinylpyrimidinyl, *tert*-butoxycarbonylpiperazinylpyrimidinyl, morpholinylpyrimidinyl, thiomorpholinylpyrimidinyl, dioxothiomorpholinylpyrimidinyl, oxodiazepanylpyrimidinyl, dioxothiadiazepanylpyrimidinyl, morpholinylmethylthienyl, morpholinylethylpyrazolyl, 2-oxa-5-azabicyclo[2.2.1]heptanylpyrimidinyl, 2-oxa-6-azaspiro[3.3]heptanylpyrimidinyl, 2-oxa-6-azaspiro[3.4]octanylpyrimidinyl, 2-oxa-6-azaspiro[3.5]nonanylpyrimidinyl and 2-oxa-7-azaspiro[3.5]nonanylpyrimidinyl.

Additional values include hydroxybutynyl, aminosulphonylphenyl, acetylaminosulphonylphenyl, methylsulphonyl-1,2,3,6-tetrahydropyridinyl, acetyl-1,2,3,6-tetrahydropyridinyl, methoxycarbonylmethyl-1,2,3,6-tetrahydropyridinyl,

[bis(methylsulphonyl)amino]pyridinyl, *N*-(carboxyethyl)-*N*-(methyl)aminopyrimidinyl, carboxycyclopentylaminopyrimidinyl, carboxycyclopropylmethylaminopyrimidinyl, ethoxycarbonylethylpyrimidinyl, carboxycyclohexylpyrimidinyl, carboxycyclohexenylpyrimidinyl, ethoxycarbonylcyclohexenylpyrimidinyl, carboxyazetidiny pyrimidinyl, carboxypyrrolidinylpyrimidinyl, (carboxy)(methyl)piperidinylpyrimidinyl, ethoxycarbonylpiperidinylpyrimidinyl, (methoxycarbonyl)(methyl)piperidinylpyrimidinyl, (ethoxycarbonyl)(methyl)piperidinylpyrimidinyl, tetrazolylpiperidinylpyrimidinyl, carboxyethylpiperazinylpyrimidinyl, tetrazolylmethylpiperazinylpyrimidinyl, carboxymorpholinylpyrimidinyl, carboxy-3-azabicyclo[3.1.0]hexanylpyrimidinyl, ethoxycarbonyl-3-azabicyclo[3.1.0]hexanylpyrimidinyl and carboxy-2-azaspiro[3.3]heptanylpyrimidinyl. Additional values include methylsulphonylphenyl, aminomethylphenyl, aminoisopropylphenyl, acetylamino methylphenyl, methoxycarbonylphenyl, (methoxycarbonyl)(methyl)pyrrolidinyl, ethoxycarbonylpiperidinyl, (methyl)[*N*-methyl-*N*-(methylsulfonyl)]pyrazolyl, hydroxyisopropylthiazolyl, dimethylimidazolyl, hydroxyisopropylpyridinyl, methylsulphonylpyridinyl, methylaminopyridinyl, fluoroisopropylpyrimidinyl, hydroxyisopropylpyrimidinyl, carboxycyclobutyl oxy-pyrimidinyl, methylthiopyrimidinyl, methylsulphonylpyrimidinyl, acetoxylisopropylpyrimidinyl, hydroxyisopropylpyrazinyl, carboxycyclohexylpyrazolyl, carboxycyclohexylpyridinyl, fluoromethylcyclopropylpyrimidinyl, acetylamino methylcyclopropylpyrimidinyl, hydroxycyclobutylpyrimidinyl, carboxycyclopentylpyrimidinyl, (carboxy)(methyl)cyclohexylpyrimidinyl, (carboxy)(hydroxy)cyclohexylpyrimidinyl, carboxymethylcyclohexylpyrimidinyl, ethoxycarbonylcyclohexylpyrimidinyl, (methoxycarbonyl)(methyl)cyclohexylpyrimidinyl, (ethoxycarbonyl)(methyl)cyclohexylpyrimidinyl, carboxycyclohexylpyrazinyl, carboxycyclohexylmethylpyrimidinyl, carboxycyclohexenylpyridinyl, carboxybicyclo[3.1.0]hexanylpyridinyl, carboxybicyclo[3.1.0]hexanylpyrimidinyl, ethoxycarbonylbicyclo[3.1.0]hexanylpyrimidinyl, carboxybicyclo[4.1.0]heptanylpyrimidinyl, carboxybicyclo[2.2.2]octanylpyrimidinyl, hydroxytetrahydropyranylpyridinyl, (carboxy)(methyl)piperidinylpyridinyl, [(carboxy)(methyl)piperidinyl](fluoro)pyridinyl, [(carboxy)(methyl)piperidinyl](chloro)pyridinyl, fluoro-octanylpyrimidinyl, hydroxy-octanylpyrimidinyl, hydroxyazetidiny pyrimidinyl, (hydroxy)(methyl)azetidiny pyrimidinyl, (*tert*-butoxycarbonyl)(hydroxy)azetidiny pyrimidinyl, tetrazolylazetidiny pyrimidinyl, hydroxytetrahydrofuranylpyrimidinyl, (carboxy)(methyl)pyrrolidinylpyrimidinyl, carboxymethylpyrrolidinylpyrimidinyl,

ethoxycarbonylpyrrolidinylpyrimidinyl, fluorotetrahydropyranylpyrimidinyl, hydroxytetrahydropyranylpyrimidinyl, difluoropiperidinylpyrimidinyl, (cyano)(methyl)-piperidinylpyrimidinyl, (hydroxy)(nitromethyl)piperidinylpyrimidinyl, (hydroxy)-(methyl)piperidinylpyrimidinyl, (hydroxy)(trifluoromethyl)piperidinylpyrimidinyl, (hydroxymethyl)(methyl)piperidinylpyrimidinyl, methylsulphonylpiperidinylpyrimidinyl, oxopiperidinylpyrimidinyl, (formyl)(methyl)piperidinylpyrimidinyl, (carboxy)(fluoro)-piperidinylpyrimidinyl, (carboxy)(ethyl)piperidinylpyrimidinyl, (carboxy)-(trifluoromethyl)piperidinylpyrimidinyl, (carboxy)(hydroxy)piperidinylpyrimidinyl, (carboxy)(hydroxymethyl)piperidinylpyrimidinyl, (carboxy)(methoxy)piperidinylpyrimidinyl, (amino)(carboxy)piperidinylpyrimidinyl, carboxymethylpiperidinylpyrimidinyl, methoxycarbonylpiperidinylpyrimidinyl, (ethoxycarbonyl)(fluoro)-piperidinylpyrimidinyl, (ethyl)(methoxycarbonyl)piperidinylpyrimidinyl, (isopropyl)-(methoxycarbonyl)piperidinylpyrimidinyl, (*n*-butoxycarbonyl)(methyl)piperidinylpyrimidinyl, (ethoxycarbonyl)(trifluoromethyl)piperidinylpyrimidinyl, (ethoxycarbonyl)-(hydroxymethyl)piperidinylpyrimidinyl, (methoxy)(methoxycarbonyl)piperidinylpyrimidinyl, (carboxy)(methoxycarbonyl)piperidinylpyrimidinyl, (methyl)-(morpholinylethoxycarbonyl)piperidinylpyrimidinyl, ethoxycarbonylmethylpiperidinylpyrimidinyl, hydroxyoxadiazolylpiperidinylpyrimidinyl, methoxyaminocarbonylpiperidinylpyrimidinyl, methylsulphonylaminocarbonylpiperidinylpyrimidinyl, aminosulphonylpiperidinylpyrimidinyl, acetylaminosulphonylpiperidinylpyrimidinyl, carboxypiperazinylpyrimidinyl, trioxohexahydro-[1,2,5]thiadiazolo[2,3-*a*]pyrazinylpyrimidinyl, dimethylmorpholinylpyrimidinyl, hydroxymethylmorpholinylpyrimidinyl, (carboxy)(methyl)morpholinylpyrimidinyl, carboxymethylmorpholinylpyrimidinyl, carboxyazepanylpyrimidinyl, carboxyoxazepanylpyrimidinyl, (oxodiazepanyl)-(trifluoromethyl)pyrimidinyl, (oxodiazepanyl)(methoxy)pyrimidinyl, (methyl)(oxo)-diazepanylpyrimidinyl, hydroxyoxetanylpyrazinyl, (carboxy)(methyl)piperidinylpyrazinyl, (ethoxycarbonyl)(methyl)piperidinylpyrazinyl, carboxy-3-azabicyclo[3.1.0]hexanylpyridinyl, carboxy-3-azabicyclo[4.1.0]heptanylpyridinyl, carboxy-3-azabicyclo[3.1.0]hexanylpyridazinyl, (carboxy)(methyl)-3-azabicyclo[3.1.0]hexanylpyrimidinyl, methoxycarbonyl-3-azabicyclo[3.1.0]hexanylpyrimidinyl, carboxy-2-oxa-5-azabicyclo[2.2.1]heptanylpyrimidinyl, carboxy-3-azabicyclo[3.1.1]heptanylpyrimidinyl, carboxy-3-azabicyclo[4.1.0]heptanylpyrimidinyl, methoxycarbonyl-3-azabicyclo[4.1.0]heptanylpyrimidinyl, ethoxycarbonyl-3-azabicyclo[4.1.0]heptanylpyrimidinyl, (hydroxy)(methyl)-

(oxo)-2-oxabicyclo[2.2.2]octanylpyrimidinyl, carboxy-3-azabicyclo[3.2.1]octanylpyrimidinyl, methoxycarbonyl-3-azabicyclo[3.2.1]octanylpyrimidinyl, oxo-8-azabicyclo[3.2.1]octanylpyrimidinyl, ethoxycarbonylmethylidenyl-8-azabicyclo[3.2.1]octanylpyrimidinyl, 3-oxa-8-azabicyclo[3.2.1]octanylpyrimidinyl, oxo-3,6-diazabicyclo[3.2.2]-nonanylpyrimidinyl, carboxy-3-oxa-7-azabicyclo[3.3.1]nonanylpyrimidinyl, carboxy-5-azaspiro[2.3]hexanylpyrimidinyl, (carboxy)(methyl)-5-azaspiro[2.3]hexanylpyrimidinyl, carboxy-5-azaspiro[2.4]heptanylpyrimidinyl and (dioxo)(methyl)-2,4,8-triazaspiro[4.5]-decanylpyrimidinyl.

Definitive values of R¹ include hydrogen, bromo, ethoxycarbonylethyl, hydroxybutynyl, methylsulfonylphenyl, aminomethylphenyl, aminoisopropylphenyl, acetylaminoethylphenyl, methoxycarbonylphenyl, aminosulphonylphenyl, acetylamino-sulphonylphenyl, (methoxycarbonyl)(methyl)pyrrolidinyl, ethoxycarbonylpiperidinyl, morpholinyl, methylsulphonyl-1,2,3,6-tetrahydropyridinyl, acetyl-1,2,3,6-tetrahydropyridinyl, *tert*-butoxycarbonyl-1,2,3,6-tetrahydropyridinyl, methoxycarbonyl-methyl-1,2,3,6-tetrahydropyridinyl, methylpyrazolyl, (methyl)[*N*-methyl-*N*-(methylsulfonyl)]pyrazolyl, dimethylisoxazolyl, hydroxyisopropylthiazolyl, dimethylimidazolyl, hydroxyisopropylpyridinyl, methoxypyridinyl, (methoxy)(methyl)pyridinyl, methylsulphonylpyridinyl, oxopyridinyl, (methyl)(oxo)pyridinyl, aminopyridinyl, methylaminopyridinyl, methylsulphonylaminopyridinyl, [bis(methylsulphonyl)amino]-pyridinyl, carboxypyridinyl, fluoroisopropylpyrimidinyl, hydroxyisopropylpyrimidinyl, carboxycyclobutylpyrimidinyl, methylthiopyrimidinyl, methylsulphonylpyrimidinyl, *N*-(carboxyethyl)-*N*-(methyl)aminopyrimidinyl, carboxycyclopentylaminopyrimidinyl, carboxycyclopropylmethylaminopyrimidinyl, acetoxisopropylpyrimidinyl, ethoxycarbonylethylpyrimidinyl, hydroxyisopropylpyrazinyl, carboxycyclohexylpyrazolyl, carboxycyclohexylpyridinyl, fluoromethylcyclopropylpyrimidinyl, acetylaminomethylcyclopropylpyrimidinyl, hydroxycyclobutylpyrimidinyl, carboxycyclopentylpyrimidinyl, carboxycyclohexylpyrimidinyl, (carboxy)(methyl)cyclohexylpyrimidinyl, (carboxy)(hydroxy)cyclohexylpyrimidinyl, carboxymethylcyclohexylpyrimidinyl, ethoxycarbonylcyclohexylpyrimidinyl, (methoxycarbonyl)(methyl)cyclohexylpyrimidinyl, (ethoxycarbonyl)(methyl)cyclohexylpyrimidinyl, carboxycyclohexylpyrazinyl, carboxycyclohexylmethylpyrimidinyl, carboxycyclohexenylpyridinyl, carboxycyclohexenylpyrimidinyl, ethoxycarbonylcyclohexenylpyrimidinyl, carboxybicyclo[3.1.0]hexanylpyridinyl, carboxybicyclo[3.1.0]hexanylpyrimidinyl,

ethoxycarbonylbicyclo[3.1.0]hexanylpyrimidinyl, carboxybicyclo[4.1.0]heptanylpyrimidinyl, carboxybicyclo[2.2.2]octanylpyrimidinyl, hydroxytetrahydropyranylpyridinyl, piperidinylpyridinyl, (carboxy)(methyl)piperidinylpyridinyl, [(carboxy)(methyl)piperidinyl](fluoro)pyridinyl, [(carboxy)(methyl)piperidinyl](chloro)pyridinyl, piperazinylpyridinyl, morpholinylpyridinyl, fluorooxetanylpyrimidinyl, hydroxyoxetanylpyrimidinyl, hydroxyazetidinympyrimidinyl, (hydroxy)(methyl)azetidinympyrimidinyl, carboxyazetidinympyrimidinyl, (*tert*-butoxycarbonyl)(hydroxy)azetidinympyrimidinyl, tetrazolylazetidinympyrimidinyl, hydroxytetrahydrofuranlypyrimidinyl, carboxypyrrolidinylpyrimidinyl, (carboxy)(methyl)pyrrolidinylpyrimidinyl, carboxymethylpyrrolidinylpyrimidinyl, ethoxycarbonylpyrrolidinylpyrimidinyl, fluoro-tetrahydropyranylpyrimidinyl, hydroxytetrahydropyranylpyrimidinyl, difluoropiperidinylpyrimidinyl, (cyano)(methyl)piperidinylpyrimidinyl, (hydroxy)(nitromethyl)piperidinylpyrimidinyl, (hydroxy)(methyl)piperidinylpyrimidinyl, (hydroxy)(trifluoromethyl)piperidinylpyrimidinyl, (hydroxymethyl)(methyl)piperidinylpyrimidinyl, methylsulphonylpiperidinylpyrimidinyl, oxopiperidinylpyrimidinyl, (formyl)(methyl)piperidinylpyrimidinyl, carboxypiperidinylpyrimidinyl, (carboxy)(fluoro)piperidinylpyrimidinyl, (carboxy)(methyl)piperidinylpyrimidinyl, (carboxy)(ethyl)piperidinylpyrimidinyl, (carboxy)(trifluoromethyl)piperidinylpyrimidinyl, (carboxy)(hydroxy)piperidinylpyrimidinyl, (carboxy)(hydroxymethyl)piperidinylpyrimidinyl, (carboxy)(methoxy)piperidinylpyrimidinyl, (amino)(carboxy)piperidinylpyrimidinyl, carboxymethylpiperidinylpyrimidinyl, methoxycarbonylpiperidinylpyrimidinyl, ethoxycarbonylpiperidinylpyrimidinyl, (ethoxycarbonyl)(fluoro)piperidinylpyrimidinyl, (methoxycarbonyl)(methyl)piperidinylpyrimidinyl, (ethyl)(methoxycarbonyl)piperidinylpyrimidinyl, (isopropyl)(methoxycarbonyl)piperidinylpyrimidinyl, (ethoxycarbonyl)(methyl)piperidinylpyrimidinyl, (*n*-butoxycarbonyl)(methyl)piperidinylpyrimidinyl, (ethoxycarbonyl)(trifluoromethyl)piperidinylpyrimidinyl, (ethoxycarbonyl)(hydroxymethyl)piperidinylpyrimidinyl, (methoxy)(methoxycarbonyl)piperidinylpyrimidinyl, (carboxy)(methoxycarbonyl)piperidinylpyrimidinyl, (methyl)(morpholinylethoxycarbonyl)piperidinylpyrimidinyl, ethoxycarbonylmethylpiperidinylpyrimidinyl, hydroxyoxadiazolylpiperidinylpyrimidinyl, tetrazolylpiperidinylpyrimidinyl, methoxyaminocarbonylpiperidinylpyrimidinyl, methylsulphonylaminocarbonylpiperidinylpyrimidinyl, aminosulphonylpiperidinylpyrimidinyl, acetylaminosulphonylpiperidinylpyrimidinyl, piperazinylpyrimidinyl, oxopiperazinylpyrimidinyl,

methylsulfonylpiperazinympyrimidinyl, carboxypiperazinympyrimidinyl, carboxyethyl-
 piperazinympyrimidinyl, *tert*-butoxycarbonylpiperazinympyrimidinyl, tetrazolylmethyl-
 piperazinympyridinyl, trioxohexahydro-[1,2,5]thiadiazolo[2,3-*a*]pyrazinympyrimidinyl,
 morpholinylpyrimidinyl, dimethylmorpholinylpyrimidinyl, hydroxymethylmorpholinyl-
 5 pyrimidinyl, carboxymorpholinylpyrimidinyl, (carboxy)(methyl)morpholinylpyrimidinyl,
 carboxymethylmorpholinylpyrimidinyl, dioxothiomorpholinylpyrimidinyl, carboxy-
 azepanylpyrimidinyl, carboxyoxazepanylpyrimidinyl, oxodiazepanylpyrimidinyl,
 (oxodiazepanyl)(trifluoromethyl)pyrimidinyl, (oxodiazepanyl)(methoxy)pyrimidinyl,
 (methyl)(oxo)diazepanylpyrimidinyl, dioxothiadiazepanylpyrimidinyl, hydroxyoxetanyl-
 10 pyrazinyl, (carboxy)(methyl)piperidinylpyrazinyl, (ethoxycarbonyl)(methyl)piperidinyl-
 pyrazinyl, carboxy-3-azabicyclo[3.1.0]hexanylpyridinyl, carboxy-3-azabicyclo[4.1.0]-
 heptanylpyridinyl, carboxy-3-azabicyclo[3.1.0]hexanylpyridazinyl, carboxy-3-
 azabicyclo[3.1.0]hexanylpyrimidinyl, (carboxy)(methyl)-3-azabicyclo[3.1.0]hexanyl-
 pyrimidinyl, methoxycarbonyl-3-azabicyclo[3.1.0]hexanylpyrimidinyl, ethoxycarbonyl-3-
 15 azabicyclo[3.1.0]hexanylpyrimidinyl, 2-oxa-5-azabicyclo[2.2.1]heptanylpyrimidinyl,
 carboxy-2-oxa-5-azabicyclo[2.2.1]heptanylpyrimidinyl, carboxy-3-azabicyclo[3.1.1]-
 heptanylpyrimidinyl, carboxy-3-azabicyclo[4.1.0]heptanylpyrimidinyl, methoxycarbonyl-
 3-azabicyclo[4.1.0]heptanylpyrimidinyl, ethoxycarbonyl-3-azabicyclo[4.1.0]heptanyl-
 pyrimidinyl, (hydroxy)(methyl)(oxo)-2-oxabicyclo[2.2.2]octanylpyrimidinyl, carboxy-3-
 20 azabicyclo[3.2.1]octanylpyrimidinyl, methoxycarbonyl-3-azabicyclo[3.2.1]octanyl-
 pyrimidinyl, oxo-8-azabicyclo[3.2.1]octanylpyrimidinyl, ethoxycarbonylmethylidenyl-8-
 azabicyclo[3.2.1]octanylpyrimidinyl, 3-oxa-8-azabicyclo[3.2.1]octanylpyrimidinyl, oxo-
 3,6-diazabicyclo[3.2.2]nonanylpyrimidinyl, carboxy-3-oxa-7-azabicyclo[3.3.1]nonanyl-
 pyrimidinyl, carboxy-5-azaspiro[2.3]hexanylpyrimidinyl, (carboxy)(methyl)-5-azaspiro-
 25 [2.3]hexanylpyrimidinyl, carboxy-5-azaspiro[2.4]heptanylpyrimidinyl, carboxy-2-
 azaspiro[3.3]heptanylpyrimidinyl and (dioxo)(methyl)-2,4,8-triazaspiro[4.5]decanyl-
 pyrimidinyl.

Particular values of R¹ include ethoxycarbonyl ethyl, hydroxybutynyl, amino-
 sulphonylphenyl, acetaminosulphonylphenyl, morpholinyl, methylsulphonyl-1,2,3,6-
 30 tetrahydropyridinyl, acetyl-1,2,3,6-tetrahydropyridinyl, *tert*-butoxycarbonyl-1,2,3,6-
 tetrahydropyridinyl, methoxycarbonylmethyl-1,2,3,6-tetrahydropyridinyl, methyl-
 pyrazolyl, methoxypyridinyl, (methoxy)(methyl)pyridinyl, oxopyridinyl, (methyl)(oxo)-
 pyridinyl, aminopyridinyl, methylsulphonylaminopyridinyl, [bis(methylsulphonyl)-

amino]pyridinyl, *N*-(carboxyethyl)-*N*-(methyl)aminopyrimidinyl, carboxycyclopentylaminopyrimidinyl, carboxycyclopropylmethylaminopyrimidinyl, ethoxycarbonylethylpyrimidinyl, carboxycyclohexylpyrimidinyl, carboxycyclohexenylpyrimidinyl, ethoxycarbonylcyclohexenylpyrimidinyl, piperazinylpyridinyl, morpholinylpyridinyl, carboxyazetidiny pyrimidinyl, carboxypyrrolidinylpyrimidinyl, carboxypiperidinylpyrimidinyl, (carboxy)(methyl)piperidinylpyrimidinyl, ethoxycarbonylpiperidinylpyrimidinyl, (methoxycarbonyl)(methyl)piperidinylpyrimidinyl, (ethoxycarbonyl)(methyl)piperidinylpyrimidinyl, tetrazolylpiperidinylpyrimidinyl, piperazinylpyrimidinyl, oxopiperazinylpyrimidinyl, carboxyethylpiperazinylpyrimidinyl, tetrazolylmethylpiperazinylpyridinyl, morpholinylpyrimidinyl, carboxymorpholinylpyrimidinyl, dioxothiomorpholinylpyrimidinyl, oxodiazepanylpyrimidinyl, dioxothiadiazepanylpyrimidinyl, carboxy-3-azabicyclo[3.1.0]hexanylpyrimidinyl, ethoxycarbonyl-3-azabicyclo[3.1.0]hexanylpyrimidinyl, 2-oxa-5-azabicyclo[2.2.1]heptanylpyrimidinyl and carboxy-2-azaspiro[3.3]heptanylpyrimidinyl.

Illustrative values of R^1 include methoxycarbonylethyl, *tert*-butoxycarbonyl-1,2,3,6-tetrahydropyridinyl, methylpyrazolyl, methoxypyridinyl, (methoxy)(methyl)pyridinyl, oxopyridinyl, (methyl)(oxo)pyridinyl, aminopyridinyl, methylsulphonylamino-pyridinyl, piperazinylpyridinyl, morpholinylpyridinyl, carboxypiperidinylpyrimidinyl, piperazinylpyrimidinyl, oxopiperazinylpyrimidinyl, morpholinylpyrimidinyl, dioxothiomorpholinylpyrimidinyl, oxodiazepanylpyrimidinyl, dioxothiadiazepanylpyrimidinyl and 2-oxa-5-azabicyclo[2.2.1]heptanylpyrimidinyl.

Typically, R^2 represents hydrogen, halogen, trifluoromethyl or optionally substituted C_{1-6} alkyl. Additionally, R^2 may represent $-OR^a$.

Typical examples of optional substituents on R^2 include C_{2-6} alkoxycarbonyl.

Typical examples of particular substituents on R^2 include ethoxycarbonyl.

In a first embodiment, R^2 represents hydrogen. In a second embodiment, R^2 represents halogen. In one aspect of that embodiment, R^2 represents fluoro. In another aspect of that embodiment, R^2 represents chloro. In a third embodiment, R^2 represents trifluoromethyl. In a fourth embodiment, R^2 represents optionally substituted C_{1-6} alkyl. In one aspect of that embodiment, R^2 represents unsubstituted methyl. In another aspect of that embodiment, R^2 represents unsubstituted ethyl. In a further aspect of that embodiment, R^2 represents monosubstituted methyl or monosubstituted ethyl. In a fifth embodiment, R^2 represents $-OR^a$.

Typical values of R^2 include hydrogen, fluoro, trifluoromethyl, methyl and ethoxycarbonyl. Additional values include chloro and $-OR^a$.

Suitable values of R^2 include hydrogen, fluoro, trifluoromethyl and methyl. Additional values include chloro and $-OR^a$.

5 Typically, R^3 represents hydrogen, halogen or C_{1-6} alkyl.

In a first embodiment, R^3 represents hydrogen. In a second embodiment, R^3 represents halogen. In one aspect of that embodiment, R^3 represents fluoro. In a third embodiment, R^3 represents C_{1-6} alkyl. In one aspect of that embodiment, R^3 represents methyl. In another aspect of that embodiment, R^3 represents ethyl.

10 In a particular embodiment, R^4 represents hydrogen.

Suitably, R^5 represents hydrogen or methyl.

In a first embodiment, R^5 represents hydrogen. In a second embodiment, R^5 represents C_{1-6} alkyl, especially methyl.

Suitably, R^6 represents hydrogen, methyl or ethyl.

15 In a first embodiment, R^6 represents hydrogen. In a second embodiment, R^6 represents C_{1-6} alkyl, especially methyl or ethyl. In one aspect of that embodiment, R^6 represents methyl. In another aspect of that embodiment, R^6 represents ethyl.

Typical examples of suitable substituents on R^a , R^b , R^c , R^d or R^e , or on the heterocyclic moiety $-NR^bR^c$, include halogen, C_{1-6} alkyl, C_{1-6} alkoxy, difluoromethoxy, trifluoromethoxy, C_{1-6} alkoxy(C_{1-6})alkyl, C_{1-6} alkylthio, C_{1-6} alkylsulphinyl, C_{1-6} alkylsulphonyl, hydroxy, hydroxy(C_{1-6})alkyl, amino(C_{1-6})alkyl, cyano, trifluoromethyl, oxo, C_{2-6} alkylcarbonyl, carboxy, C_{2-6} alkoxy carbonyl, C_{2-6} alkylcarbonyloxy, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, phenylamino, pyridinylamino, C_{2-6} alkylcarbonylamino, C_{2-6} alkylcarbonylamino(C_{1-6})alkyl, C_{2-6} alkoxy carbonylamino, C_{1-6} alkylsulphonylamino, aminocarbonyl, C_{1-6} alkylaminocarbonyl and di(C_{1-6})alkylaminocarbonyl.

Typical examples of specific substituents on R^a , R^b , R^c , R^d or R^e , or on the heterocyclic moiety $-NR^bR^c$, include fluoro, chloro, bromo, methyl, ethyl, isopropyl, methoxy, isopropoxy, difluoromethoxy, trifluoromethoxy, methoxymethyl, methylthio, ethylthio, methylsulphinyl, methylsulphonyl, hydroxy, hydroxymethyl, hydroxyethyl, aminomethyl, cyano, trifluoromethyl, oxo, acetyl, carboxy, methoxycarbonyl, ethoxycarbonyl, *tert*-butoxycarbonyl, acetoxymethyl, amino, methylamino, ethylamino, dimethylamino, phenylamino, pyridinylamino, acetoxymethyl, *tert*-butoxycarbonylamino,

acetaminomethyl, methylsulphonylamino, aminocarbonyl, methylaminocarbonyl and dimethylaminocarbonyl.

Suitably, R^a represents C₁₋₆ alkyl, aryl(C₁₋₆)alkyl or heteroaryl(C₁₋₆)alkyl, any of which groups may be optionally substituted by one or more substituents.

5 Selected values of R^a include methyl, ethyl, benzyl and isoindolylpropyl, any of which groups may be optionally substituted by one or more substituents.

Selected examples of suitable substituents on R^a include C₁₋₆ alkoxy and oxo.

Selected examples of specific substituents on R^a include methoxy and oxo.

In one embodiment, R^a represents optionally substituted C₁₋₆ alkyl. In one aspect
10 of that embodiment, R^a ideally represents unsubstituted C₁₋₆ alkyl, especially methyl. In another aspect of that embodiment, R^a ideally represents substituted C₁₋₆ alkyl, e.g. methoxyethyl. In another embodiment, R^a represents optionally substituted aryl. In one aspect of that embodiment, R^a represents unsubstituted aryl, especially phenyl. In another aspect of that embodiment, R^a represents monosubstituted aryl, especially methylphenyl.
15 In another embodiment, R^a represents optionally substituted aryl(C₁₋₆)alkyl, ideally unsubstituted aryl(C₁₋₆)alkyl, especially benzyl. In a further embodiment, R^a represents optionally substituted heteroaryl. In a further embodiment, R^a represents optionally substituted heteroaryl(C₁₋₆)alkyl, e.g. dioxoisindolylpropyl.

Specific values of R^a include methyl, methoxyethyl, benzyl and dioxoisindolyl-
20 propyl.

In a particular aspect, R^b represents hydrogen or trifluoromethyl; or C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl(C₁₋₆)alkyl, aryl, aryl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkyl(C₁₋₆)alkyl, heteroaryl or heteroaryl(C₁₋₆)alkyl, any of which groups may be optionally substituted by one or more substituents.

25 Selected values of R^b include hydrogen; or C₁₋₆ alkyl, aryl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkyl or C₃₋₇ heterocycloalkyl(C₁₋₆)alkyl, any of which groups may be optionally substituted by one or more substituents.

Typical values of R^b include hydrogen and C₁₋₆ alkyl.

Illustratively, R^b represents hydrogen or trifluoromethyl; or methyl, ethyl, *n*-propyl,
30 isopropyl, *n*-butyl, 2-methylpropyl, *tert*-butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, phenyl, benzyl, phenylethyl, azetidyl, tetrahydrofuryl, tetrahydrothienyl, pyrrolidinyl, piperidinyl, homopiperidinyl, morpholinyl,

azetidinylmethyl, tetrahydrofurylmethyl, pyrrolidinylmethyl, pyrrolidinyethyl, pyrrolidinylpropyl, thiazolidinylmethyl, imidazolidinylethyl, piperidinylmethyl, piperidinyethyl, tetrahydroquinolinylmethyl, piperazinylpropyl, morpholinylmethyl, morpholinylethyl, morpholinylpropyl, pyridinyl, indolylmethyl, pyrazolylmethyl, pyrazolyethyl, imidazolylmethyl, imidazolylethyl, benzimidazolylmethyl, triazolylmethyl, pyridinylmethyl or pyridinyethyl, any of which groups may be optionally substituted by one or more substituents.

Representative values of R^b include hydrogen; or methyl, ethyl, *n*-propyl, benzyl, pyrrolidinyl or morpholinylpropyl, any of which groups may be optionally substituted by one or more substituents.

Selected examples of suitable substituents on R^b include C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ alkylsulphinyl, C₁₋₆ alkylsulphonyl, hydroxy, cyano, C₂₋₆ alkoxycarbonyl, di-(C₁₋₆)alkylamino and C₂₋₆ alkoxycarbonylamino.

Selected examples of specific substituents on R^b include methoxy, methylthio, methylsulphinyl, methylsulphonyl, hydroxy, cyano, *tert*-butoxycarbonyl, dimethylamino and *tert*-butoxycarbonylamino.

Specific values of R^b include hydrogen, methyl, methoxyethyl, methylthioethyl, methylsulphinylethyl, methylsulphonylethyl, hydroxyethyl, cyanoethyl, dimethylaminoethyl, *tert*-butoxycarbonylaminoethyl, dihydroxypropyl, benzyl, pyrrolidinyl, *tert*-butoxycarbonylpyrrolidinyl and morpholinylpropyl.

In one embodiment, R^b represents hydrogen. In another embodiment, R^b represents C₁₋₆ alkyl, especially methyl.

Selected values of R^c include hydrogen; or C₁₋₆ alkyl, C₃₋₇ cycloalkyl or C₃₋₇ heterocycloalkyl, any of which groups may be optionally substituted by one or more substituents.

In a particular aspect, R^c represents hydrogen, C₁₋₆ alkyl or C₃₋₇ cycloalkyl.

Representative values of R^c include hydrogen; or methyl, cyclobutyl, cyclopentyl, cyclohexyl, tetrahydropyranyl and piperidinyl, any of which groups may be optionally substituted by one or more substituents.

Selected examples of suitable substituents on R^c include C₂₋₆ alkylcarbonyl and C₂₋₆ alkoxycarbonyl.

Selected examples of specific substituents on R^c include acetyl and *tert*-butoxycarbonyl.

Specific values of R^c include hydrogen, methyl, cyclobutyl, cyclopentyl, cyclohexyl, tetrahydropyranyl, acetylpiperidinyl and *tert*-butoxycarbonylpiperidinyl,

Suitably, R^c represents hydrogen or C₁₋₆ alkyl. In one embodiment, R^c is hydrogen. In another embodiment, R^c represents C₁₋₆ alkyl, especially methyl or ethyl, particularly methyl. In a further embodiment, R^c represents C₃₋₇ cycloalkyl, e.g. cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

Alternatively, the moiety -NR^bR^c may suitably represent azetidin-1-yl, pyrrolidin-1-yl, oxazolidin-3-yl, isoxazolidin-2-yl, thiazolidin-3-yl, isothiazolidin-2-yl, piperidin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, piperazin-1-yl, homopiperidin-1-yl, homomorpholin-4-yl or homopiperazin-1-yl, any of which groups may be optionally substituted by one or more substituents.

Selected examples of suitable substituents on the heterocyclic moiety -NR^bR^c include C₁₋₆ alkyl, C₁₋₆ alkylsulphonyl, hydroxy, hydroxy(C₁₋₆)alkyl, amino(C₁₋₆)alkyl, cyano, oxo, C₂₋₆ alkylcarbonyl, carboxy, C₂₋₆ alkoxycarbonyl, amino, C₂₋₆ alkylcarbonyl-amino, C₂₋₆ alkylcarbonylamino(C₁₋₆)alkyl, C₂₋₆ alkoxycarbonylamino, C₁₋₆ alkylsulphonylamino and aminocarbonyl.

Selected examples of specific substituents on the heterocyclic moiety -NR^bR^c include methyl, methylsulphonyl, hydroxy, hydroxymethyl, aminomethyl, cyano, oxo, acetyl, carboxy, ethoxycarbonyl, amino, acetylamino, acetylaminomethyl, *tert*-butoxycarbonylamino, methylsulphonylamino and aminocarbonyl.

Specific values of the moiety -NR^bR^c include azetidin-1-yl, hydroxyazetidin-1-yl, hydroxymethylazetidin-1-yl, (hydroxy)(hydroxymethyl)azetidin-1-yl, aminomethylazetidin-1-yl, cyanoazetidin-1-yl, carboxyazetidin-1-yl, aminoazetidin-1-yl, aminocarbonylazetidin-1-yl, pyrrolidin-1-yl, aminomethylpyrrolidin-1-yl, oxopyrrolidin-1-yl, acetylaminomethylpyrrolidin-1-yl, *tert*-butoxycarbonylaminopyrrolidin-1-yl, oxo-oxazolidin-3-yl, hydroxyisoxazolidin-2-yl, thiazolidin-3-yl, oxothiazolidin-3-yl, dioxo-isothiazolidin-2-yl, piperidin-1-yl, hydroxypiperidin-1-yl, hydroxymethylpiperidin-1-yl, aminopiperidin-1-yl, acetylaminopiperidin-1-yl, *tert*-butoxycarbonylaminopiperidin-1-yl, methylsulphonylaminopiperidin-1-yl, morpholin-4-yl, piperazin-1-yl, methylpiperazin-1-yl, methylsulphonylpiperazin-1-yl, oxopiperazin-1-yl, acetylpiperazin-1-yl, ethoxycarbonylpiperazin-1-yl and oxohomopiperazin-1-yl.

Suitably, R^d represents hydrogen; or C₁₋₆ alkyl, aryl or heteroaryl, any of which groups may be optionally substituted by one or more substituents.

Selected examples of suitable values for R^d include hydrogen, methyl, ethyl, isopropyl, 2-methylpropyl, *tert*-butyl, cyclopropyl, cyclobutyl, phenyl, thiazolidinyl, thienyl, imidazolyl and thiazolyl, any of which groups may be optionally substituted by one or more substituents.

- 5 Selected examples of suitable substituents on R^d include halogen, C_{1-6} alkyl, C_{1-6} alkoxy, oxo, C_{2-6} alkylcarbonyloxy and di(C_{1-6})alkylamino.

Selected examples of particular substituents on R^d include fluoro, methyl, methoxy, oxo, acetoxy and dimethylamino.

- In one embodiment, R^d represents hydrogen. In another embodiment, R^d represents optionally substituted C_{1-6} alkyl. In one aspect of that embodiment, R^d ideally represents unsubstituted C_{1-6} alkyl, e.g. methyl, ethyl, isopropyl, 2-methylpropyl or *tert*-butyl, especially methyl. In another aspect of that embodiment, R^d ideally represents substituted C_{1-6} alkyl, e.g. substituted methyl or substituted ethyl, including acetoxymethyl, dimethylaminomethyl and trifluoroethyl. In another embodiment, R^d represents optionally substituted aryl. In one aspect of that embodiment, R^d represents unsubstituted aryl, especially phenyl. In another aspect of that embodiment, R^d represents monosubstituted aryl, especially methylphenyl. In a further aspect of that embodiment, R^d represents disubstituted aryl, e.g. dimethoxyphenyl. In a further embodiment, R^d represents optionally substituted heteroaryl, e.g. thienyl, chlorothienyl, methylthienyl, methylimidazolyl or thiazolyl. In another embodiment, R^d represents optionally substituted C_{3-7} cycloalkyl, e.g. cyclopropyl or cyclobutyl. In a further embodiment, R^d represents optionally substituted C_{3-7} heterocycloalkyl, e.g. thiazolidinyl or oxo-thiazolidinyl.

- Selected examples of specific values for R^d include hydrogen, methyl, acetoxy-methyl, dimethylaminomethyl, ethyl, trifluoroethyl, isopropyl, 2-methylpropyl, *tert*-butyl, cyclopropyl, cyclobutyl, phenyl, dimethoxyphenyl, thiazolidinyl, oxothiazolidinyl, thienyl, chlorothienyl, methylthienyl, methylimidazolyl and thiazolyl.

Suitably, R^e represents C_{1-6} alkyl or aryl, either of which groups may be optionally substituted by one or more substituents.

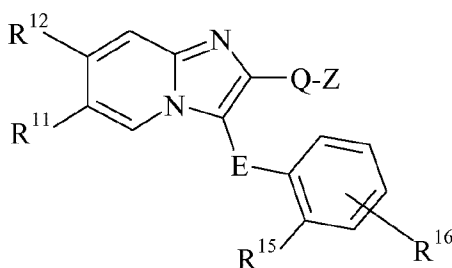
- 30 Selected examples of suitable substituents on R^e include C_{1-6} alkyl, especially methyl.

In one embodiment, R^e represents optionally substituted C_{1-6} alkyl, ideally unsubstituted C_{1-6} alkyl, e.g. methyl or propyl, especially methyl. In another embodiment,

R^e represents optionally substituted aryl. In one aspect of that embodiment, R^e represents unsubstituted aryl, especially phenyl. In another aspect of that embodiment, R^e represents monosubstituted aryl, especially methylphenyl. In a further embodiment, R^e represents optionally substituted heteroaryl.

5 Selected values of R^e include methyl, propyl and methylphenyl.

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



(IIA)

wherein

R¹¹ represents halogen or cyano; or C₁₋₆ alkyl, C₂₋₆ alkynyl, aryl, C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkenyl, heteroaryl, (C₃₋₇)heterocycloalkyl(C₁₋₆)alkyl-aryl-, heteroaryl(C₃₋₇)heterocycloalkyl-, (C₃₋₇)cycloalkyl-heteroaryl-, (C₃₋₇)cycloalkyl-(C₁₋₆)alkyl-heteroaryl-, (C₄₋₇)cycloalkenyl-heteroaryl-, (C₄₋₉) bicycloalkyl-heteroaryl-, (C₃₋₇)heterocycloalkyl-heteroaryl-, (C₃₋₇)heterocycloalkyl(C₁₋₆)alkyl-heteroaryl-, (C₃₋₇)heterocycloalkenyl-heteroaryl-, (C₄₋₉)heterobicycloalkyl-heteroaryl- or (C₄₋₉)spiroheterocycloalkyl-heteroaryl-, any of which groups may be optionally substituted by one or more substituents;

R¹² represents hydrogen, halogen, trifluoromethyl or optionally substituted C₁₋₆ alkyl;

R¹⁵ and R¹⁶ independently represent hydrogen, halogen, cyano, nitro, C₁₋₆ alkyl, trifluoromethyl, hydroxy, C₁₋₆ alkoxy, difluoromethoxy, trifluoromethoxy, C₁₋₆ alkylthio, C₁₋₆ alkylsulfinyl, C₁₋₆ alkylsulfonyl, amino, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino, arylamino, C₂₋₆ alkylcarbonylamino, C₁₋₆ alkylsulfonylamino, formyl, C₂₋₆ alkylcarbonyl, C₃₋₆ cycloalkylcarbonyl, C₃₋₆ heterocycloalkylcarbonyl, carboxy, C₂₋₆ alkoxy carbonyl,

aminocarbonyl, C₁₋₆ alkylaminocarbonyl, di(C₁₋₆)alkylaminocarbonyl, aminosulfonyl, C₁₋₆ alkylaminosulfonyl or di(C₁₋₆)alkylaminosulfonyl; and

E, Q and Z are as defined above.

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

R¹¹ represents halogen or cyano; or C₁₋₆ alkyl, C₂₋₆ alkynyl, aryl, C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkenyl, heteroaryl, (C₃₋₇)heterocycloalkyl(C₁₋₆)alkyl-aryl-, heteroaryl(C₃₋₇)heterocycloalkyl-, (C₃₋₇)cycloalkyl-heteroaryl-, (C₄₋₇)cycloalkenyl-heteroaryl-, (C₃₋₇)heterocycloalkyl-heteroaryl-, (C₃₋₇)heterocycloalkyl(C₁₋₆)alkyl-heteroaryl-, (C₃₋₇)heterocycloalkenyl-heteroaryl-, (C₄₋₉)heterobicycloalkyl-heteroaryl- or (C₄₋₉)spiroheterocycloalkyl-heteroaryl-, any of which groups may be optionally substituted by one or more substituents; and

E, Q, Z, R¹², R¹⁵ and R¹⁶ are as defined above.

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

R¹¹ represents halogen or cyano; or C₁₋₆ alkyl, aryl, C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkenyl, heteroaryl, (C₃₋₇)heterocycloalkyl(C₁₋₆)alkyl-aryl-, heteroaryl-(C₃₋₇)heterocycloalkyl-, (C₄₋₇)cycloalkenyl-heteroaryl-, (C₃₋₇)heterocycloalkyl-heteroaryl-, (C₃₋₇)heterocycloalkyl(C₁₋₆)alkyl-heteroaryl-, (C₃₋₇)heterocycloalkenyl-heteroaryl-, (C₄₋₉)heterobicycloalkyl-heteroaryl- or (C₄₋₉)spiroheterocycloalkyl-heteroaryl-, any of which groups may be optionally substituted by one or more substituents; and

E, Q, Z, R¹², R¹⁵ and R¹⁶ are as defined above.

Aptly, R¹¹ represents halogen or cyano; or C₁₋₆ alkyl, aryl, C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkenyl, heteroaryl, (C₃₋₇)heterocycloalkyl(C₁₋₆)alkyl-aryl-, heteroaryl-(C₃₋₇)heterocycloalkyl-, (C₃₋₇)heterocycloalkyl-heteroaryl-, (C₃₋₇)heterocycloalkyl-(C₁₋₆)alkyl-heteroaryl-, (C₄₋₉)heterobicycloalkyl-heteroaryl- or (C₄₋₉)spiroheterocycloalkyl-heteroaryl-, any of which groups may be optionally substituted by one or more substituents. Additionally, R¹¹ may represent C₂₋₆ alkynyl, (C₃₋₇)cycloalkyl-heteroaryl- or (C₄₋₇)cycloalkenyl-heteroaryl-, any of which groups may be optionally substituted by one or more substituents. Additionally, R¹¹ may represent (C₃₋₇)cycloalkyl(C₁₋₆)alkyl-

heteroaryl- or (C₄₋₉) bicycloalkyl-heteroaryl-, either of which groups may be optionally substituted by one or more substituents.

Examples of optional substituents which may be present on R¹¹ include one, two or three substituents independently selected from halogen, cyano, cyano(C₁₋₆)alkyl, nitro, C₁₋₆ alkyl, trifluoromethyl, trifluoroethyl, C₂₋₆ alkenyl, hydroxy, C₁₋₆ alkoxy, difluoromethoxy, trifluoromethoxy, trifluoroethoxy, C₁₋₃ alkylenedioxy, C₁₋₆ alkoxy(C₁₋₆)alkyl, C₁₋₆ alkylthio, C₁₋₆ alkylsulphonyl, (C₁₋₆)alkylsulphonyl(C₁₋₆)alkyl, oxo, amino, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino, (C₁₋₆)alkoxy(C₁₋₆)alkylamino, *N*-[(C₁₋₆)alkyl]-*N*-[hydroxy(C₁₋₆)alkyl]-amino, C₂₋₆ alkylcarbonylamino, C₂₋₆ alkoxy carbonylamino, C₁₋₆ alkylaminocarbonyl-amino, C₁₋₆ alkylsulphonylamino, formyl, C₂₋₆ alkylcarbonyl, carboxy, carboxy(C₁₋₆)alkyl, C₂₋₆ alkoxy carbonyl, C₂₋₆ alkoxy carbonyl(C₁₋₆)alkyl, a carboxylic acid isostere or prodrug moiety Ω as defined herein, aminocarbonyl, C₁₋₆ alkylaminocarbonyl, di(C₁₋₆)alkylaminocarbonyl, aminosulphonyl and di(C₁₋₆)alkylaminosulphonyl. Additional examples include bis[(C₁₋₆)alkylsulphonyl]amino, *N*-[(C₁₋₆)alkyl]-*N*-[carboxy(C₁₋₆)alkyl]amino, carboxy-(C₃₋₇)cycloalkylamino, carboxy(C₃₋₇)cycloalkyl(C₁₋₆)alkylamino and -(C₁₋₆)alkyl- Ω , in which Ω is as defined herein. Additional examples include halo(C₁₋₆)alkyl, nitro(C₁₋₆)alkyl, difluoromethyl, difluoroethyl, hydroxy(C₁₋₆)alkyl, carboxy(C₃₋₇)cycloalkyloxy, C₁₋₆ alkylsulphanyl, amino(C₁₋₆)alkyl, hydroxy(C₁₋₆)alkylamino, C₁₋₆ alkoxyamino, [(C₁₋₆)alkoxy](hydroxy)(C₁₋₆)alkylamino, [(C₁₋₆)alkylthio](hydroxy)(C₁₋₆)alkylamino, di(C₁₋₆)alkylamino(C₁₋₆)alkylamino, *N*-[di(C₁₋₆)alkylamino(C₁₋₆)alkyl]-*N*-[hydroxy(C₁₋₆)alkyl]-amino, hydroxy(C₁₋₆)alkyl(C₃₋₇)cycloalkylamino, (hydroxy)[(C₃₋₇)cycloalkyl(C₁₋₆)alkyl]-amino, (C₃₋₇)heterocycloalkyl(C₁₋₆)alkylamino, oxo(C₃₋₇)heterocycloalkyl(C₁₋₆)alkylamino, (C₁₋₆)alkylheteroaryl-amino, heteroaryl(C₁₋₆)alkylamino, (C₁₋₆)alkylheteroaryl(C₁₋₆)alkyl-amino, *N*-[(C₁₋₆)alkyl]-*N*-[(C₂₋₆)alkylcarbonyl]amino, (C₂₋₆)alkylcarbonylamino(C₁₋₆)alkyl, C₃₋₆ alkenylcarbonylamino, bis[(C₃₋₆)alkenylcarbonyl]amino, *N*-[(C₁₋₆)alkyl]-*N*-[(C₃₋₇)cycloalkylcarbonyl]amino, C₂₋₆ alkoxy carbonyl(C₁₋₆)alkylamino, *N*-[(C₁₋₆)alkyl]-*N*-[(C₁₋₆)alkylsulphonyl]amino, C₁₋₆ alkylsulphonylamino(C₁₋₆)alkyl, (C₃₋₇)cycloalkylcarbonyl, phenylcarbonyl, (C₂₋₆)alkylcarbonyloxy(C₁₋₆)alkyl, morpholinyl(C₁₋₆)alkoxy carbonyl, C₂₋₆ alkoxy carbonylmethylidenyl, hydroxy(C₁₋₆)alkylaminocarbonyl, aminocarbonyl(C₁₋₆)alkyl and C₁₋₆ alkoxyaminocarbonyl.

Examples of particular substituents on R¹¹ include fluoro, chloro, bromo, cyano, cyanoethyl, nitro, methyl, ethyl, *tert*-butyl, trifluoromethyl, trifluoroethyl, ethenyl, hydroxy, methoxy, isopropoxy, difluoromethoxy, trifluoromethoxy, trifluoroethoxy,

methylenedioxy, ethylenedioxy, methoxymethyl, methylthio, methylsulphonyl, methylsulphonylethyl, oxo, amino, methylamino, dimethylamino, methoxyethylamino, *N*-(hydroxyethyl)-*N*-(methyl)amino, acetylamino, methoxycarbonylamino, ethoxycarbonylamino, ethylaminocarbonylamino, butylaminocarbonylamino, methylsulphonylamino, formyl, acetyl, carboxy, carboxymethyl, carboxyethyl, methoxycarbonyl, ethoxycarbonyl, *tert*-butoxycarbonyl, ethoxycarbonylmethyl, ethoxycarbonylethyl, tetrazolyl, amino-carbonyl, methylaminocarbonyl, dimethylaminocarbonyl, methylsulphonylamino, aminosulphonyl, methylaminosulphonyl and dimethylaminosulphonyl. Additional examples include bis(methylsulphonyl)amino, *N*-(carboxyethyl)-*N*-(methyl)amino, carboxycyclopentylamino, carboxycyclopropylmethylamino, methoxycarbonylmethyl, tetrazolylmethyl and acetylaminosulphonyl. Additional examples include fluoromethyl, fluoroisopropyl, nitromethyl, isopropyl, isobutyl, difluoromethyl, difluoroethyl, hydroxymethyl, hydroxyisopropyl, methoxyethyl, carboxycyclobutyloxy, methylsulphinyl, aminomethyl, aminoisopropyl, ethylamino, hydroxyethylamino, hydroxypropylamino, (hydroxy)(methyl)propylamino, (hydroxy)(methoxy)(methyl)propylamino, (hydroxy)-(methylthio)butylamino, dimethylaminoethylamino, (dimethylamino)(methyl)propylamino, *N*-(dimethylaminoethyl)-*N*-(hydroxyethyl)amino, hydroxymethylcyclopentylamino, hydroxycyclobutylmethylamino, (cyclopropyl)(hydroxy)propylamino, morpholinylethylamino, oxopyrrolidinylmethylamino, ethyloxadiazolylamino, methylthiadiazolylamino, thiazolylmethylamino, thiazolyethylamino, pyrimidinylmethylamino, methylpyrazolylmethylamino, *N*-acetyl-*N*-methylamino, *N*-isopropylcarbonyl-*N*-methylamino, acetylaminomethyl, ethenylcarbonylamino, bis(ethenylcarbonyl)amino, *N*-cyclopropylcarbonyl-*N*-methylamino, *N*-(carboxymethyl)-*N*-methylamino, *tert*-butoxycarbonylamino, methoxycarbonylethylamino, *N*-methyl-*N*-(methylsulphonyl)amino, isopropylcarbonyl, cyclobutylcarbonyl, phenylcarbonyl, acetoxisopropyl, *n*-butoxycarbonyl, morpholinylethoxycarbonyl, ethoxycarbonylmethylidenyl, hydroxyoxadiazolyl, hydroxyethylaminocarbonyl and methoxyaminocarbonyl.

Generally, R¹¹ represents C₁₋₆ alkyl, aryl, C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkenyl, heteroaryl, (C₃₋₇)heterocycloalkyl(C₁₋₆)alkyl-aryl-, heteroaryl-(C₃₋₇)heterocycloalkyl-, (C₄₋₇)cycloalkenyl-heteroaryl-, (C₃₋₇)heterocycloalkyl-heteroaryl-, (C₃₋₇)heterocycloalkyl(C₁₋₆)alkyl-heteroaryl-, (C₃₋₇)heterocycloalkenyl-heteroaryl-, (C₄₋₉)heterobicycloalkyl-heteroaryl- or (C₄₋₉)spiroheterocycloalkyl-heteroaryl-, any of which groups may be optionally substituted by one or more substituents. Additionally,

R¹¹ may represent C₂₋₆ alkynyl or (C₃₋₇)cycloalkyl-heteroaryl-, either of which groups may be optionally substituted by one or more substituents. Additionally, R¹¹ may represent (C₃₋₇)cycloalkyl(C₁₋₆)alkyl-heteroaryl- or (C₄₋₉) bicycloalkyl-heteroaryl-, either of which groups may be optionally substituted by one or more substituents.

5 More generally, R¹¹ represents C₁₋₆ alkyl, aryl, C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkenyl, heteroaryl, (C₃₋₇)heterocycloalkyl(C₁₋₆)alkyl-aryl-, heteroaryl-(C₃₋₇)heterocycloalkyl-, (C₃₋₇)heterocycloalkyl-heteroaryl-, (C₃₋₇)heterocycloalkyl-(C₁₋₆)alkyl-heteroaryl-, (C₄₋₉)heterobicycloalkyl-heteroaryl- or (C₄₋₉)spiroheterocycloalkyl-heteroaryl-, any of which groups may be optionally substituted by one or more substituents. Additionally, R¹¹ may represent C₂₋₆ alkynyl, (C₃₋₇)cycloalkyl-heteroaryl- or (C₄₋₇)cycloalkenyl-heteroaryl-, any of which groups may be optionally substituted by one or more substituents. Additionally, R¹¹ may represent (C₃₋₇)cycloalkyl(C₁₋₆)alkyl-heteroaryl- or (C₄₋₉) bicycloalkyl-heteroaryl-, either of which groups may be optionally substituted by one or more substituents.

15 Still more generally, R¹¹ represents C₁₋₆ alkyl, C₂₋₆ alkynyl, aryl, C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkenyl, heteroaryl, (C₃₋₇)cycloalkyl-heteroaryl-, (C₄₋₇)cycloalkenyl-heteroaryl-, (C₃₋₇)heterocycloalkyl-heteroaryl-, (C₄₋₉)heterobicycloalkyl-heteroaryl- or (C₄₋₉)spiroheterocycloalkyl-heteroaryl-, any of which groups may be optionally substituted by one or more substituents. Additionally, R¹¹ may represent (C₃₋₇)cycloalkyl(C₁₋₆)alkyl-heteroaryl- or (C₄₋₉) bicycloalkyl-heteroaryl-, either of which groups may be optionally substituted by one or more substituents.

Even more generally, R¹¹ represents C₁₋₆ alkyl, C₃₋₇ heterocycloalkenyl, heteroaryl, (C₃₋₇)heterocycloalkyl-heteroaryl- or (C₄₋₉)heterobicycloalkyl-heteroaryl-, any of which groups may be optionally substituted by one or more substituents.

25 In a first embodiment, R¹¹ represents halogen. In one aspect of that embodiment, R¹¹ represents bromo.

In a second embodiment, R¹¹ represents cyano.

In a third embodiment, R¹¹ represents optionally substituted C₁₋₆ alkyl. In one aspect of that embodiment, R¹¹ represents optionally substituted ethyl.

30 In a fourth embodiment, R¹¹ represents optionally substituted C₂₋₆ alkynyl. In one aspect of that embodiment, R¹¹ represents optionally substituted butynyl.

In a fifth embodiment, R¹¹ represents optionally substituted aryl. In one aspect of that embodiment, R¹¹ represents optionally substituted phenyl.

In a sixth embodiment, R¹¹ represents optionally substituted C₃₋₇ heterocycloalkyl.

In a seventh embodiment, R¹¹ represents optionally substituted C₃₋₇ heterocycloalkenyl.

In an eighth embodiment, R¹¹ represents optionally substituted heteroaryl. In
5 selected aspects of that embodiment, R¹¹ represents benzofuryl, thienyl, indolyl, pyrazolyl, indazolyl, isoxazolyl, imidazolyl, pyridinyl, quinolinyl, pyridazinyl, pyrimidinyl or pyrazinyl, any of which groups may be optionally substituted by one or more substituents. In a further aspect, R¹¹ represents optionally substituted thiazolyl.

In a ninth embodiment, R¹¹ represents optionally substituted (C₃₋₇)-
10 heterocycloalkyl(C₁₋₆)alkyl-aryl-. In a first aspect of that embodiment, R¹¹ represents optionally substituted pyrrolidinylmethylphenyl-. In a second aspect of that embodiment, R¹¹ represents optionally substituted piperazinylmethylphenyl-.

In a tenth embodiment, R¹¹ represents optionally substituted heteroaryl(C₃₋₇)-
heterocycloalkyl-. In one aspect of that embodiment, R¹¹ represents optionally substituted
15 pyridinylpiperazinyl-.

In an eleventh embodiment, R¹¹ represents optionally substituted (C₃₋₇)cycloalkyl-
heteroaryl-. In a first aspect of that embodiment, R¹¹ represents optionally substituted cyclohexylpyrazolyl-. In a second aspect of that embodiment, R¹¹ represents optionally substituted cyclohexylpyridinyl-. In a third aspect of that embodiment, R¹¹ represents
20 optionally substituted cyclopropylpyrimidinyl-. In a fourth aspect of that embodiment, R¹¹ represents optionally substituted cyclobutylpyrimidinyl-. In a fifth aspect of that embodiment, R¹¹ represents optionally substituted cyclopentylpyrimidinyl-. In a sixth aspect of that embodiment, R¹¹ represents optionally substituted cyclohexylpyrimidinyl-. In a seventh aspect of that embodiment, R¹¹ represents optionally substituted cyclohexyl-
25 pyrazinyl-.

In a twelfth embodiment, R¹¹ represents optionally substituted (C₄₋₇)cycloalkenyl-
heteroaryl-.

In a thirteenth embodiment, R¹¹ represents optionally substituted (C₃₋₇)-
heterocycloalkyl-heteroaryl-. In a first aspect of that embodiment, R¹¹ represents
30 optionally substituted pyrrolidinylpyridinyl-. In a second aspect of that embodiment, R¹¹ represents optionally substituted tetrahydropyranylpyridinyl-. In a third aspect of that embodiment, R¹¹ represents optionally substituted piperidinylpyridinyl-. In a fourth aspect of that embodiment, R¹¹ represents optionally substituted piperazinylpyridinyl-. In

a fifth aspect of that embodiment, R¹¹ represents optionally substituted morpholinyl-pyridinyl-. In a sixth aspect of that embodiment, R¹¹ represents optionally substituted thiomorpholinylpyridinyl-. In a seventh aspect of that embodiment, R¹¹ represents optionally substituted diazepanylpyridinyl-. In an eighth aspect of that embodiment, R¹¹ represents optionally substituted oxetanylpurimidinyl-. In a ninth aspect of that embodiment, R¹¹ represents optionally substituted azetidinylpurimidinyl-. In a tenth aspect of that embodiment, R¹¹ represents optionally substituted tetrahydrofuranyl-purimidinyl-. In an eleventh aspect of that embodiment, R¹¹ represents optionally substituted pyrrolidinylpurimidinyl-. In a twelfth aspect of that embodiment, R¹¹ represents optionally substituted tetrahydropyranylpurimidinyl-. In a thirteenth aspect of that embodiment, R¹¹ represents optionally substituted piperidinylpurimidinyl-. In a fourteenth aspect of that embodiment, R¹¹ represents optionally substituted piperazinyl-purimidinyl-. In a fifteenth aspect of that embodiment, R¹¹ represents optionally substituted morpholinylpurimidinyl-. In a sixteenth aspect of that embodiment, R¹¹ represents optionally substituted thiomorpholinylpurimidinyl-. In a seventeenth aspect of that embodiment, R¹¹ represents optionally substituted azepanylpurimidinyl-. In an eighteenth aspect of that embodiment, R¹¹ represents optionally substituted oxazepanylpurimidinyl-. In a nineteenth aspect of that embodiment, R¹¹ represents optionally substituted diazepanylpurimidinyl-. In a twentieth aspect of that embodiment, R¹¹ represents optionally substituted thiadiazepanylpurimidinyl-. In a twenty-first aspect of that embodiment, R¹¹ represents optionally substituted piperidinylpyrazinyl-.

In a fourteenth embodiment, R¹¹ represents optionally substituted (C₃₋₇)-heterocycloalkyl(C₁₋₆)alkyl-heteroaryl-. In a first aspect of that embodiment, R¹¹ represents optionally substituted morpholinylmethylthienyl-. In a second aspect of that embodiment, R¹¹ represents optionally substituted morpholinylethylpyrazolyl-.

In a fifteenth embodiment, R¹¹ represents optionally substituted (C₃₋₇)-heterocycloalkenyl-heteroaryl-.

In a sixteenth embodiment, R¹¹ represents optionally substituted (C₄₋₉)-heterobicycloalkyl-heteroaryl-.

In a seventeenth embodiment, R¹¹ represents optionally substituted (C₄₋₉)-spiroheterocycloalkyl-heteroaryl-.

In an eighteenth embodiment, R¹¹ represents optionally substituted (C₃₋₇)-cycloalkyl(C₁₋₆)alkyl-heteroaryl-. In one aspect of that embodiment, R¹¹ represents optionally substituted cyclohexylmethylpyrimidinyl-.

In a nineteenth embodiment, R¹¹ represents optionally substituted (C₄₋₉)-bicycloalkyl-heteroaryl-.

Appositely, R¹¹ represents bromo or cyano; or ethyl, phenyl, piperidinyl, piperazinyl, morpholinyl, 1,2,3,6-tetrahydropyridinyl, benzofuryl, thienyl, indolyl, pyrazolyl, indazolyl, isoxazolyl, imidazolyl, pyridinyl, quinolinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrrolidinylmethylphenyl, piperazinylmethylphenyl, pyridinyl-
 10 piperazinyl, pyrrolidinylpyridinyl, piperidinylpyridinyl, piperazinylpyridinyl, morpholinylpyridinyl, thiomorpholinylpyridinyl, diazepanylpyridinyl, pyrrolidinylpyrimidinyl, piperidinylpyrimidinyl, piperazinylpyrimidinyl, morpholinylpyrimidinyl, thiomorpholinylpyrimidinyl, diazepanylpyrimidinyl, thiadiazepanylpyrimidinyl, morpholinylmethylthienyl, morpholinylethylpyrazolyl, 2-oxa-5-azabicyclo[2.2.1]-
 15 heptanylpyrimidinyl, 2-oxa-6-azaspiro[3.3]heptanylpyrimidinyl, 2-oxa-6-azaspiro[3.4]-octanylpyrimidinyl, 2-oxa-6-azaspiro[3.5]nonanylpyrimidinyl or 2-oxa-7-azaspiro[3.5]-nonanylpyrimidinyl, any of which groups may be optionally substituted by one or more substituents. Additionally, R¹¹ may represent butynyl, cyclohexylpyrimidinyl, cyclohexenylpyrimidinyl, azetidylpyrimidinyl, 3-azabicyclo[3.1.0]hexanylpyrimidinyl
 20 or 2-azaspiro[3.3]heptanylpyrimidinyl, any of which groups may be optionally substituted by one or more substituents. Additionally, R¹¹ may represent pyrrolidinyl, thiazolyl, cyclohexylpyrazolyl, cyclohexylpyridinyl, cyclopropylpyrimidinyl, cyclobutylpyrimidinyl, cyclopentylpyrimidinyl, cyclohexylpyrazinyl, cyclohexylmethylpyrimidinyl, cyclohexenylpyridinyl, bicyclo[3.1.0]hexanylpyridinyl, bicyclo[3.1.0]hexanyl-
 25 pyrimidinyl, bicyclo[4.1.0]heptanylpyrimidinyl, bicyclo[2.2.2]octanylpyrimidinyl, tetrahydropyranylpyridinyl, oxetanylpyrimidinyl, tetrahydrofuranylpyrimidinyl, tetrahydropyranylpyrimidinyl, hexahydro-[1,2,5]thiadiazolo[2,3-*a*]pyrazinylpyrimidinyl, azepanylpyrimidinyl, oxazepanylpyrimidinyl, piperidinylpyrazinyl, 3-azabicyclo[3.1.0]-hexanylpyridinyl, 3-azabicyclo[3.1.0]hexanylpyridazinyl, 3-azabicyclo[3.1.1]heptanyl-
 30 pyrimidinyl, 3-azabicyclo[4.1.0]heptanylpyrimidinyl, 2-oxabicyclo[2.2.2]octanylpyrimidinyl, 3-azabicyclo[3.2.1]octanylpyrimidinyl, 8-azabicyclo[3.2.1]octanylpyrimidinyl, 3-oxa-8-azabicyclo[3.2.1]octanylpyrimidinyl, 3,6-diazabicyclo[3.2.2]-nonanylpyrimidinyl, 3-oxa-7-azabicyclo[3.3.1]nonanylpyrimidinyl, 5-azaspiro[2.3]-

hexanylpyrimidinyl, 5-azaspiro[2.4]heptanylpyrimidinyl or 2,4,8-triazaspiro[4.5]decanylpyrimidinyl, any of which groups may be optionally substituted by one or more substituents.

Appropriately, R¹¹ represents ethyl, butynyl, phenyl, morpholinyl, 1,2,3,6-tetrahydropyridinyl, pyrazolyl, pyridinyl, pyrimidinyl, cyclohexylpyrimidinyl, cyclohexenylpyrimidinyl, piperazinylpyridinyl, morpholinylpyridinyl, azetidinylpyrimidinyl, pyrrolidinylpyrimidinyl, piperidinylpyrimidinyl, piperazinylpyrimidinyl, morpholinylpyrimidinyl, thiomorpholinylpyrimidinyl, diazepanylpyrimidinyl, thiadiazepanylpyrimidinyl, 3-azabicyclo[3.1.0]hexanylpyrimidinyl, 2-oxa-5-azabicyclo[2.2.1]heptanylpyrimidinyl or 2-azaspiro[3.3]heptanylpyrimidinyl, any of which groups may be optionally substituted by one or more substituents. Additionally, R¹¹ may represent pyrrolidinyl, piperidinyl, isoxazolyl, thiazolyl, imidazolyl, cyclohexylpyrazolyl, cyclohexylpyridinyl, cyclopropylpyrimidinyl, cyclobutylpyrimidinyl, cyclopentylpyrimidinyl, cyclohexylpyrazinyl, cyclohexylmethylpyrimidinyl, cyclohexenylpyridinyl, bicyclo[3.1.0]hexanylpyridinyl, bicyclo[3.1.0]hexanylpyrimidinyl, bicyclo[4.1.0]heptanylpyrimidinyl, bicyclo[2.2.2]octanylpyrimidinyl, tetrahydropyranylpyridinyl, piperidinylpyridinyl, oxetanylpyrimidinyl, tetrahydrofuranylpyrimidinyl, tetrahydropyranylpyrimidinyl, hexahydro-[1,2,5]thiadiazolo[2,3-*a*]pyrazinylpyrimidinyl, azepanylpyrimidinyl, oxazepanylpyrimidinyl, piperidinylpyrazinyl, 3-azabicyclo[3.1.0]hexanylpyridinyl, 3-azabicyclo[3.1.0]hexanylpyridazinyl, 3-azabicyclo[3.1.1]heptanylpyrimidinyl, 3-azabicyclo[4.1.0]heptanylpyrimidinyl, 2-oxabicyclo[2.2.2]octanylpyrimidinyl, 3-azabicyclo[3.2.1]octanylpyrimidinyl, 8-azabicyclo[3.2.1]octanylpyrimidinyl, 3-oxa-8-azabicyclo[3.2.1]octanylpyrimidinyl, 3,6-diazabicyclo[3.2.2]nonanylpyrimidinyl, 3-oxa-7-azabicyclo[3.3.1]nonanylpyrimidinyl, 5-azaspiro[2.3]hexanylpyrimidinyl, 5-azaspiro[2.4]heptanylpyrimidinyl or 2,4,8-triazaspiro[4.5]decanylpyrimidinyl, any of which groups may be optionally substituted by one or more substituents.

Illustratively, R¹¹ represents ethyl, 1,2,3,6-tetrahydropyridinyl, pyrazolyl, pyridinyl, piperazinylpyridinyl, morpholinylpyridinyl, piperidinylpyrimidinyl, piperazinylpyrimidinyl, morpholinylpyrimidinyl, thiomorpholinylpyrimidinyl, diazepanylpyrimidinyl, thiadiazepanylpyrimidinyl or 2-oxa-5-azabicyclo[2.2.1]heptanylpyrimidinyl, any of which groups may be optionally substituted by one or more substituents.

Typical examples of optional substituents on R¹¹ include one, two or three substituents independently selected from halogen, cyano, cyano(C₁₋₆)alkyl, C₁₋₆ alkyl, trifluoromethyl, trifluoroethyl, C₂₋₆ alkenyl, hydroxy, C₁₋₆ alkoxy, trifluoroethoxy, C₁₋₆ alkylsulphonyl, (C₁₋₆)alkylsulphonyl(C₁₋₆)alkyl, oxo, amino, di(C₁₋₆)alkylamino, (C₁₋₆)alkoxy(C₁₋₆)alkylamino, *N*-[(C₁₋₆)alkyl]-*N*-[hydroxy(C₁₋₆)alkyl]amino, C₁₋₆ alkylsulphonylamino, C₂₋₆ alkylcarbonyl, carboxy, carboxy(C₁₋₆)alkyl, C₂₋₆ alkoxy-carbonyl, C₂₋₆ alkoxycarbonyl(C₁₋₆)alkyl, a carboxylic acid isostere or prodrug moiety Ω as defined herein, and aminocarbonyl. Additional examples include bis[(C₁₋₆)alkylsulphonyl]amino, *N*-[(C₁₋₆)alkyl]-*N*-[carboxy(C₁₋₆)alkyl]amino, carboxy(C₃₋₇)cycloalkyl-amino, carboxy(C₃₋₇)cycloalkyl(C₁₋₆)alkylamino, -(C₁₋₆)alkyl- Ω , in which Ω is as defined herein, and aminosulphonyl. Additional examples include halo(C₁₋₆)alkyl, nitro(C₁₋₆)alkyl, hydroxy(C₁₋₆)alkyl, carboxy(C₃₋₇)cycloalkyloxy, C₁₋₆ alkylthio, amino(C₁₋₆)alkyl, C₁₋₆ alkylamino, (C₂₋₆)alkylcarbonylamino(C₁₋₆)alkyl, *N*-[(C₁₋₆)alkyl]-*N*-[(C₁₋₆)alkylsulphonyl]-amino, formyl, (C₂₋₆)alkylcarbonyloxy(C₁₋₆)alkyl, morpholinyl(C₁₋₆)alkoxycarbonyl, C₂₋₆ alkoxycarbonylmethylidenyl and C₁₋₆ alkoxyaminocarbonyl.

Particular examples of optional substituents on R¹¹ include one, two or three substituents independently selected from C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkylsulphonyl, oxo, amino, *N*-[(C₁₋₆)alkyl]-*N*-[carboxy(C₁₋₆)alkyl]amino, carboxy-(C₃₋₇)cycloalkylamino, carboxy(C₃₋₇)cycloalkyl(C₁₋₆)alkylamino, C₁₋₆ alkylsulphonyl-amino, bis[(C₁₋₆)alkylsulphonyl]amino, C₂₋₆ alkylcarbonyl, carboxy, carboxy(C₁₋₆)alkyl, C₂₋₆ alkoxycarbonyl, C₂₋₆ alkoxycarbonyl(C₁₋₆)alkyl, a carboxylic acid isostere or prodrug moiety Ω as defined herein, -(C₁₋₆)alkyl- Ω , and aminosulphonyl. Additional examples include halogen, halo(C₁₋₆)alkyl, cyano, nitro(C₁₋₆)alkyl, trifluoromethyl, hydroxy(C₁₋₆)alkyl, carboxy(C₃₋₇)cycloalkyloxy, C₁₋₆ alkylthio, amino(C₁₋₆)alkyl, C₁₋₆ alkylamino, (C₂₋₆)alkylcarbonylamino(C₁₋₆)alkyl, *N*-[(C₁₋₆)alkyl]-*N*-[(C₁₋₆)alkylsulphonyl]amino, formyl, (C₂₋₆)alkylcarbonyloxy(C₁₋₆)alkyl, morpholinyl(C₁₋₆)alkoxycarbonyl, C₂₋₆ alkoxycarbonylmethylidenyl and C₁₋₆ alkoxyaminocarbonyl.

Suitable examples of optional substituents on R¹¹ include one, two or three substituents independently selected from C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, oxo, amino, C₁₋₆ alkylsulphonylamino, carboxy and C₂₋₆ alkoxycarbonyl.

Typical examples of particular substituents on R¹¹ include one, two or three substituents independently selected from fluoro, chloro, cyano, cyanoethyl, methyl, trifluoromethyl, trifluoroethyl, ethenyl, hydroxy, methoxy, isopropoxy, trifluoroethoxy,

methylsulphonyl, methylsulphonylethyl, oxo, amino, dimethylamino, methoxyethylamino, *N*-(hydroxyethyl)-*N*-(methyl)amino, methylsulphonylamino, acetyl, carboxy, carboxy-methyl, carboxyethyl, methoxycarbonyl, ethoxycarbonyl, *tert*-butoxycarbonyl, ethoxycarbonylmethyl, ethoxycarbonylethyl, tetrazolyl, aminocarbonyl and methylsulphonyl-aminocarbonyl. Additional examples include bis(methylsulphonyl)amino, *N*-(carboxyethyl)-*N*-(ethyl)amino, carboxycyclopentylamino, carboxycyclopropylmethylamino, methoxycarbonylmethyl, tetrazolylmethyl, aminosulphonyl and acetylaminosulphonyl. Additional examples include fluoromethyl, fluoroisopropyl, nitromethyl, ethyl, isopropyl, hydroxymethyl, hydroxyisopropyl, carboxycyclobutyloxy, methylthio, aminomethyl, aminoisopropyl, methylamino, acetylaminomethyl, *N*-methyl-*N*-(methylsulphonyl)amino, formyl, acetoxymethyl, *n*-butoxycarbonyl, morpholinylethoxycarbonyl, ethoxycarbonylmethylidenyl, hydroxyoxadiazolyl and methoxyaminocarbonyl.

Representative examples of particular substituents on R¹¹ include one, two or three substituents independently selected from methyl, hydroxy, methoxy, methylsulphonyl, oxo, amino, methylsulphonylamino, bis(methylsulphonyl)amino, *N*-(carboxyethyl)-*N*-(ethyl)amino, carboxycyclopentylamino, carboxycyclopropylmethylamino, acetyl, carboxy, carboxyethyl, methoxycarbonyl, ethoxycarbonyl, *tert*-butoxycarbonyl, methoxycarbonylmethyl, ethoxycarbonylethyl, tetrazolyl, tetrazolylmethyl, aminosulphonyl and acetylaminosulphonyl. Additional examples include fluoro, chloro, fluoromethyl, fluoroisopropyl, cyano, nitromethyl, ethyl, isopropyl, trifluoromethyl, hydroxymethyl, hydroxyisopropyl, carboxycyclobutyloxy, methylthio, aminomethyl, aminoisopropyl, methylamino, acetylaminomethyl, *N*-methyl-*N*-(methylsulphonyl)amino, formyl, acetoxymethyl, carboxymethyl, *n*-butoxycarbonyl, morpholinylethoxycarbonyl, ethoxycarbonylmethylidenyl, hydroxyoxadiazolyl, methoxyaminocarbonyl and methylsulphonylaminocarbonyl.

Suitable examples of particular substituents on R¹¹ include one, two or three substituents independently selected from methyl, hydroxy, methoxy, oxo, amino, methylsulphonylamino, carboxy, methoxycarbonyl and *tert*-butoxycarbonyl.

In a particular embodiment, R¹¹ is substituted by hydroxy(C₁₋₆)alkyl. In one aspect of that embodiment, R¹¹ is substituted by hydroxyisopropyl, especially 2-hydroxyprop-2-yl.

Selected values of R¹¹ include bromo, cyano, methoxycarbonylethyl, ethoxycarbonylethyl, chlorophenyl, hydroxyphenyl, acetylphenyl, aminocarbonylphenyl,

oxopiperidinyl, methylsulphonylpiperazinyl, morpholinyl, *tert*-butoxycarbonyl-1,2,3,6-tetrahydropyridinyl, benzofuryl, thienyl, indolyl, pyrazolyl, methylpyrazolyl, dimethylpyrazolyl, methylindazolyl, dimethylisoxazolyl, methylimidazolyl, pyridinyl, fluoropyridinyl, cyanopyridinyl, methylpyridinyl, (cyano)(methyl)pyridinyl, dimethylpyridinyl, 5 trifluoromethylpyridinyl, ethenylpyridinyl, methoxypyridinyl, (methoxy)(methyl)pyridinyl, isopropoxypyridinyl, trifluoroethoxypyridinyl, (methyl)(trifluoroethoxy)pyridinyl, oxopyridinyl, (methyl)(oxo)pyridinyl, (dimethyl)(oxo)pyridinyl, aminopyridinyl, dimethylaminopyridinyl, methoxyethylaminopyridinyl, *N*-(hydroxyethyl)-*N*-(methyl)aminopyridinyl, methylsulphonylaminopyridinyl, carboxypyridinyl, quinolinyl, 10 hydroxypyridazinyl, pyrimidinyl, methoxypyrimidinyl, oxopyrimidinyl, aminopyrimidinyl, dimethylaminopyrimidinyl, methoxyethylaminopyrimidinyl, hydroxypyrazinyl, pyrrolidinylmethylphenyl, piperazinylmethylphenyl, pyridinylpiperazinyl, pyrrolidinylpyridinyl, hydroxypyrrolidinylpyridinyl, piperidinylpyridinyl, acetyl-piperidinylpyridinyl, piperazinylpyridinyl, (methyl)(piperazinyl)pyridinyl, cyanoethyl- 15 piperazinylpyridinyl, trifluoroethylpiperazinylpyridinyl, methylsulphonylpiperazinylpyridinyl, methylsulphonylethylpiperazinylpyridinyl, oxopiperazinylpyridinyl, acetyl-piperazinylpyridinyl, (*tert*-butoxycarbonylpiperazinyl)(methyl)pyridinyl, carboxymethylpiperazinylpyridinyl, carboxyethylpiperazinylpyridinyl, ethoxycarbonylmethylpiperazinylpyridinyl, ethoxycarbonylethylpiperazinylpyridinyl, morpholinylpyridinyl, 20 thiomorpholinylpyridinyl, oxothiomorpholinylpyridinyl, dioxothiomorpholinylpyridinyl, oxodiazepanylpyridinyl, hydroxypyrrolidinylpyrimidinyl, carboxypiperidinylpyrimidinyl, piperazinylpyrimidinyl, methylsulphonylpiperazinylpyrimidinyl, oxopiperazinylpyrimidinyl, *tert*-butoxycarbonylpiperazinylpyrimidinyl, morpholinylpyrimidinyl, thiomorpholinylpyrimidinyl, dioxothiomorpholinylpyrimidinyl, oxodiazepanyl- 25 pyrimidinyl, dioxothiadiazepanylpyrimidinyl, morpholinylmethylthienyl, morpholinylethylpyrazolyl, 2-oxa-5-azabicyclo[2.2.1]heptanylpyrimidinyl, 2-oxa-6-azaspiro[3.3]heptanylpyrimidinyl, 2-oxa-6-azaspiro[3.4]octanylpyrimidinyl, 2-oxa-6-azaspiro[3.5]nonanylpyrimidinyl and 2-oxa-7-azaspiro[3.5]nonanylpyrimidinyl. Additional values include hydroxybutynyl, aminosulphonylphenyl, acetylaminosulphonylphenyl, 30 methylsulphonyl-1,2,3,6-tetrahydropyridinyl, acetyl-1,2,3,6-tetrahydropyridinyl, methoxycarbonylmethyl-1,2,3,6-tetrahydropyridinyl, [bis(methylsulphonyl)amino]pyridinyl, *N*-(carboxyethyl)-*N*-(methyl)aminopyrimidinyl, carboxycyclopentylaminopyrimidinyl, carboxycyclopropylmethylaminopyrimidinyl, ethoxycarbonylethyl-

pyrimidinyl, carboxycyclohexylpyrimidinyl, carboxycyclohexenylpyrimidinyl,
 ethoxycarbonylcyclohexenylpyrimidinyl, carboxyazetidiny pyrimidinyl, carboxy-
 pyrrolidinylpyrimidinyl, (carboxy)(methyl)piperidinylpyrimidinyl, ethoxycarbonyl-
 piperidinylpyrimidinyl, (methoxycarbonyl)(methyl)piperidinylpyrimidinyl,
 5 (ethoxycarbonyl)(methyl)piperidinylpyrimidinyl, tetrazolylpiperidinylpyrimidinyl,
 carboxyethylpiperazinylpyrimidinyl, tetrazolylmethylpiperazinylpyrimidinyl, carboxy-
 morpholinylpyrimidinyl, carboxy-3-azabicyclo[3.1.0]hexanylpyrimidinyl,
 ethoxycarbonyl-3-azabicyclo[3.1.0]hexanylpyrimidinyl and carboxy-2-azaspiro-
 [3.3]heptanylpyrimidinyl. Additional values include methylsulphonylphenyl,
 10 aminomethylphenyl, aminoisopropylphenyl, acetylaminomethylphenyl, methoxy-
 carbonylphenyl, (methoxycarbonyl)(methyl)pyrrolidinyl, ethoxycarbonylpiperidinyl,
 (methyl)[*N*-methyl-*N*-(methylsulfonyl)]pyrazolyl, hydroxyisopropylthiazolyl, dimethyl-
 imidazolyl, hydroxyisopropylpyridinyl, methylsulphonylpyridinyl, methylaminopyridinyl,
 fluoroisopropylpyrimidinyl, hydroxyisopropylpyrimidinyl, carboxycyclobutyl-
 15 pyrimidinyl, methylthiopyrimidinyl, methylsulphonylpyrimidinyl, acetoxisopropyl-
 pyrimidinyl, hydroxyisopropylpyrazinyl, carboxycyclohexylpyrazolyl, carboxy-
 cyclohexylpyridinyl, fluoromethylcyclopropylpyrimidinyl, acetylaminomethyl-
 cyclopropylpyrimidinyl, hydroxycyclobutylpyrimidinyl, carboxycyclopentylpyrimidinyl,
 (carboxy)(methyl)cyclohexylpyrimidinyl, (carboxy)(hydroxy)cyclohexylpyrimidinyl,
 20 carboxymethylcyclohexylpyrimidinyl, ethoxycarbonylcyclohexylpyrimidinyl,
 (methoxycarbonyl)(methyl)cyclohexylpyrimidinyl, (ethoxycarbonyl)(methyl)cyclohexyl-
 pyrimidinyl, carboxycyclohexylpyrazinyl, carboxycyclohexylmethylpyrimidinyl,
 carboxycyclohexenylpyridinyl, carboxybicyclo[3.1.0]hexanylpyridinyl, carboxybicyclo-
 [3.1.0]hexanylpyrimidinyl, ethoxycarbonylbicyclo[3.1.0]hexanylpyrimidinyl, carboxy-
 25 bicyclo[4.1.0]heptanylpyrimidinyl, carboxybicyclo[2.2.2]octanylpyrimidinyl,
 hydroxytetrahydropyranylpyridinyl, (carboxy)(methyl)piperidinylpyridinyl, [(carboxy)-
 (methyl)piperidinyl](fluoro)pyridinyl, [(carboxy)(methyl)piperidinyl](chloro)pyridinyl,
 fluoroxyetanylpyrimidinyl, hydroxyoxyetanylpyrimidinyl, hydroxyazetidiny pyrimidinyl,
 (hydroxy)(methyl)azetidiny pyrimidinyl, (*tert*-butoxycarbonyl)(hydroxy)azetidiny-
 30 pyrimidinyl, tetrazolylazetidiny pyrimidinyl, hydroxytetrahydrofuranylpyrimidinyl,
 (carboxy)(methyl)pyrrolidinylpyrimidinyl, carboxymethylpyrrolidinylpyrimidinyl,
 ethoxycarbonylpyrrolidinylpyrimidinyl, fluorotetrahydropyranylpyrimidinyl,
 hydroxytetrahydropyranylpyrimidinyl, difluoropiperidinylpyrimidinyl, (cyano)(methyl)-

piperidinylpyrimidinyl, (hydroxy)(nitromethyl)piperidinylpyrimidinyl, (hydroxy)-
 (methyl)piperidinylpyrimidinyl, (hydroxy)(trifluoromethyl)piperidinylpyrimidinyl,
 (hydroxymethyl)(methyl)piperidinylpyrimidinyl, methylsulphonylpiperidinylpyrimidinyl,
 oxopiperidinylpyrimidinyl, (formyl)(methyl)piperidinylpyrimidinyl, (carboxy)(fluoro)-
 5 piperidinylpyrimidinyl, (carboxy)(ethyl)piperidinylpyrimidinyl, (carboxy)-
 (trifluoromethyl)piperidinylpyrimidinyl, (carboxy)(hydroxy)piperidinylpyrimidinyl,
 (carboxy)(hydroxymethyl)piperidinylpyrimidinyl, (carboxy)(methoxy)piperidinyl-
 pyrimidinyl, (amino)(carboxy)piperidinylpyrimidinyl, carboxymethylpiperidinyl-
 pyrimidinyl, methoxycarbonylpiperidinylpyrimidinyl, (ethoxycarbonyl)(fluoro)-
 10 piperidinylpyrimidinyl, (ethyl)(methoxycarbonyl)piperidinylpyrimidinyl, (isopropyl)-
 (methoxycarbonyl)piperidinylpyrimidinyl, (*n*-butoxycarbonyl)(methyl)piperidinyl-
 pyrimidinyl, (ethoxycarbonyl)(trifluoromethyl)piperidinylpyrimidinyl, (ethoxycarbonyl)-
 (hydroxymethyl)piperidinylpyrimidinyl, (methoxy)(methoxycarbonyl)piperidinyl-
 pyrimidinyl, (carboxy)(methoxycarbonyl)piperidinylpyrimidinyl, (methyl)-
 15 (morpholinylethoxycarbonyl)piperidinylpyrimidinyl, ethoxycarbonylmethylpiperidinyl-
 pyrimidinyl, hydroxyoxadiazolylpiperidinylpyrimidinyl, methoxyaminocarbonyl-
 piperidinylpyrimidinyl, methylsulphonylaminocarbonylpiperidinylpyrimidinyl,
 aminosulphonylpiperidinylpyrimidinyl, acetylaminosulphonylpiperidinylpyrimidinyl,
 carboxypiperazinylpyrimidinyl, trioxohexahydro-[1,2,5]thiadiazolo[2,3-*a*]pyrazinyl-
 20 pyrimidinyl, dimethylmorpholinylpyrimidinyl, hydroxymethylmorpholinylpyrimidinyl,
 (carboxy)(methyl)morpholinylpyrimidinyl, carboxymethylmorpholinylpyrimidinyl,
 carboxyazepanylpyrimidinyl, carboxyoxazepanylpyrimidinyl, (oxodiazepanyl)-
 (trifluoromethyl)pyrimidinyl, (oxodiazepanyl)(methoxy)pyrimidinyl, (methyl)(oxo)-
 diazepanylpyrimidinyl, hydroxyoxetanylpyrazinyl, (carboxy)(methyl)piperidinyl-
 25 pyrazinyl, (ethoxycarbonyl)(methyl)piperidinylpyrazinyl, carboxy-3-azabicyclo[3.1.0]-
 hexanylpyridinyl, carboxy-3-azabicyclo[4.1.0]heptanylpyridinyl, carboxy-3-azabicyclo-
 [3.1.0]hexanylpyridazinyl, (carboxy)(methyl)-3-azabicyclo[3.1.0]hexanylpyrimidinyl,
 methoxycarbonyl-3-azabicyclo[3.1.0]hexanylpyrimidinyl, carboxy-2-oxa-5-azabicyclo-
 [2.2.1]heptanylpyrimidinyl, carboxy-3-azabicyclo[3.1.1]heptanylpyrimidinyl, carboxy-3-
 30 azabicyclo[4.1.0]heptanylpyrimidinyl, methoxycarbonyl-3-azabicyclo[4.1.0]heptanyl-
 pyrimidinyl, ethoxycarbonyl-3-azabicyclo[4.1.0]heptanylpyrimidinyl, (hydroxy)(methyl)-
 (oxo)-2-oxabicyclo[2.2.2]octanylpyrimidinyl, carboxy-3-azabicyclo[3.2.1]octanyl-
 pyrimidinyl, methoxycarbonyl-3-azabicyclo[3.2.1]octanylpyrimidinyl, oxo-8-azabicyclo-

[3.2.1]octanylpyrimidinyl, ethoxycarbonylmethylidenyl-8-azabicyclo[3.2.1]octanylpyrimidinyl, 3-oxa-8-azabicyclo[3.2.1]octanylpyrimidinyl, oxo-3,6-diazabicyclo[3.2.2]-nonanylpyrimidinyl, carboxy-3-oxa-7-azabicyclo[3.3.1]nonanylpyrimidinyl, carboxy-5-azaspiro[2.3]hexanylpyrimidinyl, (carboxy)(methyl)-5-azaspiro[2.3]hexanylpyrimidinyl,
 5 carboxy-5-azaspiro[2.4]heptanylpyrimidinyl and (dioxo)(methyl)-2,4,8-triazaspiro[4.5]-decanylpyrimidinyl.

Definitive values of R¹¹ include bromo, ethoxycarbonylethyl, hydroxybutynyl, methylsulfonylphenyl, aminomethylphenyl, aminoisopropylphenyl, acetylaminomethylphenyl, methoxycarbonylphenyl, aminosulphonylphenyl, acetylaminosulphonylphenyl,
 10 (methoxycarbonyl)(methyl)pyrrolidinyl, ethoxycarbonylpiperidinyl, morpholinyl, methylsulphonyl-1,2,3,6-tetrahydropyridinyl, acetyl-1,2,3,6-tetrahydropyridinyl, *tert*-butoxycarbonyl-1,2,3,6-tetrahydropyridinyl, methoxycarbonylmethyl-1,2,3,6-tetrahydropyridinyl, methylpyrazolyl, (methyl)[*N*-methyl-*N*-(methylsulfonyl)]pyrazolyl, dimethylisoxazolyl, hydroxyisopropylthiazolyl, dimethylimidazolyl,
 15 hydroxyisopropylpyridinyl, methoxypyridinyl, (methoxy)(methyl)pyridinyl, methylsulphonylpyridinyl, oxopyridinyl, (methyl)(oxo)pyridinyl, aminopyridinyl, methylaminopyridinyl, methylsulphonylaminopyridinyl, [bis(methylsulphonyl)amino]-pyridinyl, carboxypyridinyl, fluoroisopropylpyrimidinyl, hydroxyisopropylpyrimidinyl, carboxycyclobutylloxypyrimidinyl, methylthiopyrimidinyl, methylsulphonylpyrimidinyl,
 20 *N*-(carboxyethyl)-*N*-(methyl)aminopyrimidinyl, carboxycyclopentylaminopyrimidinyl, carboxycyclopropylmethylaminopyrimidinyl, acetoxisopropylpyrimidinyl, ethoxycarbonylethylpyrimidinyl, hydroxyisopropylpyrazinyl, carboxycyclohexylpyrazolyl, carboxycyclohexylpyridinyl, fluoromethylcyclopropylpyrimidinyl, acetylaminomethylcyclopropylpyrimidinyl, hydroxycyclobutylpyrimidinyl, carboxy-
 25 cyclopentylpyrimidinyl, carboxycyclohexylpyrimidinyl, (carboxy)(methyl)cyclohexylpyrimidinyl, (carboxy)(hydroxy)cyclohexylpyrimidinyl, carboxymethylcyclohexylpyrimidinyl, ethoxycarbonylcyclohexylpyrimidinyl, (methoxycarbonyl)(methyl)-cyclohexylpyrimidinyl, (ethoxycarbonyl)(methyl)cyclohexylpyrimidinyl, carboxy-cyclohexylpyrazinyl, carboxycyclohexylmethylpyrimidinyl, carboxycyclohexenyl-
 30 pyridinyl, carboxycyclohexenylpyrimidinyl, ethoxycarbonylcyclohexenylpyrimidinyl, carboxybicyclo[3.1.0]hexanylpyridinyl, carboxybicyclo[3.1.0]hexanylpyrimidinyl, ethoxycarbonylbicyclo[3.1.0]hexanylpyrimidinyl, carboxybicyclo[4.1.0]heptanylpyrimidinyl, carboxybicyclo[2.2.2]octanylpyrimidinyl, hydroxytetrahydropyranyl-

pyridinyl, piperidinylpyridinyl, (carboxy)(methyl)piperidinylpyridinyl, [(carboxy)-(methyl)piperidinyl](fluoro)pyridinyl, [(carboxy)(methyl)piperidinyl](chloro)pyridinyl, piperazinylpyridinyl, morpholinylpyridinyl, fluorooxetanylpyrimidinyl, hydroxyoxetanylpyrimidinyl, hydroxyazetidiny pyrimidinyl, (hydroxy)(methyl)azetidiny pyrimidinyl, carboxyazetidiny pyrimidinyl, (*tert*-butoxycarbonyl)(hydroxy)azetidiny pyrimidinyl, tetrazolylazetidiny pyrimidinyl, hydroxytetrahydrofuranylpyrimidinyl, carboxypyrrolidinylpyrimidinyl, (carboxy)(methyl)pyrrolidinylpyrimidinyl, carboxymethylpyrrolidinylpyrimidinyl, ethoxycarbonylpyrrolidinylpyrimidinyl, fluoro-tetrahydropyranylpyrimidinyl, hydroxytetrahydropyranylpyrimidinyl, difluoropiperidinylpyrimidinyl, (cyano)(methyl)piperidinylpyrimidinyl, (hydroxy)(nitromethyl)piperidinylpyrimidinyl, (hydroxy)(methyl)piperidinylpyrimidinyl, (hydroxy)(trifluoromethyl)piperidinylpyrimidinyl, (hydroxymethyl)(methyl)piperidinylpyrimidinyl, methylsulphonylpiperidinylpyrimidinyl, oxopiperidinylpyrimidinyl, (formyl)(methyl)piperidinylpyrimidinyl, carboxypiperidinylpyrimidinyl, (carboxy)(fluoro)piperidinylpyrimidinyl, (carboxy)(methyl)piperidinylpyrimidinyl, (carboxy)(ethyl)piperidinylpyrimidinyl, (carboxy)(trifluoromethyl)piperidinylpyrimidinyl, (carboxy)(hydroxy)piperidinylpyrimidinyl, (carboxy)(hydroxymethyl)piperidinylpyrimidinyl, (carboxy)(methoxy)piperidinylpyrimidinyl, (amino)(carboxy)piperidinylpyrimidinyl, carboxymethylpiperidinylpyrimidinyl, methoxycarbonylpiperidinylpyrimidinyl, ethoxycarbonylpiperidinylpyrimidinyl, (ethoxycarbonyl)(fluoro)piperidinylpyrimidinyl, (methoxycarbonyl)(methyl)piperidinylpyrimidinyl, (ethyl)(methoxycarbonyl)piperidinylpyrimidinyl, (isopropyl)(methoxycarbonyl)piperidinylpyrimidinyl, (ethoxycarbonyl)(methyl)piperidinylpyrimidinyl, (*n*-butoxycarbonyl)(methyl)piperidinylpyrimidinyl, (ethoxycarbonyl)(trifluoromethyl)piperidinylpyrimidinyl, (ethoxycarbonyl)(hydroxymethyl)piperidinylpyrimidinyl, (methoxy)(methoxycarbonyl)piperidinylpyrimidinyl, (carboxy)(methoxycarbonyl)piperidinylpyrimidinyl, (methyl)(morpholinylethoxycarbonyl)piperidinylpyrimidinyl, ethoxycarbonylmethylpiperidinylpyrimidinyl, hydroxyoxadiazolylpiperidinylpyrimidinyl, tetrazolylpiperidinylpyrimidinyl, methoxyaminocarbonylpiperidinylpyrimidinyl, methylsulphonylaminocarbonylpiperidinylpyrimidinyl, aminosulphonylpiperidinylpyrimidinyl, acetylaminosulphonylpiperidinylpyrimidinyl, piperazinylpyrimidinyl, oxopiperazinylpyrimidinyl, methylsulfonylpiperazinylpyrimidinyl, carboxypiperazinylpyrimidinyl, carboxyethylpiperazinylpyrimidinyl, *tert*-butoxycarbonylpiperazinylpyrimidinyl, tetrazolylmethyl-

piperazinyipyridinyl, trioxohexahydro-[1,2,5]thiadiazolo[2,3-*a*]pyrazinyipyrimidinyl,
 morpholinyipyrimidinyl, dimethylmorpholinyipyrimidinyl, hydroxymethylmorpholiny-
 pyrimidinyl, carboxymorpholinyipyrimidinyl, (carboxy)(methyl)morpholinyipyrimidinyl,
 carboxymethylmorpholinyipyrimidinyl, dioxothiomorpholinyipyrimidinyl, carboxy-
 5 azepanyipyrimidinyl, carboxyoxazepanyipyrimidinyl, oxodiazepanyipyrimidinyl,
 (oxodiazepanyl)(trifluoromethyl)pyrimidinyl, (oxodiazepanyl)(methoxy)pyrimidinyl,
 (methyl)(oxo)diazepanyipyrimidinyl, dioxothiadiazepanyipyrimidinyl, hydroxyoxetanyl-
 pyrazinyl, (carboxy)(methyl)piperidinylpyrazinyl, (ethoxycarbonyl)(methyl)piperidinyl-
 pyrazinyl, carboxy-3-azabicyclo[3.1.0]hexanylpyridinyl, carboxy-3-azabicyclo[4.1.0]-
 10 heptanylpyridinyl, carboxy-3-azabicyclo[3.1.0]hexanylpyridazinyl, carboxy-3-
 azabicyclo[3.1.0]hexanylpyrimidinyl, (carboxy)(methyl)-3-azabicyclo[3.1.0]hexanyl-
 pyrimidinyl, methoxycarbonyl-3-azabicyclo[3.1.0]hexanylpyrimidinyl, ethoxycarbonyl-3-
 azabicyclo[3.1.0]hexanylpyrimidinyl, 2-oxa-5-azabicyclo[2.2.1]heptanylpyrimidinyl,
 carboxy-2-oxa-5-azabicyclo[2.2.1]heptanylpyrimidinyl, carboxy-3-azabicyclo[3.1.1]-
 15 heptanylpyrimidinyl, carboxy-3-azabicyclo[4.1.0]heptanylpyrimidinyl, methoxycarbonyl-
 3-azabicyclo[4.1.0]heptanylpyrimidinyl, ethoxycarbonyl-3-azabicyclo[4.1.0]heptanyl-
 pyrimidinyl, (hydroxy)(methyl)(oxo)-2-oxabicyclo[2.2.2]octanylpyrimidinyl, carboxy-3-
 azabicyclo[3.2.1]octanylpyrimidinyl, methoxycarbonyl-3-azabicyclo[3.2.1]octanyl-
 pyrimidinyl, oxo-8-azabicyclo[3.2.1]octanylpyrimidinyl, ethoxycarbonylmethylidenyl-8-
 20 azabicyclo[3.2.1]octanylpyrimidinyl, 3-oxa-8-azabicyclo[3.2.1]octanylpyrimidinyl, oxo-
 3,6-diazabicyclo[3.2.2]nonanylpyrimidinyl, carboxy-3-oxa-7-azabicyclo[3.3.1]nonanyl-
 pyrimidinyl, carboxy-5-azaspiro[2.3]hexanylpyrimidinyl, (carboxy)(methyl)-5-azaspiro-
 [2.3]hexanylpyrimidinyl, carboxy-5-azaspiro[2.4]heptanylpyrimidinyl, carboxy-2-
 azaspiro[3.3]heptanylpyrimidinyl and (dioxo)(methyl)-2,4,8-triazaspiro[4.5]decanyl-
 25 pyrimidinyl.

Particular values of R¹¹ include ethoxycarbonyl-ethyl, hydroxybutynyl, amino-
 sulphonylphenyl, acetylaminosulphonylphenyl, morpholiny, methylsulphonyl-1,2,3,6-
 tetrahydropyridinyl, acetyl-1,2,3,6-tetrahydropyridinyl, *tert*-butoxycarbonyl-1,2,3,6-
 tetrahydropyridinyl, methoxycarbonylmethyl-1,2,3,6-tetrahydropyridinyl, methyl-
 30 pyrazolyl, methoxypyridinyl, (methoxy)(methyl)pyridinyl, oxopyridinyl, (methyl)(oxo)-
 pyridinyl, aminopyridinyl, methylsulphonylaminopyridinyl, [bis(methylsulphonyl)-
 amino]pyridinyl, *N*-(carboxyethyl)-*N*-(methyl)aminopyrimidinyl, carboxycyclopentyl-
 aminopyrimidinyl, carboxycyclopropylmethylaminopyrimidinyl, ethoxycarbonyl-ethyl-

pyrimidinyl, carboxycyclohexylpyrimidinyl, carboxycyclohexenylpyrimidinyl, ethoxycarbonylcyclohexenylpyrimidinyl, piperazinylpyridinyl, morpholinylpyridinyl, carboxyazetidiny pyrimidinyl, carboxypyrrolidinylpyrimidinyl, carboxypiperidinylpyrimidinyl, (carboxy)(methyl)piperidinylpyrimidinyl, ethoxycarbonylpiperidinylpyrimidinyl, (methoxycarbonyl)(methyl)piperidinylpyrimidinyl, (ethoxycarbonyl)-(methyl)piperidinylpyrimidinyl, tetrazolylpiperidinylpyrimidinyl, piperazinylpyrimidinyl, oxopiperazinylpyrimidinyl, carboxyethylpiperazinylpyrimidinyl, tetrazolylmethylpiperazinylpyridinyl, morpholinylpyrimidinyl, carboxymorpholinylpyrimidinyl, dioxothiomorpholinylpyrimidinyl, oxodiazepanylpyrimidinyl, dioxothiadiazepanylpyrimidinyl, carboxy-3-azabicyclo[3.1.0]hexanylpyrimidinyl, ethoxycarbonyl-3-azabicyclo[3.1.0]hexanylpyrimidinyl, 2-oxa-5-azabicyclo[2.2.1]heptanylpyrimidinyl and carboxy-2-azaspiro[3.3]heptanylpyrimidinyl.

Illustrative values of R^{11} include methoxycarbonylethyl, *tert*-butoxycarbonyl-1,2,3,6-tetrahydropyridinyl, methylpyrazolyl, methoxypyridinyl, (methoxy)(methyl)-pyridinyl, oxopyridinyl, (methyl)(oxo)pyridinyl, aminopyridinyl, methylsulphonylamino-pyridinyl, piperazinylpyridinyl, morpholinylpyridinyl, carboxypiperidinylpyrimidinyl, piperazinylpyrimidinyl, oxopiperazinylpyrimidinyl, morpholinylpyrimidinyl, dioxothiomorpholinylpyrimidinyl, oxodiazepanylpyrimidinyl, dioxothiadiazepanylpyrimidinyl and 2-oxa-5-azabicyclo[2.2.1]heptanylpyrimidinyl.

Typical examples of optional substituents on R^{12} include C_{2-6} alkoxy carbonyl.

Typical examples of particular substituents on R^{12} include ethoxycarbonyl.

In a first embodiment, R^{12} represents hydrogen. In a second embodiment, R^{12} represents halogen. In one aspect of that embodiment, R^{12} represents fluoro. In another aspect of that embodiment, R^{12} represents chloro. In a third embodiment, R^{12} represents trifluoromethyl. In a fourth embodiment, R^{12} represents optionally substituted C_{1-6} alkyl. In one aspect of that embodiment, R^{12} represents unsubstituted methyl. In another aspect of that embodiment, R^{12} represents unsubstituted ethyl. In a further aspect of that embodiment, R^{12} represents monosubstituted methyl or monosubstituted ethyl.

Typical values of R^{12} include hydrogen, fluoro, trifluoromethyl, methyl and ethoxycarbonylethyl. Additionally, R^{12} may represent chloro.

Suitable values of R^{12} include hydrogen, fluoro, trifluoromethyl and methyl. Additionally, R^{12} may represent chloro.

Typically, R^{15} and R^{16} may independently represent hydrogen, fluoro, chloro, bromo, cyano, nitro, methyl, isopropyl, trifluoromethyl, hydroxy, methoxy, difluoromethoxy, trifluoromethoxy, methylthio, methylsulfinyl, methylsulfonyl, amino, methylamino, *tert*-butylamino, dimethylamino, phenylamino, acetylamino, methylsulfonylamino, formyl, acetyl, cyclopropylcarbonyl, azetidiny carbonyl, pyrrolidinylcarbonyl, piperidinylcarbonyl, piperazinylcarbonyl, morpholinylcarbonyl, carboxy, methoxycarbonyl, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, aminosulfonyl, methylaminosulfonyl and dimethylaminosulfonyl.

Typical values of R^{15} include hydrogen, halogen, C_{1-6} alkyl, trifluoromethyl, C_{1-6} alkoxy, difluoromethoxy and trifluoromethoxy.

Illustrative values of R^{15} include halogen, C_{1-6} alkyl and difluoromethoxy.

In a first embodiment, R^{15} represents hydrogen. In a second embodiment, R^{15} represents halogen. In a first aspect of that embodiment, R^{15} represents fluoro. In a second aspect of that embodiment, R^{15} represents chloro. In a third embodiment, R^{15} represents C_{1-6} alkyl. In one aspect of that embodiment, R^{15} represents methyl. In a fourth embodiment, R^{15} represents trifluoromethyl. In a fifth embodiment, R^{15} represents C_{1-6} alkoxy. In one aspect of that embodiment, R^{15} represents methoxy. In a sixth embodiment, R^{15} represents difluoromethoxy. In a seventh embodiment, R^{15} represents trifluoromethoxy.

Selected values of R^{15} include hydrogen, fluoro, chloro, methyl, trifluoromethyl, methoxy, difluoromethoxy and trifluoromethoxy.

Suitable values of R^{15} include chloro, methyl and difluoromethoxy.

Typical values of R^{16} include hydrogen, halogen, C_{1-6} alkyl, trifluoromethyl, difluoromethoxy and amino.

Illustrative values of R^{16} include hydrogen, halogen and C_{1-6} alkyl.

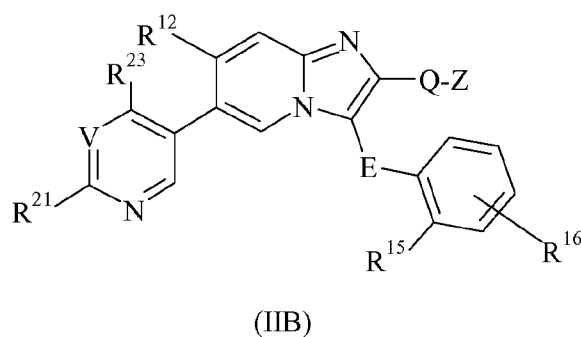
In a first embodiment, R^{16} represents hydrogen. In a second embodiment, R^{16} represents halogen. In a first aspect of that embodiment, R^{16} represents fluoro. In a second aspect of that embodiment, R^{16} represents chloro. In a third embodiment, R^{16} represents C_{1-6} alkyl. In one aspect of that embodiment, R^{16} represents methyl. In a fourth embodiment, R^{16} represents trifluoromethyl. In a fifth embodiment, R^{16} represents difluoromethoxy. In a seventh embodiment, R^{16} represents amino.

Selected values of R^{16} include hydrogen, fluoro, chloro, methyl, trifluoromethyl, difluoromethoxy and amino.

Suitable values of R¹⁶ include hydrogen, chloro and methyl.

In a particular embodiment, R¹⁶ is attached at the *para*-position of the phenyl ring relative to the integer R¹⁵.

A particular sub-group of the compounds of formula (IIA) above is represented by
 5 the compounds of formula (IIB) and *N*-oxides thereof, and pharmaceutically acceptable salts and solvates thereof, and glucuronide derivatives thereof, and co-crystals thereof:



10 wherein

V represents C-R²² or N;

R²¹ represents hydrogen, halogen, halo(C₁₋₆)alkyl, cyano, C₁₋₆ alkyl, trifluoro-methyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, hydroxy, hydroxy(C₁₋₆)alkyl, C₁₋₆ alkoxy, (C₁₋₆)alkoxy-(C₁₋₆)alkyl, difluoromethoxy, trifluoromethoxy, trifluoroethoxy, carboxy(C₃₋₇)cycloalkyl-
 15 oxy, C₁₋₆ alkylthio, C₁₋₆ alkylsulphonyl, (C₁₋₆)alkylsulphonyl(C₁₋₆)alkyl, amino, amino-(C₁₋₆)alkyl, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino, (C₁₋₆)alkoxy(C₁₋₆)alkylamino, *N*-[(C₁₋₆)-alkyl]-*N*-[hydroxy(C₁₋₆)alkyl]amino, C₂₋₆ alkylcarbonylamino, (C₂₋₆)alkylcarbonylamino-(C₁₋₆)alkyl, C₂₋₆ alkoxycarbonylamino, *N*-[(C₁₋₆)alkyl]-*N*-[carboxy(C₁₋₆)alkyl]amino, carboxy(C₃₋₇)cycloalkylamino, carboxy(C₃₋₇)cycloalkyl(C₁₋₆)alkylamino, C₁₋₆ alkyl-
 20 sulphonylamino, C₁₋₆ alkylsulphonylamino(C₁₋₆)alkyl, formyl, C₂₋₆ alkylcarbonyl, (C₂₋₆)alkylcarbonyloxy(C₁₋₆)alkyl, carboxy, carboxy(C₁₋₆)alkyl, C₂₋₆ alkoxycarbonyl, morpholinyl(C₁₋₆)alkoxycarbonyl, C₂₋₆ alkoxycarbonyl(C₁₋₆)alkyl, C₂₋₆ alkoxycarbonyl-methylidenyl, aminocarbonyl, C₁₋₆ alkylaminocarbonyl, di(C₁₋₆)alkylaminocarbonyl, aminosulphonyl, C₁₋₆ alkylaminosulphonyl or di(C₁₋₆)alkylaminosulphonyl; or R²¹
 25 represents (C₃₋₇)cycloalkyl, (C₃₋₇)cycloalkyl(C₁₋₆)alkyl, (C₄₋₇)cycloalkenyl, (C₄₋₉)bicycloalkyl, (C₃₋₇)heterocycloalkyl, (C₃₋₇)heterocycloalkenyl, (C₄₋₉)heterobicycloalkyl or (C₄₋₉)spiroheterocycloalkyl, any of which groups may be optionally substituted by one or more substituents;

R²² represents hydrogen, halogen or C₁₋₆ alkyl;

R²³ represents hydrogen, C₁₋₆ alkyl, trifluoromethyl or C₁₋₆ alkoxy; and

E, Q, Z, R¹², R¹⁵ and R¹⁶ are as defined above.

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

R²¹ represents hydrogen, halogen, cyano, C₁₋₆ alkyl, trifluoromethyl, C₂₋₆ alkenyl,
C₂₋₆ alkynyl, hydroxy, C₁₋₆ alkoxy, difluoromethoxy, trifluoromethoxy, trifluoroethoxy,
C₁₋₆ alkylthio, C₁₋₆ alkylsulphonyl, amino, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino,
10 (C₁₋₆)alkoxy(C₁₋₆)alkylamino, *N*-[(C₁₋₆)alkyl]-*N*-[hydroxy(C₁₋₆)alkyl]amino, C₂₋₆
alkylcarbonylamino, C₂₋₆ alkoxycarbonylamino, *N*-[(C₁₋₆)alkyl]-*N*-[carboxy(C₁₋₆)alkyl]-
amino, carboxy(C₃₋₇)cycloalkylamino, carboxy(C₃₋₇)cycloalkyl(C₁₋₆)alkylamino, C₁₋₆
alkylsulphonylamino, formyl, C₂₋₆ alkylcarbonyl, carboxy, carboxy(C₁₋₆)alkyl, C₂₋₆
alkoxycarbonyl, C₂₋₆ alkoxycarbonyl(C₁₋₆)alkyl, aminocarbonyl, C₁₋₆ alkylaminocarbonyl,
15 di(C₁₋₆)alkylaminocarbonyl, aminosulphonyl, C₁₋₆ alkylaminosulphonyl or di(C₁₋₆)alkyl-
aminosulphonyl; or R²¹ represents (C₃₋₇)cycloalkyl, (C₄₋₇)cycloalkenyl, (C₃₋₇)heterocyclo-
alkyl, (C₃₋₇)heterocycloalkenyl, (C₄₋₉)heterobicycloalkyl or (C₄₋₉)spiroheterocycloalkyl,
any of which groups may be optionally substituted by one or more substituents;

R²³ represents hydrogen or C₁₋₆ alkyl; and

20 E, Q, Z, V, R¹², R¹⁵ and R¹⁶ are as defined above.

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

R²¹ represents hydrogen, halogen, cyano, C₁₋₆ alkyl, trifluoromethyl, C₂₋₆ alkenyl,
25 C₂₋₆ alkynyl, hydroxy, C₁₋₆ alkoxy, difluoromethoxy, trifluoromethoxy, trifluoroethoxy,
C₁₋₆ alkylthio, C₁₋₆ alkylsulphonyl, amino, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino,
(C₁₋₆)alkoxy(C₁₋₆)alkylamino, *N*-[(C₁₋₆)alkyl]-*N*-[hydroxy(C₁₋₆)alkyl]amino, C₂₋₆
alkylcarbonylamino, C₂₋₆ alkoxycarbonylamino, C₁₋₆ alkylsulphonylamino, formyl, C₂₋₆
alkylcarbonyl, carboxy, C₂₋₆ alkoxycarbonyl, aminocarbonyl, C₁₋₆ alkylaminocarbonyl,
30 di(C₁₋₆)alkylaminocarbonyl, aminosulphonyl, C₁₋₆ alkylaminosulphonyl or di(C₁₋₆)alkyl-
aminosulphonyl; or R²¹ represents (C₄₋₇)cycloalkenyl, (C₃₋₇)heterocycloalkyl,
(C₃₋₇)heterocycloalkenyl, (C₄₋₉)heterobicycloalkyl or (C₄₋₉)spiroheterocycloalkyl, any of
which groups may be optionally substituted by one or more substituents;

R²³ represents hydrogen; and

E, Q, Z, V, R¹², R¹⁵ and R¹⁶ are as defined above.

In one embodiment, V represents C-R²². In another embodiment, V represents N.

Typically, R²¹ represents hydrogen, halogen, cyano, C₁₋₆ alkyl, trifluoromethyl, C₂₋₆ alkenyl, hydroxy, C₁₋₆ alkoxy, trifluoroethoxy, amino, di(C₁₋₆)alkylamino, (C₁₋₆)-alkoxy(C₁₋₆)alkylamino, *N*-[(C₁₋₆)alkyl]-*N*-[hydroxy(C₁₋₆)alkyl]amino, C₁₋₆ alkylsulphonyl-amino or carboxy; or R²¹ represents (C₃₋₇)heterocycloalkyl, (C₄₋₉)heterobicycloalkyl or (C₄₋₉)spiroheterocycloalkyl, any of which groups may be optionally substituted by one or more substituents. Additionally, R²¹ may represent *N*-[(C₁₋₆)alkyl]-*N*-[carboxy(C₁₋₆)alkyl]-amino, carboxy(C₃₋₇)cycloalkylamino, carboxy(C₃₋₇)cycloalkyl(C₁₋₆)alkylamino or C₂₋₆ alkoxycarbonyl(C₁₋₆)alkyl; or R²¹ may represent (C₃₋₇)cycloalkyl or (C₄₋₇)cycloalkenyl, either of which groups may be optionally substituted by one or more substituents. Additionally, R²¹ may represent halo(C₁₋₆)alkyl, hydroxy(C₁₋₆)alkyl, carboxy(C₃₋₇)-cycloalkyloxy, C₁₋₆ alkylthio, C₁₋₆ alkylsulphonyl, C₁₋₆ alkylamino, (C₂₋₆)alkylcarbonyloxy(C₁₋₆)alkyl, morpholinyl(C₁₋₆)alkoxycarbonyl, C₂₋₆ alkoxycarbonylmethylidenyl; or R²¹ may represent (C₃₋₇)cycloalkyl(C₁₋₆)alkyl or (C₄₋₉)bicycloalkyl, either of which groups may be optionally substituted by one or more substituents.

Appositely, R²¹ represents hydroxy, C₁₋₆ alkoxy, *N*-[(C₁₋₆)alkyl]-*N*-[carboxy-(C₁₋₆)alkyl]amino, carboxy(C₃₋₇)cycloalkylamino, carboxy(C₃₋₇)cycloalkyl(C₁₋₆)alkyl-amino or C₂₋₆ alkoxycarbonyl(C₁₋₆)alkyl; or R²¹ represents (C₃₋₇)cycloalkyl, (C₄₋₇)cycloalkenyl, (C₃₋₇)heterocycloalkyl, (C₄₋₉)heterobicycloalkyl or (C₄₋₉)spiroheterocycloalkyl, any of which groups may be optionally substituted by one or more substituents. Additionally, R²¹ may represent halo(C₁₋₆)alkyl, hydroxy(C₁₋₆)alkyl, carboxy(C₃₋₇)cycloalkyloxy, C₁₋₆ alkylthio, C₁₋₆ alkylsulphonyl, C₁₋₆ alkylamino, C₁₋₆ alkylsulphonylamino, (C₂₋₆)alkylcarbonyloxy(C₁₋₆)alkyl, morpholinyl(C₁₋₆)alkoxy-carbonyl, carboxy, C₂₋₆ alkoxycarbonylmethylidenyl; or R²¹ may represent (C₃₋₇)-cycloalkyl(C₁₋₆)alkyl or (C₄₋₉)bicycloalkyl, either of which groups may be optionally substituted by one or more substituents.

Suitably, R²¹ represents hydroxy or C₁₋₆ alkoxy; or R²¹ represents (C₃₋₇)heterocycloalkyl or (C₄₋₉)heterobicycloalkyl, either of which groups may be optionally substituted by one or more substituents.

Where R²¹ represents an optionally substituted (C₃₋₇)cycloalkyl group, typical values include cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, any of which groups

may be optionally substituted by one or more substituents. An additional value is cyclopropyl.

Where R²¹ represents an optionally substituted (C₃₋₇)cycloalkyl(C₁₋₆)alkyl group, a typical value is cyclohexylmethyl, which group may be optionally substituted by one or
5 more substituents.

Where R²¹ represents an optionally substituted (C₄₋₇)cycloalkenyl group, typical values include cyclobutenyl, cyclopentenyl, cyclohexenyl and cycloheptenyl, any of which groups may be optionally substituted by one or more substituents.

Where R²¹ represents an optionally substituted (C₄₋₉)bicycloalkyl group, typical
10 values include bicyclo[3.1.0]hexanyl, bicyclo[4.1.0]heptanyl and bicyclo[2.2.2]octanyl, any of which groups may be optionally substituted by one or more substituents.

Where R²¹ represents an optionally substituted (C₃₋₇)heterocycloalkyl group, typical values include azetidiny, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, diazepanyl and thiadiazepanyl, any of which groups may be optionally
15 substituted by one or more substituents. Additional values include oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, hexahydro-[1,2,5]thiadiazolo[2,3-*a*]pyrazinyl, azepanyl and oxazepanyl, any of which groups may be optionally substituted by one or more substituents.

Where R²¹ represents an optionally substituted (C₃₋₇)heterocycloalkenyl group, a
20 typical value is optionally substituted 1,2,3,6-tetrahydropyridinyl.

Where R²¹ represents an optionally substituted (C₄₋₉)heterobicycloalkyl group, typical values include 3-azabicyclo[3.1.0]hexanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, quinuclidinyl, 2-oxa-5-azabicyclo[2.2.2]octanyl, 8-azabicyclo[3.2.1]octanyl, 3,8-diaza-bicyclo[3.2.1]octanyl and 3,9-diazabicyclo[4.2.1]nonanyl, any of which groups may be
25 optionally substituted by one or more substituents. Additional values include 3-azabicyclo[3.1.1]heptanyl, 3-azabicyclo[4.1.0]heptanyl, 2-oxabicyclo[2.2.2]octanyl, 3-azabicyclo[3.2.1]octanyl, 3-oxa-8-azabicyclo[3.2.1]octanyl, 3,6-diazabicyclo[3.2.2]-nonanyl and 3-oxa-7-azabicyclo[3.3.1]nonanyl, any of which groups may be optionally substituted by one or more substituents.

Where R²¹ represents an optionally substituted (C₄₋₉)spiroheterocycloalkyl group, typical values include 2-azaspiro[3.3]heptanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 2-oxa-6-azaspiro[3.4]octanyl, 2-oxa-6-azaspiro[3.5]nonanyl and 2-oxa-7-azaspiro[3.5]nonanyl, any
30 of which groups may be optionally substituted by one or more substituents. Additional

values include 5-azaspiro[2.3]hexanyl, 5-azaspiro[2.4]heptanyl and 2,4,8-triazaspiro[4.5]-decanyl, any of which groups may be optionally substituted by one or more substituents.

Illustratively, R²¹ represents hydroxy, methoxy, *N*-[carboxyethyl]-*N*-methylamino, carboxycyclopentylamino, carboxycyclopropylmethylamino or ethoxycarbonylethyl; or
 5 R²¹ represents cyclohexyl, cyclohexenyl, azetidyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, diazepanyl, thiadiazepanyl, 3-azabicyclo[3.1.0]hexanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl or 2-azaspiro[3.3]heptanyl, any of which groups may be optionally substituted by one or more substituents. Additionally, R²¹ may represent hydroxy(C₁₋₆)alkyl, carboxycyclobutyl, methylthio, methylsulphonyl or methylamino;
 10 or R²¹ may represent cyclopropyl, cyclobutyl, cyclopentyl, cyclohexylmethyl, bicyclo[3.1.0]hexanyl, bicyclo[4.1.0]heptanyl, bicyclo[2.2.2]octanyl, oxetanyl, tetrahydrofuran, tetrahydropyran, hexahydro-[1,2,5]thiadiazolo[2,3-*a*]pyrazinyl, azepanyl, oxazepanyl, 3-azabicyclo[3.1.1]heptanyl, 3-azabicyclo[4.1.0]heptanyl, 2-oxabicyclo[2.2.2]octanyl, 3-azabicyclo[3.2.1]octanyl, 8-azabicyclo[3.2.1]octanyl, 3-oxa-8-azabicyclo[3.2.1]octanyl, 3,6-diazabicyclo[3.2.2]nonanyl, 3-oxa-7-azabicyclo[3.3.1]-
 15 nonanyl, 5-azaspiro[2.3]hexanyl or 5-azaspiro[2.4]heptanyl, any of which groups may be optionally substituted by one or more substituents.

Examples of optional substituents which may be present on R²¹ include one, two or three substituents independently selected from halogen, cyano, cyano(C₁₋₆)alkyl, C₁₋₆
 20 alkyl, trifluoromethyl, trifluoroethyl, C₂₋₆ alkenyl, hydroxy, C₁₋₆ alkoxy, difluoromethoxy, trifluoromethoxy, trifluoroethoxy, C₁₋₆ alkylthio, C₁₋₆ alkylsulphonyl, (C₁₋₆)alkylsulphonyl(C₁₋₆)alkyl, oxo, amino, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino, C₂₋₆ alkylcarbonylamino, C₂₋₆ alkoxy-carbonylamino, C₁₋₆ alkylsulphonylamino, formyl, C₂₋₆ alkylcarbonyl, carboxy, carboxy(C₁₋₆)alkyl, C₂₋₆ alkoxy-carbonyl, C₂₋₆ alkoxy-carbonyl(C₁₋₆)alkyl, a
 25 carboxylic acid isostere or prodrug moiety Ω as defined herein, aminocarbonyl, C₁₋₆ alkylaminocarbonyl, di(C₁₋₆)alkylaminocarbonyl, aminosulphonyl and di(C₁₋₆)alkylaminosulphonyl. An additional example is -(C₁₋₆)alkyl- Ω , in which Ω is as defined herein. Additional examples include halo(C₁₋₆)alkyl, nitro(C₁₋₆)alkyl, hydroxy(C₁₋₆)alkyl, (C₂₋₆)alkylcarbonylamino(C₁₋₆)alkyl, morpholinyl(C₁₋₆)alkoxy-carbonyl, C₂₋₆ alkoxy-carbonylmethylidenyl and C₁₋₆ alkoxyaminocarbonyl.
 30

Suitable examples of optional substituents on R²¹ include one, two or three substituents independently selected from fluoro, chloro, bromo, cyano, cyanomethyl, methyl, ethyl, trifluoromethyl, trifluoroethyl, ethenyl, hydroxy, methoxy, ethoxy, difluoro-

methoxy, trifluoromethoxy, trifluoroethoxy, methylthio, methylsulphonyl, methylsulphonylmethyl, oxo, amino, methylamino, dimethylamino, acetylamino, methoxycarbonylamino, ethoxycarbonylamino, *tert*-butoxycarbonylamino, methylsulphonylamino, formyl, acetyl, carboxy, carboxymethyl, carboxyethyl, methoxycarbonyl, ethoxycarbonyl, *tert*-butoxycarbonyl, methoxycarbonylmethyl, ethoxycarbonylmethyl, tetrazolyl, amino-carbonyl, methylaminocarbonyl, dimethylaminocarbonyl, methylsulphonylamino-carbonyl, aminosulphonyl, methylaminosulphonyl and dimethylaminosulphonyl. An additional example is tetrazolylmethyl. Additional examples include fluoromethyl, nitromethyl, isopropyl, hydroxymethyl, acetylamino-methyl, *n*-butoxycarbonyl, morpholinylethoxy-carbonyl, ethoxycarbonylmethylidenyl, hydroxyoxadiazolyl, methoxyaminocarbonyl and acetylaminosulphonyl.

Selected examples of optional substituents on R²¹ include one, two or three substituents independently selected from cyano(C₁₋₆)alkyl, trifluoroethyl, hydroxy, C₁₋₆ alkylsulphonyl, (C₁₋₆)alkylsulphonyl(C₁₋₆)alkyl, oxo, C₂₋₆ alkylcarbonyl, carboxy, carboxy(C₁₋₆)alkyl, C₂₋₆ alkoxycarbonyl, C₂₋₆ alkoxycarbonyl(C₁₋₆)alkyl, and a carboxylic acid isostere or prodrug moiety Ω as defined herein. Additional examples include C₁₋₆ alkyl and -(C₁₋₆)alkyl- Ω , in which Ω is as defined herein. Additional examples include halogen, halo(C₁₋₆)alkyl, cyano, nitro(C₁₋₆)alkyl, trifluoromethyl, hydroxy(C₁₋₆)alkyl, C₁₋₆ alkoxy, amino, (C₂₋₆)alkylcarbonylamino(C₁₋₆)alkyl, formyl, morpholinyl(C₁₋₆)alkoxy-carbonyl, C₂₋₆ alkoxycarbonylmethylidenyl, C₁₋₆ alkoxyaminocarbonyl and amino-sulphonyl.

Examples of particular substituents on R²¹ include one, two or three substituents independently selected from cyanoethyl, trifluoroethyl, hydroxy, methylsulphonyl, methylsulphonylethyl, oxo, acetyl, carboxy, carboxymethyl, carboxyethyl, *tert*-butoxycarbonyl, ethoxycarbonylmethyl, ethoxycarbonylethyl, tetrazolyl and methylsulphonylaminocarbonyl. Additional examples include methyl, methoxycarbonyl, ethoxycarbonyl, and tetrazolylmethyl. Additional examples include fluoro, fluoromethyl, cyano, nitromethyl, ethyl, isopropyl, trifluoromethyl, hydroxymethyl, methoxy, amino, acetylamino-methyl, formyl, *n*-butoxycarbonyl, morpholinylethoxycarbonyl, ethoxycarbonylmethylidenyl, hydroxyoxadiazolyl, methoxyaminocarbonyl, aminosulphonyl and acetylaminosulphonyl.

Particular examples of optional substituents on R²¹ include one, two or three substituents independently selected from C₁₋₆ alkyl, oxo, carboxy, carboxy(C₁₋₆)alkyl, C₂₋₆

alkoxycarbonyl, tetrazolyl and tetrazolyl(C₁₋₆)alkyl. Additional examples include halogen, halo(C₁₋₆)alkyl, cyano, nitro(C₁₋₆)alkyl, trifluoromethyl, hydroxy, hydroxy(C₁₋₆)alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylsulphonyl, amino, (C₂₋₆)alkylcarbonylamino(C₁₋₆)alkyl, formyl, morpholinyl(C₁₋₆)alkoxycarbonyl, C₂₋₆ alkoxycarbonylmethylidenyl, hydroxyoxadiazolyl, C₁₋₆ alkoxyaminocarbonyl, C₁₋₆ alkylsulphonylaminocarbonyl, aminosulphonyl and C₂₋₆ alkylcarbonylaminosulphonyl.

Typical examples of particular substituents on R²¹ include one, two or three substituents independently selected from methyl, oxo, carboxy, carboxyethyl, methoxycarbonyl, ethoxycarbonyl, tetrazolyl and tetrazolylmethyl. Additional examples include fluoro, fluoromethyl, cyano, nitromethyl, ethyl, isopropyl, trifluoromethyl, hydroxy, hydroxymethyl, methoxy, methylsulphonyl, amino, acetylaminomethyl, formyl, carboxymethyl, *n*-butoxycarbonyl, *tert*-butoxycarbonyl, morpholinylethoxycarbonyl, ethoxycarbonylmethylidenyl, hydroxyoxadiazolyl, methoxyaminocarbonyl, methylsulphonylaminocarbonyl, aminosulphonyl and acetylaminosulphonyl.

Selected examples of particular substituents on R²¹ include one, two or three substituents independently selected from oxo and carboxy.

Typically, R²¹ represents hydrogen, fluoro, cyano, methyl, trifluoromethyl, ethenyl, hydroxy, methoxy, isopropoxy, trifluoroethoxy, amino, dimethylamino, methoxyethyl-amino, *N*-(hydroxyethyl)-*N*-(methyl)amino, carboxy, pyrrolidinyl, hydroxypyrrolidinyl, piperidinyl, acetylpiperidinyl, carboxypiperidinyl, piperazinyl, cyanoethylpiperazinyl, trifluoroethylpiperazinyl, methylsulphonylpiperazinyl, methylsulphonylethylpiperazinyl, oxopiperazinyl, acetylpiperazinyl, *tert*-butoxycarbonylpiperazinyl, carboxymethylpiperazinyl, carboxyethylpiperazinyl, ethoxycarbonylmethylpiperazinyl, ethoxycarbonylethylpiperazinyl, morpholinyl, thiomorpholinyl, oxothiomorpholinyl, dioxo-thiomorpholinyl, oxodiazepanyl, dioxothiadiazepanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 2-oxa-6-azaspiro[3.4]octanyl, 2-oxa-6-azaspiro[3.5]nonanyl or 2-oxa-7-azaspiro[3.5]nonanyl. Additional values include *N*-[carboxyethyl]-*N*-methylamino, carboxycyclopentylamino, carboxycyclopropylmethylamino, ethoxycarbonylethyl, carboxycyclohexyl, carboxycyclohexenyl, ethoxycarbonylcyclohexenyl, carboxyazetidiny, carboxypyrrolidinyl, (carboxy)(methyl)piperidinyl, ethoxycarbonylpiperidinyl, (methoxycarbonyl)(methyl)piperidinyl, (ethoxycarbonyl)(methyl)piperidinyl, tetrazolylpiperidinyl, tetrazolylmethylpiperazinyl, carboxymorpholinyl, carboxy-3-azabicyclo[3.1.0]hexanyl, ethoxycarbonyl-3-azabicyclo[3.1.0]hexanyl or carboxy-2-

azaspiro[3.3]heptanyl. Additional values include fluoroisopropyl, hydroxyisopropyl, carboxycyclobutyloxy, methylthio, methylsulphonyl, methylamino, methylsulphonylamino, acetoxisopropyl, fluoromethylcyclopropyl, acetylaminomethylcyclopropyl, hydroxycyclobutyl, carboxycyclopentyl, (carboxy)(methyl)cyclohexyl, (carboxy)-

5 (hydroxy)cyclohexyl, carboxymethylcyclohexyl, ethoxycarbonylcyclohexyl, (methoxycarbonyl)(methyl)cyclohexyl, (ethoxycarbonyl)(methyl)cyclohexyl, carboxycyclohexylmethyl, carboxybicyclo[3.1.0]hexanyl, ethoxycarbonylbicyclo[3.1.0]hexanyl, carboxybicyclo[4.1.0]heptanyl, carboxybicyclo[2.2.2]octanyl, fluorooxetanyl, hydroxyoxetanyl, hydroxyazetidiny, (hydroxy)(methyl)azetidiny, (*tert*-butoxycarbonyl)-

10 (hydroxy)azetidiny, tetrazolylazetidiny, hydroxytetrahydrofuranyl, (carboxy)(methyl)pyrrolidiny, carboxymethylpyrrolidiny, ethoxycarbonylpyrrolidiny, fluorotetrahydropyranyl, hydroxytetrahydropyranyl, difluoropiperidiny, (cyano)(methyl)piperidiny, (hydroxy)(nitromethyl)piperidiny, (hydroxy)(methyl)piperidiny, (hydroxy)-(trifluoromethyl)piperidiny, (hydroxymethyl)(methyl)piperidiny, methylsulphonyl-

15 piperidiny, oxopiperidiny, (formyl)(methyl)piperidiny, (carboxy)(fluoro)piperidiny, (carboxy)(ethyl)piperidiny, (carboxy)(trifluoromethyl)piperidiny, (carboxy)(hydroxy)piperidiny, (carboxy)(hydroxymethyl)piperidiny, (carboxy)(methoxy)piperidiny, (amino)(carboxy)piperidiny, carboxymethylpiperidiny, methoxycarbonylpiperidiny, (ethoxycarbonyl)(fluoro)piperidiny, (ethyl)(methoxycarbonyl)piperidiny, (isopropyl)-

20 (methoxycarbonyl)piperidiny, (*n*-butoxycarbonyl)(methyl)piperidiny, (ethoxycarbonyl)-(trifluoromethyl)piperidiny, (ethoxycarbonyl)(hydroxymethyl)piperidiny, (methoxy)-(methoxycarbonyl)piperidiny, (carboxy)(methoxycarbonyl)piperidiny, (methyl)-(morpholinylethoxycarbonyl)piperidiny, ethoxycarbonylmethylpiperidiny, hydroxyoxadiazolylpiperidiny, methoxyaminocarbonylpiperidiny, methylsulphonyl-

25 aminocarbonylpiperidiny, aminosulphonylpiperidiny, acetylaminosulphonylpiperidiny, carboxypiperaziny, trioxohexahydro-[1,2,5]thiadiazolo[2,3-*a*]pyraziny, dimethylmorpholinyl, hydroxymethylmorpholinyl, (carboxy)(methyl)morpholinyl, carboxymethylmorpholinyl, carboxyazepanyl, carboxyoxazepanyl, (methyl)(oxo)diazepanyl, (carboxy)-(methyl)-3-azabicyclo[3.1.0]hexanyl, methoxycarbonyl-3-azabicyclo[3.1.0]hexanyl,

30 carboxy-2-oxa-5-azabicyclo[2.2.1]heptanyl, carboxy-3-azabicyclo[3.1.1]heptanyl, carboxy-3-azabicyclo[4.1.0]heptanyl, methoxycarbonyl-3-azabicyclo[4.1.0]heptanyl, ethoxycarbonyl-3-azabicyclo[4.1.0]heptanyl, (hydroxy)(methyl)(oxo)-2-oxabicyclo[2.2.2]-octanyl, carboxy-3-azabicyclo[3.2.1]octanyl, methoxycarbonyl-3-azabicyclo[3.2.1]-

octanyl, oxo-8-azabicyclo[3.2.1]octanyl, ethoxycarbonylmethylidenyl-8-azabicyclo[3.2.1]-
octanyl, 3-oxa-8-azabicyclo[3.2.1]octanyl, oxo-3,6-diazabicyclo[3.2.2]nonanyl, carboxy-
3-oxa-7-azabicyclo[3.3.1]nonanyl, carboxy-5-azaspiro[2.3]hexanyl, (carboxy)(methyl)-5-
azaspiro[2.3]hexanyl, carboxy-5-azaspiro[2.4]heptanyl and (dioxo)(methyl)-2,4,8-
5 triazaspiro[4.5]decanyl,-.

Selected values of R²¹ include fluoroisopropyl, hydroxy, hydroxyisopropyl,
methoxy, carboxycyclobutyloxy, methylthio, methylsulphonyl, methylamino,
methylsulphonylamino, *N*-[carboxyethyl]-*N*-methylamino, carboxycyclopentylamino,
carboxycyclopropylmethylamino, acetoxisopropyl, carboxy, ethoxycarbonylethyl,
10 fluoromethylcyclopropyl, acetylaminomethylcyclopropyl, hydroxycyclobutyl, carboxy-
cyclopentyl, carboxycyclohexyl, (carboxy)(methyl)cyclohexyl, (carboxy)(hydroxy)-
cyclohexyl, carboxymethylcyclohexyl, ethoxycarbonylcyclohexyl, (methoxycarbonyl)-
(methyl)cyclohexyl, (ethoxycarbonyl)(methyl)cyclohexyl, carboxycyclohexylmethyl,
carboxycyclohexenyl, ethoxycarbonylcyclohexenyl, carboxybicyclo[3.1.0]hexanyl,
15 ethoxycarbonylbicyclo[3.1.0]hexanyl, carboxybicyclo[4.1.0]heptanyl, carboxybicyclo-
[2.2.2]octanyl, fluorooxetanyl, hydroxyoxetanyl, hydroxyazetidiny, (hydroxy)(methyl)-
azetidiny, carboxyazetidiny, (*tert*-butoxycarbonyl)(hydroxy)azetidiny, tetrazolyl-
azetidiny, hydroxytetrahydrofuranyl, carboxypyrrolidiny, (carboxy)(methyl)pyrrolidiny,
carboxymethylpyrrolidiny, ethoxycarbonylpyrrolidiny, fluorotetrahydropyranyl,
20 hydroxytetrahydropyranyl, piperidiny, difluoropiperidiny, (cyano)(methyl)piperidiny,
(hydroxy)(nitromethyl)piperidiny, (hydroxy)(methyl)piperidiny, (hydroxy)-
(trifluoromethyl)piperidiny, (hydroxymethyl)(methyl)piperidiny, methylsulphonyl-
piperidiny, oxopiperidiny, (formyl)(methyl)piperidiny, carboxypiperidiny, (carboxy)-
(fluoro)piperidiny, (carboxy)(methyl)piperidiny, (carboxy)(ethyl)piperidiny, (carboxy)-
25 (trifluoromethyl)piperidiny, (carboxy)(hydroxy)piperidiny, (carboxy)(hydroxymethyl)-
piperidiny, (carboxy)(methoxy)piperidiny, (amino)(carboxy)piperidiny, carboxymethyl-
piperidiny, methoxycarbonylpiperidiny, ethoxycarbonylpiperidiny, (ethoxycarbonyl)-
(fluoro)piperidiny, (methoxycarbonyl)(methyl)piperidiny, (ethyl)(methoxycarbonyl)-
piperidiny, (isopropyl)(methoxycarbonyl)piperidiny, (ethoxycarbonyl)(methyl)-
30 piperidiny, (*n*-butoxycarbonyl)(methyl)piperidiny, (ethoxycarbonyl)(trifluoromethyl)-
piperidiny, (ethoxycarbonyl)(hydroxymethyl)piperidiny, (methoxy)(methoxycarbonyl)-
piperidiny, (carboxy)(methoxycarbonyl)piperidiny, (methyl)(morpholinyl-
ethoxycarbonyl)piperidiny, ethoxycarbonylmethylpiperidiny, hydroxyoxadiazolyl-

piperidinyl, tetrazolylpiperidinyl, methoxyaminocarbonylpiperidinyl, methylsulphonyl-
 aminocarbonylpiperidinyl, aminosulphonylpiperidinyl, acetylaminosulphonylpiperidinyl,
 piperazinyl, oxopiperazinyl, methylsulphonylpiperazinyl, carboxypiperazinyl, carboxy-
 ethylpiperazinyl, *tert*-butoxycarbonylpiperazinyl, tetrazolylmethylpiperazinyl, trioxo-
 5 hexahydro-[1,2,5]thiadiazolo[2,3-*a*]pyrazinyl, morpholinyl, dimethylmorpholinyl,
 hydroxymethylmorpholinyl, carboxymorpholinyl, (carboxy)(methyl)morpholinyl,
 carboxymethylmorpholinyl, dioxothiomorpholinyl, carboxyazepanyl, carboxyoxazepanyl,
 oxodiazepanyl, (methyl)(oxo)diazepanyl, dioxothiadiazepanyl, carboxy-3-azabicyclo-
 [3.1.0]hexanyl, (carboxy)(methyl)-3-azabicyclo[3.1.0]hexanyl, methoxycarbonyl-3-
 10 azabicyclo[3.1.0]hexanyl, ethoxycarbonyl-3-azabicyclo[3.1.0]hexanyl, 2-oxa-5-
 azabicyclo[2.2.1]heptanyl, carboxy-2-oxa-5-azabicyclo[2.2.1]heptanyl, carboxy-3-
 azabicyclo[3.1.1]heptanyl, carboxy-3-azabicyclo[4.1.0]heptanyl, methoxycarbonyl-3-
 azabicyclo[4.1.0]heptanyl, ethoxycarbonyl-3-azabicyclo[4.1.0]heptanyl, (hydroxy)-
 (methyl)(oxo)-2-oxabicyclo[2.2.2]octanyl, carboxy-3-azabicyclo[3.2.1]octanyl,
 15 methoxycarbonyl-3-azabicyclo[3.2.1]octanyl, oxo-8-azabicyclo[3.2.1]octanyl,
 ethoxycarbonylmethylidenyl-8-azabicyclo[3.2.1]octanyl, 3-oxa-8-azabicyclo[3.2.1]-
 octanyl, oxo-3,6-diazabicyclo[3.2.2]nonanyl, carboxy-3-oxa-7-azabicyclo[3.3.1]nonanyl,
 (carboxy)(methyl)-5-azaspiro[2.3]hexanyl, carboxy-5-azaspiro[2.3]hexanyl, carboxy-5-
 azaspiro[2.4]heptanyl, carboxy-2-azaspiro[3.3]heptanyl and (dioxo)(methyl)-2,4,8-
 20 triazaspiro[4.5]decanyl.

Particular values of R²¹ include hydroxy, methoxy, *N*-[carboxyethyl]-*N*-methyl-
 amino, carboxycyclopentylamino, carboxycyclopropylmethylamino, ethoxycarbonylethyl,
 carboxycyclohexyl, carboxycyclohexenyl, ethoxycarbonylcyclohexenyl, carboxy-
 azetidyl, carboxypyrrolidinyl, carboxypiperidinyl, (carboxy)(methyl)piperidinyl,
 25 ethoxycarbonylpiperidinyl, (methoxycarbonyl)(methyl)piperidinyl, (ethoxycarbonyl)-
 (methyl)piperidinyl, tetrazolylpiperidinyl, piperazinyl, oxopiperazinyl, carboxyethyl-
 piperazinyl, tetrazolylmethylpiperazinyl, morpholinyl, carboxymorpholinyl, dioxo-
 thiomorpholinyl, oxodiazepanyl, dioxothiadiazepanyl, carboxy-3-azabicyclo[3.1.0]-
 hexanyl, ethoxycarbonyl-3-azabicyclo[3.1.0]hexanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl
 30 and carboxy-2-azaspiro[3.3]heptanyl.

Illustrative values of R²¹ include hydroxy, methoxy, carboxypiperidinyl,
 piperazinyl, oxopiperazinyl, morpholinyl, dioxothiomorpholinyl, oxodiazepanyl,
 dioxothiadiazepanyl and 2-oxa-5-azabicyclo[2.2.1]heptanyl.

In a particular embodiment, R^{21} represents hydroxy(C_{1-6})alkyl. In one aspect of that embodiment, R^{21} represents hydroxyisopropyl, especially 2-hydroxyprop-2-yl.

Generally, R^{22} represents hydrogen or C_{1-6} alkyl.

Suitably, R^{22} represents hydrogen, chloro or methyl.

5 Typically, R^{22} represents hydrogen or methyl.

In one embodiment, R^{22} represents hydrogen. In another embodiment, R^{22} represents C_{1-6} alkyl, especially methyl. In a further embodiment, R^{22} represents halogen. In one aspect of that embodiment, R^{22} represents fluoro. In another aspect of that embodiment, R^{22} represents chloro.

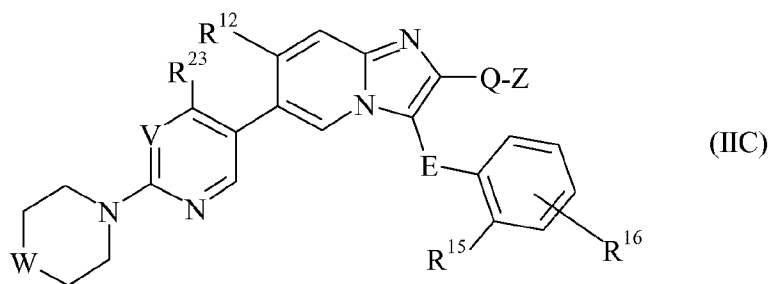
10 Generally, R^{23} represents hydrogen or C_{1-6} alkyl.

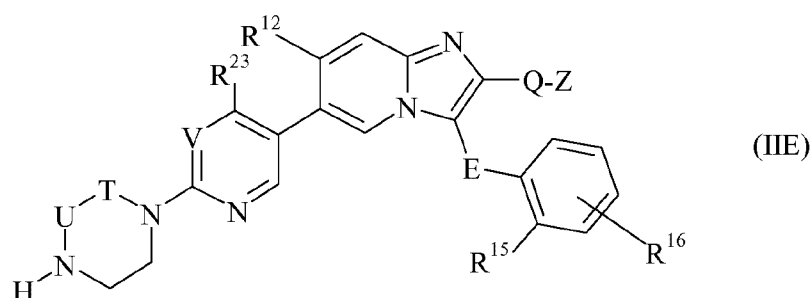
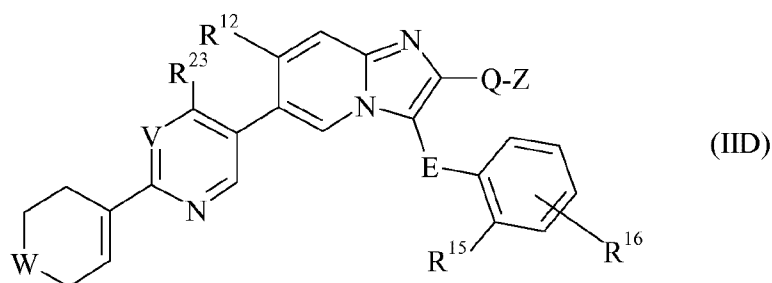
Suitably, R^{23} represents hydrogen, methyl, trifluoromethyl or methoxy.

Typically, R^{23} represents hydrogen or methyl.

In one embodiment, R^{23} represents hydrogen. In another embodiment, R^{23} represents C_{1-6} alkyl, especially methyl. In a further embodiment, R^{23} represents trifluoromethyl. In an additional embodiment, R^{23} represents C_{1-6} alkoxy, especially methoxy.

Particular sub-groups of the compounds of formula (IIB) above are represented by the compounds of formula (IIC), (IID) and (IIE) and *N*-oxides thereof, and pharmaceutically acceptable salts and solvates thereof, and glucuronide derivatives thereof, and co-crystals thereof:





5 wherein

T represents -CH₂- or -CH₂CH₂-;

U represents C(O) or S(O)₂;

W represents O, S, S(O), S(O)₂, N(R³¹) or C(R³²)(R³³);

10 R³¹ represents hydrogen, cyano(C₁₋₆)alkyl, C₁₋₆ alkyl, trifluoromethyl, trifluoroethyl, C₁₋₆ alkylsulphonyl, (C₁₋₆)alkylsulphonyl(C₁₋₆)alkyl, formyl, C₂₋₆ alkylcarbonyl, carboxy, carboxy(C₁₋₆)alkyl, C₂₋₆ alkoxycarbonyl, C₂₋₆ alkoxycarbonyl(C₁₋₆)alkyl, a carboxylic acid isostere or prodrug moiety Ω, -(C₁₋₆)alkyl-Ω, aminocarbonyl, C₁₋₆ alkylaminocarbonyl, di(C₁₋₆)alkylaminocarbonyl, aminosulphonyl or di(C₁₋₆)alkylaminosulphonyl;

15 R³² represents hydrogen, halogen, cyano, hydroxy, hydroxy(C₁₋₆)alkyl, C₁₋₆ alkylsulphonyl, formyl, C₂₋₆ alkylcarbonyl, carboxy, carboxy(C₁₋₆)alkyl, C₂₋₆ alkoxycarbonyl, C₂₋₆ alkoxycarbonyl(C₁₋₆)alkyl, aminosulphonyl, a carboxylic acid isostere or prodrug moiety Ω, or -(C₁₋₆)alkyl-Ω;

20 R³³ represents hydrogen, halogen, C₁₋₆ alkyl, trifluoromethyl, hydroxy, hydroxy-(C₁₋₆)alkyl, C₁₋₆ alkoxy, amino or carboxy; and

V, E, Q, Z, R¹², R¹⁵, R¹⁶, R²³ and Ω are as defined above.

In a first embodiment, T represents -CH₂-. In a second embodiment, T represents -CH₂CH₂-.

In a first embodiment, U represents C(O). In a second embodiment, U represents S(O)₂.

In one aspect, W represents O, S, S(O), S(O)₂, N(R³¹), CF₂, CH(CO₂H) or CH(tetrazolyl).

5 Generally, W represents O, S(O)₂, N(R³¹) or C(R³²)(R³³).

Suitably, W represents O, S, S(O), S(O)₂, N(R³¹) or CH(CO₂H).

Typically, W represents O, S(O)₂, N(R³¹) or CH(CO₂H).

In a first embodiment, W represents O. In a second embodiment, W represents S. In a third embodiment, W represents S(O). In a fourth embodiment, W represents S(O)₂.

10 In a fifth embodiment, W represents N(R³¹). In a sixth embodiment, W represents C(R³²)(R³³).

In a first aspect of the sixth embodiment, W represents CF₂. In a second aspect of the sixth embodiment, W represents CH(CO₂H). In a third aspect of the sixth embodiment, W represents CH(tetrazolyl).

15 In one aspect, R³¹ represents hydrogen, cyano(C₁₋₆)alkyl, C₁₋₆ alkyl, trifluoromethyl, trifluoroethyl, C₁₋₆ alkylsulphonyl, (C₁₋₆)alkylsulphonyl(C₁₋₆)alkyl, formyl, C₂₋₆ alkylcarbonyl, carboxy, carboxy(C₁₋₆)alkyl, C₂₋₆ alkoxy carbonyl, C₂₋₆ alkoxy carbonyl-(C₁₋₆)alkyl, aminocarbonyl, C₁₋₆ alkylaminocarbonyl, di(C₁₋₆)alkylaminocarbonyl, aminosulphonyl, C₁₋₆ alkylaminosulphonyl or di(C₁₋₆)alkylaminosulphonyl.

20 Suitably, R³¹ represents hydrogen, cyano(C₁₋₆)alkyl, trifluoroethyl, C₁₋₆ alkylsulphonyl, (C₁₋₆)alkylsulphonyl(C₁₋₆)alkyl, C₂₋₆ alkylcarbonyl, carboxy(C₁₋₆)alkyl, C₂₋₆ alkoxy carbonyl or C₂₋₆ alkoxy carbonyl(C₁₋₆)alkyl. Additionally, R³¹ may represent tetrazolyl(C₁₋₆)alkyl. Additionally, R³¹ may represent C₁₋₆ alkyl.

Appositely, R³¹ represents hydrogen, C₁₋₆ alkyl, C₁₋₆ alkylsulphonyl, carboxy-(C₁₋₆)alkyl, C₂₋₆ alkoxy carbonyl or tetrazolyl(C₁₋₆)alkyl.

Typically, R³¹ represents hydrogen, carboxy(C₁₋₆)alkyl or tetrazolyl(C₁₋₆)alkyl.

Typical values of R³¹ include hydrogen, cyanoethyl, methyl, ethyl, isopropyl, trifluoromethyl, trifluoroethyl, methylsulphonyl, methylsulphonylethyl, formyl, acetyl, carboxy, carboxymethyl, carboxyethyl, methoxycarbonyl, ethoxycarbonyl, *tert*-butoxycarbonyl, ethoxycarbonylmethyl, ethoxycarbonylethyl, aminocarbonyl, methylamino-
30 carbonyl, dimethylaminocarbonyl, aminosulphonyl, methylaminosulphonyl and dimethylaminosulphonyl. An additional value is tetrazolylmethyl.

Selected values of R^{31} include hydrogen, cyanoethyl, trifluoroethyl, methylsulphonyl, methylsulphonylethyl, acetyl, carboxymethyl, carboxyethyl, *tert*-butoxycarbonyl, ethoxycarbonylmethyl and ethoxycarbonylethyl. An additional value is tetrazolylmethyl. An additional value is methyl.

5 Apposite values of R^{31} include hydrogen, methyl, methylsulphonyl, carboxymethyl, carboxyethyl, *tert*-butoxycarbonyl and tetrazolylmethyl.

Suitable values of R^{31} include hydrogen, carboxyethyl and tetrazolylmethyl.

A particular value of R^{31} is hydrogen.

Generally, R^{32} represents halogen, carboxy, carboxy(C_{1-6})alkyl, C_{2-6} alkoxy carbonyl, C_{2-6} alkoxy carbonyl(C_{1-6})alkyl, a carboxylic acid isostere or prodrug moiety Ω , or $-(C_{1-6})$ alkyl- Ω .

Suitably, R^{32} represents hydrogen, halogen, cyano, hydroxy, hydroxy(C_{1-6})alkyl, C_{1-6} alkylsulphonyl, formyl, carboxy, carboxy(C_{1-6})alkyl, C_{2-6} alkoxy carbonyl, C_{2-6} alkoxy carbonyl(C_{1-6})alkyl, aminosulphonyl, (C_{1-6})alkoxyaminocarbonyl, (C_{1-6})alkylsulphonylaminocarbonyl, (C_{2-6})alkylcarbonylaminosulphonyl, hydroxyoxadiazolyl or tetrazolyl.

Typically, R^{32} represents carboxy, C_{2-6} alkoxy carbonyl or tetrazolyl.

Selected values of R^{32} include hydrogen, fluoro, cyano, hydroxy, hydroxymethyl, methylsulphonyl, formyl, carboxy, carboxymethyl, methoxycarbonyl, ethoxycarbonyl, *tert*-butoxycarbonyl, ethoxycarbonylmethyl, aminosulphonyl, methoxyaminocarbonyl, methylsulphonylaminocarbonyl, acetylaminosulphonyl, hydroxyoxadiazolyl or tetrazolyl.

Typical values of R^{32} include fluoro, carboxy, carboxymethyl, carboxyethyl, methoxycarbonyl, ethoxycarbonyl, methoxycarbonylmethyl, methoxycarbonylethyl, ethoxycarbonylmethyl, ethoxycarbonylethyl, tetrazolyl, tetrazolylmethyl and tetrazolylethyl.

Particular values of R^{32} include carboxy, methoxycarbonyl, ethoxycarbonyl and tetrazolyl.

In a selected embodiment, R^{32} represents carboxy.

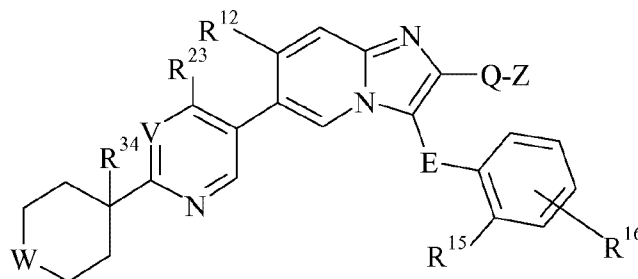
Generally, R^{33} represents hydrogen, halogen or C_{1-6} alkyl.

Suitably, R^{33} represents hydrogen or C_{1-6} alkyl.

Selected values of R^{33} include hydrogen, fluoro, methyl, ethyl, isopropyl, trifluoromethyl, hydroxy, hydroxymethyl, methoxy, amino and carboxy.

In a first embodiment, R^{33} represents hydrogen. In a second embodiment, R^{33} represents halogen. In one aspect of that embodiment, R^{33} represents fluoro. In a third embodiment, R^{33} represents C_{1-6} alkyl. In a first aspect of that embodiment, R^{33} represents methyl. In a second aspect of that embodiment, R^{33} represents ethyl. In a third aspect of that embodiment, R^{33} represents isopropyl. In a fourth embodiment, R^{33} represents trifluoromethyl. In a fifth embodiment, R^{33} represents hydroxy. In a sixth embodiment, R^{33} represents hydroxy(C_{1-6})alkyl. In one aspect of that embodiment, R^{33} represents hydroxymethyl. In a seventh embodiment, R^{33} represents C_{1-6} alkoxy. In one aspect of that embodiment, R^{33} represents methoxy. In an eighth embodiment, R^{33} represents amino. In a ninth embodiment, R^{33} represents carboxy.

Another sub-group of the compounds of formula (IIB) above is represented by the compounds of formula (IIF) and *N*-oxides thereof, and pharmaceutically acceptable salts and solvates thereof, and glucuronide derivatives thereof, and co-crystals thereof:



(IIF)

wherein

R^{34} represents hydrogen, halogen, halo(C_{1-6})alkyl, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulphinyl, C_{1-6} alkylsulphonyl, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, (C_{2-6})alkylcarbonylamino, (C_{2-6})alkylcarbonylamino(C_{1-6})alkyl, (C_{1-6})alkylsulphonylamino or (C_{1-6})alkylsulphonylamino(C_{1-6})alkyl; and

E, Q, Z, V, W, R^{12} , R^{15} , R^{16} and R^{23} are as defined above.

In a first embodiment, R^{34} represents hydrogen. In a second embodiment, R^{34} represents halogen. In one aspect of that embodiment, R^{34} represents fluoro. In a third embodiment, R^{34} represents halo(C_{1-6})alkyl. In one aspect of that embodiment, R^{34} represents fluoromethyl. In a fourth embodiment, R^{34} represents hydroxy. In a fifth embodiment, R^{34} represents C_{1-6} alkoxy, especially methoxy. In a sixth embodiment, R^{34} represents C_{1-6} alkylthio, especially methylthio. In a seventh embodiment, R^{34} represents

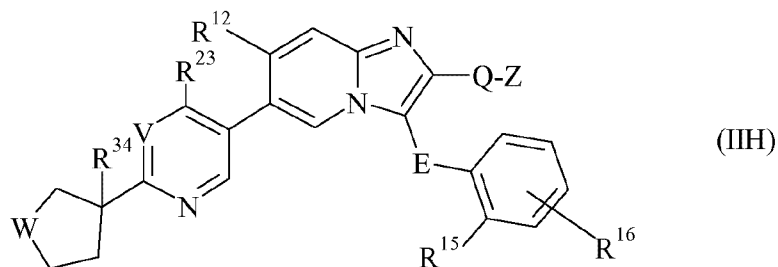
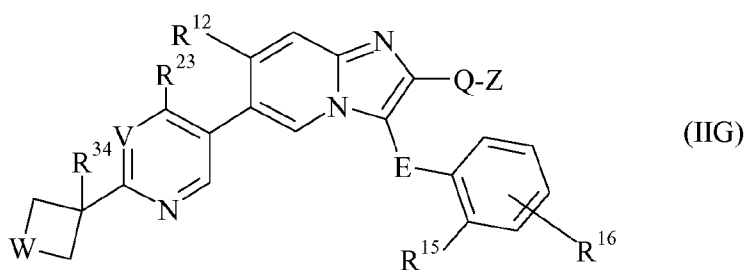
- C₁₋₆ alkylsulphinyl, especially methylsulphinyl. In an eighth embodiment, R³⁴ represents C₁₋₆ alkylsulphonyl, especially methylsulphonyl. In a ninth embodiment, R³⁴ represents amino. In a tenth embodiment, R³⁴ represents C₁₋₆ alkylamino, especially methylamino. In an eleventh embodiment, R³⁴ represents di(C₁₋₆)alkylamino, especially dimethylamino.
- 5 In a twelfth embodiment, R³⁴ represents (C₂₋₆)alkylcarbonylamino, especially acetylamino. In a thirteenth embodiment, R³⁴ represents (C₂₋₆)alkylcarbonylamino(C₁₋₆)alkyl, especially acetylaminomethyl. In a fourteenth embodiment, R³⁴ represents (C₁₋₆)alkylsulphonylamino, especially methylsulphonylamino. In a fifteenth embodiment, R³⁴ represents (C₁₋₆)alkylsulphonylamino(C₁₋₆)alkyl, especially methylsulphonylaminomethyl.
- 10 Typically, R³⁴ represents hydrogen, halogen, halo(C₁₋₆)alkyl, hydroxy or (C₂₋₆)alkylcarbonylamino(C₁₋₆)alkyl.

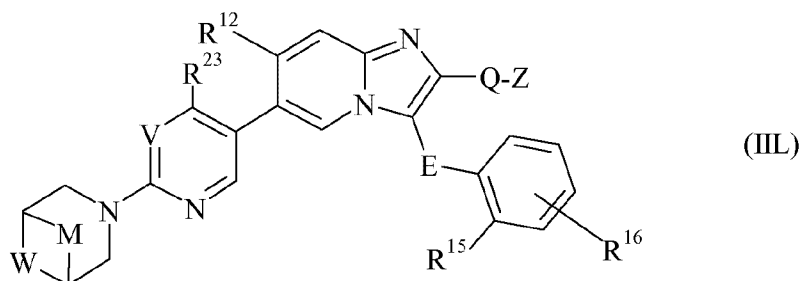
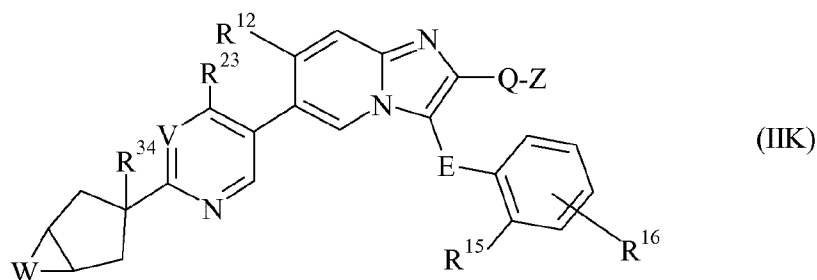
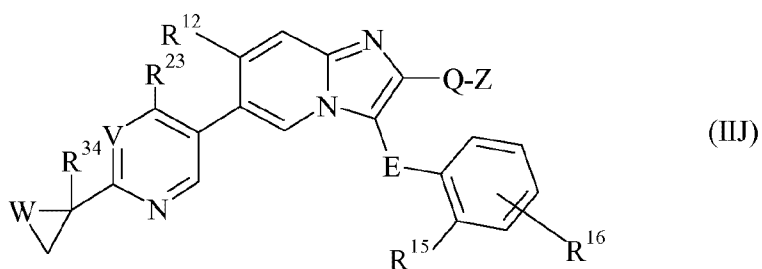
Selected values of R³⁴ include hydrogen, fluoro, fluoromethyl, hydroxy, methoxy, methylthio, methylsulphinyl, methylsulphonyl, amino, methylamino, dimethylamino and acetylaminomethyl.

- 15 Particular values of R³⁴ include hydrogen, fluoro, fluoromethyl, hydroxy and acetylaminomethyl.

Suitably, R³⁴ represents hydrogen or hydroxy.

- Further sub-groups of the compounds of formula (IIB) above are represented by the compounds of formula (IIG), (IIH), (IIJ), (IIK) and (IIL) and *N*-oxides thereof, and
- 20 pharmaceutically acceptable salts and solvates thereof, and glucuronide derivatives thereof, and co-crystals thereof:





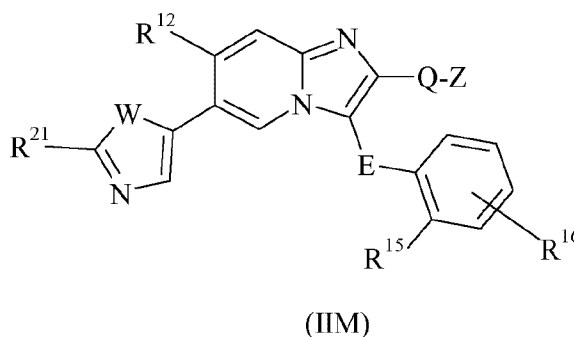
5 wherein

-M- represents -CH₂- or -CH₂CH₂-; and

E, Q, Z, V, W, R¹², R¹⁵, R¹⁶, R²³ and R³⁴ are as defined above.

In one embodiment, -M- represents -CH₂-. In another embodiment, -M- represents -CH₂CH₂-.

10 An alternative sub-class of compounds according to the invention is represented by the compounds of formula (IIM) and *N*-oxides thereof, and pharmaceutically acceptable salts and solvates thereof, and glucuronide derivatives thereof, and co-crystals thereof:



wherein

E, Q, Z, W, R¹², R¹⁵, R¹⁶ and R²¹ are as defined above.

5 With specific reference to formula (IIM), the integer W is suitably O, S or N-R³¹, especially S or N-R³¹.

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, and co-crystals thereof.

10 The compounds in accordance with the present invention are beneficial in the treatment and/or prevention of various human ailments. These include autoimmune and inflammatory disorders; neurological and neurodegenerative disorders; pain and nociceptive disorders; cardiovascular disorders; metabolic disorders; ocular disorders; and oncological disorders.

15 Inflammatory and autoimmune disorders include systemic autoimmune disorders, autoimmune endocrine disorders and organ-specific autoimmune disorders. Systemic autoimmune disorders include systemic lupus erythematosus (SLE), psoriasis, psoriatic arthropathy, vasculitis, polymyositis, scleroderma, multiple sclerosis, systemic sclerosis, ankylosing spondylitis, rheumatoid arthritis, non-specific inflammatory arthritis, juvenile
20 inflammatory arthritis, juvenile idiopathic arthritis (including oligoarticular and polyarticular forms thereof), anaemia of chronic disease (ACD), Still's disease (juvenile and/or adult onset), Behçet's disease and Sjögren's syndrome. Autoimmune endocrine disorders include thyroiditis. Organ-specific autoimmune disorders include Addison's disease, haemolytic or pernicious anaemia, acute kidney injury (AKI; including cisplatin-
25 induced AKI), diabetic nephropathy (DN), obstructive uropathy (including cisplatin-induced obstructive uropathy), glomerulonephritis (including Goodpasture's syndrome, immune complex-mediated glomerulonephritis and antineutrophil cytoplasmic antibodies

(ANCA)-associated glomerulonephritis), lupus nephritis (LN), minimal change disease, Graves' disease, idiopathic thrombocytopenic purpura, inflammatory bowel disease (including Crohn's disease, ulcerative colitis, indeterminate colitis and pouchitis), pemphigus, atopic dermatitis, autoimmune hepatitis, primary biliary cirrhosis, autoimmune
 5 pneumonitis, autoimmune carditis, myasthenia gravis, spontaneous infertility, osteoporosis, osteopenia, erosive bone disease, chondritis, cartilage degeneration and/or destruction, fibrosing disorders (including various forms of hepatic and pulmonary fibrosis), asthma, rhinitis, chronic obstructive pulmonary disease (COPD), respiratory distress syndrome, sepsis, fever, muscular dystrophy (including Duchenne muscular
 10 dystrophy) and organ transplant rejection (including kidney allograft rejection).

Neurological and neurodegenerative disorders include Alzheimer's disease, Parkinson's disease, Huntington's disease, ischaemia, stroke, amyotrophic lateral sclerosis, spinal cord injury, head trauma, seizures and epilepsy.

Cardiovascular disorders include thrombosis, cardiac hypertrophy, hypertension,
 15 irregular contractility of the heart (e.g. during heart failure), and sexual disorders (including erectile dysfunction and female sexual dysfunction). Modulators of TNF α function may also be of use in the treatment and/or prevention of myocardial infarction (see J.J. Wu *et al.*, *JAMA*, 2013, **309**, 2043-2044).

Metabolic disorders include diabetes (including insulin-dependent diabetes mellitus
 20 and juvenile diabetes), dyslipidemia and metabolic syndrome.

Ocular disorders include retinopathy (including diabetic retinopathy, proliferative retinopathy, non-proliferative retinopathy and retinopathy of prematurity), macular oedema (including diabetic macular oedema), age-related macular degeneration (ARMD), vascularisation (including corneal vascularisation and neovascularisation), retinal vein
 25 occlusion, and various forms of uveitis and keratitis.

Oncological disorders, which may be acute or chronic, include proliferative disorders, especially cancer, and cancer-associated complications (including skeletal complications, cachexia and anaemia). Particular categories of cancer include haematological malignancy (including leukaemia and lymphoma) and non-haematological
 30 malignancy (including solid tumour cancer, sarcoma, meningioma, glioblastoma multiforme, neuroblastoma, melanoma, gastric carcinoma and renal cell carcinoma). Chronic leukaemia may be myeloid or lymphoid. Varieties of leukaemia include lymphoblastic T cell leukaemia, chronic myelogenous leukaemia (CML), chronic

lymphocytic/lymphoid leukaemia (CLL), hairy-cell leukaemia, acute lymphoblastic leukaemia (ALL), acute myelogenous leukaemia (AML), myelodysplastic syndrome, chronic neutrophilic leukaemia, acute lymphoblastic T cell leukaemia, plasmacytoma, immunoblastic large cell leukaemia, mantle cell leukaemia, multiple myeloma, acute megakaryoblastic leukaemia, acute megakaryocytic leukaemia, promyelocytic leukaemia and erythroleukaemia. Varieties of lymphoma include malignant lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, lymphoblastic T cell lymphoma, Burkitt's lymphoma, follicular lymphoma, MALT1 lymphoma and marginal zone lymphoma. Varieties of non-haematological malignancy include cancer of the prostate, lung, breast, rectum, colon, lymph node, bladder, kidney, pancreas, liver, ovary, uterus, cervix, brain, skin, bone, stomach and muscle. Modulators of TNF α function may also be used to increase the safety of the potent anticancer effect of TNF (see F.V. Hauwermeiren *et al.*, *J. Clin. Invest.*, 2013, **123**, 2590-2603).

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.

5 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
10 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.

15 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
20 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
25 dispensing device may be accompanied by instructions for administration.

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

carriers include, for example, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, benzyl alcohol, 2-octyldodecanol and water.

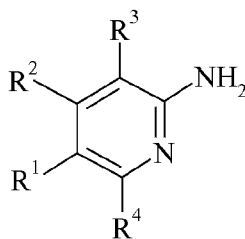
For ophthalmic administration the compounds of use in the present invention may be conveniently formulated as micronized suspensions in isotonic, pH-adjusted sterile saline, either with or without a preservative such as a bactericidal or fungicidal agent, for example phenylmercuric nitrate, benzylalkonium chloride or chlorhexidine acetate. Alternatively, for ophthalmic administration compounds may be formulated in an ointment such as petrolatum.

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

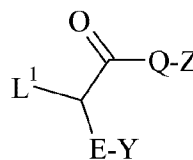
The quantity of a compound of use in the invention required for the prophylaxis or treatment of a particular condition will vary depending on the compound chosen and the condition of the patient to be treated. In general, however, daily dosages may range from around 10 ng/kg to 1000 mg/kg, typically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

If desired, a compound in accordance with the present invention may be co-administered with another pharmaceutically active agent, e.g. an anti-inflammatory molecule such as methotrexate or prednisolone.

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)

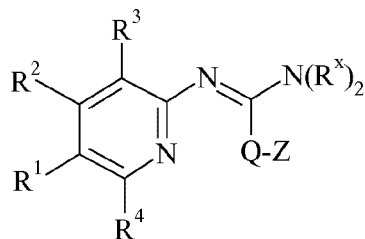
wherein E, Q, Y, Z, R¹, R², R³ and R⁴ are as defined above, and L¹ represents a suitable leaving group.

The leaving group L¹ is typically a halogen atom, e.g. bromo.

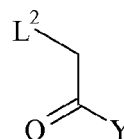
- 5 The reaction is conveniently effected at an elevated temperature in a suitable solvent, e.g. a C₁₋₄ alkanol such as ethanol, or a cyclic ether such as 1,4-dioxane.

The compounds of formula (I) above wherein E represents -C(O)- may be prepared by a process which comprises reacting a compound of formula (V) with a compound of formula (VI):

10



(V)



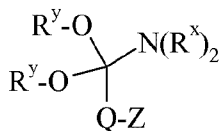
(VI)

wherein Q, Y, Z, R¹, R², R³ and R⁴ are as defined above, R^x represents a C₁₋₄ alkyl group, e.g. methyl, and L² represents a suitable leaving group.

- 15 The leaving group L² is typically a halogen atom, e.g. bromo.

The reaction is conveniently effected at ambient or elevated temperature in a suitable solvent, e.g. a dipolar aprotic solvent such as *N,N*-dimethylformamide, a hydrocarbon solvent such as toluene, or a C₁₋₄ alkanol such as ethanol.

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

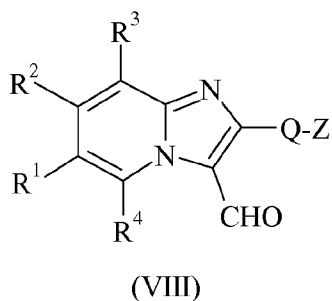


(VII)

wherein Q, Z and R^x are as defined above, and R^y represents a C₁₋₄ alkyl group, e.g. methyl.

The reaction is conveniently effected at an elevated temperature in a suitable solvent, e.g. a hydrocarbon solvent such as toluene, or a C₁₋₄ alkanol such as methanol.

- 5 The compounds of formula (I) above wherein E represents -CH(OH)- may be prepared by a process which comprises reacting a compound of formula Y-MgHal with a compound of formula (VIII):



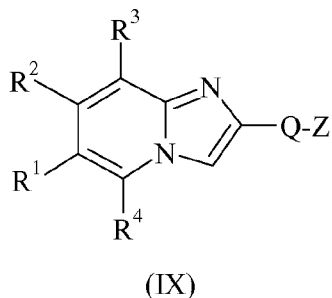
10

wherein Q, Y, Z, R¹, R², R³ and R⁴ are as defined above, and Hal represents a halogen atom.

The halogen atom Hal is typically bromo.

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

The intermediates of formula (VIII) above may be prepared by treating a compound of formula (IX):

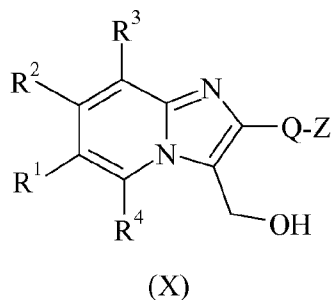


20

wherein Q, Z, R¹, R², R³ and R⁴ are as defined above; with (chloromethylene)dimethyliminium chloride (Vilsmeier reagent).

The reaction is conveniently effected at an elevated temperature in a suitable solvent, e.g. a dipolar aprotic solvent such as *N,N*-dimethylformamide.

The compounds of formula (I) above wherein E represents -CH₂- and Y represents optionally substituted aryl or heteroaryl may be prepared by a process which comprises
 5 reacting a compound of formula Y¹-H with a compound of formula (X):

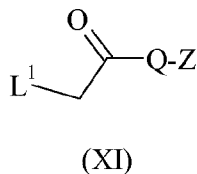


wherein Q, Z, R¹, R², R³ and R⁴ are as defined above, and Y¹ represents aryl or heteroaryl,
 10 either of which groups may be optionally substituted by one or more substituents; in the presence of a sulfonic acid derivative.

The sulfonic acid derivative of use in the foregoing reaction is suitably an organic sulfonic acid derivative such as methanesulfonic acid. The reaction is conveniently effected at an elevated temperature in a suitable solvent, e.g. water.

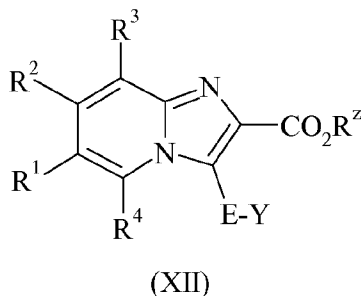
15 The intermediates of formula (X) above may be prepared by treating a compound of formula (IX) as defined above with formaldehyde. The reaction is conveniently effected at an elevated temperature in a suitable solvent, e.g. water.

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



wherein Q, Z and L¹ are as defined above; under conditions analogous to those described above for the reaction between compounds (III) and (IV).

The compounds of formula (I) above wherein -Q-Z represents -CH₂OH may be prepared by a process which comprises treating a compound of formula (XII):



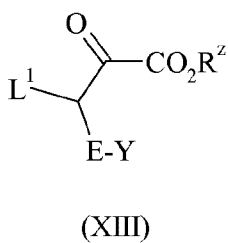
5

wherein E, Y, R¹, R², R³ and R⁴ are as defined above, and R^z represents a C₁₋₄ alkyl group, e.g. methyl; with a reducing agent.

The reducing agent of use in the foregoing reaction is suitably an alkali metal borohydride such as lithium borohydride. The reaction is conveniently effected at ambient
10 temperature in a suitable solvent, e.g. a cyclic ether such as tetrahydrofuran, or a C₁₋₄ alkanol such as methanol, or a mixture thereof.

Alternatively, the reducing agent of use in the foregoing reaction may suitably be diisobutylaluminium hydride. The reaction is conveniently effected at a temperature in the region of 0°C in a suitable solvent, e.g. a cyclic ether such as tetrahydrofuran.

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



20 wherein E, Y, R^z and L¹ are as defined above; under conditions analogous to those described above for the reaction between compounds (III) and (IV).

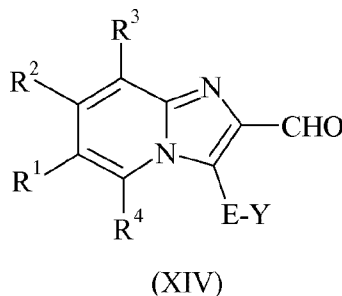
The compounds of formula (I) above wherein E represents -N(H)- may be prepared by a process which comprises reacting a compound of formula (III) as defined above with

an isocyanide derivative of formula Y-NC and an aldehyde derivative of formula OHC-Q-Z; in the presence of a transition metal catalyst.

The transition metal catalyst of use in the foregoing reaction is suitably a zirconium derivative, e.g. a zirconium halide such as zirconium(IV) chloride. The reaction is
5 conveniently effected at an elevated temperature in a suitable solvent, e.g. a C₁₋₄ alkanol such as *n*-butanol.

The compounds of formula (I) above wherein Q represents -CH₂N(H)- may be prepared by a process which comprises reacting a compound of formula Z-NH₂ with a compound of formula (XIV):

10



wherein E, Y, R¹, R², R³ and R⁴ are as defined above; in the presence of a reducing agent.

The reducing agent of use in the above reaction is suitably sodium borohydride.

15 The intermediates of formula (XIV) may be prepared from the corresponding compound of formula (I) wherein Q-Z represents -CH₂OH by treatment with an oxidising agent such as Dess-Martin periodinane.

Where they are not commercially available, the starting materials of formula (III), (IV), (VI), (VII), (XI) and (XIII) may be prepared by methods analogous to those
20 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
25 compound of formula (I) wherein E represents -C(O)- may be converted into the corresponding compound wherein E represents -CH(OH)- by treatment with a reducing agent such as sodium borohydride.

A compound of formula (I) wherein E represents -CH(OH)- may be converted into the corresponding compound wherein E represents -CH₂- by heating with elemental iodine and phosphinic acid in acetic acid; or by treating with triethylsilane and an acid, e.g. an organic acid such as trifluoroacetic acid, or a Lewis acid such as boron trifluoride diethyl etherate; or by a two-step procedure which comprises: (i) treatment with thionyl bromide; and (ii) treatment of the product thereby obtained with a transition metal catalyst, e.g. (2,2'-bipyridine)dichlororuthenium(II) hydrate, in the presence of diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate (Hantzsch ester) and a base, e.g. an organic base such as *N,N*-diisopropylethylamine.

10 A compound of formula (I) wherein E represents -CH₂- may be converted into the corresponding compound wherein E represents -CH(CH₃)- by treatment with a methyl halide, e.g. methyl iodide, in the presence of a base such as lithium hexamethyldisilazide.

A compound of formula (I) which contains a hydroxy group may be alkylated by treatment with the appropriate alkyl halide in the presence of a base, e.g. sodium hydride, or silver oxide. A compound of formula (I) wherein -Q-Z represents -CH₂OH may be arylated in a two-step procedure which comprises: (i) treatment with thionyl chloride; and (ii) treatment of the chloro derivative thereby obtained with the appropriate aryl or heteroaryl hydroxide. A compound of formula (I) wherein -Q-Z represents -CH₂OH may be converted into the corresponding compound of formula (I) wherein -Q-Z represents -CH₂S-Z via a two-step procedure which comprises: (i) treatment with thionyl chloride; and (ii) treatment of the chloro derivative thereby obtained with a compound of formula Z-SH, typically in the presence of a base, e.g. an inorganic base such as potassium carbonate. A compound of formula (I) wherein -Q-Z represents -CH₂OH may be converted into the corresponding compound of formula (I) wherein -Q-Z represents -CH₂CN via a two-step procedure which comprises: (i) treatment with thionyl chloride; and (ii) treatment of the chloro derivative thereby obtained with a cyanide salt such as sodium cyanide. A compound of formula (I) which contains hydroxy may be converted into the corresponding fluoro-substituted compound by treatment with diethylaminosulfur trifluoride (DAST) or bis(2-methoxyethyl)aminosulfur trifluoride (BAST). A compound of formula (I) which contains hydroxy may be converted into the corresponding difluoro-substituted compound via a two-step procedure which comprises: (i) treatment with an oxidising agent, e.g. manganese dioxide; and (ii) treatment of the carbonyl-containing compound thereby obtained with DAST.

A compound of formula (I) which contains an N-H moiety may be alkylated by treatment with the appropriate alkyl halide, typically at an elevated temperature in an organic solvent such as acetonitrile; or at ambient temperature in the presence of a base, e.g. an alkali metal carbonate such as potassium carbonate or cesium carbonate, in a suitable solvent, e.g. a dipolar aprotic solvent such as *N,N*-dimethylformamide. Alternatively, a compound of formula (I) which contains an N-H moiety may be alkylated by treatment with the appropriate alkyl tosylate in the presence of a base, e.g. an inorganic base such as sodium hydride, or an organic base such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

10 A compound of formula (I) which contains an N-H moiety may be methylated by treatment with formaldehyde in the presence of a reducing agent, e.g. sodium triacetoxyborohydride.

A compound of formula (I) which contains an N-H moiety may be acylated by treatment with the appropriate acid chloride, e.g. acetyl chloride, or with the appropriate carboxylic acid anhydride, e.g. acetic anhydride, typically at ambient temperature in the presence of a base, e.g. an organic base such as triethylamine.

15 A compound of formula (I) which contains an N-H moiety may be converted into the corresponding compound wherein the nitrogen atom is substituted by C₁₋₆ alkylsulphonyl, e.g. methylsulphonyl, by treatment with the appropriate C₁₋₆ alkylsulphonic acid anhydride, e.g. methanesulphonic anhydride, typically at ambient temperature in the presence of a base, e.g. an organic base such as *N,N*-diisopropylethylamine.

A compound of formula (I) substituted by amino (-NH₂) may be converted into the corresponding compound substituted by C₁₋₆ alkylsulphonylamino, e.g. methylsulphonylamino, or bis[(C₁₋₆)alkylsulphonyl]amino, e.g. bis(methylsulphonyl)amino, by treatment with the appropriate C₁₋₆ alkylsulphonyl halide, e.g. a C₁₋₆ alkylsulphonyl chloride such as methanesulphonyl chloride. Similarly, a compound of formula (I) substituted by hydroxy (-OH) may be converted into the corresponding compound substituted by C₁₋₆ alkylsulphonyloxy, e.g. methylsulphonyloxy, by treatment with the appropriate C₁₋₆ alkylsulphonyl halide, e.g. a C₁₋₆ alkylsulphonyl chloride such as methanesulphonyl chloride.

25 A compound of formula (I) containing the moiety -S- may be converted into the corresponding compound containing the moiety -S(O)- by treatment with 3-chloroperoxybenzoic acid. Likewise, a compound of formula (I) containing the moiety -S(O)- may be converted into the corresponding compound containing the moiety -S(O)₂- by treatment

with 3-chloroperoxybenzoic acid. Alternatively, a compound of formula (I) containing the moiety -S- may be converted into the corresponding compound containing the moiety -S(O)₂- by treatment with Oxone® (potassium peroxymonosulfate).

5 A compound of formula (I) containing an aromatic nitrogen atom may be converted into the corresponding *N*-oxide derivative by treatment with 3-chloroperoxybenzoic acid.

A bromophenyl derivative of formula (I) may be converted into the corresponding optionally substituted 2-oxopyrrolidin-1-ylphenyl or 2-oxooxazolidin-3-ylphenyl derivative by treatment with pyrrolidin-2-one or oxazolidin-2-one, or an appropriately substituted analogue thereof. The reaction is conveniently effected at an elevated
10 temperature in the presence of copper(I) iodide, *trans*-*N,N'*-dimethylcyclohexane-1,2-diamine and an inorganic base such as potassium carbonate.

A compound of formula (I) wherein R¹ represents halogen, e.g. bromo, may be converted into the corresponding compound wherein R¹ represents an optionally substituted aryl or heteroaryl moiety by treatment with the appropriately substituted aryl or
15 heteroaryl boronic acid or a cyclic ester thereof formed with an organic diol, e.g. pinacol, 1,3-propanediol or neopentyl glycol. The reaction is typically effected in the presence of a transition metal catalyst, e.g. [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), tetrakis(triphenylphosphine)palladium(0), or bis[3-(diphenylphosphanyl)cyclopenta-2,4-
20 dien-1-yl]iron-dichloropalladium-dichloromethane complex, or tetrakis(triphenylphosphine)palladium(0), and a base, e.g. an inorganic base such as sodium carbonate or potassium carbonate, or potassium phosphate.

A compound of formula (I) wherein R¹ represents halogen, e.g. bromo, may be converted into the corresponding compound wherein R¹ represents an optionally substituted aryl, heteroaryl or heterocycloalkenyl moiety via a two-step procedure which
25 comprises: (i) reaction with bis(pinacolato)diboron or bis(neopentyl glycolato)diboron; and (ii) reaction of the compound thereby obtained with an appropriately functionalised halo- or tosyloxy-substituted aryl, heteroaryl or heterocycloalkenyl derivative. Step (i) is conveniently effected in the presence of a transition metal catalyst such as [1,1'-bis-
30 (diphenylphosphino)ferrocene]dichloropalladium(II), or bis[3-(diphenylphosphanyl)cyclopenta-2,4-dien-1-yl]iron-dichloropalladium-dichloromethane complex. Step (ii) is conveniently effected in the presence of a transition metal catalyst such as tetrakis-(triphenylphosphine)palladium(0), or bis[3-(diphenylphosphanyl)cyclopenta-2,4-dien-1-

yl]iron-dichloropalladium-dichloromethane complex, and a base, e.g. an inorganic base such as sodium carbonate or potassium carbonate.

A compound of formula (I) wherein R¹ represents halogen, e.g. bromo, may be converted into the corresponding compound wherein R¹ represents an optionally substituted C₂₋₆ alkynyl moiety by treatment with an appropriately substituted alkyne derivative, e.g. 2-hydroxybut-3-yne. The reaction is conveniently accomplished with the assistance of a transition metal catalyst, e.g. tetrakis(triphenylphosphine)palladium(0), typically in the presence of copper(I) iodide and a base, e.g. an organic base such as triethylamine.

A compound of formula (I) wherein R¹ represents halogen, e.g. bromo, may be converted into the corresponding compound wherein R¹ represents an optionally substituted imidazol-1-yl moiety by treatment with the appropriately substituted imidazole derivative, typically in the presence of copper(II) acetate and an organic base such as *N,N,N',N'*-tetramethylethylenediamine (TMEDA).

A compound of formula (I) wherein R¹ represents halogen, e.g. bromo, may be converted into the corresponding compound wherein R¹ represents 2-(methoxycarbonyl)-ethyl via a two-step procedure which comprises: (i) reaction with methyl acrylate; and (ii) catalytic hydrogenation of the alkenyl derivative thereby obtained, typically by treatment with a hydrogenation catalyst, e.g. palladium on charcoal, under an atmosphere of hydrogen gas. Step (i) is typically effected in the presence of a transition metal catalyst, e.g. palladium(II) acetate or bis(dibenzylideneacetone)palladium(0), and a reagent such as tri(*ortho*-tolyl)phosphine.

In general, a compound of formula (I) containing a -C=C- functionality may be converted into the corresponding compound containing a -CH-CH- functionality by catalytic hydrogenation, typically by treatment with a hydrogenation catalyst, e.g. palladium on charcoal, under an atmosphere of hydrogen gas, optionally in the presence of a base, e.g. an alkali metal hydroxide such as sodium hydroxide.

A compound of formula (I) wherein R¹ represents 6-methoxypyridin-3-yl may be converted into the corresponding compound wherein R¹ represents 2-oxo-1,2-dihydro-pyridin-5-yl by treatment with pyridine hydrochloride; or by heating with a mineral acid such as hydrochloric acid. By utilising similar methodology, a compound of formula (I) wherein R¹ represents 6-methoxy-4-methylpyridin-3-yl may be converted into the corresponding compound wherein R¹ represents 4-methyl-2-oxo-1,2-dihydropyridin-5-yl;

and a compound of formula (I) wherein R¹ represents 6-methoxy-5-methylpyridin-3-yl may be converted into the corresponding compound wherein R¹ represents 3-methyl-2-oxo-1,2-dihydropyridin-5-yl.

5 A compound of formula (I) wherein R¹ represents 2-oxo-1,2-dihydropyridin-5-yl may be converted into the corresponding compound wherein R¹ represents 2-oxopiperidin-5-yl by catalytic hydrogenation, typically by treatment with gaseous hydrogen in the presence of a hydrogenation catalyst such as platinum(IV) oxide.

A compound of formula (I) containing an ester moiety, e.g. a C₂₋₆ alkoxycarbonyl group such as methoxycarbonyl or ethoxycarbonyl, may be converted into the
10 corresponding compound containing a carboxy (-CO₂H) moiety by treatment with an acid, e.g. a mineral acid such as hydrochloric acid.

A compound of formula (I) containing an *N*-(*tert*-butoxycarbonyl) moiety may be converted into the corresponding compound containing an N-H moiety by treatment with an acid, e.g. a mineral acid such as hydrochloric acid, or an organic acid such as
15 trifluoroacetic acid.

A compound of formula (I) containing an ester moiety, e.g. a C₂₋₆ alkoxycarbonyl group such as methoxycarbonyl or ethoxycarbonyl, may alternatively be converted into the corresponding compound containing a carboxy (-CO₂H) moiety by treatment with a base, e.g. an alkali metal hydroxide selected from lithium hydroxide, sodium hydroxide and
20 potassium hydroxide; or an organic base such as sodium methoxide or sodium ethoxide.

A compound of formula (I) containing a carboxy (-CO₂H) moiety may be converted into the corresponding compound containing an amide moiety by treatment with the appropriate amine in the presence of a condensing agent such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide.

25 A compound of formula (I) containing a carbonyl (C=O) moiety may be converted into the corresponding compound containing a -C(CH₃)(OH)- moiety by treatment with methylmagnesium bromide. Similarly, a compound of formula (I) containing a carbonyl (C=O) moiety may be converted into the corresponding compound containing a -C(CF₃)(OH)- moiety by treatment with (trifluoromethyl)trimethylsilane and cesium
30 fluoride. A compound of formula (I) containing a carbonyl (C=O) moiety may be converted into the corresponding compound containing a -C(CH₂NO₂)(OH)- moiety by treatment with nitromethane.

A compound of formula (I) containing a hydroxymethyl moiety may be converted into the corresponding compound containing a formyl (-CHO) moiety by treatment with an oxidising agent such as Dess-Martin periodinane. A compound of formula (I) containing a hydroxymethyl moiety may be converted into the corresponding compound
5 containing a carboxy moiety by treatment with an oxidising agent such as tetrapropylammonium perruthenate.

A compound of formula (I) wherein R^1 represents a substituent containing at least one nitrogen atom, which substituent is linked to the remainder of the molecule via a nitrogen atom, may be prepared by reacting a compound of formula (I) wherein R^1
10 represents halogen, e.g. bromo, with the appropriate compound of formula R^1-H [e.g. 1-(pyridin-3-yl)piperazine or morpholine]. The reaction is conveniently effected with the assistance of a transition metal catalyst, e.g. tris(dibenzylideneacetone)dipalladium(0), in the presence of an amination ligand such as 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (XPhos) or 2,2'-bis(diphenylphosphino)-1,1'-binaphthalene (BINAP) and a base,
15 e.g. an inorganic base such as sodium *tert*-butoxide. Alternatively, the reaction may be effected using palladium diacetate, in the presence of a reagent such as [2',6'-bis(propan-2-yloxy)biphenyl-2-yl](dicyclohexyl)phosphane and a base, e.g. an inorganic base such as cesium carbonate.

A compound of formula (I) containing an oxo moiety can be converted into the
20 corresponding compound containing an ethoxycarbonylmethylidene moiety by treatment with triethyl phosphonoacetate in the presence of a base such as sodium hydride.

A compound of formula (IIB) wherein R^{21} represents ethenyl may be prepared by reacting a compound of formula (IIB) wherein R^{21} represents halogen, e.g. chloro, with potassium vinyl trifluoroborate. The reaction is typically effected in the presence of a
25 transition metal catalyst, e.g. [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), and a base, e.g. an organic base such as triethylamine.

A compound of formula (IIB) wherein R^{21} represents halogen, e.g. chloro, may be converted into the corresponding compound wherein R^{21} represents an optionally substituted C_{4-7} cycloalkenyl moiety by treatment with the appropriately substituted
30 cycloalkenyl boronic acid or a cyclic ester thereof formed with an organic diol, e.g. pinacol, 1,3-propanediol or neopentyl glycol. The reaction is typically effected in the presence of a transition metal catalyst, e.g. bis[3-(diphenylphosphanyl)cyclopenta-2,4-

dien-1-yl]iron-dichloropalladium-dichloromethane complex, and a base, e.g. an inorganic base such as potassium carbonate.

A compound of formula (IIB) wherein R^{21} represents a substituent containing at least one nitrogen atom, which substituent is linked to the remainder of the molecule via a nitrogen atom, may be prepared by reacting a compound of formula (IIB) wherein R^{21} represents halogen, e.g. chloro, with the appropriate compound of formula R^{21} -H [e.g. 2-methoxyethylamine, *N*-methyl-*L*-alanine, 2-aminocyclopentanecarboxylic acid, 3-aminocyclopentanecarboxylic acid, 1-(aminomethyl)cyclopropanecarboxylic acid, methyl azetidine-3-carboxylate, pyrrolidin-3-ol, pyrrolidine-3-carboxylic acid, piperidine-2-carboxylic acid, piperidine-3-carboxylic acid, 4-(1*H*-tetrazol-5-yl)piperidine, piperazine, 1-(methylsulfonyl)piperazine, piperazin-2-one, 2-(piperazin-1-yl)propanoic acid, morpholine, morpholine-2-carboxylic acid, thiomorpholine, thiomorpholine 1,1-dioxide, 1,4-diazepan-5-one, 2-oxa-5-azabicyclo[2.2.1]heptane or an appropriately substituted azaspiroalkane], optionally in the presence of a base, e.g. an organic base such as triethylamine or *N,N*-diisopropylethylamine and/or 1-methyl-2-pyrrolidinone, or pyridine, or an inorganic base such as potassium carbonate.

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.

- 5 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
10 *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.

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

The compounds in accordance with this invention potently inhibit TNF α -induced NF- κ B activation in the following assay.

20 *Inhibition of TNF α -induced NF- κ B activation*

- Stimulation of HEK-293 cells by TNF α leads to activation of the NF- κ B pathway. The reporter cell line used to determine TNF α activity was purchased from InvivoGen. HEK-BlueTM CD40L is a stable transfectant expressing SEAP (secreted alkaline phosphatase) under the control of the IFN β minimal promoter fused to five NF- κ B
25 binding sites. Secretion of SEAP by these cells is stimulated in a dose-dependent manner by TNF α (0.5 ng/mL). Compounds were diluted from 10 mM DMSO stocks (final assay concentration 0.3%) to generate a 10-point 3-fold serial dilution curve (30,000 nM to 2 nM final concentration). They were mixed with cells and stimulating ligand in a 384-well microtitre plate and incubated for 18 h. SEAP activity was determined in the supernatant
30 using the colorimetric substrate QUANTI-BlueTM (InvivoGen). Percentage inhibitions for compound dilutions were calculated between a DMSO control and maximum inhibition (by excess control compound) and an IC₅₀ calculated using XLfitTM (4 parameter logistic model) in ActivityBase.

When tested in the above assay, the compounds of the accompanying Examples were all found to exhibit IC₅₀ values of 50 µM or better.

EXAMPLES

5

Abbreviations

	DCM: dichloromethane	EtOAc: ethyl acetate
	DMF: <i>N,N</i> -dimethylformamide	MeOH: methanol
	DMSO: dimethylsulfoxide	EtOH: ethanol
10	THF: tetrahydrofuran	AcOH: acetic acid
	DME: 1,2-dimethoxyethane	Et ₃ N: triethylamine
	NBS: <i>N</i> -bromosuccinimide	NMP: 1-methyl-2-pyrrolidinone
	LDA: lithium diisopropylamide	DIPEA: <i>N,N</i> -diisopropylethylamine
	MeCN: acetonitrile	TFA: trifluoroacetic acid
15	TBME: <i>tert</i> -butyl methyl ether	TBAF: tetrabutylammonium fluoride
	DIBAL: diisobutylaluminium hydride	KHMDS: potassium hexamethyldisilazide
	DAST: diethylaminosulfur trifluoride	DMP: Dess-Martin periodinane
	SiO ₂ : silica	h: h
	r.t.: room temperature	RT: retention time
20	br: broad	M: mass
	SCX: strong cation exchange	SAX: strong anion exchange
	FCC: flash column chromatography	
	HPLC: High Performance Liquid Chromatography	
	LCMS: Liquid Chromatography Mass Spectrometry	
25	ES+: Electrospray Positive Ionisation	
	Pd(PPh ₃) ₄ : tetrakis(triphenylphosphine)palladium(0)	
	Pd(dba) ₂ : bis(dibenzylideneacetone)palladium(0)	
	Pd ₂ (dba) ₃ : tris(dibenzylideneacetone)dipalladium(0)	
	Pd(dppf)Cl ₂ : [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)	
30	PdCl ₂ (PPh ₃) ₂ : dichlorobis(triphenylphosphine)palladium(II)	
	Xantphos: 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene	
	BINAP: 2,2'-bis(diphenylphosphino)-1,1'-binaphthalene	
	BAST: bis(2-methoxyethyl)aminosulfur trifluoride	

Nomenclature

Compounds were named with the aid of ACD/Name Batch (Network) version 11.01, and/or Accelrys Draw 4.0.

5

Analytical Conditions

NMR spectra were obtained using a Bruker DPX 250 MHz NMR spectrometer; a Bruker Fourier 300 MHz NMR spectrometer; a Bruker AVIII 400 MHz NMR spectrometer; a Bruker DRX 500 MHz NMR spectrometer; or an AV 600MHz NMR spectrometer. Chemical shift values are reported in ppm (δ) with zero corresponding to the corrected residual deuterated solvent shift as an internal reference, or with zero corresponding to tetramethylsilane as an internal standard. The NMR spectra were recorded at a temperature ranging from 5 to 110°C. When more than one conformer was detected the chemical shifts for the most abundant conformer are reported.

15

Analytical HPLC***Method A***

Column: Waters Atlantis dC18 (2.1 x 100 mm, 3 μ m column)
Flow rate: 0.6 mL/minute
20 Solvent A: 0.1% formic acid/water
Solvent B: 0.1% formic acid/acetonitrile
Injection volume: 3 μ L
Column temperature: 40°C
UV detection wavelength: 215 nm
25 Eluent: 0.00-5.00 minutes, constant gradient from 95% solvent A + 5% solvent B to 100% solvent B; 5.00-5.40 minutes, 100% solvent B; 5.40-5.42 minutes, constant gradient from 100% solvent B to 95% solvent A + 5% solvent B; 5.42-7.00 minutes, 95% solvent A + 5% solvent B.

30 ***Method B***

Column: Waters Atlantis dC18 (2.1 x 50 mm, 3 μ m column)
Flow rate: 1.0 mL/minute
Solvent A: 0.1% formic acid/water

Solvent B: 0.1% formic acid/acetonitrile

Injection volume: 3 μ L

UV detection wavelength: 215 nm

Eluent: 0.00-2.50 minutes, constant gradient from 95% solvent A + 5% solvent B to

- 5 100% solvent B; 2.50-2.70 minutes, 100% solvent B; 2.71-3.00 minutes, 95% solvent A + 5% solvent B.

Method C

Column: Waters Atlantis dC18 (2.1 x 30 mm, 3 μ m column)

- 10 Flow rate: 1.0 mL/minute

Solvent A: 0.1% formic acid/water

Solvent B: 0.1% formic acid/acetonitrile

Injection volume: 3 μ L

UV detection wavelength: 215 nm

- 15 Eluent: 0.00-1.50 minutes, constant gradient from 95% solvent A + 5% solvent B to 100% solvent B; 1.50-1.60 minutes, 100% solvent B; 1.60-1.61 minutes, constant gradient from 100% solvent B to 95% solvent A + 5% solvent B; 1.61-2.00 minutes, 95% solvent A + 5% solvent B.

MS detection using Waters LCT or LCT Premier, or ZQ or ZMD.

- 20 UV detection using Waters 2996 photodiode array or Waters 2787 UV or Waters 2788 UV.

Method D (uPLC)

Column: Phenomenex, Kinetex-XB C18 (2.1 mm x 100 mm, 1.7 μ m column)

- 25 Flow rate: 0.6 mL/minute

Solvent A: 0.1% formic acid/water

Solvent B: 0.1% formic acid/acetonitrile

Injection volume: 3 μ L

Column temperature: 40°C

- 30 UV detection wavelength: 215 nm

Eluent: 0.00-5.30 minutes, constant gradient from 95% solvent A + 5% solvent B to 100% solvent B; 5.30-5.80 minutes, 100% solvent B; 5.80-5.82 minutes, constant gradient from 100% solvent B to 95% solvent A + 5% solvent B.

MS detection using Waters LCT or LCT Premier, or ZQ or ZMD.

UV detection using Waters 2996 photodiode array or Waters 2787 UV or Waters 2788 UV.

5 *Method E (high pH)*

Column: Phenomenex, Gemini C18 (2.0 mm x 100 mm, 3 µm column)

Flow rate: 0.5 mL/minute

Solvent A: 2 mM ammonium hydrogencarbonate in water

Solvent B: acetonitrile

10 Injection volume: 3 µL

Column temperature: 50°C

UV detection wavelength: 215 nm

Eluent: 0.00-5.50 minutes, constant gradient from 95% solvent A + 5% solvent B to 100% solvent B; 5.50-5.90 minutes, 100% solvent B.

15 MS detection using Waters LCT or LCT Premier, or ZQ or ZMD.

UV detection using Waters 2996 photodiode array or Waters 2787 UV or Waters 2788 UV.

Method F

20 Waters Acquity SQD (QC LCMS)

The Waters Acquity SQD system comprises an Acquity PDA, Acquity Column Manager, Acquity Sample Manager and Acquity Sample Organiser, Acquity Binary Solvent 30 Manager and a Waters SQD mass spectrometer. The system is controlled via MassLynx PDA C11UPD846A.

25 Column Manager C11UPM180G

Sample Manager M10UPA441M

Sample Organiser F11UPO132M

Binary Solvent Manager E11UPB007A

SQD Mass Spectrometer LBA746

30 ***SQD Mass Spectrometer - ESI Source***

Capillary Voltage 0.56 kV

Cone Voltage 55 V

Extractor Voltage 6 V

RF Lens 0.2 V

Source Temperature 150°C

Desolvation Temperature 350°C

Desolvation Gas 700 L/hour

5 Cone Gas 0 L/hour

Mass Range 150-650 amu

Scan Time 0.1 seconds

Chromatography

Column: Waters Acquity UPLC BEH C18, 2.1 x 50 mm, 1.7 µm

10 Injection Volume: 1-5 µL

UV data: 210 to 400 nm

Sample Temperature: Ambient

Column Temperature: 40°C

Flow Rate: 1 mL/min

15 Solvent A: 10 mM ammonium formate + 0.1% ammonia

Solvent B: 95% MeCN + 5% H₂O + 0.1% ammonia

Gradient: Time A% B%

0.00 95.0 5.0

0.50 95.0 5.0

20 1.75 5.0 95.0

2.00 5.0 95.0

2.25 95.0 5.0

Preparative HPLC

25 *Preparative Method A*

Flow rate: 40 mL/minute

Mobile Phase A: water with 0.1% formic acid

Mobile Phase B: acetonitrile with 0.1% formic acid

Column: Waters Sunfire, C18, 30 mm x 100 mm

30 Particle Size: 10 µm

Runtime: 25.5 minutes

Inlet method: LC7_40ml_7030_tubes.w60

5	Method Gradient:	Time (min)	% A	% B
		0.00	75	25
		2.00	75	25
		2.50	70	30
		18.50	0	100
		21.50	0	100
		22.50	99	1
		23.00	99	1
10	ACD Flow: 2 mL/minute (acetonitrile with 0.1% formic acid) throughout run.			
	Primary wavelength (collection): 215 nm			
	Equipment:	Gilson 215 Liquid Handler with 819 valve, Gilson 307 pump (at Column Dilution), Waters 2487 Detector (prep cell), Waters FC II (waste collection), Knauer degasser, Waters 600 pump/controller (No. 3 pump heads).		
15	Software:	Masslynx v4.0 sp4		

Preparative Method B

	Flow rate:	40 mL/minute
20	Mobile Phase A:	water with 0.1% formic acid
	Mobile Phase B:	acetonitrile with 0.1% formic acid
	Column:	Waters Sunfire, C18, 30 mm x 100 mm
	Particle Size:	10 µm
	Runtime:	25.5 minutes
25	Inlet method:	LC7_40ml_9010_tubes.w60

30	Method Gradient:	Time (min)	% A	% B
		0.00	95	5
		2.00	95	5
		2.50	90	10
		18.50	0	100
		21.50	0	100
		22.50	95	5

23.00 95 5

ACD Flow: 2 mL/minute (acetonitrile with 0.1% formic acid) throughout run.

Primary wavelength (collection): 215 nm

- 5 Equipment: Gilson 215 Liquid Handler with 819 valve, Gilson 307 pump (at Column Dilution), Waters 2487 Detector (prep cell), Waters FC II (waste collection), Knauer degasser, Waters 600 pump/controller (No. 3 pump heads).

Software: Masslynx v4.0 sp4

10

Preparative Method C

Flow rate: 20 mL/minute

Mobile Phase A: water

Mobile Phase B: acetonitrile

- 15 Column: Waters Sunfire, C18, 30 mm x 100 mm

Particle Size: 5 µm

Runtime: 19 minutes

	Method Gradient:	Time (min)	% A	% B
20		0.00	95	5
		2.00	95	5
		2.50	90	10
		14.50	0	100
		16.50	0	100
25		17.00	95	5
		19.00	95	5

Primary wavelength (collection): 215 nm

Secondary wavelength : 254 nm

- 30 Equipment: Gilson 215 Liquid Handler, Gilson 321 Pumps, Gilson 151 UV/Vis Detector.

Software: Gilson Unipoint V5.11

Preparative Method D (high pH)

	Flow rate:	40 mL/minute
	Mobile Phase A:	acetonitrile + 0.2% ammonium hydroxide
	Mobile Phase B:	acetonitrile + 0.2% ammonium hydroxide
5	Column:	Waters Sunfire, C18, 30 mm x 100 mm
	Particle Size:	5 µm
	Runtime:	15.5 minutes

	Method Gradient (isocratic):	Time (min)	% A	% B
10		0.00	95	5
		2.00	85	15
		12.00	70	30
		12.50	5	95
		15.00	5	95
15		15.50	95	5

Primary wavelength (collection): 215 nm

Secondary wavelength: 254 nm

20 **INTERMEDIATE 1**

5-(6-Methoxypyridin-3-yl)pyridin-2-amine

A degassed mixture of 2-amino-5-bromopyridine (3.5 g, 20.23 mmol), 6-methoxy-pyridin-3-ylboronic acid (3.71 g, 24.28 mmol) and bis[3-(diphenylphosphanyl)-cyclopenta-2,4-dien-1-yl]iron-dichloropalladium-dichloromethane complex (413 mg, 0.51 mmol) in 1,4-dioxane (36 mL) and a 2M aqueous potassium carbonate solution (36.4 mL) was heated at 90°C under a nitrogen atmosphere for approximately 16 h. The reaction mixture was allowed to cool to room temperature and diluted with diethyl ether (100 mL). The organic phase was separated off, washed with brine, dried over sodium sulfate and concentrated under vacuum. The crude product was triturated with DCM (10 mL) and filtered, to afford the *title compound* (3.36 g, 83%) as a light brown solid. Method C LCMS: MH⁺ *m/z* 202, RT 0.60 minutes.

INTERMEDIATE 2

1-[2-(Difluoromethoxy)phenyl]ethan-1-one

Potassium hydroxide (105 g, 1872 mmol) was suspended in a mixture of
5 acetonitrile (200 mL) and water (200 mL) and cooled to approximately -20°C. 1-(2-Hydroxyphenyl)ethanone (11.28 mL, 93.7 mmol) was added dropwise, followed by diethyl [bromo(difluoro)methyl]phosphonate (33.27 mL, 187.3 mmol) over 15 minutes. The mixture was then allowed to warm to room temperature over 1 h. The mixture was extracted with ethyl acetate (3 x 200 mL), then the combined organic layers were washed
10 with brine (50 mL), dried over magnesium sulfate and concentrated under vacuum. The mixture was purified by flash chromatography to afford the *title compound* (16.0 g, 92%) as a colourless oil. Method B HPLC-MS: MH⁺ *m/z* 187, RT 1.77 minutes.

INTERMEDIATE 3

15

N'-(5-Bromopyridin-2-yl)-N,N-dimethylethenimide

2-Amino-5-bromopyridine (10 g, 57.8 mmol) was suspended in methanol (100 mL) and *N,N*-dimethylacetamide dimethyl acetal (25.5 mL, 174.4 mmol) was added. The mixture was heated to reflux at 80°C for 16 h. The mixture was concentrated under
20 vacuum and ethyl acetate (80 mL) was added. The resulting material was washed with saturated aqueous sodium bicarbonate solution (50 mL) followed by water (3 x 50 mL) and then brine (50 mL). The organic layer was dried over sodium sulfate and concentrated under vacuum to afford the *title compound* (13.72 g, 98%) as a dark red oil. δ_{H} (500 MHz, CDCl₃) 8.34 (d, *J* 2.4 Hz, 1H), 7.62 (d, *J* 7.8 Hz, 1H), 6.69 (br s, 1H), 3.08
25 (s, 6H), 2.01 (s, 3H).

INTERMEDIATE 4

2-Bromo-1-[2-(difluoromethoxy)phenyl]ethan-1-one

30 A solution of bromine (1.25 mL, 24.44 mmol) in glacial acetic acid (20 mL) was added dropwise over 60 minutes to a stirring solution of *Intermediate 2* (4.6 g, 24.4 mmol) in glacial acetic acid (20 mL) in the dark. When the addition was complete the reaction was diluted with DCM (200 mL) and washed with water (200 mL). The aqueous

layer was then extracted with DCM (50 mL). To the combined organic layers was added saturated aqueous sodium carbonate solution (100 mL), and further solid sodium carbonate was added portionwise with vigorous stirring until the mixture was neutralised. The organic phase was separated and the aqueous layer was extracted with DCM (2 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over sodium sulphate, filtered and concentrated under vacuum to afford the *title compound* (6.48 g, 82%) as a light yellow oil. δ_{H} (500 MHz, CDCl_3) 7.83 (m, 1H), 7.58 (td, J 8.3, 1.7 Hz, 1H), 7.34 (m, 1H), 7.20 (d, J 8.3 Hz, 1H), 6.64 (t, J 72.9 Hz, 1H), 4.53 (s, 2H). Method C HPLC-MS: MH^+ m/z 265/267, RT 1.32 minutes (80%).

INTERMEDIATE 5

6-Bromo-3-{[2-(difluoromethoxy)phenyl]carbonyl}-2-methylimidazo[1,2-*a*]pyridine

Intermediate 3 (9.94 g, 41.1 mmol) and *Intermediate 4* (10.9 g, 41.1 mmol) were combined in toluene (120 mL) and heated at 140°C for 10 minutes. The mixture was then allowed to cool gradually in the heating block for 1 h, before being cooled to room temperature. The volatiles were removed under vacuum and the residue was taken up in ethyl acetate (300 mL) and methanol (30 mL). The organic phase was washed with saturated aqueous sodium bicarbonate solution (150 mL) and the organic layer was dried over sodium sulphate, filtered and concentrated under vacuum to afford a red oil (~15 g). The residue was purified by flash chromatography, eluting with a gradient of 0-100% ethyl acetate in heptane, to afford the *title compound* (9.94 g, 63.5%) as a pink solid. δ_{H} (500 MHz, CDCl_3) 9.96 (s, 1H), 7.58 (m, 3H), 7.38 (m, 3H), 6.52 (t, J 73.5 Hz, 1H), 2.03 (s, 3H).

INTERMEDIATE 6

(6-Bromo-2-methylimidazo[1,2-*a*]pyridin-3-yl)[2-(difluoromethoxy)phenyl]methanol

Intermediate 5 (9.94 g, 26.1 mmol) was suspended in methanol (200 mL). The mixture was then cooled to 0°C in an ice bath and sodium borohydride (1.03 g, 27.4 mmol) was added. After 10 minutes the mixture was warmed to room temperature and stirred for 1 h, after which time a light-coloured precipitate had formed. The mixture was reduced in volume *in vacuo* by approximately two-thirds and then diluted with ethyl

acetate (400 mL). The organic phase was washed with saturated aqueous sodium bicarbonate solution (200 mL), dried over sodium sulphate and filtered, then concentrated *in vacuo*, to afford the *title compound* (9.8 g, 98%) as a cream-coloured solid. δ_{H} (500 MHz, CD_3OD) 8.54 (s, 1H), 7.94 (m, 1H), 7.39 (m, 4H), 7.12 (m, 1H), 6.54 (m, 2H), 2.29 (s, 3H).

INTERMEDIATE 7

6-Bromo-3-[2-(difluoromethoxy)benzyl]-2-methylimidazo[1,2-a]pyridine

Intermediate 6 (9.6 g, 25.1 mmol) was suspended in DCM (200 mL). Boron trifluoride diethyl etherate (7.5 mL, 60.8 mmol) and triethylsilane (8 mL, 50.1 mmol) were added and the mixture was stirred at room temperature for 6 h, before being left to stand at room temperature over the weekend. LCMS analysis indicated incomplete conversion, so further boron trifluoride diethyl etherate (3 mL, 24.3 mmol) and triethylsilane (2 mL, 12.5 mmol) were added and the mixture was stirred at room temperature for 6 h. The mixture was diluted with methanol (30 mL) to dissolve a small amount of precipitate, then the mixture was washed with saturated aqueous sodium bicarbonate solution (100 mL). The organic layer was dried over sodium sulfate and concentrated under vacuum to afford an orange gum. DCM (50 mL) was added, which caused a white precipitate to form. This was filtered off and washed further with DCM (100 mL) and methanol (20 mL) to afford the *title compound* (5.58 g, 54%) as a white solid. The filtrate was concentrated under vacuum and purified by flash chromatography, eluting with a gradient of 30-100% ethyl acetate in heptane, to afford a further quantity of the *title compound* (1.18 g, 12%) as a pale orange solid. Method C HPLC-MS: MH^+ m/z 367/369, RT 1.01 minutes (90%).

INTERMEDIATE 8

tert-Butyl 4-(5-{3-[2-(difluoromethoxy)benzyl]-2-methylimidazo[1,2-a]pyridin-6-yl}-pyridin-2-yl)piperazine-1-carboxylate

Intermediate 7 (200 mg, 0.54 mmol) and *tert*-butyl 4-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]piperazine-1-carboxylate (316 mg, 0.81 mmol) were dissolved in 1,4-dioxane (20 mL) and a 2M aqueous solution of potassium carbonate (1

mL) was added. The mixture was flushed with nitrogen and bis[3-(diphenylphosphanyl)-cyclopenta-2,4-dien-1-yl]iron-dichloropalladium-dichloromethane complex (12 mg, 0.01 mmol) was added. The mixture was heated at 90°C under nitrogen for 16 h. LCMS indicated incomplete conversion so additional *tert*-butyl 4-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]piperazine-1-carboxylate (150 mg, 0.39 mmol) and bis[3-(diphenylphosphanyl)cyclopenta-2,4-dien-1-yl]iron-dichloropalladium-dichloromethane complex (12 mg, 0.01 mmol) were added and the mixture was heated at 90°C under nitrogen for 4 h. The mixture was diluted with ethyl acetate (30 mL) and washed with water (2 x 10 mL), then brine (10 mL). The organic layer was dried over sodium sulphate, filtered and concentrated under vacuum to yield a dark grey solid. This was purified by flash chromatography, eluting with a gradient of 0-100% ethyl acetate in heptane, followed by 0-20% methanol in ethyl acetate. The resultant material was further purified by flash chromatography, eluting with a gradient of 0-5% methanol in DCM. The resultant material was then further purified by preparative HPLC (*Preparative Method B*) to afford the *title compound* (66 mg, 22%) as an off-white solid. δ_{H} (250 MHz, CD_3OD) 8.35-8.17 (m, 2H), 7.81-7.58 (m, 3H), 7.42-6.59 (m, 6H), 4.42 (s, 2H), 3.55 (br s, 8H), 2.48 (br s, 3H), 1.49 (s, 9H).

INTERMEDIATE 9

20

6-Bromo-2-methylimidazo[1,2-*a*]pyridine

2-Amino-5-bromopyridine (10 g, 57.8 mmol) was dissolved in ethanol (100 mL) and chloroacetone (9.3 mL, 115.59 mmol) was added. The mixture was heated to reflux at 90°C for 16 h. The reaction mixture was concentrated under vacuum and the residue was purified by flash chromatography, eluting with a gradient of 0-20% methanol in DCM, to afford the *title compound* (9 g, 66.4%) as a yellow solid. δ_{H} (500 MHz, CD_3OD) 9.03 (s, 1H), 8.02 (m, 1H), 7.93 (s, 1H), 7.79 (d, *J* 9.4 Hz, 1H), 2.56 (s, 3H).

INTERMEDIATE 10

30

6-Bromo-2-methylimidazo[1,2-*a*]pyridine-3-carbaldehyde

(Chloromethylene)dimethyliminium chloride (1.03 g, 8.05 mmol) was added to *N,N*-dimethylformamide (10 mL) at 0°C and stirred for 5 minutes. *Intermediate 9* (85%

pure, 1 g, 4.03 mmol) was added. The mixture was warmed to room temperature and then heated at 80°C for 1 h. The mixture was cooled to room temperature and quenched by adding saturated aqueous sodium bicarbonate solution. The mixture was extracted with ethyl acetate (3 x 100 mL) and the combined organic layers were washed with water (50 mL) followed by brine (50 mL), then dried over magnesium sulphate and concentrated under vacuum. The residue was purified by flash chromatography to afford the *title compound* (500 mg, 47%) as an orange solid. Method B HPLC-MS: MH⁺ *m/z* 239/241, RT 1.49 minutes (83%).

10

INTERMEDIATE 11

(6-Bromo-2-methylimidazo[1,2-*a*]pyridin-3-yl)(3-methylthien-2-yl)methanol

Intermediate 10 (100 mg, 0.42 mmol) was suspended in THF (1 mL) and added dropwise to a stirred 0.5M solution of 3-methylthien-2-ylmagnesium bromide in THF (1 mL, 0.50 mmol) at 0°C. The mixture was then warmed to room temperature and stirred for 2 h. The mixture was quenched by adding saturated aqueous ammonium chloride solution, then the mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with water and brine (20 mL), then dried over magnesium sulfate and concentrated under vacuum. The residue was purified by flash chromatography to afford the *title compound* (100 mg, 71%) as a pale yellow solid. Method B HPLC-MS: MH⁺ *m/z* 337/339, RT 1.37 minutes (84%).

20

INTERMEDIATE 12

6-Bromo-2-methyl-3-[(3-methylthien-2-yl)methyl]imidazo[1,2-*a*]pyridine

Intermediate 11 (100 mg, 0.3 mmol) was suspended in DCM (5 mL) and cooled to 0°C. Boron trifluoride diethyl etherate (73.53 μ L, 0.6 mmol) was added dropwise, followed by triethylsilane (94.54 μ L, 0.59 mmol), then the mixture was warmed to room temperature and stirred for 3 h. The mixture was washed with saturated aqueous sodium bicarbonate solution (5 mL), dried over magnesium sulfate and concentrated under vacuum. The residue was purified by flash chromatography to afford the *title compound* (80 mg, 71.4%) of as a brown solid. Method B HPLC-MS: MH⁺ *m/z* 321/323, RT 1.47 minutes (81%).

30

INTERMEDIATE 13**(E)-N'-[5-Bromo-4-(trifluoromethyl)pyridin-2-yl]-N,N-dimethylethenimidamide**

5 2-Amino-5-bromo-4-(trifluoromethyl)pyridine (5 g, 20.75 mmol) was suspended in methanol (50 mL) and *N,N*-dimethylacetamide dimethyl acetal (9.15 mL, 62.6 mmol) was added. The mixture was heated to reflux at 80°C for 8 h. The mixture was concentrated under vacuum and diluted with ethyl acetate (150 mL), then washed with saturated aqueous sodium bicarbonate solution (50 mL), followed by water (3 x 50 mL)
10 and brine (50 mL). The organic layers were dried over sodium sulfate and concentrated under vacuum to afford the *title compound* (6.45 g, 96%) as a dark red oil. δ_{H} (500 MHz, CDCl_3) 8.49 (s, 1H), 7.14-6.93 (m, 1H), 3.10 (s, 6H), 2.07 (s, 3H). Method C HPLC-MS: MH+ m/z 310/312, RT 1.23 minutes (96%).

15

INTERMEDIATE 14**6-Bromo-3-{[2-(difluoromethoxy)phenyl]carbonyl}-2-methyl-7-(trifluoromethyl)-imidazo[1,2-*a*]pyridine**

Intermediate 13 (6.4 g, 19.4 mmol) and *Intermediate 4* (6.73 g, 21.34 mmol) were
20 dissolved in DMF (100 mL) and heated at 80°C under a nitrogen atmosphere for 8 h. The mixture was cooled to room temperature, then diluted with water (150 mL) and extracted with ethyl acetate (3 x 150 mL). The combined organic layers were washed with water (4 x 100 mL) and brine (50 mL), then dried over magnesium sulfate and concentrated under vacuum. The resulting dark brown solid was purified by biotage, eluting with a gradient
25 of 25-50% ethyl acetate in heptane, to afford the *title compound* (5.4 g, 62%) as a beige solid. δ_{H} (500 MHz, CDCl_3) 10.06 (s, 1H), 8.04 (s, 1H), 7.58 (ddd, J 8.4, 7.3, 2.1 Hz, 1H), 7.44-7.37 (m, 2H), 7.34 (d, J 8.3 Hz, 1H), 6.50 (t, J 73.2 Hz, 1H), 2.08 (s, 3H). Method C HPLC-MS: MH+ m/z 449/451, RT 2.34 minutes (99%).

INTERMEDIATE 15

[6-Bromo-2-methyl-7-(trifluoromethyl)imidazo[1,2-*a*]pyridin-3-yl][2-(difluoromethoxy)-phenyl]methanol

- 5 *Intermediate 14* (3.6 g, 0.01 mol) was dissolved in methanol (40 mL). Sodium borohydride (0.3 g, 8.01 mmol) was then added portionwise at room temperature and the resulting mixture was stirred for 2 h. The mixture was concentrated under vacuum to afford the *title compound* (3.6 g, 100%) as a light pink solid. δ_{H} (500 MHz, CD₃OD) 10.32 (s, 1H), 9.53 (dd, *J* 6.9, 2.1 Hz, 1H), 9.45 (s, 1H), 9.00-8.87 (m, 2H), 8.69 (d, *J* 8.1
10 Hz, 1H), 8.30 (t, *J* 73.9 Hz, 1H), 8.06 (s, 1H), 4.91 (s, 1H), 3.90 (s, 3H). Method C HPLC-MS: MH⁺ *m/z* 451/453, RT 2.04 minutes (98%).

INTERMEDIATE 16

- 15 6-Bromo-3-[2-(difluoromethoxy)benzyl]-2-methyl-7-(trifluoromethyl)imidazo[1,2-*a*]pyridine

- Boron trifluoride diethyl etherate (3.9 mL, 31.9 mmol) was added dropwise to a stirred solution of *Intermediate 15* (3.6 g, 7.98 mmol) in DCM (40 mL) at room temperature. Triethylsilane (5.1 mL, 31.92 mmol) was then added, and the mixture was
20 heated at 45°C for 5 h. The mixture was cooled to room temperature and washed with saturated aqueous NaHCO₃ solution (50 mL), water (50 mL) and brine (50 mL), then dried over magnesium sulfate and concentrated under vacuum. The resulting brownish oil was purified by biotage, eluting with a gradient of 25-50% ethyl acetate in heptane, to afford the *title compound* (1.78 g, 51%) as a light grey solid. δ_{H} (500 MHz, CDCl₃) 8.13
25 (s, 1H), 8.06 (s, 1H), 7.31 (t, *J* 7.8 Hz, 1H), 7.21-7.06 (m, 2H), 6.90 (d, *J* 7.7 Hz, 1H), 6.64 (t, *J* 73.4 Hz, 1H), 4.28 (s, 2H), 2.55 (s, 3H). Method C HPLC-MS: MH⁺ *m/z* 435/437, RT 2.16 minutes (98%).

INTERMEDIATE 17

30

(*E*)-*N'*-(5-Bromo-4-methylpyridin-2-yl)-*N,N*-dimethylethenimidamide

2-Amino-5-bromo-4-methylpyridine (5 g, 26.7 mmol) was dissolved in methanol (50 mL) and *N,N*-dimethylacetamide dimethyl acetal (12 mL, 82.1 mmol) was added.

The mixture was heated at 80°C for 16 h. Methanol was removed under vacuum and the residue was dissolved in ethyl acetate (100 mL), then washed with saturated aqueous sodium bicarbonate solution (50 mL). The organic layer was dried over sodium sulfate and concentrated under vacuum to afford the *title compound* (6.2 g, 90%) as a brown oil.

- 5 δ_{H} (500 MHz, CDCl_3) 8.32 (s, 1H), 6.66 (s, 1H), 3.07 (s, 6H), 2.32 (s, 3H), 2.00 (s, 3H).
Method B HPLC-MS: MH^+ m/z 256/258, RT 0.92 minutes (97%).

INTERMEDIATE 18

- 10 6-Bromo-3-{[2-(difluoromethoxy)phenyl]carbonyl}-2,7-dimethylimidazo[1,2-*a*]pyridine
Intermediate 17 (2 g, 7.8 mmol) and *Intermediate 4* (2.5 g, 7.8 mmol) were dissolved in toluene (30 mL) and heated at 100°C for 100 minutes. The reaction mixture was diluted with EtOAc (50 mL), then washed with saturated aqueous NaHCO_3 solution (30 mL), dried over Na_2SO_4 and concentrated under vacuum. The crude residue was
15 purified by flash chromatography on silica, eluting with 0 to 90% EtOAc in heptane, to yield the *title compound* (2.4 g, 78%) as a beige solid. δ_{H} (250 MHz, CDCl_3) 9.98 (s, 1H), 7.53 (m, 2H), 7.36 (m, 3H), 6.52 (t, J 73.6 Hz, 1H), 2.55 (s, 3H), 2.01 (s, 3H).
Method B HPLC-MS: MH^+ m/z 395/397, RT 2.04 minutes (100%).

20

INTERMEDIATE 19

- (6-Bromo-2,7-dimethylimidazo[1,2-*a*]pyridin-3-yl)[2-(difluoromethoxy)phenyl]methanol
Intermediate 18 (2.4 g, 6.1 mmol) was dissolved in methanol (30 mL) and cooled to 0°C in an ice bath. Sodium borohydride (0.24 g, 6.4 mmol) was added and the mixture
25 was stirred at 0°C for 75 minutes. A white precipitate was filtered off and washed with ethyl acetate (20 mL). The filtrate was concentrated under vacuum and was then diluted with ethyl acetate (50 mL). The organic phase was washed with brine (50 mL), and the organic layer was dried over sodium sulfate and concentrated under vacuum. The resultant solids were combined with the collected precipitate to afford the *title compound*
30 (2.17 g, 90%). δ_{H} (500 MHz, $\text{DMSO}-d_6$) 8.55 (s, 1H), 7.90 (dd, J 6.7, 2.4 Hz, 1H), 7.45 (s, 1H), 7.37 (m, 2H), 7.11 (m, 2H), 6.34 (s, 1H), 6.23 (d, J 2.8 Hz, 1H), 2.35 (s, 3H), 2.13 (s, 3H). Method B HPLC-MS: MH^+ m/z 397/399, RT 1.45 minutes (100%).

INTERMEDIATE 20**6-Bromo-3-[2-(difluoromethoxy)benzyl]-2,7-dimethylimidazo[1,2-*a*]pyridine**

Intermediate 19 (2.2 g, 5.46 mmol) was suspended in DCM (35 mL) under nitrogen. Boron trifluoride diethyl etherate (2.3 mL, 18.6 mmol) was added, followed by triethylsilane (2.2 mL, 13.8 mmol), and the mixture was stirred at ambient temperature under nitrogen for 4 h. The reaction mixture was treated again with boron trifluoride diethyl etherate (1 mL) and the reaction mixture was stirred at ambient temperature for 16 h. The mixture was washed with saturated aqueous sodium bicarbonate solution (30 mL). The organic layer was dried over sodium sulfate and concentrated under vacuum. The resulting beige solid was triturated with DCM to yield the *title compound* (915 mg, 43.9%) as a white solid. The filtrate was purified by flash chromatography on silica, eluting with 25-100% EtOAc in heptanes, to yield a further quantity of the *title compound* (371 mg, 17.8%). δ_{H} (500 MHz, CD₃OD) 8.23 (s, 1H), 7.40 (s, 1H), 7.31 (t, *J* 7.8 Hz, 1H), 7.22 (d, *J* 8.0 Hz, 1H), 7.14 (t, *J* 7.5 Hz, 1H), 7.01 (d, *J* 7.7 Hz, 1H), 6.94 (t, *J* 7.4 Hz, 1H), 4.32 (s, 2H), 2.45 (s, 3H), 2.40 (s, 3H). Method B HPLC-MS: MH⁺ *m/z* 381/383, RT 1.52 minutes (92%).

INTERMEDIATE 21

20

2-Bromo-1-(2,5-dichlorophenyl)ethanone

2,5-Dichloroacetophenone (20.9 g, 0.11 mol) was dissolved in diethyl ether (300 mL) and the reaction mixture was cooled to 0°C. Bromine (5.66 mL, 0.11 mol) was added slowly dropwise and the reaction mixture was allowed to warm to room temperature over 20 minutes. The reaction mixture was treated with saturated aqueous NaHCO₃ solution (250 mL). The organic layer was separated, dried over MgSO₄ and concentrated *in vacuo*, yielding the *title compound* (20.0 g, 68%) as a yellow oil. δ_{H} (d₆-DMSO) 7.94 (dd, *J* 2.2, 0.3 Hz, 1H), 7.61 (m, 2H), 4.88 (s, 2H).

INTERMEDIATE 22**(E)-Ethyl 4-[2-(difluoromethoxy)phenyl]-2-oxobut-3-enoate**

A suspension of 2-(difluoromethoxy)benzaldehyde (295 g, 1714 mmol) and ethyl
5 (triphenylphosphoranylidene)pyruvate (279.1 g, 742 mmol) was heated at 100°C. The
dark red aldehyde immediately decolorized, and a yellow suspension was obtained, which
slowly changed to a dark brown solution. 2-(Difluoromethoxy)benzaldehyde (52.5 g, 305
mmol) was added to the reaction mixture. Residual aldehyde was separated from the
reaction mixture by distillation. The resulting mixture was stirred in heptane (500 mL)
10 and diethyl ether (500 mL). The brown solid precipitate was filtered off, and washed with
a 1:1 mixture of heptane and diethyl ether (3 x 250 mL). The filtrate was concentrated,
yielding a brown oil (218.5 g). Purification by flash column chromatography (1.5 kg
silica, 2-20% EtOAc in heptane, 125 mL/minute) gave the *title compound* (91 g) as a
yellow oil. δ_{H} (CDCl₃, 300 MHz) 1.42 (t, *J* 7.1 Hz, 3H), 4.40 (q, *J* 7.1 Hz, 2H), 6.59 (t, *J*
15 72.9 Hz, 1H), 7.20 (dd, *J* 7.3, 1.0 Hz, 1H), 7.28 (br t, *J* 7.6 Hz, 1H), 7.38 (d, *J* 16.3 Hz,
1H), 7.46 (dt, *J* 7.8, 1.7 Hz, 1H), 7.75 (dt, *J* 7.8, 1.6 Hz, 1H), 8.13 (d, *J* 16.3 Hz, 1H). MS
[ES⁺] *m/z* 271 [M+H]⁺.

INTERMEDIATE 23

20

Ethyl 4-[2-(difluoromethoxy)phenyl]-2-[(triethylsilyl)oxy]but-2-enoate

To a nitrogen-flushed solution of *Intermediate 22* (50 g, 185 mmol) in
dichloromethane (500 mL) were added rhodium(II) acetate dimer (0.818 g, 1.85 mmol)
and triethylsilane (35.5 mL, 25.8 g, 222 mmol). The resulting mixture was stirred at
25 reflux. Additional triethylsilane (10 mL, 7.28 g, 62.6 mmol) and rhodium(II) acetate
dimer (0.2 g, 0.453 mmol) were added after 4 h. Heating at reflux was continued for 16
h. The reaction mixture was cooled to room temperature and filtered over a tight pad of
kieselguhr. The resulting material was rinsed with DCM and concentrated *in vacuo* to
yield the *title compound* (61 g) as a clear yellow oil that was employed in subsequent
30 steps with no further purification.

INTERMEDIATE 24Ethyl 3-bromo-4-[2-(difluoromethoxy)phenyl]-2-oxobutanoate

To a stirred solution of *Intermediate 23* (69 g, 179 mmol) in anhydrous tetrahydrofuran (700 mL) at room temperature was added NBS (35.0 g, 196 mmol). The resulting mixture was stirred at reflux for 2 h before being cooled to room temperature. The reaction mixture was concentrated to approximately one-third of its original volume. DCM (500 mL) was added and the resulting mixture was washed with saturated aqueous NaHCO₃ solution (700 mL), then extracted with DCM (250 mL), dried over Na₂SO₄ and concentrated *in vacuo*, to yield a crude yellow oil (97 g). After storage overnight at room temperature under nitrogen, the product had partly solidified. The resulting material was triturated in diisopropyl ether (300 mL) for 1 h at room temperature. The precipitate was removed by filtration. The filtrate was concentrated *in vacuo* yielding a clear yellow-brown oil (88 g). Purification by flash column chromatography (1.5 kg silica, 2-20% EtOAc in heptane) afforded the *title compound* (58.3 g) as a light brown oil. δ_{H} (CDCl₃, 300 MHz) 1.38 (t, *J* 7.1 Hz, 3H), 3.32 (dd, *J* 14.5, 7.8 Hz, 1H), 3.55 (dd, *J* 14.5, 7.1 Hz, 1H), 4.36 (q, *J* 7.1 Hz, 2H), 5.37 (dd, *J* 7.8, 7.1 Hz, 1H), 6.58 (t, *J* 73.5 Hz, 1H), 7.09-7.19 (m, 2H), 7.26-7.33 (m, 2H). MS [ES⁺] *m/z* 271 [M-Br]⁺.

INTERMEDIATE 25Ethyl 3-[2-(difluoromethoxy)benzyl]-6-(6-methoxypyridin-3-yl)imidazo[1,2-*a*]pyridine-2-carboxylate

Intermediate 1 (0.355 g, 1.76 mmol) and *Intermediate 24* (0.62 g, 1.76 mmol) were dissolved in ethanol (5 mL) and heated at reflux for 18 h. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between aqueous NaHCO₃ solution (20 mL) and EtOAc (50 mL). The organics were extracted and dried over MgSO₄, then concentrated *in vacuo*. The residue was purified by column chromatography (SiO₂, 0-100% EtOAc/hexane), yielding the *title compound* (0.26 g, 33%) as a cream solid. δ_{H} (d₆-DMSO) 8.53 (s, 1H), 8.49 (d, *J* 2.4 Hz, 1H), 8.03 (dd, *J* 8.7, 2.6 Hz, 1H), 7.77 (m, 1H), 7.72 (m, 1H), 7.29 (m, 2H), 7.21 (m, 1H), 7.09 (m, 1H), 6.94 (d, *J* 8.6 Hz, 1H), 6.84 (dd, *J* 7.6, 1.1 Hz, 1H), 4.80 (s, 2H), 4.29 (q, *J* 7.1 Hz, 2H), 3.90 (s, 3H), 1.27 (t, *J* 7.1 Hz, 3H). LCMS (ES⁺) 454.0 (M+H)⁺.

INTERMEDIATE 26**(6-Bromo-2-methylimidazo[1,2-*a*]pyridin-3-yl)(2,5-dichlorophenyl)methanone**

5 A mixture of *Intermediate 21* (5.2 g, 19 mmol) and *Intermediate 3* (3.6 g, 15 mmol) in ethanol (25 mL) was heated at 75°C for 4 h, then stood at room temperature overnight. The mixture was concentrated *in vacuo*, then the residue was partitioned between EtOAc and saturated aqueous NaHCO₃ solution. The organic layer was separated and extracted into EtOAc. The combined organic layers were washed with
10 water and brine, then dried (MgSO₄), filtered and concentrated *in vacuo*. The resulting material was subjected to column chromatography (SiO₂, eluent hexane to 50% EtOAc). The resulting material was washed with diethyl ether to give the *title compound* (3.6 g, 63%) as a beige solid. δ_{H} (400 MHz, DMSO-*d*₆) 9.80 (d, 1H, *J* 1.4 Hz), 7.90 (dd, 1H, *J* 9.4, 2.0 Hz), 7.81 (d, 1H, *J* 9.4 Hz), 7.72 (s, 1H), 7.70 (m, 2H), 1.92 (s, 3H). MH⁺ 383.0.

15

INTERMEDIATE 27**(2,5-Dichlorophenyl)[2-methyl-6-(1-methylpyrazol-4-yl)imidazo[1,2-*a*]pyridin-3-yl]-methanone**

20 A mixture of *Intermediate 26* (1.0 g, 2.6 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (0.59 g, 2.8 mmol) and Pd(dppf)Cl₂ (84 mg, 5 mol %) in 2M aqueous Na₂CO₃ solution (5 mL) and 1,4-dioxane (20 mL) was degassed with nitrogen. The mixture was heated at 100°C for 15 minutes and then at 90°C for 5 h. The mixture was partitioned between EtOAc (100 mL) and water (50 mL), then the aqueous
25 phase was separated and re-extracted into EtOAc (50 mL). The combined organic fractions were washed with water (20 mL) and brine (20 mL), then dried (Na₂SO₄), filtered and concentrated *in vacuo*. The resulting dark oil was purified by column chromatography (SiO₂, eluent hexane to 100% EtOAc) to give the *title compound* (0.80 g, 81%) as a white foam. δ_{H} (400 MHz, DMSO-*d*₆) 9.84 (d, 1H, *J* 0.7 Hz), 8.33 (s, 1H),
30 7.99 (dd, 1H, *J* 9.2, 1.8 Hz), 7.96 (d, 1H, *J* 0.4 Hz), 7.85 (d, 1H, *J* 0.6 Hz), 7.84 (dd, 1H, *J* 9.1, 0.6 Hz), 7.76 (d, 1H, *J* 2.1 Hz), 7.70 (m, 1H), 3.92 (s, 3H), 1.92 (s, 3H). MH⁺ 385.0.

INTERMEDIATE 28

tert-Butyl 4-(5-{3-[2-(difluoromethoxy)benzyl]-2-methylimidazo[1,2-*a*]pyridin-6-yl}-pyrimidin-2-yl)piperazine-1-carboxylate

- 5 *Intermediate* 7 (250 mg, 0.68 mmol) and *tert*-butyl 4-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidin-2-yl]piperazine-1-carboxylate (319 mg, 0.82 mmol) were dissolved in 1,4-dioxane (3 mL). A 2M aqueous solution of potassium carbonate (1.2 mL) was added and the reaction mixture was degassed with nitrogen for 5 minutes. Bis[3-(diphenylphosphanyl)cyclopenta-2,4-dien-1-yl]iron-dichloropalladium-dichloro-
- 10 methane complex (28 mg, 0.03 mmol) was added and the reaction mixture was heated at 90°C in a pressure tube for 18 h. The reaction mixture was diluted with EtOAc, washed with water and brine, then dried over sodium sulfate and concentrated under vacuum. The residue obtained was purified by flash column chromatography, eluting with 0-10% methanol in DCM, to yield the *title compound* (324 mg, 86%). δ_{H} (500 MHz, DMSO- d_6)
- 15 8.69 (s, 2H), 8.40 (s, 1H), 7.55 (d, *J* 9.3 Hz, 1H), 7.48 (d, *J* 10.7 Hz, 1H), 7.46-7.10 (m, 4H), 7.04 (d, *J* 6.8 Hz, 1H), 4.36 (s, 2H), 3.81-3.74 (m, 4H), 3.47-3.39 (m, 4H), 2.32 (s, 3H), 1.43 (s, *J* 3.5 Hz, 9H). Method B HPLC-MS: MH^+ *m/z* 551, RT 1.72 minutes (80%).

20

INTERMEDIATE 29

2-Chloro-5-{3-[2-(difluoromethoxy)benzyl]-2-methylimidazo[1,2-*a*]pyridin-6-yl}-pyrimidine

- 25 *Intermediate* 7 (1.0 g, 2.72 mmol) and 2-chloropyrimidin-5-ylboronic acid (517 mg, 3.3 mmol) were dissolved in 1,4-dioxane (10 mL) and a 2M aqueous solution of potassium carbonate (4.9 mL) was added. The reaction mixture was degassed with nitrogen for 5 minutes, then bis[3-(diphenylphosphanyl)cyclopenta-2,4-dien-1-yl]iron-dichloropalladium-dichloromethane complex (111.2 mg, 0.14 mmol) was added. The reaction mixture was heated at 90°C under nitrogen for 18 h. The reaction mixture was
- 30 re-treated with additional 2-chloropyrimidin-5-ylboronic acid (517.5 mg, 3.27 mmol) and heated at 90°C under nitrogen for a further 24 h. The reaction mixture was diluted with EtOAc, washed with water (x 2) and brine, filtered to remove a black solid, then dried over sodium sulfate and dried under vacuum. The residue obtained was purified by

column chromatography, eluting with 0-90% EtOAc in heptanes, to yield the *title compound* (130 mg, 12%). δ_{H} (500 MHz, DMSO- d_6) 9.14 (s, 2H), 8.73 (s, 1H), 7.64 (s, 2H), 7.46-7.09 (m, 5H), 4.40 (s, 2H), 2.30 (s, 3H). Method B HPLC-MS: MH+ m/z 401/403, RT 1.47 minutes (88%).

5

INTERMEDIATE 30

2-Chloro-5-{3-[2-(difluoromethoxy)benzyl]-2-methylimidazo[1,2-*a*]pyridin-6-yl}-pyridine

10 *Intermediate 7* (250 mg, 0.68 mmol) and 6-chloropyridin-3-ylboronic acid (130 mg, 0.83 mmol) were dissolved in 1,4-dioxane (15 mL) and a 2M aqueous solution of potassium carbonate (1.25 mL) was added. The mixture was flushed with nitrogen and bis[3-(diphenylphosphanyl)cyclopenta-2,4-dien-1-yl]iron-dichloropalladium-dichloromethane complex (15 mg, 0.02 mmol) was added. The mixture was heated at 90°C under
15 nitrogen for 16 h. The mixture was diluted with ethyl acetate (30 mL), then washed with water (2 x 10 mL) and brine (10 mL). The organic layer was dried over sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography, eluting with a gradient of 0-10% methanol in DCM. The crude product was further purified by preparative HPLC (*Method B*) to afford the *title compound* (295 mg, 92%) as
20 a brown solid. Method C HPLC-MS: MH+ m/z 400, RT 1.00 minutes (85%).

INTERMEDIATE 31

3-[2-(Difluoromethoxy)benzyl]-2-methylimidazo[1,2-*a*]pyridin-6-ylboronic acid

25 *Intermediate 7* (2.5 g, 6.81 mmol), bis(neopentyl glycolato)diboron (1.85 g, 8.17 mmol) and potassium acetate (2.6 g, 27.2 mmol) were combined in anhydrous DMSO (50 mL) and the mixture was degassed under nitrogen. Bis[3-(diphenylphosphanyl)cyclopenta-2,4-dien-1-yl]iron-dichloropalladium-dichloromethane complex (278 mg, 0.34 mmol) was added and the mixture was heated at 100°C under nitrogen for 2 h. The
30 mixture was diluted with ethyl acetate (100 mL) and filtered through celite™, then the solids were washed with further ethyl acetate (50 mL). The filtrate was washed with water (3 x 50 mL) and brine (50 mL). The organic layer was then washed with 1M aqueous sodium hydroxide solution (3 x 50 mL). The aqueous layer was neutralised to

approximately pH 6 by adding 6M hydrochloric acid. The aqueous layer was then extracted with ethyl acetate (3 x 100 mL). The combined organic layers were dried over sodium sulfate and concentrated under vacuum to afford the *title compound* (1.61 g, 50%) as a brown solid. Method C HPLC-MS: MH⁺ *m/z* 333, RT 0.89 minutes (93%).

5

INTERMEDIATE 32

2-Bromo-1-(2,4-dimethyl-1,3-thiazol-5-yl)ethanone

N,N,N-Trimethylanilinium bromide-bromine (1:1:1) (1.84 g, 4.9 mmol) was added to a solution of 1-(2,4-dimethyl-1,3-thiazol-5-yl)ethanone (800 mg, 5.15 mmol) in diethyl ether (9 mL) and acetonitrile (3 mL), and HBr in acetic acid (33% w/w, 4 mL). The mixture was stirred for 1 h. The reaction mixture was diluted with diethyl ether (25 mL) and washed with aqueous Na₂S₂O₅ solution (5% w/v, 20 mL). The organic phase was separated off, and the aqueous phase was extracted with diethyl ether (25 mL). The organic phases were combined, then washed with saturated aqueous NaHCO₃ solution (2 x 25 mL) and brine. The residue was dried over sodium sulfate, then filtered and concentrated under vacuum, to give the *title compound* (764 mg, 63%) as a light brown oil. δ_H (250 MHz, CDCl₃) 4.22 (s, 2H), 2.69-2.76 (br s, 6H).

20

INTERMEDIATE 33

(1*E*)-*N'*-(6'-Methoxy-3,3'-bipyridin-6-yl)-*N,N*-dimethylethanimidamide

A mixture of *Intermediate 1* (626 mg, 3.11 mmol) and *N,N*-dimethylacetamide dimethyl acetal (2.27 mL, 15.55 mmol) in MeOH (3 mL) was heated at 80°C in a sealed tube for 1 h. The reaction mixture was allowed to cool to ambient temperature, and concentrated under vacuum. The crude mixture was taken up in DCM (20 mL), then washed with saturated aqueous NaHCO₃ solution (2 x 25 mL) and brine. The residue was dried over sodium sulfate, filtered and concentrated under vacuum, to afford the *title compound* (810 mg, 87%) as a brown viscous oil. Method C HPLC-MS: MH⁺ *m/z* 271, RT 0.81 minutes (90%).

30

INTERMEDIATE 34

(2,4-Dimethyl-1,3-thiazol-5-yl)[6-(6-methoxypyridin-3-yl)-2-methylimidazo[1,2-
a]pyridin-3-yl]methanone

- 5 A mixture of *Intermediate 33* (2.56 mmol) and *Intermediate 32* (600 mg, 2.56 mmol) in DMF (6 mL) was stirred at ambient temperature for 1 h. The reaction mixture was diluted with diethyl ether (6 mL) and filtered. The solid residue was washed with diethyl ether (2 x 6 mL) and air-dried, to give the *title compound* (1.41 g, 77%) as an off-white solid. δ_{H} (250 MHz, CDCl_3) 9.53-9.58 (m, 1H), 8.38-8.45 (m, 1H), 7.66-7.86 (m, 10 3H), 6.83-6.91 (m, 1H), 4.00 (s, 3H), 2.76 (s, 3H), 2.50 (s, 3H), 2.40 (s, 3H). Method C HPLC-MS: MH^+ m/z 379, RT 1.16 minutes (97%).

INTERMEDIATE 35

- 15 (2,4-Dimethyl-1,3-thiazol-5-yl)[6-(6-methoxypyridin-3-yl)-2-methylimidazo[1,2-
a]pyridin-3-yl]methanol

- Sodium borohydride (74.7 mg, 1.97 mmol) was added to *Intermediate 34* (1.41 g, 1.97 mmol) in MeOH (14 mL) and the mixture was stirred at ambient temperature for 1 h. The reaction mixture was concentrated under vacuum. The crude mixture was taken up in 20 saturated aqueous NaHCO_3 solution (20 mL) and chloroform (20 mL). The organic phase was separated off, and the aqueous phase was extracted with chloroform (20 mL). The organic phases were combined, washed with brine, dried over sodium sulfate, filtered, and concentrated under vacuum, to afford the *title compound* (865 mg, 97%) as a light brown solid. Method C HPLC-MS: MH^+ m/z 381, RT 0.87 minutes (95%).

25

INTERMEDIATE 36

Methyl (2E)-3-{3-[2-(difluoromethoxy)benzyl]-2-methylimidazo[1,2-a]pyridin-6-
yl}prop-2-enoate

- 30 Methyl prop-2-enoate (63.3 mg, 0.74 mmol) was added to a stirred suspension of *Intermediate 7* (200 mg, 0.49 mmol), $\text{Pd}(\text{dba})_2$ (28 mg, 0.05 mmol), tris(2-methylphenyl)-phosphine (27 mg, 0.09 mmol) and triethylamine (74 mg, 0.74 mmol) in DMF (2 mL) at ambient temperature. The reaction mixture was thoroughly degassed under a stream of

nitrogen and was then sealed and heated at 120°C for 18 h. The reaction mixture was cooled, diluted with DCM (5 mL), washed with saturated aqueous NaHCO₃ solution (2 x 5 mL) and dried over sodium sulfate. The solvent was removed under vacuum and the resulting brown oil (220 mg) was purified by column chromatography, eluting with 25-
100% EtOAc in heptanes, to afford the *title compound* (136 mg, 63%) as a pale brown oil. δ_{H} (500 MHz, CDCl₃) 7.79 (s, 1H), 7.57-7.46 (m, 2H), 7.35 (dd, *J* 9.4, 1.5 Hz, 1H), 7.25 (d, *J* 7.6 Hz, 1H), 7.17 (d, *J* 8.2 Hz, 1H), 7.09-7.03 (m, 1H), 6.85-6.46 (m, 2H), 6.34 (d, *J* 15.9 Hz, 1H), 4.27 (s, 2H), 3.78 (s, 3H), 2.48 (s, 3H).

INTERMEDIATE 37

1-(5-Boronopyrimidin-2-yl)piperidine-4-carboxylic acid

2-Chloropyrimidin-5-ylboronic acid (2.00 g, 12.6 mmol) and isonipecotic acid (1.63 g, 12.6 mmol) were suspended in ethanol (25 mL). Triethylamine (1.78 mL, 12.6
mmol) was added and the mixture was heated at 80°C for 16 h. The reaction mixture was cooled and concentrated *in vacuo* to dryness. Water (30 mL) was added and the reaction mixture was swirled until the product completely dissolved. On standing, crystallisation occurred. The mixture was cooled in an ice bath for 30 minutes, then filtered. The resultant solid was washed sparingly with water and dried under suction, then freeze-
dried, to give the *title compound* (1.90 g, 7.6 mmol, 60%) as a white solid. δ_{H} (d₆-DMSO) 8.60 (s, 2H), 8.06 (br s, 2H), 4.60-4.52 (m, 2H), 3.14-3.02 (m, 2H), 2.60-2.54 (m, 1H), 1.90-1.80 (m, 2H), 1.55-1.39 (m, 2H). LCMS (ES⁺) 252 (M+H)⁺.

INTERMEDIATE 38

2-(Morpholin-4-yl)pyrimidin-5-ylboronic acid

A mixture of 2-chloropyrimidin-5-ylboronic acid (3 g, 19.0 mmol), morpholine (1.66 mL, 19 mmol) and triethylamine (1.67 mL, 19.19 mmol) in EtOH (20 mL) was stirred at 80°C for 5 h. LCMS indicated completion of the reaction. The reaction mixture was concentrated *in vacuo* and the residue was taken up in ethanol (approximately 5 mL). Diethyl ether was added, and the triethylamine hydrochloride salt that crystallised out was filtered and discarded. The filtrate was concentrated *in vacuo* and water (approximately 10 mL) was added. The mixture was placed in a refrigerator for 1 h, after which time the

resulting solid was filtered off, washed with the minimum amount of water and dried by suction, to give the *title compound* (2.7 g, 68%) as an off-white solid. δ_{H} (DMSO- d_6) 8.64 (s, 2H), 8.08 (s, 2H), 3.73 (m, 4H), 3.65 (m, 4H). LCMS (ES+) 210 (M+H)⁺, RT 0.15 minutes.

5

INTERMEDIATE 39

6-Iodo-2-methylimidazo[1,2-*a*]pyridine

- 2-Amino-5-iodopyridine (5 g, 22.73 mmol) was dissolved in ethanol (20 mL).
10 Chloroacetone (2.29 mL, 25 mmol) was added and the mixture was heated at reflux overnight. The reaction mixture was evaporated to dryness. The residue was dissolved in DCM (50 mL) and washed with saturated aqueous sodium bicarbonate solution (20 mL). The organic layer was dried over MgSO₄, filtered and evaporated. The resulting crude residue (4.8 g) was triturated with ethyl acetate to afford pure *title compound* (2.2 g). The
15 filtrate was concentrated to dryness, yielding an additional quantity of less pure *title compound* (2.0 g). δ_{H} (CDCl₃) 7.33 (m, 4H), 2.48 (s, 3H). LCMS: MH+ 259.

INTERMEDIATE 40

(6-Iodo-2-methylimidazo[1,2-*a*]pyridin-3-yl)methanol

- Intermediate 39* (1 g, 3.88 mmol) and formaldehyde (0.23 g, 7.75 mmol) were dissolved in water (120 mL) and placed in a vial. The vial was sealed and heated at 110°C over 4 h. After cooling to room temperature, the resulting solid was filtered off. The precipitate was dissolved in MeOH (20 mL) and concentrated to dryness to give the
25 *title compound* (1.1 g). δ_{H} (DMSO- d_6) 8.60 (m, 1H), 7.39 (m, 1H), 7.31 (m, 1H), 5.12 (t, *J* 5.5 Hz, 1H), 4.76 (d, *J* 5.4 Hz, 2H), 2.32 (m, 3H). LCMS: MH+ 289.

INTERMEDIATE 41

3-(2,5-Dimethylbenzyl)-6-iodo-2-methylimidazo[1,2-*a*]pyridine

Intermediate 40 (0.15 g, 0.5 mmol), *p*-xylene (10 mL), water (1 mL) and methanesulfonic acid (0.2 mL, 1.4 mmol) were introduced into a vial. The mixture was heated for 1 h at 100°C, until no more starting material was observed. The reaction

mixture was concentrated under reduced pressure. The crude residue was dissolved in DCM (10 mL) and washed with saturated aqueous sodium bicarbonate solution (10 mL). The organic layer was dried over MgSO_4 , filtered and evaporated, to afford the *title compound* (230 mg). δ_{H} (CDCl_3) 7.77 (m, 1H), 7.27 (m, 1H), 7.19 (m, 1H), 7.04 (m, 1H), 6.88 (m, 1H), 6.37 (s, 1H), 4.00 (s, 2H), 2.31 (s, 3H), 2.27 (s, 3H), 2.08 (s, 3H). LCMS: MH+ 377.

INTERMEDIATE 42

10 *tert*-Butyl *N*-[2-(vinylsulfonylamino)ethyl]carbamate

tert-Butyl *N*-(2-aminoethyl)carbamate (5.00 g, 31.2 mmol) was dissolved in dry dichloromethane (50 mL). Triethylamine (7.02 g, 68.7 mmol) was added and the mixture was cooled in an ice bath, with stirring. 2-Chloroethanesulfonyl chloride (5.09 g, 31.2 mmol) was added dropwise, and the ice bath was removed. The mixture was stirred and allowed to warm to room temperature, stirring overnight. The mixture was partitioned between dichloromethane (150 mL) and 1.5M aqueous sodium carbonate solution (75 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to give the *title compound* (7.81 g, quantitative, contains 0.4 equivalents of triethylamine) as a colourless oil. δ_{H} (d_6 -DMSO) 6.53 (dd, 1H, J 16.6, 9.9 Hz), 6.24 (d, 1H, J 16.6 Hz), 5.95 (d, 1H, J 9.9 Hz), 5.06 (br s, 2H), 3.31-3.27 (m, 2H), 3.16-3.12 (m, 2H), 1.45 (s, 9H). LCMS (ES^+) 251 ($\text{M}+\text{H}$)⁺.

INTERMEDIATE 43

25 *N*-(2-Aminoethyl)ethenesulfonamide hydrochloride

Intermediate 42 (7.81 g, 31.2 mmol) was dissolved in 1,4-dioxane (30 mL) and 4.0M hydrochloric acid (100 mL) in 1,4-dioxane was added with stirring. After stirring at room temperature for 2 h, the mixture was concentrated *in vacuo* to give the *title compound* (6.50 g, quantitative, contains 0.4 equivalents of triethylamine hydrochloride) as a colourless gum. δ_{H} (d_6 -DMSO) 8.25 (br s, 3H), 7.79 (br t, 1H, NH), 6.75 (dd, 1H, J 16.6, 10.0 Hz), 6.09-6.03 (m, 2H), 3.10-3.05 (m, 2H), 2.92-2.84 (m, 2H).

INTERMEDIATE 44**1,2,5-Thiadiazepane 1,1-dioxide**

Intermediate 43 (5.82 g, 31.2 mmol) was dissolved in methanol (250 mL).

- 5 Triethylamine (4.40 mL, 31.2 mmol) was added and the mixture was stirred at room temperature for 3.5 days. The mixture was pre-adsorbed onto silica (45 g) and subjected to flash chromatography (silica, 120 g, 4% conc. ammonia in acetonitrile, eluted with 2 L volume). Fractions were analysed by TLC, eluting with the foregoing solvent mix, and stained with potassium permanganate solution. Fractions in the middle of the
- 10 chromatography showed two spots which co-eluted. These fractions were concentrated *in vacuo*. The resulting damp white solid was azeotrope with toluene (50 mL) to give the *title compound* (5.46 g, 70%, ¹H NMR showed 1 equivalent of triethylamine) as a dry white solid. δ_{H} (d₆-DMSO) 7.50 (br s, 1H), 3.58-3.53 (m, 2H), 3.24-3.19 (m, 2H), 3.20-3.10 (m, 4H), 3.05 (q, Et₃N), 1.22 (t, Et₃N). LCMS (ES⁺) 151 (M+H)⁺.

15

INTERMEDIATE 45**2-(1,1-Dioxo-1,2,5-thiadiazepan-5-yl)pyrimidin-5-ylboronic acid**

- 2-Chloropyrimidin-5-ylboronic acid (1.00 g, 6.32 mmol) and *Intermediate 44*
- 20 (1.75 g, 6.96 mmol) were dissolved in ethanol (25 mL) and heated at reflux overnight. Analysis by LCMS showed the major UV visible component to have the desired mass. The mixture was concentrated *in vacuo*, re-dissolved in water (20 mL) and acidified with acetic acid (1 mL). The mixture was concentrated *in vacuo* again and purified by chromatography (silica, 50 g, eluted with 82% DCM, 15% MeOH, 2% AcOH, 1% water)
- 25 to give the *title compound* (1.40 g). The product was used in the next step without further purification.

INTERMEDIATE 46

- 30 **tert-Butyl 4-(5-{3-[2-(difluoromethoxy)benzyl]-2,7-dimethylimidazo[1,2-a]pyridin-6-yl}pyridin-2-yl)piperazine-1-carboxylate**

Intermediate 20 (60 mg, 0.16 mmol) and *tert*-butyl 4-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]piperazine-1-carboxylate (61 mg, 0.16 mmol) were

dissolved in 1,4-dioxane (1 mL). A 2M aqueous potassium carbonate solution (0.28 mL) was added and the reaction mixture was degassed with nitrogen for 5 minutes. Bis[3-(diphenylphosphanyl)cyclopenta-2,4-dien-1-yl]iron-dichloropalladium-dichloromethane complex (6 mg, 0.01 mmol) was added and the reaction mixture was heated at 90°C in a pressure tube for 90 minutes. The reaction mixture was diluted with EtOAc and washed with water and brine, then dried (Na₂SO₄), filtered and concentrated to dryness. The residue obtained was purified by column chromatography (eluting with 40-100% EtOAc in heptane) to yield the *title compound* (50 mg, 56%). δ_{H} (250 MHz, CDCl₃) 8.03 (d, *J* 2.3 Hz, 1H), 7.49 (s, 1H), 7.45-7.35 (m, 2H), 7.21 (d, *J* 7.0 Hz, 1H), 7.15-6.98 (m, 2H), 6.90-6.23 (m, 3H), 4.23 (s, 2H), 3.59-3.54 (m, 7H), 2.46 (s, 3H), 2.33-2.16 (m, 4H), 1.49 (s, 9H). MH⁺ 564.

INTERMEDIATE 47

2-Chloro-5-{3-[2-(difluoromethoxy)benzyl]-2,7-dimethylimidazo[1,2-*a*]pyridin-6-yl}-pyrimidine

Intermediate 20 (371 mg, 0.97 mmol) and 2-chloropyrimidin-5-ylboronic acid (462 mg, 2.92 mmol) were dissolved in 1,4-dioxane (3 mL) and a 2M aqueous sodium carbonate solution (1.5 mL) was added. The resulting mixture was degassed with nitrogen for 5 minutes. Bis(triphenylphosphine)palladium(II) dichloride (34 mg, 0.05 mmol) and tri-*tert*-butylphosphine (10 mg, 0.05 mmol) were added and the reaction mixture was heated at 110°C under microwave irradiation for 30 minutes. Additional 2-chloropyrimidin-5-ylboronic acid (462 mg, 2.92 mmol) was added and the reaction mixture was heated at 120°C under microwave irradiation for 30 minutes. The reaction mixture was diluted with EtOAc, and washed with water and brine, then dried (Na₂SO₄), filtered and concentrated to dryness. The residue obtained was purified by column chromatography to yield the *title compound* (280 mg, 52%). δ_{H} NMR (500 MHz, CDCl₃) 8.55 (s, 2H), 7.61 (s, 1H), 7.45 (s, 1H), 7.26 (m, 1H), 7.13 (d, *J* 8.0 Hz, 1H), 7.08 (t, *J* 7.6 Hz, 1H), 6.87 (d, *J* 7.7 Hz, 1H), 6.60 (t, *J* 73.7 Hz, 1H), 4.26 (s, 2H), 2.50 (d, *J* 4.3 Hz, 3H), 2.28 (s, 3H). MH⁺ 415.

INTERMEDIATE 48

tert-Butyl 4-(5-{3-[2-(difluoromethoxy)benzyl]-2-methyl-7-(trifluoromethyl)-imidazo[1,2-*a*]pyridin-6-yl}pyridin-2-yl)piperazine-1-carboxylate

- 5 A mixture of *Intermediate 16* (150 mg, 0.34 mmol), *tert*-butyl 4-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]piperazine-1-carboxylate (148 mg, 0.38 mmol) and 2M aqueous potassium carbonate solution (0.69 mL) in 1,4-dioxane (4 mL) was degassed with nitrogen for 5 minutes. Bis[3-(diphenylphosphanyl)cyclopenta-2,4-dien-1-yl]iron-dichloropalladium-dichloromethane complex (14 mg, 0.02 mmol) was
- 10 added and the reaction mixture was heated at 120°C for 8 h. The mixture was treated again with bis[3-(diphenylphosphanyl)cyclopenta-2,4-dien-1-yl]iron-dichloropalladium-dichloromethane complex (14 mg, 0.02 mmol) and heated for a further 3 h. The mixture was cooled to room temperature, filtered through Celite and purified by preparative HPLC (*Method C*) to afford the *title compound* (33 mg, 16%) as a clear oil. δ_{H} (500
- 15 MHz, CDCl_3) 8.09-7.90 (m, 2H), 7.65 (s, 1H), 7.46 (d, J 9.0 Hz, 1H), 7.26 (s, 1H), 7.14-7.03 (m, 2H), 6.82 (d, J 7.5 Hz, 1H), 6.74-6.32 (m, 2H), 4.27 (s, 2H), 3.58 (m, 8H), 2.53 (s, 3H), 1.49 (s, 9H). MH^+ 618.

INTERMEDIATE 49

- 20 2-Chloro-5-{3-[2-(difluoromethoxy)benzyl]-2-methyl-7-(trifluoromethyl)imidazo[1,2-*a*]pyridin-6-yl}pyrimidine

- A mixture of *Intermediate 16* (1 g, 2.3 mmol), 2-chloropyrimidin-5-ylboronic acid (1.09 g, 6.89 mmol) and 2M aqueous sodium carbonate solution (4.6 mL) in 1,4-dioxane
- 25 (50 mL) was degassed with nitrogen for 5 minutes. Tri-*tert*-butylphosphine (23 mg, 0.11 mmol) and bis(triphenylphosphine)palladium(II) dichloride (81 mg, 0.11 mmol) were added and the reaction mixture was heated at 120°C for 8 h. The mixture was cooled to room temperature and concentrated under reduced pressure. The resulting dark brown gum was purified by column chromatography, eluting with 30-80% ethyl acetate in
- 30 heptanes, to afford the *title compound* (604 mg, 56%). δ_{H} (500 MHz, CDCl_3) 8.58 (s, 2H), 8.18 (d, J 18.6 Hz, 1H), 7.85 (s, 1H), 7.31 (t, J 7.1 Hz, 1H), 7.20-7.05 (m, 2H), 6.97 (d, J 7.4 Hz, 1H), 6.57 (t, J 73.5 Hz, 1H), 4.31 (s, 2H), 2.61 (s, 3H). MH^+ 469/471.

INTERMEDIATE 50*tert*-Butyl 4-fluoropyridin-2-ylcarbamate

Palladium (II) acetate (1.69 g, 7.53 mmol) and Xantphos (8.71 g, 15.05 mmol) were dissolved/suspended in degassed 1,4-dioxane (1200 mL) in a nitrogen atmosphere. 2-Chloro-4-fluoropyridine (99 g, 753 mmol) and *tert*-butyl carbamate (97 g, 828 mmol) in 1,4-dioxane (550 mL) were added, followed by sodium hydroxide (45.2 g, 1.12 mol) and water (20 mL). The resulting mixture was heated at 100°C for 2 h. The mixture was cooled to ambient temperature and filtered over celite. The residue was washed with 1,4-dioxane and the filtrate was concentrated to afford a yellow solid (206 g). The crude material was recrystallized from 2-propanol (400 mL) and dried to afford the *title compound* (120.8 g) as a white solid. LCMS 213 [M+H], RT 1.96 minutes, purity 94%.

INTERMEDIATE 514-Fluoropyridin-2-amine

Intermediate 50 (120 g, 565 mmol) was dissolved in DCM (1250 mL) and cooled with an ice bath. Trifluoroacetic acid (250 mL) was added dropwise. The resulting mixture was stirred overnight at ambient temperature. The mixture was concentrated and partitioned between saturated aqueous sodium bicarbonate solution and EtOAc. The aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with brine, dried with sodium sulphate, filtered and concentrated, to afford the *title compound* (65.5 g) as a yellow solid. LCMS 113 [M+H], RT 0.17 minutes.

INTERMEDIATE 525-Bromo-4-fluoropyridin-2-amine

In an aluminium foil-covered flask, *Intermediate 51* (62.3 g, 506 mmol) was dissolved in acetonitrile (1500 mL), and NBS (86 g, 481 mmol) was added. The mixture was stirred at ambient temperature for 2 h. The mixture was concentrated to afford a yellow solid. The crude material was dissolved in EtOAc (1000 mL), washed twice with saturated aqueous sodium bicarbonate solution, then with brine, dried with sodium sulphate, filtered and concentrated *in vacuo*, to afford a light brown solid (71.2 g). The

crude material was crystallized from EtOAc (300 mL) and heptane (300 mL) to give the *title compound* (34.3 g) as brown crystals. LCMS 191(⁷⁹Br)/193(⁸¹Br) [M+H], RT 0.79 minutes.

5

INTERMEDIATE 53

Ethyl 6-bromo-3-[2-(difluoromethoxy)benzyl]-7-fluoroimidazo[1,2-a]pyridine-2-carboxylate

A solution of *Intermediate 24* (5.07 g, 14.4 mmol) in 1,4-dioxane (30 mL) was treated with magnesium sulphate (5.1 g, 42 mmol), followed by *Intermediate 52* (5.6 g, 29 mmol). The resulting suspension was heated at reflux under a nitrogen atmosphere for 24 h. The mixture was cooled and filtered, and the solid was washed with 1,4-dioxane (30 mL) and concentrated *in vacuo*. The resulting residue was partitioned between EtOAc (150 mL) and 10% aqueous Na₂CO₃ solution (150 mL). The aqueous layer was extracted with further EtOAc (150 mL), and the combined organic layers were washed with brine (100 mL), dried over MgSO₄, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel, eluting with EtOAc in DCM (0% to 10%), to give the *title compound* (3.84 g, 62%) as a yellow solid. δ_H (DMSO-d₆) 8.81 (d, 1H), 7.76 (d, 1H), 7.29 (t, 1H), 7.26 (t, 1H), 7.19 (d, 1H), 7.08 (t, 1H), 6.81 (d, 1H), 4.67 (s, 2H), 4.25 (q, 2H), 1.23 (t, 3H). LCMS 445 (M+H)⁺, RT 1.14 minutes.

INTERMEDIATE 54

{6-Bromo-3-[2-(difluoromethoxy)benzyl]-7-fluoroimidazo[1,2-a]pyridin-2-yl} methanol

A solution of *Intermediate 53* (3.7 g, 8.3 mmol) in THF (50 mL) was cooled to 0°C under a nitrogen atmosphere and treated with diisobutylaluminium hydride (1.0 mol/L in DCM, 33 mL, 33 mmol), added slowly via a syringe. The reaction mixture was stirred at 0°C for 20 minutes. The reaction mixture was quenched by the addition of MeOH (3 mL) and allowed to warm to ambient temperature, then 2M HCl solution (50 mL) was added. The mixture was extracted with DCM (2 x 100 mL). The combined organic layers were washed with saturated aqueous NaHCO₃ solution (200 mL) and brine (150 mL), then dried over MgSO₄. Filtration and concentration *in vacuo* gave the *title*

compound (2.3 g, 69%) as a yellow powder, containing approximately 10% starting material. δ_{H} (DMSO- d_6) 8.71 (d, 1H), 7.75 (d, 1H), 7.42 (d, 1H), 7.40 (t, 1H), 7.33 (d, 1H), 7.24 (t, 1H), 7.07 (d, 1H), 4.69 (s, 2H), 4.54 (s, 2H). LCMS 403 (M+H)⁺, RT 0.99 minutes.

5

INTERMEDIATE 55

6-Bromo-3-[2-(difluoromethoxy)benzyl]-7-fluoro-2-(methoxymethyl)imidazo[1,2-*a*]-pyridine

10 A solution of *Intermediate 54* (450 mg, 1.08 mmol) in DMF (7 mL) was cooled to 0°C under a nitrogen atmosphere, then treated with iodomethane (120 μ L, 1.92 mmol) followed by sodium hydride (60% suspension in mineral oil, 80 mg, 2.00 mmol) and stirred at 0°C for 40 minutes. The mixture was quenched with water (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organic extracts were washed with
15 water (50 mL) and brine (50 mL), and dried over MgSO₄. Filtration and concentration *in vacuo* gave the *title compound* (450 mg, 87%) as a yellow solid. δ_{H} (DMSO- d_6) 8.62 (d, 1H), 7.64 (d, 1H), 7.30 (t, 1H), 7.25 (t, 1H), 7.20 (d, 1H), 7.12 (t, 1H), 6.93 (d, 1H), 4.44 (s, 2H), 4.38 (d, 2H), 3.02 (s, 3H). LCMS 415.0 (M+H)⁺, RT 1.07 minutes.

20

INTERMEDIATE 56

Ethyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-ene-1-carboxylate

Lithium hexamethyldisilazide in THF/ethylbenzene (1M, 5.55 mL) was added dropwise to a stirred solution of ethyl 4-oxocyclohexanecarboxylate (900 mg, 5.29 mmol)
25 in anhydrous THF (5 mL) under an inert atmosphere at -78°C, and the mixture was stirred for 1 h. 1,1,1-Trifluoro-*N*-phenyl-*N*-[(trifluoromethyl)sulfonyl]methanesulfonamide (1.98 g, 5.55 mmol) in THF (5 mL) was added over 5 minutes, and the mixture was stirred for 30 minutes. The reaction mixture was then warmed to room temperature and stirred for 12 h. The mixture was quenched with NaHSO₄ and diluted with ethyl acetate
30 (250 mL), then washed with 0.5M aqueous NaOH solution (2 x 20 mL), saturated aqueous NH₄Cl solution (20 mL) and brine (20 mL). The organic fraction was then dried over MgSO₄ and concentrated under reduced pressure to afford the intermediate triflate (1.9 g, 83%). This material was dissolved in 1,4-dioxane (30 mL), bis(pinacolato)diboron

(1.68 g, 6.6 mmol) and 1,1'-bis(diphenylphosphino)ferrocene (73 mg, 0.13 mmol) were added and the mixture was degassed with N₂ for 5 minutes. Bis[3-(diphenylphosphanyl)-cyclopenta-2,4-dien-1-yl]iron-dichloropalladium-dichloromethane complex (108 mg, 0.13 mmol) was added and the mixture was heated at 90°C for 18 h. The mixture was diluted with water (100 mL) and extracted with ethyl acetate (2 x 100 mL). The combined organic layers were washed with brine (50 mL), dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by silica gel chromatography, eluting with 10-20% ethyl acetate in heptane, to afford the *title compound* in two batches (440 mg, 26% yield, 73% purity; and 362 mg, 12% yield, 42% purity) as a colourless oil.

Method B HPLC-MS: MH⁺ *m/z* 281, RT 2.37 minutes (73%).

INTERMEDIATE 57

[2-(4-Methoxycarbonyl-4-methylpiperidin-1-yl)pyrimidin-5-yl]boronic acid

Prepared from 4-methylpiperidine-4-carboxylic acid methyl ester and (2-chloro-pyrimidin-5-yl)boronic acid according to the method of *Intermediate 45*.

INTERMEDIATE 58

[2-(4-Ethoxycarbonyl-4-methylpiperidin-1-yl)pyrimidin-5-yl]boronic acid

To 2-chloropyrimidine-5-boronic acid (4.00 g, 25.3 mmol) were added ethyl 4-methylpiperidine-4-carboxylate hydrochloride (4.09 g, 23.9 mmol), ethanol (40 mL) and triethylamine (9.0 mL, 64.0 mmol). The mixture was heated at 80°C for 3 h before being concentrated *in vacuo*. The reaction mixture was partitioned between water (100 mL) and ethyl acetate (100 mL), then the aqueous layer was separated and extracted with ethyl acetate (2 x 100 mL). The organic layers were combined and washed with brine (100 mL), then dried (Na₂SO₄). The solvent was then removed under reduced pressure and the crude reaction mixture was purified by flash column chromatography on silica (Biotage SNAP 100 g, Isolera). Gradient elution, with 100% dichloromethane to 30% methanol/dichloromethane, afforded the *title compound* (4.27 g, 43% yield, 74% purity) as a brown oil. LCMS (pH 10): MH⁺ *m/z* 294.1, RT 0.652 minutes.

INTERMEDIATE 59

4-(3-{[2-(Difluoromethoxy)phenyl]methyl}-2-methylimidazo[1,2-a]pyridin-6-yl)-1,2,3,6-tetrahydropyridine dihydrochloride

- 5 *Example 19* (650 mg, 1.4 mmol) was suspended in 4M HCl in 1,4-dioxane (3.46 mL) and stirred at room temperature for 2 h. The mixture was concentrated under reduced pressure and dried under vacuum to provide the *title compound* (630 mg, quantitative) as an off-white solid. The crude material was used directly in the next step. Method B HPLC-MS: MH⁺ *m/z* 370, RT 1.04 minutes (93%).

10

INTERMEDIATE 60

{2-[(1*R*,5*S*,6*r*)-6-(Ethoxycarbonyl)-3-azabicyclo[3.1.0]hexan-3-yl]pyrimidin-5-yl}boronic acid

- 15 (2-Chloropyrimidin-5-yl)boronic acid (250 mg, 1.6 mmol), ethyl (1*R*,5*S*,6*r*)-3-azabicyclo[3.1.0]hexane-6-carboxylate hydrochloride (303 mg, 1.6 mmol) and triethylamine (0.22 mL, 1.6 mmol) were dissolved in ethanol (8 mL) and stirred at 80°C overnight. The reaction mixture was cooled and concentrated under vacuum. Water (30 mL) was added and the resulting material was filtered and dried to afford the *title*
- 20 *compound* (253 mg, 58%) as a pale brown solid. Method B HPLC-MS: MH⁺ *m/z* 278, RT 1.35 minutes (100%).

INTERMEDIATE 61

- 25 {2-[4-(Ethoxycarbonyl)piperidin-1-yl]pyrimidin-5-yl}boronic acid

- (2-Chloropyrimidin-5-yl)boronic acid (2 g, 13 mmol) and ethyl piperidine-4-carboxylate (1.94 mL, 13 mmol) were dissolved in 1,4-dioxane (20 mL) and heated to 60°C under microwave irradiation for 1 h. The reaction mixture was concentrated to dryness and partitioned between EtOAc and water. The organic layer was separated,
- 30 washed with brine, dried over Na₂SO₄ and concentrated to dryness, to afford the *title compound* (1.79 g, 51%) as a yellow gum. Method C HPLC-MS: MH⁺ *m/z* 280, RT 0.94 minutes (89%).

INTERMEDIATE 62

Ethyl 2-(5-bromopyrimidin-2-yl)propanoate

Ethyl 2-(5-bromopyrimidin-2-yl)acetate (500 mg, 2.04 mmol) was dissolved in THF (8 mL) and the mixture was cooled to -78°C under nitrogen. LDA in THF/heptane/ethylbenzene (2M, 1.25 mL) was added dropwise, then the mixture was stirred for 15 minutes. Iodomethane (0.22 mL, 3.53 mmol) was added, then the reaction mixture was warmed to room temperature and stirred for a further 2 h. Water (10 mL) was added and the mixture was extracted with ethyl acetate (20 mL). The aqueous layer was acidified to pH ~5 with 1M HCl, then extracted with additional ethyl acetate (2 x 20 mL). The combined organic layers were dried over Na₂SO₄ and concentrated under vacuum. The residue was purified by silica gel chromatography, eluting with a gradient of 0-50% ethyl acetate in heptane, to afford the *title compound* (417 mg, 79%) as a yellow oil. δ_H (500 MHz, CDCl₃) 8.75 (s, 2H), 4.18 (m, 2H), 4.08 (q, *J* 7.2 Hz, 1H), 1.60 (d, *J* 7.3 Hz, 3H), 1.22 (t, *J* 7.1 Hz, 3H).

INTERMEDIATE 63

[2-(1-Ethoxy-1-oxopropan-2-yl)pyrimidin-5-yl]boronic acid

Intermediate 62 (417 mg, 1.6 mmol), bis(pinacolato)diboron (613 mg, 2.4 mmol) and potassium acetate (474 mg, 4.8 mmol) were combined in 1,4-dioxane (8 mL) and the mixture was degassed under nitrogen. Bis[3-(diphenylphosphanyl)cyclopenta-2,4-dien-1-yl]iron-dichloropalladium-dichloromethane complex (119 mg, 0.16 mmol) was added and the mixture was heated at 85°C under nitrogen for 16 h. Water (20 mL) was added and the mixture was extracted with ethyl acetate (3 x 30 mL). The combined organic layers were dried over sodium sulfate and concentrated under vacuum to afford the *title compound* (0.86 g) as a dark brown oil, which was used without purification. Method B HPLC-MS: MH⁺ *m/z* 225, RT 1.15 minutes (76%).

INTERMEDIATE 64

(2S)-4-[5-(Dihydroxyboranyl)pyrimidin-2-yl]morpholine-2-carboxylic acid
bis(triethylamine) dihydrochloride

- 5 Prepared from 2(S)-morpholine-2-carboxylic acid and (2-chloropyrimidin-5-yl)boronic acid according to the method of *Intermediate 45*.

INTERMEDIATE 65

- 10 N-(5-Bromo-4-fluoropyridin-2-yl)-N,N-dimethylacetamide

The *title compound* can be prepared from 5-bromo-4-fluoropyridin-2-amine according to the method of *Intermediate 3*.

INTERMEDIATE 66

15

(6-Bromo-7-fluoro-2-methylimidazo[1,2-a]pyridin-3-yl)[2-(difluoromethoxy)phenyl]-methanone

- The *title compound* can be prepared from *Intermediate 4* and *Intermediate 65* according to the method of *Intermediate 5*. δ_{H} (400 MHz, DMSO- d_6) 9.89 (d, 1H, *J* 7.0 Hz), 7.95 (d, 1H, *J* 9.1 Hz), 7.66 (m, 1H), 7.54 (dd, 1H, *J* 7.5, 1.7 Hz), 7.43 (m, 2H), 7.26 (t, 1H, *J* 7.4 Hz), 1.89 (s, 3H). LCMS RT 1.51 minutes, MH^+ 399.
- 20

INTERMEDIATE 67

- 25 (6-Bromo-7-fluoro-2-methylimidazo[1,2-a]pyridin-3-yl)[2-(difluoromethoxy)phenyl]-methanol

- The *title compound* can be prepared from *Intermediate 66* according to the method of *Intermediate 6*. δ_{H} (400 MHz, DMSO- d_6) 8.70 (d, 1H, *J* 6.8 Hz), 7.91 (dd, 1H, *J* 6.9, 2.2 Hz), 7.55 (d, 1H, *J* 9.6 Hz), 7.38 (m, 2H), 7.13 (m, 1H), 7.09 (t, 1H, *J* 7.4 Hz), 6.38 (m, 1H), 6.24 (d, 1H, *J* 4.4 Hz), 2.10 (s, 3H). LCMS RT 1.41 minutes, MH^+ 401.
- 30

INTERMEDIATE 68

6-Bromo-3-{{2-(difluoromethoxy)phenyl}methyl}-7-fluoro-2-methylimidazo[1,2-a]-pyridine

5 The *title compound* can be prepared from *Intermediate 67* according to the method of *Intermediate 7*. δ_{H} (400 MHz, DMSO- d_6) 8.61 (d, 1H, J 6.7 Hz), 7.55 (d, 1H, J 9.7 Hz), 7.31 (m, 1H), 7.26 (t, 1H, J 74.1 Hz), 7.20 (d, 1H, J 7.9 Hz), 7.14 (td, 1H, J 7.5, 1.0 Hz), 7.00 (dd, 1H, J 7.6, 1.3 Hz), 4.31 (s, 2H), 2.26 (s, 3H). LCMS 1.53 minutes, MH^+ 385.

10

INTERMEDIATE 69

tert-Butyl 4-[5-(3-{{2-(difluoromethoxy)phenyl}methyl}-2,7-dimethylimidazo[1,2-a]-pyridin-6-yl)pyrimidin-2-yl]piperazine-1-carboxylate

15 *Intermediate 20* (150 mg, 0.39 mmol) and (2-{4-[(*tert*-butoxy)carbonyl]piperazin-1-yl}pyrimidin-5-yl)boronic acid (133 mg, 0.43 mmol) were dissolved in 1,4-dioxane (1.5 mL) and 2M aqueous potassium carbonate solution (0.69 mL) was added. The reaction mixture was degassed with nitrogen for 5 minutes, then bis[3-(diphenylphosphanyl)-cyclopenta-2,4-dien-1-yl]iron-dichloropalladium-dichloromethane complex (16 mg, 0.02 mmol) was added. The mixture was heated at 90°C for 3 h in a sealed tube under nitrogen. Further (2-{4-[(*tert*-butoxy)carbonyl]piperazin-1-yl}pyrimidin-5-yl)boronic acid (61 mg, 0.2 mmol), 2M aqueous potassium carbonate solution (0.3 mL) and bis[3-(diphenylphosphanyl)cyclopenta-2,4-dien-1-yl]iron-dichloropalladium-dichloromethane complex (8 mg, 0.01 mmol) were added. The mixture was degassed, then heated at 90°C for 2 h in a sealed tube under nitrogen. The mixture was diluted with water (5 mL) and extracted into EtOAc (3 x 10 mL), then washed with brine (10 mL), dried over magnesium sulfate and concentrated under vacuum. The crude product was purified by flash column chromatography, eluting with 0-10% (7M ammonia in methanol) in DCM followed by 10-50% MeOH in DCM, to afford the *title compound* (160 mg, 69%).

25

30 Method C HPLC-MS: MH^+ m/z 565, RT 1.18 minutes (90%).

INTERMEDIATE 70

5-(3-{[2-(Difluoromethoxy)phenyl]methyl}-2,7-dimethylimidazo[1,2-a]pyridin-6-yl)-2-(piperazin-1-yl)pyrimidine

5 Trifluoroacetic acid (0.21 mL, 2.72 mmol) was added to a solution of *Intermediate*
69 (96% pure, 160 mg, 0.27 mmol) in DCM (0.5 mL) and the mixture was stirred for 30
minutes. The mixture was loaded onto an SCX cartridge which was washed with MeOH,
followed by 7M ammonia in MeOH. Product fractions were concentrated to afford the
title compound (109 mg, 86%). Method C HPLC-MS: MH+ *m/z* 465, RT 0.85 minutes
10 (83%).

INTERMEDIATE 71

[2-(3-Oxopiperazin-1-yl)pyrimidin-5-yl]boronic acid

15 (2-Chloropyrimidin-5-yl)boronic acid (1.0 g, 6.32 mmol) and piperazin-2-one (1.6
g, 16.0 mmol) were suspended in 1,4-dioxane (10 mL) and the mixture was heated at
100°C under microwave irradiation for 45 minutes. The supernatant liquid was decanted
from the suspension and the residue was triturated with methanol and diethyl ether. The
resultant solids were filtered off and dried under vacuum to afford the *title compound*
20 (706 mg, 30%) as a pale pink solid. Method B HPLC-MS: MH+ *m/z* 223, RT 0.25
minutes.

INTERMEDIATE 72

25 [2-(5-Oxo-1,4-diazepan-1-yl)pyrimidin-5-yl]boronic acid

(2-Chloropyrimidin-5-yl)boronic acid (200 mg, 1.26 mmol) and 1,4-diazepan-5-
one (288.34 mg, 2.53 mmol) were suspended in 1,4-dioxane (3 mL) and the mixture was
heated at 100°C under microwave irradiation for 45 minutes. The resulting slurry was
concentrated under vacuum and triturated with MeOH to afford the *title compound* (145
30 mg, 30%) as a cream precipitate, which was used without further purification. Method C
HPLC-MS: MH+ *m/z* 237, RT 0.40 minutes.

INTERMEDIATE 73**4-(3-{[2-(Difluoromethoxy)phenyl]methyl}-2-methylimidazo[1,2-a]pyridin-6-yl)-2-fluoropyridine**

5 In a pressure tube *Intermediate 7* (1.7 g, 4.63 mmol) and (2-fluoropyridin-4-yl)-boronic acid (935 mg, 6.64 mmol) were dissolved in 1,4-dioxane (10 mL) and a 2M solution of K₂CO₃ in water (7 mL) was added. The mixture was flushed with nitrogen and bis[3-(diphenylphosphanyl)cyclopenta-2,4-dien-1-yl]iron dichloropalladium dichloromethane complex (300 mg, 0.37 mmol) was added. The mixture was heated at
10 90°C for 4 h. The mixture was diluted with ethyl acetate (20 mL), then washed with water (2 x 10 mL) and brine (10 mL). The organic layer was dried over sodium sulfate and concentrated under vacuum. The resulting dark brown solid was purified by FCC, eluting with a gradient of 70-100% ethyl acetate in heptane followed by 0-10% methanol in DCM, to afford the *title compound* (1.55 g, 87%) as a light pink solid. δ_{H} (250 MHz, CD₃OD) 8.52-8.49 (m, 1H), 8.24 (d, *J* 5.4 Hz, 1H), 7.63 (d, *J* 1.8 Hz, 1H), 7.60 (d, *J* 0.9 Hz, 1H), 7.56-7.52 (m, 1H), 7.33 (s, 1H), 7.31-7.25 (m, 1H), 7.24-6.64 (m, 4H), 4.43 (s, 2H), 2.44 (s, 3H). Method D HPLC-MS: MH⁺ *m/z* 384, RT 3.29 minutes.

INTERMEDIATE 74

20

Methyl 1-benzyl-2,5-dihydro-1H-pyrrole-3-carboxylate

To a stirred solution of benzyl(methoxymethyl)[(trimethylsilyl)methyl]amine (7.3 g, 0.03 mol) and methyl prop-2-ynoate (3.1 mL, 0.04 mol) in dichloromethane (150 mL) at 0°C under nitrogen was added dropwise a solution of trifluoroacetic acid (0.12 mL, 0.002 mol) in dichloromethane (1 mL). The reaction mixture was allowed to stir at 0°C
25 for 20 minutes, then the ice bath was removed and the solution was allowed to warm to room temperature. The solution was stirred at room temperature for 2 h, then the solvent was evaporated. The residue was purified by FCC, eluting with 0-20% ethyl acetate in heptane, to afford the *title compound* (2.37 g, 29%) as a yellow oil. δ_{H} (250 MHz, CDCl₃) 7.35-7.15 (5H, m), 6.70 (1H, s), 3.79 (3H, s), 3.75-3.60 (6H, m).
30

INTERMEDIATE 75Methyl 3-benzyl-3-azabicyclo[3.1.0]hexane-1-carboxylate

To a stirred suspension of sodium hydride (60%, 0.71 g, 0.02 mol) in anhydrous DMSO (20 mL) under nitrogen at 0°C was added portionwise trimethylsulfoxonium iodide (4.16 g, 0.02 mol). The mixture was stirred until gas evolution had ceased, then warmed to 40°C. The mixture was cooled to 0°C, then a solution of *Intermediate 74* (1.94 g, 0.01 mol) in DMSO (1 mL) was added dropwise. The mixture was warmed to room temperature, stirred for 10 minutes, then warmed to 50°C and stirred for 2 h. The mixture was cooled to room temperature, then poured into water (20 mL) and ethyl acetate (20 mL). The phases were separated, and the aqueous phase was extracted twice with ethyl acetate (20 mL). The combined organic extracts were washed with water (2 x 10 mL) and concentrated under vacuum. The residue was purified by FCC, eluting with 0-25% ethyl acetate in heptane, to afford the *title compound* (411 mg, 20%) as a colourless oil. δ_{H} (500 MHz, CDCl_3) 7.26 (5H, m), 3.66 (3H, s), 3.57 (m, 2H), 3.27-2.98 (1H, m), 2.98-2.92 (1H, m), 2.72 (1H, m), 2.42 (1H, m), 1.93 (1H, m), 1.52-1.39 (1H, m), 1.28 (1H, m).

INTERMEDIATE 76Methyl 3-azabicyclo[3.1.0]hexane-1-carboxylate hydrochloride

To palladium on carbon under nitrogen was added a solution of *Intermediate 75* (0.4 g, 1.73 mmol) in methanol (10 mL). The flask was cycled thrice between vacuum and nitrogen, then filled with hydrogen and stirred vigorously for 5 h. The mixture was filtered through celite, washing with methanol. The filtrate was concentrated under vacuum, then treated with 4M hydrogen chloride in 1,4-dioxane (1 mL, 4 mmol). The solution was evaporated to dryness under a stream of nitrogen, then dried further in a vacuum oven at 40°C for 5 h, to afford the *title compound* (291 mg, 95%) as a white solid. δ_{H} (500 MHz, DMSO-d_6) 9.67 (1H, s), 9.35 (1H, s), 3.62 (3H, s), 3.58-3.48 (1H, m), 3.39 (1H, d, J 11.5 Hz), 3.35 (1H, m), 3.26 (1H, d, J 11.5 Hz), 2.19 (1H, dt, J 9.1, 5.0 Hz), 1.56-1.41 (1H, m), 1.37 (1H, t, J 5.7 Hz).

INTERMEDIATE 77Methyl 2-[1-(diphenylmethyl)azetidin-3-ylidene]acetate

Methyl (triphenylphosphoranylidene)acetate (2.77 g, 8.29 mmol) was added to a mixture of 1-(diphenylmethyl)azetidin-3-one (1.64 g, 6.91 mmol) in THF (24 mL) and the resultant mixture was left to stir overnight. The mixture was concentrated under vacuum, then the residue was dissolved in hot 1:4 EtOAc/heptane (40 mL) and allowed to cool to room temperature. The resultant solid was filtered off and the filtrate was concentrated under vacuum. The crude residue was purified by FCC, eluting with 20% EtOAc in heptane, to afford the *title compound* (917 mg, 44%) as a pale yellow solid. Method B HPLC-MS: MH⁺ *m/z* 294, RT 1.43 minutes.

INTERMEDIATE 7815 Methyl 5-(diphenylmethyl)-5-azaspiro[2.3]hexane-1-carboxylate

A mixture of potassium *tert*-butoxide (1.33 g, 11.9 mmol) and trimethylsulfoxonium iodide (2.78 g, 12.5 mmol) in DMSO (10 mL) was heated at 50°C until a solution resulted. Then a solution of *Intermediate 77* (917 mg, 3.13 mmol) in DMSO (5 mL) was added dropwise. Upon complete addition, the mixture was heated for a further 2 h, then allowed to cool to room temperature. The mixture was diluted with water (90 mL) and extracted with diethyl ether (2 x 50 mL). The organic phases were combined, washed with water (50 mL) and brine, then dried over sodium sulfate and concentrated under vacuum. The crude product was purified by FCC, eluting with a gradient of 0-20% EtOAc in heptane, to afford the *title compound* (455 mg, 44%) as a yellow viscous oil. Method B HPLC-MS: MH⁺ *m/z* 308, RT 1.44 minutes (93%).

INTERMEDIATE 79Methyl 5-azaspiro[2.3]hexane-1-carboxylate hydrochloride

30 A mixture of *Intermediate 78* (570 mg, 1.85 mmol) and palladium(II) dihydroxide (12%, 109 mg, 0.09 mmol) in MeOH (20 mL) was stirred under an atmosphere of hydrogen overnight. A 1M solution of HCl in MeOH (10 mL) was added, and the mixture was filtered through celite. The filtrate was concentrated *in vacuo*, and the

residue was washed with heptane (2 x 20 mL), to afford the *title compound* (351 mg, >100%) as a light brown viscous oil. δ_H (250 MHz, $CDCl_3$) 3.99-4.28 (m, 4H), 3.74-3.87 (m, 5H), 1.75-1.94 (m, 1H), 1.14-1.39 (m, 2H).

5

INTERMEDIATE 80

Methyl 5-[5-(3-{[2-(difluoromethoxy)phenyl]methyl}-2-methylimidazo[1,2-a]pyridin-6-yl)pyrimidin-2-yl]-5-azaspiro[2.3]hexane-1-carboxylate

A mixture of (2-chloropyrimidin-5-yl)boronic acid (261 mg, 1.65 mmol),
 10 *Intermediate 79* (351 mg, 1.98 mmol) and triethylamine (0.83 mL, 5.93 mmol) in EtOH (2 mL) were heated under microwave irradiation at 80°C for 1 h. *Intermediate 7* (403 mg, 1.1 mmol), 1,2-dimethoxyethane (18 mL) and 2M aqueous sodium carbonate solution (4 mL) were added and the reaction mixture was thoroughly degassed. Tetrakis(triphenylphosphine)palladium(0) (190 mg, 0.16 mmol) was added and the mixture was heated in a
 15 sealed tube at 80°C under nitrogen overnight. The mixture was allowed to cool to room temperature, then water (10 mL) and EtOAc (15 mL) were added. The organic phase was separated and the aqueous phase was extracted with EtOAc (15 mL). The organic phases were combined, washed with brine, dried over sodium sulfate and concentrated under vacuum. The crude residue was purified by FCC, eluting with 0-10% MeOH in DCM, to
 20 afford the *title compound* (160 mg, 13%) as a light brown gummy solid. Method B HPLC-MS: MH^+ m/z 506, RT 1.52 minutes (80%).

INTERMEDIATE 81

25 2-Bromo-5-(3-{[2-(difluoromethoxy)phenyl]methyl}-2-methylimidazo[1,2-a]pyridin-6-yl)pyrazine

Intermediate 31 (200 mg, 0.602 mmol), 2-bromo-5-iodopyrazine (172 mg, 0.602 mmol), 2M aqueous sodium carbonate solution (0.903 mL, 1.807 mmol) and anhydrous DMSO (2 mL) were charged to a sealed tube. The mixture was degassed by bubbling
 30 with nitrogen for 5 minutes before the addition of tetrakis(triphenylphosphine)-palladium(0) (35 mg, 0.03 mmol). The mixture was sealed under nitrogen, then stirred at 100°C for 1 h. The reaction mixture was partitioned between water (25 mL) and EtOAc (50 mL), then the organic phase was washed with saturated aqueous $NaHCO_3$ solution

(10 mL) and brine (10 mL), dried over sodium sulfate and concentrated under vacuum. The residue was purified by FCC, eluting with a gradient of 17-100% EtOAc in heptane, to afford the *title compound* (160 mg, 42%) as an off white solid. δ_{H} (500 MHz, CDCl_3) 8.72-8.68 (m, 2H), 7.93 (s, 2H), 7.33-7.26 (m, 2H), 7.18 (d, J 8.0 Hz, 1H), 7.13 (t, J 7.5 Hz, 1H), 7.01 (t, J 8.3 Hz, 1H), 6.82-6.52 (t, 1H), 4.36 (s, 2H), 2.61 (s, 3H).

INTERMEDIATE 82

N-(5-Bromo-1-methyl-1*H*-pyrazol-3-yl)methanesulfonamide

10 5-Bromo-1-methyl-1*H*-pyrazol-3-amine (500 mg, 2.84 mmol) and DIPEA (2.47 mL, 14.2 mmol) were stirred in anhydrous 1,2-dichloroethane (8 mL) at room temperature, then mesyl chloride (550 μL , 7.1 mmol) in 1,2-dichloroethane (1.5 mL) was added dropwise. The mixture was stirred at room temperature for 3 h, then partitioned between DCM and water. The organic phases were separated and washed with brine, 15 then dried over sodium sulfate and concentrated. To the resulting orange/brown solid was added 1M tetrabutylammonium fluoride in THF (10.5 mL) and the mixture was heated at reflux for 4 h. The reaction mixture was concentrated and diluted with DCM (40 mL), then washed with water (4 x 25 mL), followed by brine (25 mL). The organic layers were dried over sodium sulfate and concentrated under vacuum. The residue was purified by 20 FCC, eluting with 35-50% EtOAc in heptane followed by 5-10% MeOH in DCM, to afford the *title compound* (388 mg, 54%) as a white solid. δ_{H} (250 MHz, CDCl_3) 6.33 (s, 1H), 3.85 (s, 3H), 3.02 (s, 3H).

INTERMEDIATE 83

25

N-(5-Bromo-1-methyl-1*H*-pyrazol-3-yl)-*N*-methylmethanesulfonamide

Potassium carbonate (422 mg, 3.05 mmol) was added to a solution of *Intermediate* 82 (388 mg, 1.53 mmol) in anhydrous MeCN (5.5 mL) in a round-bottom flask fitted with a condenser and a potassium hydroxide scrubber. Dimethyl sulfate (290 μL , 3.05 mmol) 30 was added slowly. The reaction mixture was heated at 50°C and stirred for 17 h. The mixture was concentrated under vacuum and the crude residue was purified by FCC, eluting with 25-50% EtOAc in heptane, to afford the *title compound* (350 mg, 86%) as a

colourless oil. δ_{H} (250 MHz, DMSO- d_6) 6.35 (s, 1H), 3.80 (s, 3H), 3.29 (s, 3H), 2.90 (s, 3H).

INTERMEDIATE 84

5

3-Chloro-6-(3-{[2-(difluoromethoxy)phenyl]methyl}-2-methylimidazo[1,2-*a*]pyridin-6-yl)pyridazine

Intermediate 31 (150 mg, 0.45 mmol), 3-chloro-6-iodopyridazine (109 mg, 0.45 mmol), 2M aqueous sodium carbonate solution (677 μL) and anhydrous DMSO (2 mL) were charged to a sealed tube. The mixture was degassed by bubbling with nitrogen for 5 minutes before the addition of tetrakis(triphenylphosphine)palladium(0) (26 mg, 0.023 mmol). The reaction mixture was sealed under nitrogen, then stirred at 90°C for 2 h. The mixture was diluted with water (2 mL), extracted into EtOAc (3 x 10 mL) and washed with brine (10 mL), then dried over sodium sulfate and concentrated under vacuum. The crude residue was purified by FCC, eluting with 0-100% ethyl acetate in heptane followed by 0-10% methanolic ammonia in DCM, to afford the *title compound* (108 mg, 50%). Method C HPLC-MS: MH^+ m/z 401, RT 1.06 minutes.

INTERMEDIATE 85

20

Ethyl (1*R*,5*S*,6*r*)-3-[6-(3-{[2-(difluoromethoxy)phenyl]methyl}-2-methylimidazo[1,2-*a*]pyridin-6-yl)pyridazin-3-yl]-3-azabicyclo[3.1.0]hexane-6-carboxylate (*cis* isomer)

Intermediate 84 (84%, 108 mg, 0.23 mmol), ethyl (1*R*,5*S*,6*r*)-3-azabicyclo[3.1.0]hexane-6-carboxylate hydrochloride (43 mg, 0.23 mmol) and triethylamine (32 μL , 0.23 mmol) were stirred in 1,4-dioxane (2 mL) at 90°C for 2.5 h, then at 120°C for 1.5 h, then at 130°C for a total of 9 h. Further ethyl (1*R*,5*S*,6*r*)-3-azabicyclo[3.1.0]hexane-6-carboxylate hydrochloride (43 mg, 0.23 mmol) and triethylamine (63 μL , 0.45 mmol) were added and the reaction mixture was heated for 6 h at 150°C. The mixture was concentrated and diluted with EtOAc (25mL), then washed with water (2 x 10 mL) and brine. The aqueous phase was basified with saturated aqueous sodium carbonate solution, then extracted with EtOAc (3 x 25 mL). The organic layers were washed with brine, dried over sodium sulfate and concentrated under vacuum, to afford the *title compound*

(134 mg, 52%), which was used without purification. Method C HPLC-MS: MH⁺ *m/z* 520, RT 1.09 minutes.

INTERMEDIATE 86

5

5-(3-{[2-(Difluoromethoxy)phenyl]methyl}-2-methylimidazo[1,2-*a*]pyridin-6-yl)pyridin-2-amine

Tetrakis(triphenylphosphine)palladium(0) (190 mg, 0.16 mmol) was added to a thoroughly degassed mixture of 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (225 mg, 1.02 mmol) and *Intermediate 7* (250 mg, 0.68 mmol) in 1,2-dimethoxyethane (8 mL) and 2M aqueous sodium carbonate solution (2 mL). The reaction mixture was heated in a sealed tube at 80°C under nitrogen for 4 h. The mixture was allowed to cool to room temperature, then diluted with water (15 mL) and 9:1 chloroform/isopropanol (20 mL). The organic phase was separated and the aqueous phase was extracted with 9:1 chloroform/isopropanol (25 mL). The organic phases were combined, washed with brine, dried over sodium sulfate and concentrated under vacuum. The crude residue was purified by FCC, eluting with 0-10% MeOH in DCM, to afford the *title compound* (219 mg, 85%) as an orange solid. δ_H (250 MHz, CDCl₃) 8.15 (d, *J* 2.13 Hz, 1H), 7.77-7.85 (m, 1H), 7.48-7.65 (m, 2H), 7.27 (s, 4H), 6.31-6.97 (m, 3H), 4.56 (br s, 2H), 4.31 (s, 2H), 2.52 (s, 3H). Method B HPLC-MS: MH⁺ *m/z* 381, RT 1.17 minutes.

INTERMEDIATE 87

Methyl 1-[5-(3-{[2-(difluoromethoxy)phenyl]methyl}-2-methylimidazo[1,2-*a*]pyridin-6-yl)pyrimidin-2-yl]-3-methylpyrrolidine-3-carboxylate

(2-Chloropyrimidin-5-yl)boronic acid (194 mg, 1.23 mmol), methyl 3-methylpyrrolidine-3-carboxylate (234 mg, 1.63 mmol) and K₂CO₃ (226 mg, 1.63 mmol) were stirred in *N,N*-dimethylformamide (4 mL) in a sealed tube at 80°C for 1 h. *Intermediate 7* (300 mg, 0.82 mmol) in 1,4-dioxane (6 mL) was added and the mixture was degassed with nitrogen for 5 minutes. Degassed 2M aqueous potassium carbonate solution (1.3 mL) and bis[3-(diphenylphosphanyl)cyclopenta-2,4-dien-1-yl]iron dichloropalladium dichloromethane complex (34 mg, 0.04 mmol) were added and the mixture was heated at 80°C for 3 h in a sealed tube under nitrogen. The mixture was diluted with water (10

mL), extracted with EtOAc (3 x 20 mL), washed with brine (10 mL), dried over magnesium sulfate and concentrated under vacuum. The crude residue was purified by FCC, eluting with 0-2% ammonia/methanol in DCM, to afford the *title compound* (296 mg, 61%). δ_{H} (500 MHz, CDCl_3) 8.41 (s, 2H), 7.78 (s, 1H), 7.69 (d, J 9.2 Hz, 1H), 7.32-7.29 (m, 1H), 7.28-7.25 (m, 1H), 7.19 (d, J 8.1 Hz, 1H), 7.10 (t, J 7.5 Hz, 1H), 6.88 (d, J 6.9 Hz, 1H), 6.65 (t, J 73.7 Hz, 1H), 4.32 (s, 2H), 4.10 (d, J 11.4 Hz, 1H), 3.73 (d, J 9.7 Hz, 5H), 3.51 (d, J 11.4 Hz, 1H), 2.55 (s, 3H), 2.52 (dd, J 13.1, 6.5 Hz, 1H), 2.00-1.94 (m, 1H), 1.44 (s, 3H). Method C HPLC-MS: MH^+ m/z 508, RT 1.12 minutes.

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INTERMEDIATE 88

1-(tert-Butyl) 3-ethyl 4-hydroxypiperidine-1,3-dicarboxylate

1-(tert-Butyl) 3-ethyl 4-oxopiperidine-1,3-dicarboxylate (10 g, 36.86 mmol) was suspended in EtOH (200 mL) and cooled to 0°C under a nitrogen atmosphere. Sodium borohydride (0.7 g, 18.43 mmol) was then added portionwise over 15 minutes and the reaction mixture was stirred for 0.5 h at 25°C. The mixture was evaporated to dryness, the residue was partitioned between EtOAc (200 mL) and saturated aqueous sodium bicarbonate solution (200 mL), then the aqueous layer was washed with EtOAc (2 x 100 mL). The combined organic layers were washed with brine (200 mL), dried over magnesium sulfate and concentrated. The residue was purified by FCC, eluting with 0-100% EtOAc in heptane, to afford the *title compound* (7.26 g, 85%) as a clear yellow oil. δ_{H} (500 MHz, CDCl_3) 4.32-4.25 (m, 1H), 4.19 (q, J 7.12 Hz, 2H), 4.13-3.85 (m, 1H), 3.71 (dt, J 13.35, 3.62 Hz, 1H), 3.51-3.34 (m, 1H), 3.21-2.82 (m, 1H), 2.67-2.56 (m, 1H), 1.89-1.76 (m, 1H), 1.73-1.60 (m, 1H), 1.46 (s, 9H), 1.28 (t, J 7.17 Hz, 3H).

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INTERMEDIATE 89

1-(tert-Butyl) 3-ethyl 1,2,5,6-tetrahydropyridine-1,3-dicarboxylate

Intermediate 88 (7.26 g, 0.03 mol) and triethylamine (22.21 mL, 159.37 mmol) were dissolved in DCM (150 mL) at 0°C under a nitrogen atmosphere and methanesulfonyl chloride (6.17 mL, 79.69 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 3 days. The mixture was then partitioned between DCM (200 mL) and water (200 mL), and the aqueous layer was washed with

DCM (2 x 100 mL). The combined organic layers were dried over magnesium sulfate and concentrated. The residue was purified by FCC, eluting with 0-50% EtOAc in heptane, to afford the *title compound* (3.62 g, 52%) as a yellow oil. δ_{H} (500 MHz, CDCl_3) 7.12-7.02 (m, 1H), 4.22 (q, J 7.07 Hz, 2H), 4.17-4.03 (m, 2H), 3.48 (t, J 5.65 Hz, 2H), 2.31 (m, 2H), 1.48 (s, 9H), 1.30 (t, J 7.10 Hz, 3H).

INTERMEDIATE 90

3-(*tert*-Butyl) 1-ethyl 3-azabicyclo[4.1.0]heptane-1,3-dicarboxylate

Trimethylsulfoxonium iodide (5.39 g, 24.25 mmol) was slurried in DMSO (18 mL) under nitrogen. Potassium *tert*-butoxide (2.65 g, 23.65 mmol) was added in two portions and the mixture was stirred for 2 h at room temperature. A solution of *Intermediate 89* (3.16 g, 12.13 mmol) in DMSO (9 mL) was heated at 80°C and the pre-formed ylide was added slowly over 2 h. LCMS showed incomplete conversion so further ylide was formed as follows: trimethylsulfoxonium iodide (2.69 g, 12.13 mmol) was slurried in DMSO (9 mL) under nitrogen. Potassium *tert*-butoxide (1.3 g, 11.5 mmol) was added in two portions and the mixture was stirred for 2 h. This was added to the reaction mixture over 1 h at 80°C, then the mixture was stirred at 80°C for 2 h. The reaction mixture was diluted with water (15 mL) and extracted with EtOAc (2 x 25 mL). The organic layers were combined, washed with brine (25 mL), dried over sodium sulfate and concentrated under vacuum. The residue was purified by FCC, eluting with 0-50% EtOAc in heptane, to afford the *title compound* (468 mg, 14%) as a yellow oil. δ_{H} (500 MHz, CDCl_3) 4.13 (q, J 7.1 Hz, 2H), 4.00-3.82 (m, 2H), 3.51-3.38 (m, 1H), 2.94 (ddd, J 13.3, 9.2, 5.6 Hz, 1H), 2.07-1.90 (m, 1H), 1.85-1.62 (m, 2H), 1.45 (s, 9H), 1.38 (dd, J 9.4, 4.4 Hz, 1H), 1.25 (t, J 7.1 Hz, 3H), 0.72 (dd, J 6.5, 4.4 Hz, 1H).

INTERMEDIATE 91

Ethyl 3-azabicyclo[4.1.0]heptane-1-carboxylate

Intermediate 90 (468 mg, 1.74 mmol) was stirred in DCM (2.5 mL), then TFA (2.5 mL) was added and the mixture was stirred at room temperature for 30 minutes. The mixture was concentrated. The residue was dissolved in EtOAc (30 mL), washed with aqueous sodium bicarbonate solution (2 x 10 mL) and brine (10 mL), then dried over

sodium sulfate and concentrated, to afford the *title compound* (280 mg, 95%) as a yellow oil. δ_{H} (500 MHz, CDCl_3) 4.10 (q, J 7.1 Hz, 2H), 3.73-3.65 (m, 1H), 3.03 (d, J 13.2 Hz, 1H), 2.60-2.54 (m, 2H), 1.95-1.87 (m, 1H), 1.75-1.58 (m, 2H), 1.37 (dd, J 9.6, 3.9 Hz, 1H), 1.23 (t, J 7.1 Hz, 3H), 0.88 (dd, J 6.7, 4.0 Hz, 1H).

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INTERMEDIATE 92

4-(3-{[2-(Difluoromethoxy)phenyl]methyl}-2-methylimidazo[1,2-*a*]pyridin-6-yl)-1*H*-pyrazole

10 *Intermediate 7* (250 mg, 0.681 mmol), 1*H*-pyrazol-4-ylboronic acid (84 mg, 0.749 mmol), 2M aqueous sodium carbonate solution (1.02 mL, 2.04 mmol) and anhydrous DMSO (2 mL) were charged to a sealed tube and degassed. Bis[3-(diphenylphosphanyl)-cyclopenta-2,4-dien-1-yl]iron dichloropalladium dichloromethane complex (28 mg, 0.034 mmol) was added. The reaction mixture was sealed under nitrogen and stirred at 100°C

15 for 18 h. Further 1*H*-pyrazol-4-ylboronic acid (42 mg, 0.37 mmol), 2M aqueous sodium carbonate solution (0.51 mL, 1.02 mmol) and anhydrous DMSO (1 mL) were added and the mixture was degassed. Bis[3-(diphenylphosphanyl)cyclopenta-2,4-dien-1-yl]iron dichloropalladium dichloromethane complex (28 mg, 0.034 mmol) was added, then the reaction mixture was sealed under nitrogen and stirred at 100°C for 2 h. The reaction

20 mixture was diluted with EtOAc (40 mL), washed with water (3 x 15 mL) followed by saturated aqueous sodium bicarbonate solution (15 mL) and brine (15 mL), then dried over sodium sulfate and concentrated. The residue was purified by FCC, eluting with 0-3% (7M NH_3 in MeOH) in DCM, to afford the *title compound* (220 mg, 91%) as a black solid. Method C HPLC-MS: MH^+ m/z = 355, RT 1.00 minutes.

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INTERMEDIATE 93

Ethyl 4-[4-(3-{[2-(difluoromethoxy)phenyl]methyl}-2-methylimidazo[1,2-*a*]pyridin-6-yl)-1*H*-pyrazol-1-yl]cyclohexane-1-carboxylate

30 *Intermediate 92* (117 mg, 0.33 mmol), ethyl 4-(methanesulfonyloxy)cyclohexane-1-carboxylate (79 mg, 0.31 mmol), cesium carbonate (151 mg, 0.46 mmol) and anhydrous *N,N*-dimethylformamide (3 mL) were charged to a sealed tube under nitrogen. The mixture was stirred at 80°C for 18 h, then at 100°C for 3 h. Further ethyl 4-(methane-

sulfonyloxy)cyclohexane-1-carboxylate (79 mg, 0.31 mmol) and cesium carbonate (102 mg, 0.31 mmol) were added and the mixture was stirred at 100°C for 6 h. Further ethyl 4-(methanesulfonyloxy)cyclohexane-1-carboxylate (79 mg, 0.31 mmol) and cesium carbonate (102 mg, 0.31 mmol) were added and the mixture was stirred at 100°C for 4 h.

5 The reaction mixture was diluted with EtOAc (50 mL), washed with water (3 x 10 mL) followed by saturated aqueous sodium carbonate solution (10 mL) and brine (10 mL), then dried over sodium sulfate and concentrated. The resulting material was purified by FCC, eluting with 0-2% MeOH in DCM. The residue was then further purified by FCC, eluting with 10-100% EtOAc in heptane, to afford the *title compound* (60 mg, 29%) as a

10 brown gum. Method D HPLC-MS: MH+ *m/z* 508, RT 2.57 minutes.

INTERMEDIATE 94

2-Chloro-5-(3-{[2-(difluoromethoxy)phenyl]methyl}-2-methylimidazo[1,2-*a*]pyridin-6-yl)pyrazine

15 *Intermediate 31* (350 mg, 1.05 mmol), 2-chloro-5-iodopyrazine (252 mg, 1.05 mmol), 2M aqueous sodium carbonate solution (1.58 mL, 3.16 mmol) and anhydrous DMSO (5 mL) were charged to a sealed tube. The mixture was degassed by bubbling with nitrogen for 5 minutes before the addition of tetrakis(triphenylphosphine)-

20 palladium(0) (61 mg, 0.05 mmol). The reaction mixture was sealed under nitrogen and stirred at 110°C for 1 h. The mixture was diluted with water (40 mL) and extracted with EtOAc (3 x 20 mL). The organic phase was washed with saturated aqueous sodium bicarbonate solution (2 x 10 mL) followed by brine (10 mL), then dried over sodium sulfate and concentrated under vacuum. The residue was purified by FCC, eluting with

25 17-80% EtOAc in heptane, to afford the *title compound* (285 mg, 54% at 80% purity) as an off white solid. δ_H (500 MHz, CDCl₃) 8.73-8.64 (m, 2H), 8.63-8.59 (m, 1H), 7.92 (s, 2H), 7.33-7.27 (m, 1H), 7.17 (d, *J* 8.2 Hz, 1H), 7.15-7.07 (m, 1H), 7.00 (d, *J* 6.6 Hz, 1H), 6.67 (t, *J* 73.5 Hz, 1H), 4.36 (s, 2H), 2.60 (s, 3H). Method C HPLC-MS: MH+ *m/z* 401, RT 1.10 minutes.

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INTERMEDIATE 95Ethyl 2-[1-(diphenylmethyl)azetidin-3-ylidene]propanoate

Sodium hydride (60%, 202 mg, 5.06 mmol) was suspended in anhydrous THF (15 mL) and cooled in an ice bath. Ethyl 2-(diethoxyphosphoryl)propanoate (1.2 g, 5.06 mmol) was added dropwise under nitrogen and the mixture was stirred in an ice bath for 1 h. 1-(Diphenylmethyl)azetidin-3-one (1 g, 4.21 mmol) was added in portions as a solid and the mixture was stirred at room temperature for 1 h, then left to stir at room temperature overnight. Water (50 mL) was added and the mixture was extracted with DCM (3 x 50 mL). Brine was added, and the aqueous and organic layers were separated. The organic layer was dried over sodium sulfate and concentrated. The resulting crude yellow oil was purified by FCC, eluting with 0-50% EtOAc, to afford a clear oil which crystallised upon standing. The solids were sonicated with heptane and the remaining solid was collected by filtration. The filtrate was concentrated and sonicated with heptane to afford a second crop of solid. The filtrate was concentrated and the residue was sonicated with heptane to afford a further crop of solid material. The resultant solids were collected and combined to afford the *title compound* (892 mg, 66%) as a white solid. δ_{H} (250 MHz, CDCl_3) 7.56-7.39 (m, 4H), 7.38-7.15 (m, 6H), 4.63-4.45 (m, 1H), 4.24-4.01 (m, 4H), 3.96-3.76 (m, 2H), 1.72-1.58 (m, 3H), 1.27-1.14 (m, 3H).

INTERMEDIATE 96Ethyl 5-(diphenylmethyl)-1-methyl-5-azaspiro[2.3]hexane-1-carboxylate

Trimethylsulfoxonium iodide (920 mg, 4.14 mmol) and potassium *tert*-butoxide (442 mg, 3.94 mmol) were heated in anhydrous DMSO (5 mL) at 50°C for 20 minutes. *Intermediate 95* (333 mg, 1.04 mmol) in DMSO (5 mL) was added dropwise at 50°C and the mixture was stirred for 2 h. Water (50 mL) was added and the mixture was extracted with EtOAc (3 x 50 mL), then dried over sodium sulfate and concentrated to afford a clear oil. The procedure was then repeated using *Intermediate 95* (559 mg, 1.75 mmol) with a heating time of 30 minutes, and worked up as described above, to afford a clear/yellow oil. The batches of crude material were combined and purified by FCC, eluting with 0-50% EtOAc in heptane, to afford the *title compound* (700 mg, 75%) as a clear oil which solidified to a white solid upon standing. δ_{H} (500 MHz, CDCl_3) 7.51-7.40 (m, 4H),

7.33-7.25 (m, 4H), 7.25-7.15 (m, 2H), 4.49 (s, 1H), 4.08 (q, J 7.1 Hz, 2H), 3.55-3.37 (m, 1H), 3.37-3.07 (m, 3H), 1.57-1.50 (m, 1H), 1.21 (t, J 7.1 Hz, 3H), 1.16 (s, 3H), 0.86-0.77 (m, 1H). Method B HPLC-MS: MH^+ m/z 336, RT 1.48 minutes.

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INTERMEDIATE 97

Ethyl 1-methyl-5-azaspiro[2.3]hexane-1-carboxylate hydrochloride

Intermediate 96 (700 mg, 2.09 mmol) was dissolved in EtOH (20 mL) and palladium dihydroxide (12%, 122 mg, 0.10 mmol) was added. The mixture was purged with nitrogen (x 3) followed by hydrogen (x 3), then stirred under a hydrogen atmosphere for 2.5 h. The mixture was filtered, then 1M HCl in EtOAc (4 mL) was added to the filtrate and the mixture was concentrated. Further 1M HCl in EtOAc (1 mL) was added and the mixture was concentrated. The resulting clear oil was sonicated in heptane, then concentrated, to afford a white solid with a moist appearance. The residue was then sonicated in diethyl ether, and the resultant solids were collected by filtration, to afford the *title compound* (393 mg, 92%) as a white solid. δ_H (500 MHz, DMSO- d_6) 9.45 (s, 1H), 9.08 (s, 1H), 4.15-3.97 (m, 5H), 3.97-3.87 (m, 1H), 1.35 (d, J 5.2 Hz, 1H), 1.18 (t, J 7.1 Hz, 3H), 1.15 (s, 3H), 1.09 (d, J 5.2 Hz, 1H). Method B HPLC-MS: MH^+ m/z 336, RT 1.48 minutes.

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INTERMEDIATE 98

Ethyl 5-[5-(3-{[2-(difluoromethoxy)phenyl]methyl}-2-methylimidazo[1,2-*a*]pyridin-6-yl)pyrimidin-2-yl]-1-methyl-5-azaspiro[2.3]hexane-1-carboxylate

Intermediate 29 (85% pure, 229 mg, 0.49 mmol) and *Intermediate 97* (110 mg, 0.53 mmol) were dissolved in 1-methyl-2-pyrrolidinone, then triethylamine (149 μ L, 1.07 mmol) was added and the mixture was heated under microwave irradiation at 120°C for 45 minutes. Water (10 mL) was added. The mixture was extracted with EtOAc (2 x 20 mL) and washed with brine, then dried over sodium sulfate and concentrated. The residue was purified by FCC, eluting with 0-3% MeOH in DCM, then further purified by preparative HPLC (Method C), to afford the *title compound* (22 mg). δ_H (500 MHz, DMSO- d_6) 8.67 (s, 2H), 8.39 (s, 1H), 7.59-7.52 (m, 1H), 7.50-7.41 (m, 1H), 7.33-7.26 (m, 2H) 7.23-7.17 (m, 1H), 7.17-7.10 (m, 1H), 7.08-7.01 (m, 1H), 4.37 (s, 2H), 4.22-4.17 (m,

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1H), 4.17-3.99 (m, 5H), 2.32 (s, 3H), 1.48 (d, *J* 4.8 Hz, 1H), 1.22-1.16 (m, 6H), 1.07 (d, *J* 4.8 Hz, 1H).

INTERMEDIATE 99

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5-Bromo-2-(3-{[2-(difluoromethoxy)phenyl]methyl}-2-methylimidazo[1,2-*a*]pyridin-6-yl)pyrimidine

Intermediate 31 (320 mg, 0.964 mmol), 5-bromo-2-iodopyrimidine (275 mg, 0.964 mmol), 2M aqueous sodium carbonate solution (1.45 mL, 2.89 mmol) and anhydrous DMSO (5 mL) were charged to a sealed tube. The mixture was degassed by bubbling with nitrogen for 5 minutes before the addition of tetrakis(triphenylphosphine)-palladium(0) (56 mg, 0.048 mmol). The reaction mixture was sealed under nitrogen, then stirred at 100°C for 2 h. The reaction mixture was treated with 5-bromo-2-iodopyrimidine (30 mg, 0.1 mmol), then degassed as above, sealed under nitrogen and stirred at 100°C for 2 h. The mixture was partitioned between water (25 mL) and EtOAc (70 mL). The organic phase was washed with saturated aqueous sodium bicarbonate solution (12 mL) followed by brine (12 mL), then dried over sodium sulfate and concentrated under vacuum. The residue was purified by FCC, eluting with 17-80% EtOAc in heptane, to afford the *title compound* (195 mg) as a white solid. Method A HPLC-MS: MH⁺ *m/z* 445/447, RT 3.45 minutes.

INTERMEDIATE 100

Ethyl 1-[2-(3-{[2-(difluoromethoxy)phenyl]methyl}-2-methylimidazo[1,2-*a*]pyridin-6-yl)pyrimidin-5-yl]-4-methylpiperidine-4-carboxylate

[2',6'-Bis(propan-2-yloxy)biphenyl-2-yl](dicyclohexyl)phosphane (12 mg, 0.026 mmol) and palladium diacetate (5 mg, 0.021 mmol) were charged to a sealed tube with anhydrous 1,4-dioxane (2 mL) and heated at 80°C for 5 minutes, then cooled to room temperature. A solution of *Intermediate 99* (190 mg, 0.43 mmol) in 1,4-dioxane (3 mL) was added, together with ethyl 4-methylpiperidine-4-carboxylate hydrochloride (89 mg, 0.43 mmol) and cesium carbonate (278 mg, 0.85 mmol). The mixture was degassed, sealed under nitrogen and stirred at 110°C for 2 h. Further [2',6'-bis(propan-2-yloxy)-biphenyl-2-yl](dicyclohexyl)phosphane (24 mg, 0.052 mmol) and palladium diacetate (10

mg, 0.042 mmol) were added. The mixture was thoroughly degassed, then heated at 110°C for a total of 6 h. The mixture was diluted with water (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with water (10 mL) followed by brine (10 mL), then dried over sodium sulfate and concentrated under vacuum. The residue was purified by FCC, eluting with 0-3% MeOH in DCM, to afford the *title compound* (125 mg) as a light brown solid. δ_{H} (500 MHz, CDCl_3) 8.78 (s, 1H), 8.35 (s, 2H), 8.09 (dd, J 9.4, 1.5 Hz, 1H), 7.57 (d, J 9.4 Hz, 1H), 7.23-7.18 (m, 1H), 7.14 (d, J 8.6 Hz, 1H), 7.06-6.99 (m, 1H), 6.90-6.86 (m, 1H), 6.85-6.53 (m, 1H), 4.33 (s, 2H), 4.18 (q, J 7.1 Hz, 2H), 3.50 (dt, J 12.9, 4.1 Hz, 2H), 3.04-2.92 (m, 2H), 2.46 (s, 3H), 2.25 (d, J 13.6 Hz, 2H), 1.60 (ddd, J 14.2, 10.9, 4.1 Hz, 2H), 1.25 (s, 6H). Method C HPLC-MS: MH^+ m/z 536, RT 1.23 minutes.

INTERMEDIATE 101

5-(3-{[2-(Difluoromethoxy)phenyl]methyl}-2-methylimidazo[1,2-*a*]pyridin-6-yl)-2-fluoropyridine

Intermediate 7 (500 mg, 1.36 mmol) and (6-fluoropyridin-3-yl)boronic acid (230 mg, 1.63 mmol) were dissolved in 1,4-dioxane (6 mL) and 2M aqueous potassium carbonate solution (2 mL) was added. The mixture was degassed for 10 minutes with nitrogen, then bis[3-(diphenylphosphanyl)cyclopenta-2,4-dien-1-yl]iron dichloropalladium dichloromethane complex (55 mg, 0.068 mmol) was added and the mixture was heated at 80°C for 1 h. Further (6-fluoropyridin-3-yl)boronic acid (40 mg, 0.284 mmol) was added and the mixture was degassed for 10 minutes, then bis[3-(diphenylphosphanyl)cyclopenta-2,4-dien-1-yl]iron dichloropalladium dichloromethane complex (55 mg, 0.068 mmol) was added and the mixture was heated at 90°C overnight. The mixture was diluted with EtOAc (20 mL), then washed with water (50 mL) and brine (20 mL), before being dried over sodium sulfate and concentrated under vacuum. The residue was purified by FCC, eluting with 90-100% EtOAc in heptane, to afford the *title compound* (293 mg, 51%) as an off-white solid. Method C HPLC-MS: MH^+ m/z 384, RT 1.06 minutes.

INTERMEDIATE 102

Ethyl 1-[5-(3-{[2-(difluoromethoxy)phenyl]methyl}-2-methylimidazo[1,2-a]pyridin-6-yl)pyridin-2-yl]-4-methylpiperidine-4-carboxylate

5 *Intermediate 101* (300 mg, 0.493 mmol), ethyl 4-methylpiperidine-4-carboxylate (205 mg, 0.986 mmol) and pyridine (3 mL) were charged to a microwave tube and stirred under microwave irradiation at 180°C for a total of 4 h. After this time, further ethyl 4-methylpiperidine-4-carboxylate (102 mg, 0.493 mmol) was added and the mixture was heated for a total of 3 h at 180°C under microwave irradiation. Water (50 mL) was added, and the mixture was extracted with EtOAc (50 mL), then washed with more water (2 x 50 mL) and brine (50 mL). The organic layer was concentrated under vacuum. The resulting brown oil was combined with further crude product (80 mg at 81% purity) for purification. The residue was purified by FCC, eluting with 0-10% methanol in DCM, to afford the *title compound* (382 mg) as a brown oil. Method C HPLC-MS: MH⁺ *m/z* 535, 15 RT 1.16 minutes.

INTERMEDIATE 103

5-Bromo-2-(3-{[2-(difluoromethoxy)phenyl]methyl}-2-methylimidazo[1,2-a]pyridin-6-yl)pyridine

20 *Intermediate 31* (600 mg, 1.807 mmol) and 5-bromo-2-iodopyridine (615 mg, 2.168 mmol) were dissolved in 1,4-dioxane (5 mL) and 2M aqueous potassium carbonate solution (3 mL) was added. The mixture was flushed with nitrogen and tetrakis-(triphenylphosphine)palladium(0) (104 mg, 0.09 mmol) was added. The mixture was 25 heated at 90°C overnight. 5-Bromo-2-iodopyridine (512 mg, 1.807 mmol) was added and the mixture was degassed for 10 minutes, then tetrakis(triphenylphosphine)palladium(0) (104 mg, 0.09mmol) was added and the mixture was heated at 90°C for 2 h. Aqueous potassium carbonate solution (2M, 3 mL) was added and the reaction mixture was heated at 90°C for 1 h. The mixture was cooled to room temperature, diluted with EtOAc (100 30 mL) and washed with brine (100 mL), then dried over sodium sulfate and concentrated. The resulting brown solid (1.3 g) was purified by FCC, eluting with 70-100% EtOAc in heptane, to afford the *title compound* (363 mg, 43%) as an off-white solid. Method C HPLC-MS: MH⁺ *m/z* 444/446, RT 1.15 minutes.

INTERMEDIATE 104

Ethyl 1-[6-(3-{[2-(difluoromethoxy)phenyl]methyl}-2-methylimidazo[1,2-*a*]pyridin-6-yl)pyridin-3-yl]-4-methylpiperidine-4-carboxylate

- 5 [2',6'-Bis(propan-2-yloxy)biphenyl-2-yl](dicyclohexyl)phosphane (14 mg, 0.031 mmol) and palladium(II) acetate (5.7 mg, 0.026 mmol) were dissolved in degassed 1,4-dioxane (2 mL) and heated at 80°C for 5 minutes. The mixture was then cooled to room temperature and a solution of *Intermediate 103* (363 mg, 0.515 mmol) in 1,4-dioxane (6 mL) was added, followed by ethyl 4-methylpiperidine-4-carboxylate hydrochloride (117 mg, 0.566 mmol) and cesium carbonate (335 mg, 1.03 mmol). The reaction mixture was flushed with nitrogen for 10 minutes, then further [2',6'-bis(propan-2-yloxy)biphenyl-2-yl](dicyclohexyl)phosphane (14 mg, 0.031 mmol) and palladium(II) acetate (5.7 mg, 0.026 mmol) were added and the mixture was heated at 120°C for 2 h. The reaction mixture was flushed with nitrogen for 10 minutes, then [2',6'-bis(propan-2-yloxy)-biphenyl-2-yl](dicyclohexyl)phosphane (30 mg, 0.062 mmol) and palladium(II) acetate (10 mg, 0.052 mmol) were added and the mixture was heated at 120°C for 3 h. Further ethyl 4-methylpiperidine-4-carboxylate hydrochloride (117 mg, 0.566 mmol) and cesium carbonate (335 mg, 1.03 mmol) were added and the mixture was degassed for 10 minutes, before the addition of further [2',6'-bis(propan-2-yloxy)biphenyl-2-yl](dicyclohexyl)-phosphane (30 mg, 0.062 mmol) and palladium(II) acetate (10 mg, 0.052 mmol), and the mixture was heated at 120°C for 2.5 h. The crude mixture was filtered through celite and washed with EtOAc (80 mL). The organic phase was washed with water (30 mL) and brine (30 mL), then dried over sodium sulfate and concentrated to dryness under vacuum. The crude material was purified by FCC, then further purified by preparative HPLC, to afford the *title compound* (139 mg, 51%) as a clear glass. Method C HPLC-MS: MH+ *m/z* 535, RT 1.25 minutes.

INTERMEDIATE 105

1-(6-Bromo-2,7-dimethylimidazo[1,2-*a*]pyridin-3-yl)-1-[2-(difluoromethoxy)phenyl]-ethanol

- 5 *Intermediate 18* (2 g, 5.06 mmol) was dissolved in THF (20 mL) and cooled to 0°C under nitrogen. Methylmagnesium bromide in THF/toluene (1.4M, 6.51 mL) was added at 0°C under nitrogen and the reaction mixture was stirred for 1 h at 0°C under nitrogen. The reaction mixture was then allowed to warm to room temperature and stirred under nitrogen for 1 h. The reaction mixture was cooled to 0°C under nitrogen and
- 10 further methylmagnesium bromide in THF/toluene (1.4M, 1.81 mL) was added. The reaction mixture was stirred under nitrogen at 0°C for 10 minutes, then at room temperature for 1 h. The reaction mixture was carefully quenched by the addition of saturated aqueous ammonium chloride solution (15 mL) at 0°C, and extracted into EtOAc (30 mL). The organic layer was separated, washed with brine (10 mL), dried over sodium
- 15 sulfate and concentrated to dryness. The residue was triturated with 1:1 DCM/TBME (10 mL), and the solid was washed with TBME, to afford the *title compound* (1.51 g, 73%) as a pale yellow solid. Method C HPLC-MS: MH⁺ *m/z* 411/413, RT 1.00 minutes.

INTERMEDIATE 106

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1-[6-(2-Chloropyrimidin-5-yl)-2,7-dimethylimidazo[1,2-*a*]pyridin-3-yl]-1-[2-(difluoromethoxy)phenyl]ethanol

- Intermediate 105* (477 mg, 1.16 mmol) and (2-chloropyrimidin-5-yl)boronic acid (552 mg, 3.48 mmol) were dissolved in 1,4-dioxane (7 mL) and 2M sodium carbonate in
- 25 water (1.74 mL) was added. The resulting mixture was degassed with nitrogen for 5 minutes, then dichlorobis(triphenylphosphine)palladium(II) (41 mg, 0.058 mmol) and tri-*tert*-butylphosphine (12 mg, 0.058 mmol) were added. The reaction mixture was heated at 120°C under microwave irradiation for a total of 70 minutes. The reaction was repeated on the same scale and the two reaction mixtures were combined, diluted with
- 30 EtOAc (25 mL), washed with water (20 mL) and brine (20 mL), then dried over sodium sulfate and concentrated to dryness. The residue was purified by FCC, eluting with 50-100% EtOAc in heptane followed by 0-5% MeOH in EtOAc, to afford the *title compound* (585 mg, 57%) as a yellow gum. δ_{H} (500 MHz, CDCl₃) 8.40 (s, 2H), 8.11 (s, 1H), 7.66

(d, J 7.4 Hz, 1H), 7.40 (s, 1H), 7.38-7.34 (m, 1H), 7.26 (t, J 7.6 Hz, 1H), 7.08 (d, J 8.0 Hz, 1H), 6.19 (t, J 73.5 Hz, 1H), 2.45 (s, 3H), 2.26 (s, 3H), 2.17 (s, 3H). Method C HPLC-MS: MH⁺ m/z 445, RT 0.97 minutes.

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INTERMEDIATE 107

2-Chloro-5-(3-{1-[2-(difluoromethoxy)phenyl]ethenyl}-2,7-dimethylimidazo[1,2-*a*]-pyridin-6-yl)pyrimidine

Intermediate 106 (585 mg, 1.32 mmol) was dissolved in DCM (10 mL) under nitrogen and boron trifluoride diethyl etherate (600 μ L, 4.86 mmol) was added. The reaction mixture was stirred for 30 minutes at room temperature. The reaction mixture was washed with saturated aqueous sodium bicarbonate solution (6 mL). The aqueous layer was re-extracted with DCM (6 mL), then the combined organic layers were dried over sodium sulfate and concentrated to dryness. The residue was triturated with 1:1 DCM/heptane (~4 mL) to afford the *title compound* (310 mg, 55%) as an off-white solid. δ_H (250 MHz, CD₃OD) 8.67 (s, 2H), 8.26 (s, 1H), 7.84 (s, 1H), 7.72-7.63 (m, 1H), 7.58-7.44 (m, 1H), 7.43-7.30 (m, 1H), 7.15 (d, J 8.1 Hz, 1H), 6.66 (t, J 73.9 Hz, 1H), 6.21 (s, 1H), 5.99 (s, 1H), 2.46 (s, 3H), 2.39 (s, 3H). Method C HPLC-MS: MH⁺ m/z 427, RT 1.06 minutes.

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INTERMEDIATE 108

2-Chloro-5-(3-{1-[2-(difluoromethoxy)phenyl]ethyl}-2,7-dimethylimidazo[1,2-*a*]pyridin-6-yl)pyrimidine

Intermediate 107 (310 mg, 0.73 mmol) was dissolved in EtOAc (10 mL) and platinum oxide (35 mg, 0.15 mmol) was added. The reaction mixture was placed under a hydrogen atmosphere and stirred for a total of 42 h. Further platinum oxide (35 mg, 0.15 mmol) was added and the mixture was stirred under a hydrogen atmosphere for a total of 24 h. The reaction mixture was filtered and concentrated to dryness, to afford the *title compound* (311 mg, 100%) as an off-white solid, which was used without further purification. δ_H (250 MHz, CD₃OD) 8.72 (s, 2H), 8.22 (s, 1H), 7.57-7.49 (m, 1H), 7.44 (s, 1H), 7.40-7.19 (m, 2H), 7.18-7.10 (m, 1H), 6.71 (t, J 74.2 Hz, 1H), 2.36-2.21 (m, 7H), 1.78 (d, J 7.3 Hz, 3H). Method C HPLC-MS: MH⁺ m/z 429, RT 1.07 minutes.

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INTERMEDIATE 109

Ethyl (1*R*,5*S*,6*r*)-3-[5-(3-{1-[2-(difluoromethoxy)phenyl]ethyl}-2,7-dimethylimidazo-
5 [1,2-*a*]pyridin-6-yl)pyrimidin-2-yl]-3-azabicyclo[3.1.0]hexane-6-carboxylate

Intermediate 108 (312 mg, 0.73 mmol) and ethyl (1*R*,5*S*,6*r*)-3-azabicyclo[3.1.0]-hexane-6-carboxylate hydrochloride (209 mg, 1.09 mmol) were dissolved in 1-methyl-2-pyrrolidinone (3 mL) and triethylamine (203 μ L, 1.46 mmol) was added. The reaction mixture was heated at 150°C under microwave irradiation for 1 h. The reaction mixture
10 was diluted with water (3 mL) and extracted with EtOAc (3 mL). The resulting organic layer was washed with brine (1 mL), dried over sodium sulfate and concentrated to dryness. Purification was attempted by FCC, to afford the *title compound* (175 mg, 44%) as a yellow gum, which was used without further purification. Method C HPLC-MS: MH⁺ *m/z* 548, RT 1.16 minutes.

15

INTERMEDIATE 110

Ethyl 1-benzyl-4-methyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate

Benzyl(methoxymethyl)[(trimethylsilyl)methyl]amine (10.78 mL, 42.12 mmol)
20 and ethyl but-2-ynoate (5.89 mL, 50.54 mmol) were stirred in DCM (500 mL) at 0°C under nitrogen, then trifluoroacetic acid (161 μ L, 2.11 mmol) was added dropwise. The reaction mixture stirred at 0°C for 20 minutes, then the ice bath was removed and the solution was allowed to warm to room temperature. The solution was stirred at room temperature overnight. The mixture was concentrated and purified by FCC, eluting with
25 0-70% EtOAc in heptane, to afford the *title compound* (2.76 g, 27%). δ_{H} (500 MHz, DMSO-*d*₆) 7.38-7.32 (m, 4H), 7.30-7.23 (m, 1H), 4.13 (q, *J* 7.1 Hz, 2H), 3.75 (s, 2H), 3.60-3.51 (m, 4H), 2.05 (s, 3H), 1.22 (t, *J* 7.1 Hz, 3H).

INTERMEDIATE 111

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Ethyl 3-benzyl-5-methyl-3-azabicyclo[3.1.0]hexane-1-carboxylate

Trimethylsulfoxonium iodide (3.62 g, 16.31 mmol) and potassium *tert*-butoxide (1.74 g, 15.49 mmol) were heated in anhydrous DMSO (5 mL) at 50°C for 30 minutes

until all had dissolved. *Intermediate 110* (1 g, 4.08 mmol) in DMSO (5 mL) was added dropwise and the mixture was stirred at 50°C for 2.5 h. Water (20 mL) was added and the mixture was extracted with EtOAc (2 x 30 mL). The organic layers were washed with brine, dried over sodium sulfate and concentrated. The resulting yellow oil was purified by FCC, eluting with 0-50% EtOAc in heptane, to afford the *title compound* (483 mg, 46%). δ_{H} (500 MHz, DMSO- d_6) 7.35-7.21 (m, 5H), 4.15-3.99 (m, 2H), 3.65-3.53 (m, 2H), 2.93 (d, J 8.9 Hz, 1H), 2.88 (d, J 8.9 Hz, 1H), 2.71 (d, J 8.9 Hz, 1H), 2.22 (d, J 8.9 Hz, 1H), 1.48 (d, J 3.5 Hz, 1H), 1.22 (s, 3H), 1.17 (t, J 7.1 Hz, 3H), 1.09 (d, J 3.5 Hz, 1H).

INTERMEDIATE 112

Ethyl 5-methyl-3-azabicyclo[3.1.0]hexane-1-carboxylate hydrochloride

Intermediate 111 (983 mg, 3.79 mmol) was dissolved in EtOH (20 mL) and palladium on carbon (10%, 225 mg, 0.21 mmol) was added. The mixture was flushed with nitrogen, then hydrogen, and stirred under a hydrogen atmosphere for 18 h. The mixture was filtered through celite and washed through with further EtOH. To this solution was added 1M HCl in EtOAc (10 mL), and the mixture was concentrated, to afford the *title compound* (784 mg, 100%) as a brown gum which solidified upon standing. δ_{H} (500 MHz, DMSO- d_6) 9.85 (s, 1H), 9.39 (s, 1H), 4.22-4.07 (m, 2H), 3.69-3.59 (m, 1H), 3.47-3.33 (m, 2H), 3.26-3.17 (m, 1H), 1.55 (d, J 5.8 Hz, 1H), 1.34 (d, J 5.8 Hz, 1H), 1.31 (s, 3H), 1.21 (t, J 7.1 Hz, 3H).

INTERMEDIATE 113

Ethyl 3-[5-(3-{[2-(difluoromethoxy)phenyl]methyl}-2-methylimidazo[1,2-*a*]pyridin-6-yl)pyrimidin-2-yl]-5-methyl-3-azabicyclo[3.1.0]hexane-1-carboxylate

Intermediate 29 (85% pure, 240 mg, 0.51 mmol) and *Intermediate 112* (115 mg, 0.56 mmol) were dissolved in 1-methyl-2-pyrrolidinone (3 mL) and triethylamine (160 μ L, 1.12 mmol) was added. The mixture was heated under microwave irradiation at 120°C for 45 minutes. Water (30 mL) was added, and the mixture was extracted with EtOAc (3 x 30mL) and washed with brine, then dried over sodium sulfate and concentrated. The resulting crude brown liquid was purified by FCC, eluting with 0-3%

MeOH in DCM, then further purified by preparative HPLC (Method C), to afford the *title compound* (129 mg, 47%) as a brown solid. δ_{H} (500 MHz, DMSO- d_6) 8.65 (s, 2H), 8.37 (s, 1H), 7.54 (d, J 9.3 Hz, 1H), 7.46 (dd, J 9.3, 1.6 Hz, 1H), 7.33-7.26 (m, 1H), 7.29 (t, J 74.1 Hz, 1H), 7.20 (d, J 8.1 Hz, 1H), 7.17-7.10 (m, 1H), 7.07-7.01 (m, 1H), 4.36 (s, 2H),
 5 4.24-4.08 (m, 2H), 4.05-3.95 (m, 2H), 3.92 (d, J 11.2 Hz, 1H), 3.40 (d, J 11.1 Hz, 1H), 2.32 (s, 3H), 1.44 (d, J 4.4 Hz, 1H), 1.39 (s, 3H), 1.24 (t, J 7.1 Hz, 3H), 1.03 (d, J 4.6 Hz, 1H).

INTERMEDIATE 114

10

Methyl 3-azabicyclo[4.1.0]heptane-6-carboxylate hydrochloride (*Racemic*)

3-[(*tert*-Butoxy)carbonyl]-3-azabicyclo[4.1.0]heptane-6-carboxylic acid (5 g, 20.72 mmol) was dissolved in MeOH (200 mL) and 4M HCl in 1,4-dioxane (25.9 mL) was added. The reaction mixture was heated at 60°C for 4 h. The reaction mixture was
 15 cooled to room temperature, then concentrated, to afford the *title compound* (4.0 g, 101%) as a pale yellow solid. δ_{H} (250 MHz, CDCl_3) 3.69 (s, 3H), 3.42 (br s, 1H), 2.11 (br s, 5H), 1.84 (br s, 1H), 1.62 (d, J 4.2 Hz, 1H), 1.29 (br s, 1H).

INTERMEDIATE 115

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3-Benzyl 6-methyl 3-azabicyclo[4.1.0]heptane-3,6-dicarboxylate (*Racemic*)

Intermediate 114 (4 g, 20.87 mmol) was stirred in DCM (100 mL) and 1-[[[(benzyloxy)carbonyl]oxy]pyrrolidine-2,5-dione (5.20 g, 20.87 mmol) was added, followed by triethylamine (7.29 mL, 52.18 mmol). The reaction mixture was stirred at
 25 room temperature overnight. The mixture was washed with 1M HCl (2 x 30 mL), saturated sodium bicarbonate solution (50 mL) and brine (50 mL), then dried over sodium sulfate and concentrated. The resulting yellow oil was purified by FCC, eluting with 0-50% EtOAc in heptane, to afford the *title compound* (4.72 g, 78%) as a pale yellow oil.
 δ_{H} (500 MHz, CDCl_3) 7.40-7.29 (m, 5H), 5.12 (s, 2H), 3.91 (d, J 13.6 Hz, 1H), 3.66 (s, 3H), 3.59 (dd, J 13.6, 4.4 Hz, 1H), 3.48 (br s, 1H), 3.09 (s, 1H), 2.56 (dt, J 14.5, 5.6 Hz, 1H), 1.91-1.66 (m, 2H), 1.44 (s, 1H), 0.75 (dd, J 6.4, 4.8 Hz, 1H).
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INTERMEDIATE 116Methyl 3-azabicyclo[4.1.0]heptane-6-carboxylate hydrochloride (*Enantiomer A*)

Intermediate 115 (4.72 g, 16.31 mmol) was separated using chiral preparative HPLC (Lux Amylose-2 column, 21.2 x 250 mm, 5 μ m; 70% heptane/20% ethanol/10% isopropanol eluent; 21 mL/minute flow rate) and the first-eluting enantiomer was isolated (1.85 g, 6.38 mmol). This was dissolved in MeOH (20 mL) and 10% palladium on carbon (0.38 g) was added. The mixture was flushed with nitrogen (x 3) and hydrogen (x 3), then stirred under a hydrogen atmosphere for 18 h. The mixture was filtered through celite and washed through with MeOH. The filtrate was concentrated to near dryness and diethyl ether (10 mL) was added, followed by 4M HCl in 1,4-dioxane (3 mL). The mixture was allowed to stand for ~30 minutes and the resultant precipitate was collected by filtration, washed with diethyl ether and dried under vacuum, to afford the *title compound* (1.1 g, 90%) as a white solid. δ_{H} (250 MHz, DMSO- d_6) 8.91 (s, 1H), 8.79 (s, 1H), 3.60 (s, 3H), 3.52-3.43 (m, 1H), 3.16-2.98 (m, 1H), 2.98-2.68 (m, 2H), 2.67-2.53 (m, 1H), 1.96-1.81 (m, 1H), 1.79-1.64 (m, 1H), 1.33 (dd, J 9.4, 4.8 Hz, 1H), 1.22 (dd, J 6.7, 4.8 Hz, 1H).

INTERMEDIATE 117Methyl 3-azabicyclo[4.1.0]heptane-6-carboxylate hydrochloride (*Enantiomer B*)

Intermediate 115 (4.72 g, 16.31 mmol) was separated using chiral preparative HPLC (Lux Amylose-2 column, 21.2 x 250 mm, 5 μ m; 70% heptane/20% ethanol/10% isopropanol eluent; 21 mL/minute flow rate) and the second-eluting enantiomer was isolated (1.63 g, 5.64 mmol). This was dissolved in MeOH (20 mL) and 10% palladium on carbon (0.34 g) was added. The mixture was flushed with nitrogen (x 3) and hydrogen (x 3), then stirred under a hydrogen atmosphere for 18 h. The mixture was filtered through celite and washed through with MeOH. The filtrate was concentrated to near dryness and diethyl ether (10 mL) was added, followed by 4M HCl in 1,4-dioxane (3 mL). The mixture was allowed to stand for ~30 minutes and the resultant precipitate was collected by filtration, washed with diethyl ether and dried under vacuum, to afford the *title compound* (980 mg, 91%) as a white solid. δ_{H} (250 MHz, DMSO- d_6) 8.97 (s, 1H), 8.83 (s, 1H), 3.60 (s, 3H), 3.50-3.33 (m, 1H), 3.16-2.99 (m, 1H), 2.98-2.69 (m, 2H), 2.67-

2.52 (m, 1H), 1.96-1.80 (m, 1H), 1.77-1.63 (m, 1H), 1.32 (dd, *J* 9.4, 4.7 Hz, 1H), 1.24 (dd, *J* 6.8, 4.8 Hz, 1H).

INTERMEDIATE 118

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3-Benzyl 1-ethyl 3-azabicyclo[4.1.0]heptane-1,3-dicarboxylate (*Racemic*)

The hydrochloride salt of *Intermediate 91* (1.6 g, 7.78 mmol) was suspended in DCM (60 mL) at 25°C under a nitrogen atmosphere and triethylamine (2.72 mL, 19.45 mmol) was added. 1-[[*(Benzyloxy)carbonyl*]oxy]pyrrolidine-2,5-dione (1.94 g, 7.78 mmol) was added, and the reaction mixture was stirred for 2 h. The mixture was diluted with DCM (60 mL), washed with 1M HCl (60 mL), saturated aqueous sodium bicarbonate solution (50 mL) and brine (50 mL), then dried over sodium sulfate and concentrated. The residue was purified by FCC, eluting with 0-50% EtOAc in heptane, to afford the *title compound* (2.36 g, 82%) as a yellow oil. δ_{H} (500 MHz, CDCl_3) 7.45-7.33 (m, 5H), 5.13 (s, 2H), 4.18-4.09 (m, 2H), 4.08-3.88 (m, 2H), 3.50 (dt, *J* 12.2, 5.7 Hz, 1H), 3.11-3.01 (m, 1H), 2.02 (dd, *J* 13.3, 6.3 Hz, 1H), 1.87-1.66 (m, 2H), 1.39 (dd, *J* 9.4, 4.5 Hz, 1H), 1.23 (t, *J* 6.7 Hz, 3H), 0.79-0.68 (m, 1H). Method D HPLC-MS: MH^+ *m/z* 508, RT 2.27 minutes.

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INTERMEDIATE 119

Ethyl 3-azabicyclo[4.1.0]heptane-1-carboxylate hydrochloride (*Enantiomer A*)

Intermediate 118 (90% pure, 1.72 g, 5.10 mmol) was separated using chiral preparative HPLC (Lux Cellulose 4 column, 21.2 x 250 mm, 5 μm ; 80% heptane/20% isopropanol eluent; 20 mL/minute flow rate) and the first-eluting enantiomer was isolated (561 mg, 1.85 mmol). This was dissolved in ethanol (15 mL) and the mixture was degassed and purged with nitrogen. Palladium on carbon (10%, 98 mg, 0.09 mmol) was added, and the reaction mixture was stirred under a hydrogen balloon at room temperature for 18 h. The reaction mixture was filtered through celite and the solids were washed with excess methanol. The filtrate was concentrated to ~10 mL volume, then 2M hydrochloric acid in ether (8 mL) was added and the mixture was stirred at room temperature for 10 minutes. The reaction mixture was evaporated and the resulting residue was sonicated in diethyl ether for 1 h. The resultant precipitate was filtered,

washed with diethyl ether and dried, to afford the *title compound* (255 mg, 67%) as an off-white solid. δ_{H} (500 MHz, DMSO- d_6) 9.11 (s, 1H), 8.79 (s, 1H), 4.08 (q, J 7.1 Hz, 2H), 3.97 (d, J 13.6 Hz, 1H), 3.10 (d, J 13.6 Hz, 1H), 2.97 (dt, J 11.2, 5.2 Hz, 1H), 2.76-2.66 (m, 1H), 2.17 (ddt, J 12.2, 10.3, 6.1 Hz, 1H), 1.94-1.83 (m, 1H), 1.83-1.67 (m, 1H), 1.41 (dd, J 9.6, 4.7 Hz, 1H), 1.29 (dd, J 7.2, 4.8 Hz, 1H), 1.19 (t, J 7.1 Hz, 3H).

INTERMEDIATE 120

Ethyl 3-azabicyclo[4.1.0]heptane-1-carboxylate hydrochloride (*Enantiomer B*)

Intermediate 118 (90% pure, 1.72 g, 5.10 mmol) was separated using chiral preparative HPLC (Lux Cellulose 4 column, 21.2 x 250 mm, 5 μ m; 80% heptane/20% isopropanol eluent; 20 mL/minute flow rate) and the second-eluting enantiomer was isolated (608 mg, 2.00 mmol). This was dissolved in ethanol (15 mL) and the mixture was degassed and purged with nitrogen. Palladium on carbon (10%, 106 mg, 0.10 mmol) was added, and the reaction mixture was stirred under a hydrogen balloon at room temperature for 18 h. The reaction mixture was filtered through celite and the solids were washed with excess methanol. The filtrate was concentrated to ~10 mL volume, then 2M HCl in ether (8 mL) was added and the mixture was stirred at room temperature for 10 minutes. The reaction mixture was evaporated and the resulting residue was sonicated in diethyl ether for 1 h. The resultant precipitate was filtered, washed with diethyl ether and dried, to afford the *title compound* (316 mg, 76%) as an off-white solid. δ_{H} (500 MHz, DMSO- d_6) 8.90 (d, J 134.2 Hz, 2H), 4.08 (q, J 7.1 Hz, 2H), 3.98 (d, J 13.6 Hz, 1H), 3.10 (d, J 13.6 Hz, 1H), 2.97 (dt, J 11.1, 5.2 Hz, 1H), 2.70 (td, J 12.9, 11.7, 4.5 Hz, 1H), 2.16 (ddd, J 16.2, 11.2, 6.2 Hz, 1H), 1.93-1.83 (m, 1H), 1.78 (q, J 7.4 Hz, 1H), 1.42 (dd, J 9.6, 4.7 Hz, 1H), 1.28 (dd, J 7.1, 4.9 Hz, 1H), 1.19 (t, J 7.1 Hz, 3H).

INTERMEDIATE 121

Methyl 2-{4-[5-(3-{[2-(difluoromethoxy)phenyl]methyl}-2-methylimidazo[1,2-*a*]pyridin-6-yl)pyrimidin-2-yl]morpholin-3-yl}acetate

Intermediate 29 (150 mg, 0.37 mmol), methyl 2-(morpholin-3-yl)acetate hydrochloride (125 mg, 0.64 mmol) and triethylamine (0.26 mL, 1.87 mmol) were suspended in 1-methyl-2-pyrrolidinone (3 mL) and the reaction mixture was heated for a

total of 3 h at 160°C under microwave irradiation. The reaction mixture was allowed to cool to room temperature, then diluted with DCM (20 mL) and saturated aqueous sodium bicarbonate solution (10 mL). The organic phase was separated, washed with brine, dried over sodium sulfate and concentrated under vacuum. The residue was purified by preparative HPLC (Method C) to afford the *title compound* (50 mg, 15%) as a brown oil. δ_{H} (500 MHz, CD₃OD) 8.50 (s, 2H), 8.13 (s, 1H), 7.52 (d, *J* 9.3 Hz, 1H), 7.43 (d, *J* 9.3 Hz, 1H), 7.27 (t, *J* 7.7 Hz, 1H), 7.19 (d, *J* 8.2 Hz, 1H), 7.12 (t, *J* 7.5 Hz, 1H), 7.07-6.75 (m, 2H), 5.04 (d, *J* 5.9 Hz, 1H), 4.41 (d, *J* 13.7 Hz, 1H), 4.37 (s, 2H), 3.96 (dd, *J* 11.4, 3.5 Hz, 1H), 3.91 (d, *J* 11.8 Hz, 1H), 3.66 (dd, *J* 11.8, 2.9 Hz, 1H), 3.56 (s, 3H), 3.53 (dd, *J* 11.6, 3.0 Hz, 1H), 3.25 (td, *J* 13.1, 3.7 Hz, 1H), 2.88 (dd, *J* 15.0, 8.5 Hz, 1H), 2.64 (dd, *J* 15.0, 6.1 Hz, 1H), 2.43 (s, 3H).

INTERMEDIATE 122

Methyl 1-[5-(3-{[2-(difluoromethoxy)phenyl]methyl}-2-methylimidazo[1,2-*a*]pyridin-6-yl)pyrimidin-2-yl]azepane-4-carboxylate

Intermediate 29 (85% pure, 150 mg, 0.32 mmol), methyl azepane-4-carboxylate (75 mg, 0.48 mmol) and 1M aqueous potassium carbonate solution (1 mL) were suspended in 1-methyl-2-pyrrolidinone (3 mL) and the reaction mixture was heated for 1 h at 120°C under microwave irradiation. The mixture was allowed to cool to room temperature, then diluted with ethyl acetate (20 mL) and saturated aqueous sodium bicarbonate solution (10 mL). The organic phase was separated, washed with brine, dried over sodium sulfate and concentrated under vacuum. The product was purified by preparative HPLC (Method C) to afford the *title compound* (130 mg, 39%) as a light brown solid. δ_{H} (500 MHz, DMSO-*d*₆) 8.63 (s, 2H), 8.38 (s, 1H), 7.53 (d, *J* 9.2 Hz, 1H), 7.48-7.10 (m, 5H), 7.03-6.99 (m, 1H), 4.35 (s, 2H), 3.92 (ddd, *J* 14.1, 6.1, 4.6 Hz, 1H), 3.82 (dt, *J* 13.8, 5.1 Hz, 1H), 3.72-3.63 (m, 2H), 3.56 (s, 3H), 3.16 (d, *J* 5.1 Hz, 1H), 2.30 (s, 3H), 2.07 (dq, *J* 14.2, 4.3 Hz, 1H), 1.90 (td, *J* 12.3, 10.2, 5.4 Hz, 2H), 1.79 (ddq, *J* 14.3, 10.1, 4.4 Hz, 1H), 1.68 (dq, *J* 11.1, 5.5 Hz, 1H), 1.56-1.46 (m, 1H).

INTERMEDIATE 123

5-(3-{[2-(Difluoromethoxy)phenyl]methyl}-2-methylimidazo[1,2-a]pyridin-6-yl)-2,3-difluoropyridine

- 5 *Intermediate 7* (250 mg, 0.68 mmol) and (5,6-difluoropyridin-3-yl)boronic acid (165 mg, 1.02 mmol) were suspended in acetonitrile (2.5 mL). Aqueous sodium carbonate solution (2M, 520 μ L) was added and mixture was de-gassed for 5 minutes. Pd(dppf)Cl₂ complex with DCM (30 mg, 0.03 mmol) was added. The reaction mixture was heated under microwave irradiation for 30 minutes at 150°C. The reaction mixture
- 10 was diluted with water (20 mL) and extracted with ethyl acetate (2 x 50 mL). The organic extracts were combined, washed with brine, dried over sodium sulfate and concentrated. The resulting black solid was purified by column chromatography, using 0-3% MeOH in DCM on 50g silica isolate, to afford the *title compound* (170 mg) as a pink solid. δ_{H} (500 MHz, DMSO-d₆) 8.63 (s, 1H), 8.45 (ddd, *J* 11.1, 9.2, 2.1 Hz, 1H), 8.42-
- 15 8.39 (m, 1H), 7.62-7.56 (m, 2H), 7.33-7.26 (m, 1H), 7.48-7.12 (m, 1H), 7.23-7.17 (m, 1H), 7.16-7.08 (m, 1H), 7.04-6.97 (m, 1H), 4.41 (s, 2H), 2.30 (s, 3H). Method B HPLC-MS: MH⁺ *m/z* 402, RT 1.69 minutes.

INTERMEDIATE 124

- 20 Ethyl 1-[5-(3-{[2-(difluoromethoxy)phenyl]methyl}-2-methylimidazo[1,2-a]pyridin-6-yl)-3-fluoropyridin-2-yl]-4-methylpiperidine-4-carboxylate
- Intermediate 123* (86% purity, 110 mg, 0.24 mmol) and ethyl 4-methylpiperidine-4-carboxylate hydrochloride (98 mg, 0.47 mmol) in pyridine (4 mL) were heated under
- 25 microwave irradiation at 180°C for 4 h. To the reaction mixture were added 1M HCl (30 mL), ethyl acetate (50 mL) and brine (100 mL). The phases were separated and the aqueous phase was extracted with ethyl acetate (3 x 50 mL). The organic extracts were combined and washed with brine. The brine wash was extracted with ethyl acetate (20 mL). The organic extracts were combined, dried over sodium sulphate and concentrated.
- 30 The crude residue was successively purified by column chromatography, using 0-4% MeOH in DCM, and by preparative HPLC (Method C), to afford the *title compound* (41 mg) as a yellow solid. δ_{H} (500 MHz, DMSO-d₆) 8.47-8.40 (m, 1H), 8.35-8.29 (m, 1H), 7.88 (dd, *J* 14.8, 2.0 Hz, 1H), 7.56-7.50 (m, 2H), 7.47-7.10 (m, 1H), 7.33-7.25 (m, 1H),

7.22-7.18 (m, 1H), 7.16-7.09 (m, 1H), 7.03-6.96 (m, 1H), 4.38 (s, 2H), 4.13 (q, *J* 7.1 Hz, 2H), 3.75 (dt, *J* 13.3, 4.2 Hz, 2H), 3.17-3.06 (m, 2H), 2.30 (s, 3H), 2.12-2.03 (m, 2H), 1.58-1.48 (m, 2H), 1.23-1.17 (m, 6H).

5

INTERMEDIATE 125

tert-Butyl 4-[5-(3-{[2-(difluoromethoxy)phenyl]methyl}-2-methylimidazo[1,2-*a*]pyridin-6-yl)pyrimidin-2-yl]-1,2,3,6-tetrahydropyridine-1-carboxylate

Intermediate 29 (0.70 g, 1.46 mmol), {1-[(*tert*-butoxy)carbonyl]-1,2,3,6-tetrahydropyridin-4-yl}boronic acid (0.59 g, 2.62 mmol) and a 2M sodium carbonate solution in water (5.59 mL) were combined in DME (27.5 mL) in a sealed tube and degassed thoroughly under nitrogen for 15 minutes. Pd(PPh₃)₄ (202 mg, 0.17 mmol) was added and the mixture was heated at 90°C for 120 minutes. The reaction mixture was cooled to r.t., then diluted using DCM (40 mL). The mixture was washed using an aqueous saturated solution of sodium bicarbonate (2 x 40 mL) and brine (40 mL). The organic phase was dried over sodium sulfate and concentrated under vacuum. The crude residue was successively purified using Biotage (50 g cartridge; eluent: 0-10% MeOH/DCM) and Biotage (50 g cartridge; eluent: 0-7% MeOH/DCM with the gradient held steady at 4% MeOH/DCM), to afford the *title compound* (1.13 g, 94%) as a pink oil.

Method C HPLC-MS: MH⁺ *m/z* 548, RT 1.82, 1.88 minutes.

INTERMEDIATE 126

5-(3-{[2-(Difluoromethoxy)phenyl]methyl}-2-methylimidazo[1,2-*a*]pyridin-6-yl)-2-(1,2,3,6-tetrahydropyridin-4-yl)pyrimidine hydrochloride

Intermediate 125 (80%, 1.13 g, 1.65 mmol) was dissolved in 1,4-dioxane (10 mL) and 4M HCl in 1,4-dioxane (2.06 mL) was added. The reaction mixture was stirred at r.t. for 2 h. Additional 4M HCl in 1,4 dioxane (5 equivalents) was added and the reaction mixture was stirred at r.t. over the weekend. The solvent was removed under vacuum and the crude residue was triturated using ethyl acetate, to afford the *title compound* (1.01 g, 94%) as a pale orange solid. Method C HPLC-MS: MH⁺ *m/z* 448, RT 0.77 minutes.

INTERMEDIATE 127

Ethyl 2-{4-[5-(3-{[2-(difluoromethoxy)phenyl]methyl}-2-methylimidazo[1,2-a]pyridin-6-yl)pyrimidin-2-yl]-1,2,3,6-tetrahydropyridin-1-yl}acetate

5 *Intermediate 126* (75%, 1.01 g, 1.57 mmol) was stirred in DMF (30 mL) and potassium carbonate (0.65 g, 4.71 mmol) was added. The reaction mixture was stirred for 5 minutes at r.t. before the addition of ethyl 2-bromoacetate (0.17 mL, 1.57 mmol). The reaction mixture was stirred at r.t. for 90 minutes. Water (30 mL) and EtOAc (30 mL) were added, the layers were shaken and separated, then the organic layer was further
10 washed using water (2 x 20 mL) and brine (20 mL). The organic layer was dried over sodium sulfate and concentrated. The crude residue was purified using Biotage (50 g cartridge), with an eluent of 0-8% MeOH/DCM over 18 column volumes, to afford the *title compound* (254 mg, 33%) as a pale pink solid. δ_{H} (250 MHz, CDCl_3) 8.75 (s, 2H), 7.92 (s, 1H), 7.70 (d, J 9.5 Hz, 1H), 7.35 (d, J 9.2 Hz, 1H), 7.24 (s, 1H), 7.17 (d, J 8.0 Hz,
15 1H), 7.09 (t, J 7.4 Hz, 1H), 6.89 (m, 1H), 6.98-6.30 (t, J 73.5 Hz, 1H), 4.32 (s, 2H), 4.22 (q, J 7.1 Hz, 2H), 3.47 (d, J 3.4 Hz, 2H), 3.41 (s, 2H), 2.89 (d, J 4.8 Hz, 2H), 2.81 (s, 2H), 2.54 (s, 3H), 1.30 (t, J 7.1 Hz, 3H). Method B HPLC-MS: MH^+ m/z 534, RT 1.39 minutes.

20

INTERMEDIATE 128

Ethyl 2-{4-[5-(3-{[2-(difluoromethoxy)phenyl]methyl}-2-methylimidazo[1,2-a]pyridin-6-yl)pyrimidin-2-yl]piperidin-1-yl}acetate

Intermediate 127 (100 mg, 0.18 mmol) was dissolved in ethanol (10 mL), then
25 palladium on carbon was added. The suspension was de-gassed using vacuum/nitrogen/hydrogen, and the reaction mixture was stirred under hydrogen at ambient temperature and atmospheric pressure for 2 h. The reaction mixture was flushed with nitrogen, then the catalyst was filtered and washed with ethanol (70 mL). The filtrate was concentrated under vacuum. The resulting crude yellow oil was purified using Biotage (25 g
30 cartridge), with an eluent of 0-10% MeOH/DCM with the gradient held steady at 4% MeOH/DCM for 3 column volumes, to afford the *title compound* (40 mg, 40%) as a pink oil. δ_{H} (250 MHz, CDCl_3) 8.74 (s, 2H), 7.90 (d, J 0.8 Hz, 1H), 7.67 (dd, J 9.3, 0.8 Hz, 1H), 7.31 (dd, J 9.3, 1.8 Hz, 1H), 7.23 (d, J 1.7 Hz, 1H), 7.16 (d, J 7.2 Hz, 1H), 7.08 (td, J

7.4, 1.4 Hz, 1H), 6.87 (dd, *J* 7.6, 1.4 Hz, 1H), 6.64 (t, *J* 73.5 Hz, 1H), 4.32 (s, 2H), 4.20 (q, *J* 7.1 Hz, 2H), 3.28 (s, 2H), 3.09 (d, *J* 11.4 Hz, 2H), 2.99-2.84 (m, 1H), 2.53 (s, 3H), 2.47-2.32 (m, 2H), 2.07 (q, *J* 5.5 Hz, 4H), 1.28 (t, *J* 7.1 Hz, 3H).

5

INTERMEDIATE 129

tert-Butyl(cyclopent-3-en-1-yloxy)dimethylsilane

Cyclopent-3-en-1-ol (10 g, 118.9 mmol) was dissolved in DMF (100 mL) at 0°C, then 1*H*-imidazole (17.29 mL, 261.5 mmol) was added, followed by *tert*-butyl(chloro)-
 10 dimethylsilane (21.5 g, 142.7 mmol). The mixture was warmed to room temperature and stirred for 14 h. The mixture was diluted with ethyl acetate (300 mL), washed with 5% aqueous LiCl solution (2 x 100 mL) and brine (50 mL), then dried over sodium sulfate, filtered, and concentrated. The crude residue was purified by chromatography, eluting with 0-10% EtOAc in hexane, to afford the *title compound* (17.2 g, 73%) as a colourless
 15 clear liquid. δ_{H} (250 MHz, CDCl_3) 5.66 (s, 2H), 4.53 (tt, *J* 7.0, 3.6 Hz, 1H), 2.57 (dd, *J* 15.2, 6.8 Hz, 2H), 2.27 (dd, *J* 15.3, 3.6 Hz, 2H), 0.89 (s, 9H), 0.06 (s, 6H).

INTERMEDIATE 130

20 Ethyl 3-[(*tert*-butyldimethylsilyl)oxy]bicyclo[3.1.0]hexane-6-carboxylate

1-(2-Ethoxy-2-oxoethylidene)diazonium (6.07 mL, 48.4 mmol) in DCM (4 mL) was added slowly via syringe pump over 6 h to a stirred solution of *Intermediate 129* (8 g, 40.3 mmol) and rhodium(II) acetate (178.24 mg, 0.4 mmol) in DCM (150 mL) under nitrogen at room temperature. The mixture was stirred for 14 h, then filtered through
 25 celite and concentrated under reduced pressure. The resulting crude light brown oil was purified by column chromatography, eluting with 5-30% ethyl acetate in heptane, to afford the *title compound* (7.15 g, 59%) as a mixture of isomers (*exo:endo* 2.5:1) as a colourless clear oil. δ_{H} (500 MHz, CDCl_3) 4.12-4.03 (m, 2H), 2.13 (dd, *J* 13.0, 7.2 Hz, 1H), 2.05 (ddd, *J* 13.2, 5.8, 3.4 Hz, 1H), 1.88-1.69 (m, 4H), 1.51 (d, *J* 14.7 Hz, 1H), 1.28-
 30 1.19 (m, 4H), 0.88-0.82 (m, 9H), 0.04-0.03 (m, 6H).

INTERMEDIATE 131Ethyl 3-hydroxybicyclo[3.1.0]hexane-6-carboxylate

TBAF (1M, 68.13 mL) was added dropwise to a stirred solution of *Intermediate 130* (95% pure, 10.2 g, 34.06 mmol) in THF (100 mL) at room temperature, then the mixture was heated at 50°C for 1 h. The mixture was cooled to room temperature and concentrated under reduced pressure. The resulting light brownish oil was diluted with ethyl acetate (300 mL), washed with water (2 x 100 mL) and brine (50 mL), then dried over magnesium sulfate and concentrated under reduced pressure, to provide the *title compound* (9.4 g crude) as a light reddish oil. δ_{H} (500 MHz, CDCl_3) 4.15-4.05 (m, 2H), 2.26 (dd, J 13.1, 7.1 Hz, 1H), 2.20-2.11 (m, 1H), 1.99-1.93 (m, 1H), 1.92-1.84 (m, 4H), 1.84-1.75 (m, 1H), 1.64-1.53 (m, 1H), 1.30-1.20 (m, 3H).

INTERMEDIATE 132Ethyl 3-oxobicyclo[3.1.0]hexane-6-carboxylate

Intermediate 131 (60% pure, 9.4 g, 33.14 mmol) was dissolved in DCM (100 mL), then DMP (28.11 g, 0.07 mol) was added as a solid and the mixture was stirred at room temperature for 15 h. The mixture was diluted with DCM (200 mL), washed with saturated aqueous sodium bicarbonate solution (2 x 100 mL), water (100 mL) and brine (50 mL), then dried over sodium sulfate and concentrated under reduced pressure. The resulting crude sticky off-white solid was purified by flash chromatography, eluting with 30-100% ethyl acetate in heptane, to afford the *title compound* (3.15g, 56%) as a light brown oil. δ_{H} (500 MHz, CDCl_3) 4.15 (q, J 7.1 Hz, 2H), 2.66 (ddt, J 18.5, 3.9, 1.6 Hz, 2H), 2.31 (d, J 1.8 Hz, 1H), 2.27 (d, J 1.7 Hz, 2H), 2.18 (td, J 3.4, 1.6 Hz, 2H), 1.31-1.23 (m, 4H).

INTERMEDIATE 133Ethyl 3-(trifluoromethanesulfonyloxy)bicyclo[3.1.0]hex-2-ene-6-carboxylate

Intermediate 132 (3 g, 17.84 mmol) was dissolved in dry toluene (60 mL), then DIPEA (12.5 mL, 71.35 mmol) was added and the reaction mixture was heated at 45°C. Trifluoromethanesulfonic anhydride (12 mL, 71.35 mmol) was added, the temperature

rose to 70°C and the reaction mixture was cooled using an ice bath. The mixture was stirred for 1.5 h at 45°C. The reaction mixture was diluted with ethyl acetate (200 mL) and washed with saturated aqueous sodium bicarbonate solution (2 x 100 mL). The aqueous washes were extracted with ethyl acetate (200 mL) and washed with saturated aqueous sodium bicarbonate solution (2 x 100 mL). The aqueous washes were extracted (100 mL), then the organic extracts were combined, washed with brine (50 mL), dried over sodium sulfate and concentrated. The crude product was purified by chromatography, eluting with 0-20% ethyl acetate (200 mL), then washed with saturated aqueous sodium bicarbonate solution (2 x 100 mL). The aqueous washes were extracted in heptane to afford the *title compound* (2.73 g, 51%). δ_{H} (250 MHz, CDCl_3) 5.87 (d, J 1.9 Hz, 1H), 4.14 (q, J 7.1 Hz, 2H), 3.00 (dd, J 17.2, 6.2 Hz, 1H), 2.75-2.60 (m, 1H), 2.46-2.31 (m, 1H), 2.23-2.11 (m, 1H), 1.39-1.32 (m, 1H), 1.32-1.16 (m, 3H).

INTERMEDIATE 134

Ethyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)bicyclo[3.1.0]hex-2-ene-6-carboxylate

Intermediate 133 (2.73 g, 9.09 mmol) was dissolved in 1,4-dioxane (60 mL) and degassed using nitrogen for 5 minutes. Bis(pinacolato)diborane (3.46 g, 13.64 mmol), potassium acetate (2.68 g, 27.28 mmol), 1,1'-bis(diphenylphosphanyl)ferrocene (0.15 g, 0.27 mmol) and Pd(dppf)Cl_2 complex with dichloromethane (0.22 g, 0.27 mmol) were added, and the reaction mixture was heated under nitrogen at 90°C for 18 h. The reaction mixture was diluted with ethyl acetate (200 mL) and washed with a saturated aqueous solution of sodium bicarbonate (2 x 100 mL). The aqueous washes were re-extracted with ethyl acetate (50 mL). The organic extracts were combined, washed with brine, dried over sodium sulfate and concentrated. The crude residue was purified by chromatography, eluting with 0-40% ethyl acetate in heptane, to afford the *title compound* (2.0 g, 59%) containing bis(pinacolato)diborane impurity. δ_{H} (250 MHz, CDCl_3) 6.66 (d, J 1.9 Hz, 1H), 4.11 (q, J 7.1 Hz, 2H), 2.88-2.73 (m, 1H), 2.66-2.44 (m, 2H), 2.33-2.22 (m, 1H), 1.34-1.18 (m, 16H).

INTERMEDIATE 135

Ethyl 3-[5-(3-{[2-(difluoromethoxy)phenyl]methyl}-2-methylimidazo[1,2-*a*]-pyridin-6-yl)pyrimidin-2-yl]bicyclo[3.1.0]hex-2-ene-6-carboxylate

- 5 *Intermediate 134* (70%, 230 mg, 0.58 mmol) and *Intermediate 29* (230 mg, 0.58 mmol) were dissolved in 1,4-dioxane (3 mL). Aqueous potassium carbonate solution (2M, 0.87 mL) was added. The reaction mixture was degassed with nitrogen for 5 minutes. Tetrakis(triphenylphosphine)palladium(0) (67 mg, 0.06 mmol) was added and the reaction mixture was heated under microwave irradiation for 2 h at 120°C. The
- 10 reaction mixture was allowed to cool, diluted with ethyl acetate (50 mL), washed with aqueous sodium bicarbonate solution (20 mL) and brine (20 mL), dried over sodium sulfate and concentrated. The resulting black oil was successively purified by column chromatography, using 0-10% methanol in dichloromethane, and preparative HPLC, to afford the *title compound* (85 mg, 28%) as a white sticky solid. Method B HPLC-MS:
- 15 MH+ *m/z* 517, RT 1.70 minutes.

INTERMEDIATE 136

4-(*tert*-Butyl) 2-methyl morpholine-2,4-dicarboxylate

- 20 4-(*tert*-Butoxycarbonyl)morpholine-2-carboxylic acid (500 mg, 2.16 mmol) and potassium carbonate (900 mg, 6.51 mmol) were placed in a round-bottom flask. The flask was flushed with nitrogen and DMF (5 mL) was added. The mixture was cooled to 0°C while stirring and iodomethane (0.54 mL, 8.67 mmol) was added dropwise. The reaction mixture was allowed to warm to r.t. and stirred for 15 h. The reaction mixture
- 25 was quenched with saturated aqueous ammonium chloride solution (15 mL), diluted with water (30 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organic layers were washed with brine (25 mL), dried over sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography (0-25% ethyl acetate in heptane) to afford the *title compound* (478 mg, 90%). δ_{H} (500 MHz, DMSO-*d*₆) 4.18 (dd, *J* 8.4, 3.4 Hz, 1H), 3.84 (dt, *J* 11.6, 4.1 Hz, 2H), 3.67 (s, 3H), 3.54-3.44 (m, 2H), 3.31 (s, 1H), 3.09 (ddd, *J* 13.2, 9.1, 3.4 Hz, 1H), 1.40 (s, 9H).
- 30

INTERMEDIATE 137**4-tert-Butyl 2-methyl 2-methylmorpholine-2,4-dicarboxylate**

Diisopropylamine (0.35 mL, 2.48 mmol) was added dropwise to 2.5M
5 butyllithium solution (1 mL) in THF (2 mL) at -74°C. The mixture was allowed to warm to r.t. whilst stirring for 1 h. The mixture was re-cooled and *Intermediate 136* (478 mg, 1.95 mmol) in THF (5 mL) was added dropwise at -78°C. The reaction mixture was allowed to stir for 1 h, then iodomethane (0.15 mL, 2.41 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature and was stirred for 16 h. The
10 reaction mixture was cooled to -78°C and 2M lithium dipropan-2-ylazanide (10 mL) was added dropwise. The reaction mixture was allowed to stir for 1 h. Iodomethane (0.05 mL, 0.8 mmol) was added dropwise at -78°C. The reaction mixture was allowed to stir at r.t. overnight. The reaction mixture was cooled to 0°C and quenched with saturated aqueous ammonium chloride solution (10 mL), diluted with water (20 mL) and extracted
15 with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine (25 mL), dried over sodium sulfate and concentrated under vacuum. The crude residue was purified onto a 25g silica cartridge, eluting with a gradient of 0-25% ethyl acetate in heptane, to afford the *title compound* (110 mg, 22%) as a pale yellow oil. δ_{H} (500 MHz, CD₃OD) 4.39 (d, *J* 13.2 Hz, 1H), 3.79-3.70 (m, 6H), 2.99 (s, 1H), 2.85 (d, *J* 12.3 Hz, 1H),
20 1.46 (s, 9H), 1.33 (s, 3H).

INTERMEDIATE 138**Methyl 2-methylmorpholine-2-carboxylate hydrochloride**

25 *Intermediate 137* (110 mg, 0.42 mmol) was dissolved in a 4M solution of hydrogen chloride in 1,4-dioxane (3 mL) and allowed to stir for 18 h at r.t. The reaction mixture was concentrated under vacuum to afford the *title compound* (83 mg, 100%) as a yellow oil. δ_{H} (500 MHz, CD₃OD) 4.01-3.96 (m, 1H), 3.86 (s, 3H), 3.83-3.79 (m, 1H), 3.66 (s, 2H), 3.21 (d, *J* 2.8 Hz, 1H), 3.08 (d, *J* 13.1 Hz, 1H), 1.44 (s, 3H).

INTERMEDIATE 139

Methyl 4-[5-(3-{[2-(difluoromethoxy)phenyl]methyl}-2-methylimidazo[1,2-a]pyridin-6-yl)pyrimidin-2-yl]-2-methylmorpholine-2-carboxylate

- 5 *Intermediate 29* (85%, 130 mg, 0.28 mmol), *Intermediate 138* (80 mg, 0.41 mmol) and a 1M solution of potassium carbonate in water (0.85 mL) were suspended in NMP (3 mL). The reaction mixture was heated at 120°C under microwave irradiation (2 x 1 h). The reaction mixture was allowed to cool to r.t., diluted with DCM (20 mL) and acidified using 1M HCl (5 mL). The organic phase was separated, washed with brine and dried
- 10 over sodium sulphate, then filtered and concentrated under vacuum. The residue was purified by preparative HPLC (Method C) to afford the *title compound* (48 mg, 17%) as a light brown solid. δ_{H} (500 MHz, CD₃OD) 8.51 (d, *J* 2.1 Hz, 2H), 8.31 (s, 1H), 7.64 (s, 2H), 7.32-7.27 (m, 1H), 7.22-7.12 (m, 3H), 6.93 (t, *J* 74.0 Hz, 1H), 5.05 (d, *J* 13.3 Hz, 1H), 4.40 (d, 3H), 3.88-3.82 (m, 2H), 3.67 (s, 3H), 3.17 (dt, *J* 13.8, 7.5 Hz, 1H), 3.03 (d, *J*
- 15 13.3 Hz, 1H), 2.46 (s, 3H), 1.40 (s, 3H).

INTERMEDIATE 140

Ethyl 3-azabicyclo[4.1.0]heptane-6-carboxylate hydrochloride (*Racemic*)

- 20 A 4M solution of hydrogen chloride in 1,4-dioxane (2.07 mL, 8 mmol) was added to a solution of 3-(*tert*-butyl) 6-ethyl 3-azabicyclo[4.1.0]heptane-3,6-dicarboxylate (1 g, 4 mmol) in ethanol (10 mL) at room temperature. The mixture was stirred at room temperature for 2.5 h. Additional ethanol (10 mL) and 4M solution of hydrogen chloride in 1,4-dioxane (4.14 mL) were added and the mixture was heated at 50°C for 1.5 h. The
- 25 reaction mixture was cooled and evaporated under vacuum. A second reaction batch was prepared whereby a 4M solution of hydrogen chloride in 1,4-dioxane (10.4 mL, 40 mmol) was added to a solution of 3-(*tert*-butyl) 6-ethyl 3-azabicyclo[4.1.0]heptane-3,6-dicarboxylate (1 g, 4 mmol) in ethanol (40 mL) and the reaction mixture was warmed to 75°C and stirred at this temperature overnight. The reaction mixture was cooled to r.t.
- 30 The batches were combined, then concentrated under vacuum, to afford the *title compound* (3.1 g) as a pale yellow solid. δ_{H} (250 MHz, DMSO-*d*₆) 9.07 (d, *J* 37.9 Hz, 2H), 4.05 (q, *J* 7.1 Hz, 2H), 3.08 (d, *J* 13.1 Hz, 1H), 2.83 (s, 2H), 2.61 (dt, *J* 13.7, 6.5 Hz, 1H), 2.00-1.81 (m, 1H), 1.71 (q, *J* 7.0 Hz, 1H), 1.36-1.22 (m, 2H), 1.18 (q, *J* 7.1, 6.4 Hz,

3H).

INTERMEDIATE 141

5 Methyl 4-[5-(3-{[2-(difluoromethoxy)phenyl]methyl}-2-methylimidazo[1,2-*a*]pyridin-6-yl)pyridin-2-yl]cyclohex-3-ene-1-carboxylate

Intermediate 30 (470 mg, 1.17 mmol), *Intermediate 56* (375 mg, 1.41 mmol) and 2M aqueous dipotassium carbonate solution (1.76 mL) were added to 1,4-dioxane (4 mL) in a microwave tube. The mixture was degassed for 10 minutes, then Bedford's catalyst
10 (126 mg, 0.12 mmol) was added. The reaction mixture was heated under microwave irradiation for 30 minutes at 150°C, then filtered through celite. The celite was washed with ethyl acetate. The filtrate was washed with water (50 mL) and brine (25 mL), dried with sodium sulphate and concentrated under vacuum. The crude brown oil was purified on Biotage using 100g SNAP cartridge (loaded with DCM, eluent: 95% EtOAc/heptane
15 to 100% EtOAc) to afford the *title compound* (262 mg, 40%) as an off-white solid. Method C HPLC-MS: MH⁺ *m/z* 504, RT 1.09 minutes.

INTERMEDIATE 142

20 Methyl 1-[(1*R*)-1-phenylethyl]-2,5-dihydro-1*H*-pyrrole-3-carboxylate

To a stirred solution of (1*R*)-*N*-(methoxymethyl)-1-phenyl-*N*-[(trimethylsilyl)-methyl]ethanamine (55.83 mL, 205.62 mmol) and methyl prop-2-ynoate (22.5 mL, 252.9 mmol) in dichloromethane (500 mL) at 0°C under nitrogen was added trifluoroacetic acid (800 µL, 10.45 mmol). The reaction mixture was allowed to stir at 0°C for 20 minutes,
25 then the ice bath was removed and the solution was allowed to warm to room temperature. The solution was stirred at room temperature for 1 h. The reaction mixture was concentrated to dryness and the residue was purified by FCC, eluting with 0-70% EtOAc in heptane, to afford the *title compound* (26.5 g, 56%) as a yellow oil. δ_H (500 MHz, CDCl₃) 7.41-7.29 (m, 4H), 7.28-7.21 (m, 1H), 6.77-6.70 (m, 1H), 3.72 (s, 3H),
30 3.71-3.65 (m, 1H), 3.65-3.42 (m, 4H), 1.40 (d, *J* 6.6 Hz, 3H). Method F HPLC-MS: MH⁺ *m/z* 232, RT 1.62 minutes.

INTERMEDIATE 143Methyl 3-[(1*R*)-1-phenylethyl]-3-azabicyclo[3.1.0]hexane-1-carboxylate

To a stirred suspension of potassium *tert*-butoxide (12.86 g, 114.57 mmol) in anhydrous DMSO (80 mL) under nitrogen in a cold water bath (~5°C) was added trimethylsulfoxonium iodide (26.72 g, 120.3 mmol) portionwise. The mixture was stirred for 15 minutes, then warmed to 40°C. The mixture was cooled to approximately 5°C with a cold water bath, then a solution of *Intermediate 142* (13.25 g, 57.30 mmol) in DMSO (40 mL) was added portionwise. The mixture was stirred for 1 minute, then warmed to 50°C and stirred for 1 h. The mixture was cooled to room temperature, then poured into water (120 mL) and ethyl acetate (120 mL). The phases were separated and the organic layer was washed with brine (80 mL), dried over sodium sulfate and concentrated to dryness. The residue was purified by FCC, eluting with 0-30% EtOAc in heptane. The procedure was repeated on the same scale as above, and the purified products were combined, to afford the *title compound* (11.9 g, 42%) as a colourless oil. Method F HPLC-MS: MH⁺ *m/z* 246, RT 1.77 minutes.

INTERMEDIATE 144Methyl 3-azabicyclo[3.1.0]hexane-1-carboxylate hydrochloride (*Enantiomer A*)

Intermediate 143 (5 g, 20 mmol) was separated using chiral preparative HPLC (Chiracel OJ column, 20 x 250 mm, 5 µm; 100% acetonitrile eluent; 20 mL/minute flow rate) and the second-eluting diastereomer was isolated (1.87 g, 7.62 mmol). This was dissolved in methanol (55 mL) and the mixture was degassed with nitrogen, then palladium on carbon (10%, 195 mg, 0.18 mmol) was added. The reaction mixture was stirred under a hydrogen balloon at room temperature for 5 h. The reaction mixture was filtered through celite and the solids were washed with excess methanol. The filtrate was concentrated by evaporation. To the residue was added 4M hydrochloric acid in diethyl ether (10 mL) and the mixture was stirred at room temperature for 10 minutes. The resulting precipitate was filtered, washed with diethyl ether and dried, to afford the *title compound* (1.21 g, 93%) as an off-white solid. δ_H (500 MHz, CD₃OD) 3.83 (dd, *J* 11.8, 1.3 Hz, 1H), 3.75 (s, 3H), 3.59-3.52 (m, 2H), 3.44 (d, *J* 11.7 Hz, 1H), 2.40-2.30 (m, 1H), 1.76-1.69 (m, 1H), 1.17 (t, *J* 5.9 Hz, 1H).

INTERMEDIATE 145

5 3-Chloro-5-(3-{[2-(difluoromethoxy)phenyl]methyl}-2-methylimidazo[1,2-*a*]pyridin-6-yl)-2-fluoropyridine

A mixture of *Intermediate 7* (100 mg, 0.27 mmol), 3-chloro-2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (105 mg, 0.41 mmol) and aqueous 2M sodium carbonate solution (0.2 mL) in acetonitrile (1 mL) was purged with nitrogen for 5 minutes. Bis[3-(diphenylphosphanyl)cyclopenta-2,4-dien-1-yl]iron dichloropalladium
 10 dichloromethane complex (11 mg, 0.01 mmol) was then added and the reaction mixture was heated at 150°C under microwave irradiation for 30 minutes. The reaction mixture was combined and partitioned between ethyl acetate (50 mL) and water (30 mL). The aqueous layer was separated and extracted with ethyl acetate (50 mL). The combined organic extracts were washed with brine (15 mL), dried over sodium sulfate and
 15 concentrated by evaporation. The residue was purified by FCC, using a KP-NH cartridge (Biotage®) and eluting with 0-50% ethyl acetate in heptane. The material was then triturated with dichloromethane/heptane to afford the *title compound* (0.14 g, 39%) as a white solid. δ_{H} (500 MHz, CDCl_3) 8.18 (dd, J 2.2, 1.3 Hz, 1H), 7.97 (s, 1H), 7.91 (dd, J 8.4, 2.3 Hz, 1H), 7.76 (d, J 9.4 Hz, 1H), 7.39-7.30 (m, 2H), 7.20 (d, J 7.8 Hz, 1H), 7.13 (t, J 7.5 Hz, 1H), 6.96 (d, J 7.7 Hz, 1H), 6.67 (t, J 73.6 Hz, 1H), 4.35 (s, 2H), 2.59 (s, 3H).
 20 Method C HPLC-MS: MH^+ m/z 418, RT 1.11 minutes.

INTERMEDIATE 146

25 Ethyl 1-[3-chloro-5-(3-{[2-(difluoromethoxy)phenyl]methyl}-2-methylimidazo[1,2-*a*]pyridin-6-yl)pyridin-2-yl]-4-methylpiperidine-4-carboxylate

A mixture of *Intermediate 145* (97% pure, 50 mg, 0.12 mmol) and ethyl 4-methylpiperidine-4-carboxylate hydrochloride (48 mg, 0.23 mmol) in pyridine (2 mL) was heated at 180°C under microwave irradiation for a total of 4 h. The reaction mixture
 30 was concentrated under vacuum. The residue was purified by FCC, using a KP-NH cartridge (Biotage®) and eluting with 0-30% ethyl acetate in heptane followed by 100% EtOAc. The material was then triturated with MeCN/water, and purified by preparative HPLC (Method C), to afford the *title compound* (56 mg, 32%) as an orange oil. δ_{H} (500

MHz, DMSO-d₆) 8.55-8.44 (m, 2H), 8.12 (d, *J* 2.2 Hz, 1H), 7.54 (d, *J* 1.1 Hz, 2H), 7.46-7.05 (m, 4H), 7.05-6.93 (m, 1H), 4.39 (s, 2H), 4.13 (q, *J* 7.1 Hz, 2H), 3.59-3.46 (m, 2H), 3.09-2.90 (m, 2H), 2.30 (s, 3H), 2.11 (d, *J* 14.0 Hz, 2H), 1.58 (ddd, *J* 13.4, 10.2, 3.5 Hz, 2H), 1.27-1.11 (m, 6H). Method A HPLC-MS: MH⁺ *m/z* 569, RT 4.15 minutes.

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INTERMEDIATE 147

Ethyl 3-methyl-4-oxocyclohexane-1-carboxylate

Lithium hexamethyldisilazanide in THF/ethylbenzene (1M, 117.5 mL) was added dropwise to a stirred solution of ethyl 4-oxocyclohexane-1-carboxylate (20 g, 0.12 mol) in THF (100 mL) at -78°C. The mixture was stirred for 30 minutes. Iodomethane (7.32 mL, 0.12 mol) was added dropwise, then the mixture was gradually warmed to room temperature over 1 h and stirred for 4 h. The mixture was quenched with water (200 mL) and extracted with ethyl acetate (2 x 200 mL). The combined organic layers were washed with brine (100 mL), dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified twice by FCC, eluting with 20-70% ethyl acetate in cyclohexane, to afford the *title compound* (3.3 g, 15%) as a colourless oil. δ_{H} (500 MHz, CDCl₃) 4.15 (q, *J* 7.1 Hz, 2H), 2.82 (tt, *J* 12.2, 3.5 Hz, 1H), 2.50-2.40 (m, 2H), 2.40-2.27 (m, 3H), 1.91-1.78 (m, 1H), 1.59 (q, *J* 13.0 Hz, 1H), 1.27 (t, *J* 7.1 Hz, 3H), 1.05 (d, *J* 6.5 Hz, 3H).

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INTERMEDIATE 148

Ethyl 5-methyl-4-(trifluoromethanesulfonyloxy)cyclohex-3-ene-1-carboxylate

Lithium hexamethyldisilazanide in THF/ethylbenzene (1M, 18.64 mL) was added dropwise to a stirred solution of *Intermediate 147* (3.27 g, 17.75 mmol) in THF (15 mL) at -78°C. The mixture was stirred for 1 h. 1,1,1-Trifluoro-*N*-phenyl-*N*-[(trifluoromethyl)sulfonyl]methanesulfonamide (6.66 g, 18.64 mmol) in THF (25 mL) was added over 10 minutes and the mixture was stirred for another 30 minutes. The mixture was warmed to room temperature and stirred for 12 h. The mixture was quenched with aqueous sodium hydrogensulfate solution (100 mL), extracted into ethyl acetate (300 mL), and washed with 0.5M aqueous NaOH solution (2 x 50 mL), saturated ammonium chloride (50 mL) and brine (50 mL), then dried over magnesium sulfate and concentrated under reduced

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pressure. The residue was purified by FCC, eluting with 5-10% ethyl acetate in heptane, to afford the *title compound* (5.3g, 90%) as a colourless oil. δ_{H} (500 MHz, CDCl_3) 5.79-5.66 (m, 1H), 4.16 (q, J 7.1 Hz, 2H), 2.75-2.54 (m, 2H), 2.52-2.34 (m, 2H), 2.33-2.22 (m, 1H), 1.58-1.44 (m, 1H), 1.27 (t, J 7.1 Hz, 3H), 1.17 (d, J 6.9 Hz, 3H).

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INTERMEDIATE 149

Ethyl 5-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-ene-1-carboxylate

10 *Intermediate 148* (95% pure, 5.3 g, 15.92 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (6.06 g, 23.88 mmol) and potassium acetate (4.69 g, 47.76 mmol) were suspended in 1,4-dioxane (80 mL) and degassed for 15 minutes. 1,1'-Bis(diphenylphosphanyl)ferrocene (0.26 g, 0.48 mmol) was added, followed by bis[3-(diphenylphosphanyl)cyclopenta-2,4-dien-1-yl]iron
15 dichloropalladium dichloromethane complex (0.39 g, 0.48 mmol), and the mixture was heated at 90°C for 2 h. The mixture was cooled to room temperature, diluted with water (100 mL) and extracted with ethyl acetate (2 x 150 mL). The combined organic layers were washed with brine (50 mL), dried over magnesium sulfate and concentrated. The residue was purified by FCC, eluting with 10-50% ethyl acetate in heptane, to afford the
20 *title compound* (3.4 g, 69%) as a colourless thick oil. δ_{H} (500 MHz, CDCl_3) 6.52-6.45 (m, 1H), 4.17-4.08 (m, 2H), 2.54-2.45 (m, 1H), 2.45-2.36 (m, 1H), 2.35-2.18 (m, 2H), 2.13-2.05 (m, 1H), 1.26 (d, J 5.5 Hz, 16H), 1.10 (d, J 7.0 Hz, 3H).

INTERMEDIATE 150

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Ethyl 4-[5-(3-{[2-(difluoromethoxy)phenyl]methyl}-2-methylimidazo[1,2-*a*]pyridin-6-yl)pyrimidin-2-yl]-5-methylcyclohex-3-ene-1-carboxylate

Intermediate 29 (430 mg, 0.86 mmol), *Intermediate 149* (73% pure, 395 mg, 1.03 mmol) and 2M aqueous potassium carbonate solution (1.72 mL) were suspended in 1,4-
30 dioxane (15 mL) and the mixture was degassed with nitrogen for 10 minutes. Tetrakis-(triphenylphosphine)palladium(0) (64 mg, 0.06 mmol) was added and the mixture was heated at 120°C for 8 h. The mixture was cooled to room temperature, diluted with water (100 mL) and extracted with ethyl acetate (3 x 100 mL). The combined organic layers

were washed with water (50 mL), dried over magnesium sulfate and concentrated. The residue was purified by FCC, eluting with 2-10% methanol in DCM, to afford the *title compound* (120 mg, 20%) as a brownish oil. δ_{H} (500 MHz, CDCl_3) 8.76 (s, 2H), 7.92 (s, 1H), 7.68 (d, J 9.2 Hz, 1H), 7.33 (dd, J 9.3, 1.7 Hz, 1H), 7.29-7.23 (m, 1H), 7.17 (d, J 7.9 Hz, 1H), 7.13-7.04 (m, 1H), 6.95-6.86 (m, 2H), 6.64 (t, J 73.7 Hz, 1H), 4.32 (s, 2H), 4.17 (q, J 7.1 Hz, 2H), 3.20-3.06 (m, 1H), 2.67-2.57 (m, 1H), 2.54 (s, 4H), 2.52-2.43 (m, 1H), 2.40-2.28 (m, 1H), 1.58 (ddd, J 13.1, 12.1, 10.3 Hz, 1H), 1.29 (t, J 7.1 Hz, 3H), 1.11 (d, J 6.8 Hz, 3H). Method B HPLC-MS: MH^+ m/z 533.5, RT 1.77 minutes.

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INTERMEDIATE 151

Ethyl 4-[5-(3-{[2-(difluoromethoxy)phenyl]methyl}-2-methylimidazo[1,2-*a*]pyridin-6-yl)pyrimidin-2-yl]-3-methylcyclohexane-1-carboxylate (unknown isomer)

To a stirring solution of *Intermediate 150* (50 mg, 0.09 mmol) in ethanol (5 mL), degassed and purged with nitrogen, was added palladium on carbon (10%, 10 mg, 0.01 mmol). The reaction mixture was degassed and purged with nitrogen, then stirred under a hydrogen balloon at room temperature for 4 h. The reaction mixture was filtered through celite and the solids were washed with excess methanol. The filtrate was concentrated by evaporation. The resulting pale oil was purified by preparative HPLC (Method D), and the second-eluting peak was isolated, to afford the *title compound* (13 mg, 26%) as a pale oil. δ_{H} (500 MHz, CDCl_3) 8.74 (s, 2H), 7.92 (s, 1H), 7.71 (d, J 9.2 Hz, 1H), 7.35 (dd, J 9.2, 1.6 Hz, 1H), 7.30-7.27 (m, 1H), 7.18 (d, J 7.9 Hz, 1H), 7.09 (t, J 7.5 Hz, 1H), 6.88 (d, J 6.6 Hz, 1H), 6.65 (t, J 73.7 Hz, 1H), 4.33 (s, 2H), 4.15 (q, J 7.1 Hz, 2H), 3.30 (q, J 4.8 Hz, 1H), 2.54 (s, 3H), 2.46 (tt, J 11.1, 3.8 Hz, 1H), 2.35-2.23 (m, 1H), 2.18-2.00 (m, 3H), 1.86 (ddd, J 13.4, 9.8, 5.3 Hz, 1H), 1.74 (ddd, J 16.9, 8.7, 4.4 Hz, 2H), 1.27 (t, J 7.1 Hz, 3H), 0.86 (d, J 7.0 Hz, 3H). Method E HPLC-MS: MH^+ m/z 535, RT 5.32 minutes.

INTERMEDIATE 152

2-Chloro-5-(3-{[2-(difluoromethoxy)phenyl]methyl}-7-fluoro-2-methylimidazo[1,2-*a*]pyridin-6-yl)pyrimidine

Intermediate 68 (5.5 g, 14.28 mmol) and 2-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine (6.85 g, 28.48 mmol) were dissolved in 1,4-dioxane (180

mL) and DMSO (50 mL). Sodium carbonate in water (2M, 21 mL) was added and the resulting mixture was degassed with nitrogen for 45 minutes. Dichlorobis(triphenylphosphine)palladium(II) (505 mg, 0.72 mmol) and tri-*tert*-butylphosphonium tetrafluoroborate (410 mg, 1.41 mmol) were added and the reaction mixture was heated at 120°C under nitrogen for 6.5 h. The reaction mixture was diluted with water (200 mL) and extracted with EtOAc (3 x 200 mL). The combined organic layers were dried over sodium sulphate, filtered and concentrated to dryness. The residue was purified by FCC, using a KP-NH cartridge (Biotage®) and eluting with 0-50% EtOAc in heptane, to afford the *title compound* (3.52 g, 59%) as a white solid. δ_{H} (500 MHz, CDCl_3) 8.67 (d, *J* 1.4 Hz, 2H), 7.81 (d, *J* 7.2 Hz, 1H), 7.35 (d, *J* 10.7 Hz, 1H), 7.30-7.26 (m, 1H), 7.16 (d, *J* 7.9 Hz, 1H), 7.11 (t, *J* 7.5 Hz, 1H), 6.97-6.91 (m, 1H), 6.62 (t, *J* 73.6 Hz, 1H), 4.29 (s, 2H), 2.52 (s, 3H). Method C HPLC-MS: MH^+ *m/z* 419, RT 1.03 minutes.

INTERMEDIATE 153

Ethyl 4-{[5-(3-{[2-(difluoromethoxy)phenyl]methyl}-2-methylimidazo[1,2-*a*]pyridin-6-yl)pyrimidin-2-yl]methyl}cyclohexane-1-carboxylate

Ethyl 4-methylidenecyclohexanecarboxylate (50 mg, 0.3 mmol) was stirred with 0.5M 9-borabicyclo[3.3.1]nonane in THF (0.89 mL), which was added slowly under nitrogen. The reaction mixture was stirred at room temperature overnight. The crude mixture was cooled to 0°C and *Intermediate 29* (203 mg, 0.51 mmol) in DMF (3 mL) was added, followed by bis[3-(diphenylphosphanyl)cyclopenta-2,4-dien-1-yl]iron dichloropalladium dichloromethane complex (24 mg, 0.03 mmol) and 2M aqueous potassium carbonate solution (0.22 mL). The reaction mixture was stirred at room temperature over the weekend, then heated at 60°C for 1.5 h. Further bis[3-(diphenylphosphanyl)cyclopenta-2,4-dien-1-yl]iron dichloropalladium dichloromethane complex (50 mg, 0.061 mmol) was added and the mixture was heated at 80°C overnight under nitrogen. The reaction mixture was added to cold water and 0.5M aqueous NaOH solution (0.5 mL) was added. The mixture was extracted with DCM (100 mL), dried over sodium sulphate, filtered and concentrated under vacuum. The resulting brown oil was purified twice by FCC, eluting with 0-30% MeOH in DCM. The material was further purified by preparative HPLC (Method C), to afford the *title compound* (11.4 mg, 7%) as a brown oil. Method B HPLC-MS: MH^+ *m/z* 535, RT 1.72 minutes.

INTERMEDIATE 154**1,4-Dioxaspiro[4.5]dec-7-en-8-yl trifluoromethanesulfonate**

5 Lithium hexamethyldisilazide in THF/ethylbenzene (1M, 6.75 mL) was added dropwise to a stirred solution of 1,4-dioxaspiro[4.5]decan-8-one (1 g, 6.41 mmol) in THF (5 mL) at -78°C. The mixture was stirred for 1 h. 1,1,1-Trifluoro-*N*-phenyl-*N*-[(trifluoromethyl)sulfonyl]methanesulfonamide (2.4 g, 6.75 mmol) in THF (5 mL) was added over 5 minutes and the mixture was stirred for another 30 minutes. The reaction
10 mixture was warmed to room temperature and stirred for 12 h. The reaction mixture was quenched with aqueous sodium hydrogensulfate solution, extracted with ethyl acetate (100 mL) and washed with 0.5M aqueous NaOH solution (50 mL), saturated aqueous ammonium chloride solution (50 mL) and brine (50 mL), then dried over magnesium sulfate and concentrated under reduced pressure, to afford the *title compound* (2.3 g, 87%
15 yield at 70% purity) as a yellow oil, which was used without further purification. δ_{H} (500 MHz, CDCl_3) 5.53 (t, *J* 4.1 Hz, 1H), 3.91-3.80 (m, 4H), 2.46-2.37 (m, 2H), 2.32-2.24 (m, 2H), 1.78 (t, *J* 6.6 Hz, 2H).

INTERMEDIATE 155

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Methyl 1,4-dioxaspiro[4.5]dec-7-ene-8-carboxylate

Palladium diacetate (125 mg, 0.555 mmol, 10 mol %) was added to a mixture of *Intermediate 154* (1.6 g, 5.55 mmol), triphenylphosphine (291 mg, 1.11 mmol, 20 mol %), triethylamine (1.53 mL, 11.04 mmol) and MeOH (20 mL, 624 mmol) in DMF (20
25 mL). The mixture was placed under a carbon monoxide atmosphere at 5 bar pressure and stirred at room temperature for 16 h. The reaction mixture was quenched with water (100 mL), extracted with diethyl ether (2 x 100 mL), dried over MgSO_4 and concentrated. The resulting brown oil (1.85 g) was redissolved in EtOAc, washed with water (6 times), dried over MgSO_4 and concentrated, to afford the *title compound* (900 mg, 82%) as a brown
30 oil. δ_{H} (500 MHz, CDCl_3) 6.79 (tt, *J* 3.8, 1.6 Hz, 1H), 3.91 (s, 4H), 3.65 (s, 3H), 2.45 (tq, *J* 6.5, 2.3 Hz, 2H), 2.38-2.34 (m, 2H), 1.72 (t, *J* 6.6 Hz, 2H).

INTERMEDIATE 156**1,4-Dioxaspiro[4.5]dec-7-en-8-ylmethanol**

To a 1.2M solution of DIBAL in toluene (10.64 mL) in DCM (10 mL) at -78°C was added *Intermediate 155* (1.1 g, 5.55 mmol) in DCM (10 mL) over 2 minutes. After 1.5 h, the reaction mixture was quenched with methanol (10 mL) and diluted with 10% w/v aqueous NaOH solution (30 mL). The resulting slurry was allowed to warm to room temperature, and after 30 minutes the layers were separated. The aqueous layer was washed with DCM (2 x 50 mL), and the combined organic phases were dried over sodium sulphate, then filtered and concentrated under vacuum, to afford the *title compound* (840 mg, 85%) as a yellow-orange oil, which was used without further purification. δ_{H} (500 MHz, DMSO- d_6) 5.44 (tt, J 3.5, 1.5 Hz, 1H), 4.65 (t, J 5.5 Hz, 1H), 3.87 (s, 4H), 3.78 (d, J 3.9 Hz, 2H), 2.15 (s, 2H), 2.06 (t, J 5.8 Hz, 2H), 1.65 (t, J 6.6 Hz, 2H).

INTERMEDIATE 157**Spiro[bicyclo[4.1.0]heptane-3,2'-[1,3]dioxolane]-6-ylmethanol**

Diethylzinc in toluene (1.1M, 17.76 mL) was added to DCM (20 mL) under a stream of nitrogen at 0°C. Diiodomethane (1.57 mL, 19.54 mmol) in DCM (10 mL) was added and stirring was continued at 0°C for 30 minutes. *Intermediate 156* (95% pure, 1.75 g, 9.77 mmol) in DCM (20 mL) was added dropwise over 20 minutes, then the reaction mixture was warmed to room temperature and stirred for 2 h. DCM (50 mL) was added, together with 1N HCl (50 mL), and the layers were separated. The organic layers were washed with water (50 mL), saturated NaHCO₃ solution (50 mL) and brine (50 mL), then dried over sodium sulfate and concentrated, to afford the *title compound* (1.57 g, 79% yield at 90% purity) as a yellow oil, which was used without further purification. δ_{H} (500 MHz, DMSO- d_6) 4.40 (t, J 5.8 Hz, 1H), 3.84-3.73 (m, 4H), 3.24-3.18 (m, 1H), 3.11 (dd, J 10.9, 5.8 Hz, 1H), 1.92 (tdd, J 9.8, 4.9, 2.7 Hz, 2H), 1.74 (dt, J 13.5, 5.6 Hz, 1H), 1.59 (d, J 14.3 Hz, 1H), 1.41 (dtd, J 11.7, 5.8, 1.8 Hz, 1H), 1.30 (ddd, J 13.3, 10.0, 5.2 Hz, 1H), 0.82-0.76 (m, 1H), 0.48 (dd, J 9.0, 4.0 Hz, 1H), 0.29 (t, J 4.7 Hz, 1H).

INTERMEDIATE 158Methyl 4-oxobicyclo[4.1.0]heptane-1-carboxylate

Intermediate 157 (90% pure, 1.57 g, 7.67 mmol) was suspended in water (100 mL), then KMnO₄ (4.61 g, 29.14 mmol) and 2M aqueous KOH solution (14.6 mL) were added. The mixture was heated under reflux for 2 h. The hot solution was filtered through celite and the solids were washed with water. The filtrate was acidified to pH 2 with 1N HCl, extracted into EtOAc (3 x 150 mL), dried over sodium sulfate and concentrated. The resulting orange oil (0.84 g) was dissolved in DCM (28 mL) and MeOH (12 mL) under a nitrogen atmosphere. (Diazomethyl)(trimethyl)silane in diethyl ether (2M, 4.22 mL) was added, and the reaction mixture was stirred at room temperature for 16 h. Acetic acid was added to the reaction mixture until the yellow colour disappeared, then the mixture was evaporated to dryness. The residue was dissolved in MeOH (50 mL) and concentrated HCl (4 mL) was added dropwise. The reaction mixture was stirred at 70°C for 1.5 h before the solvent was removed under vacuum. The residue was partitioned between ethyl acetate (100 mL) and 2M aqueous KOH solution (100 mL). The organic layer was separated and washed with brine (2 x 50 mL), then dried over sodium sulfate and concentrated. The residue was purified by FCC, eluting with 0-100% EtOAc in heptane, to afford the *title compound* (423 mg, 31%) as a yellow oil. 3.61 (s, 3H), 2.71 (dd, *J* 18.1, 5.5 Hz, 1H), 2.50 (p, *J* 1.7 Hz, 1H), 2.42 (dd, *J* 18.1, 3.1 Hz, 1H), 2.24-2.10 (m, 2H), 2.01 (dt, *J* 14.0, 5.8 Hz, 1H), 1.68 (dtd, *J* 9.0, 5.8, 3.2 Hz, 1H), 1.31 (dd, *J* 9.2, 5.0 Hz, 1H), 1.15-1.10 (m, 1H).

INTERMEDIATE 159Methyl 4-(trifluoromethanesulfonyloxy)bicyclo[4.1.0]heptene-1-carboxylate

Lithium hexamethyldisilazide in THF/ethylbenzene (1M, 2.52 mL) was added dropwise to a stirred solution of *Intermediate 158* (423 mg, 2.52 mmol) in THF (15 mL) at -78°C. Stirring was continued at this temperature for 1 h, then 1,1,1-trifluoro-*N*-phenyl-*N*-[(trifluoromethyl)sulfonyl]methanesulfonamide (943 mg, 2.64 mmol) in THF (5 mL) was added over 5 minutes and stirring was continued for another 30 minutes. The reaction mixture was allowed to warm to room temperature and was stirred for 16 h. The reaction mixture was quenched with saturated ammonium chloride solution (20 mL), the

layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 50 mL). The organic phase was sequentially washed with 0.5M aqueous NaOH solution (2 x 25 mL), saturated aqueous ammonium chloride solution (50 mL) and brine (50 mL), then dried over sodium sulphate, filtered and concentrated *in vacuo*, to afford the *title compound* (1.27 g, 100% yield at 60% purity) as an orange oil, which was used without further purification. δ_{H} (500 MHz, DMSO- d_6) 6.25 (dd, J 6.2, 2.0 Hz, 1H), 3.62 (s, 3H), 2.33-2.20 (m, 3H), 2.14 (ddd, J 13.5, 11.3, 7.1 Hz, 1H), 1.91 (dt, J 9.0, 5.9 Hz, 1H), 1.52 (dd, J 9.0, 4.5 Hz, 1H), 1.28-1.25 (m, 1H).

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INTERMEDIATE 160

Methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)bicyclo[4.1.0]heptene-1-carboxylate (unknown regioisomer)

To a flask were added bis(pinacolato)diboron (0.71 g, 2.79 mmol), potassium acetate (0.75 g, 7.61 mmol), bis[3-(diphenylphosphanyl)cyclopenta-2,4-dien-1-yl]iron dichloropalladium (42 mg, 0.076 mmol) and 1,1'-bis(diphenylphosphanyl)ferrocene (56 mg, 0.076 mmol), and the contents were flushed with nitrogen. A solution of *Intermediate 159* (60% pure, 1.27 g, 2.54 mmol) in 1,4-dioxane (20 mL) was added and the mixture was stirred at 80°C for 16 h. The reaction mixture was cooled to room temperature and filtered through a pad of celite. The solids were washed with EtOAc and the filtrate was evaporated to dryness. The residue was purified by FCC, eluting with 0-50% EtOAc in heptane, to afford the *title compound* (270 mg, 38%) as a colourless oil. δ_{H} (500 MHz, DMSO- d_6) 6.74 (dd, J 5.5, 2.9 Hz, 1H), 3.60 (s, 3H), 2.19-2.11 (m, 1H), 2.09-2.01 (m, 1H), 1.85-1.62 (m, 3H), 1.40 (dd, J 9.2, 4.1 Hz, 1H), 1.37-1.32 (m, 1H), 1.18 (d, J 2.0 Hz, 12H).

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INTERMEDIATE 161

Methyl 4-[5-(3-{[2-(difluoromethoxy)phenyl]methyl}-7-fluoro-2-methylimidazo[1,2-a]-pyridin-6-yl)pyrimidin-2-yl]bicyclo[4.1.0]heptene-1-carboxylate (unknown regioisomer)

30

A mixture of *Intermediate 152* (97% pure, 315 mg, 0.73 mmol), *Intermediate 160* (99% pure, 205 mg, 0.73 mmol) and 2M aqueous sodium carbonate solution (1.1 mL) in 1,4-dioxane (4.0 mL) was degassed with nitrogen for 5 minutes. Tetrakis(triphenyl-

phosphine)palladium(0) (84 mg, 0.073 mmol) was added, then the reaction mixture was heated at 120°C under microwave irradiation for 2 h. The reaction mixture was filtered through a pad of celite, then the solids were washed with EtOAc and the filtrate was evaporated to dryness. The residue was purified by FCC, eluting with 0-100% EtOAc in heptane. The resulting yellow oil was further purified by FCC, eluting with 80-100% EtOAc in heptane, to afford the *title compound* (155 mg, 38%) as a yellow-orange oil. δ_{H} (500 MHz, DMSO- d_6) 8.91 (dd, J 7.4, 1.4 Hz, 2H), 8.54 (d, J 7.4 Hz, 1H), 7.61 (dd, J 6.0, 2.7 Hz, 1H), 7.53 (d, J 11.4 Hz, 1H), 7.44-7.09 (m, 4H), 7.04 (d, J 6.6 Hz, 1H), 4.35 (s, 2H), 3.65 (d, J 2.6 Hz, 3H), 3.14-3.07 (m, 1H), 2.28 (s, 4H), 2.13-2.02 (m, 2H), 1.93 (td, J 13.2, 5.8 Hz, 1H), 1.57 (dd, J 9.2, 4.1 Hz, 1H), 1.49 (t, J 4.7 Hz, 1H). Method D HPLC-MS: MH+ m/z 535, RT 2.67 minutes.

INTERMEDIATE 162

Methyl 4-[5-(3-{[2-(difluoromethoxy)phenyl]methyl}-7-fluoro-2-methylimidazo[1,2-*a*]pyridin-6-yl)pyrimidin-2-yl]bicyclo[4.1.0]heptane-1-carboxylate

Intermediate 161 (95% pure, 26 mg, 0.05 mmol) was dissolved in ethanol (3 mL) and the reaction vessel was purged and evacuated thrice with nitrogen. Palladium on carbon (10%, 50% wet, 15 mg, 0.01 mmol) was added and the reaction vessel was purged and evacuated thrice with nitrogen gas, then purged and evacuated thrice with hydrogen gas. The reaction was stirred at room temperature under a hydrogen atmosphere for 3 days. The vessel was evacuated and purged with nitrogen gas. The mixture was filtered through a pad of Celite, then the solids were washed with MeOH (50 mL) and the filtrate was evaporated to dryness. The residue was purified by FCC, eluting with 0-100% MeOH in DCM, to afford the *title compound* (13 mg, 47%) as a yellow oil. Method D HPLC-MS: MH+ m/z 537, RT 2.54-2.55 minutes.

INTERMEDIATE 163

Methyl 6-[5-(3-{[2-(difluoromethoxy)phenyl]methyl}-2-methylimidazo[1,2-*a*]pyridin-6-yl)pyrimidin-2-yl]bicyclo[4.1.0]heptane-3-carboxylate

A solution of trimethylsulfoxonium iodide (176 mg, 0.79 mmol) and potassium *tert*-butoxide (85 mg, 0.75 mmol) in DMSO (2 mL) was stirred at 50°C for 45 minutes. A

solution of methyl 4-[5-(3-{[2-(difluoromethoxy)phenyl]methyl}-2-methylimidazo[1,2-
a]pyridin-6-yl)pyrimidin-2-yl]cyclohex-3-ene-1-carboxylate (prepared in an analogous
manner to that described for *Example 39*, 100 mg, 0.2 mmol) in DMSO (2 mL) was added
and the mixture was stirred at 50°C for 4 h, then at room temperature for 3 days. The
5 reaction mixture was diluted with DCM (10 mL) and washed with water (3 x 3 mL). The
aqueous washes were combined and further extracted with DCM (2 x 3 mL). The organic
extracts were combined, dried over sodium sulfate and evaporated. The resulting crude
brown residue was diluted with DCM (3 mL) and washed with 1N aqueous NaOH
solution (3 x 1 mL). The organic phase was dried over sodium sulfate and evaporated.
10 The resulting pale brown residue was purified by preparative TLC, eluting with 1%
MeOH in DCM, to afford the *title compound* (38.3 mg, 37%) as an off-white solid.
Method B HPLC-MS: MH⁺ *m/z* 519, RT 1.80 minutes.

INTERMEDIATE 164

15 2-Bromo-5-(3-{[2-(difluoromethoxy)phenyl]methyl}-2-methylimidazo[1,2-*a*]pyridin-6-
yl)pyrazine

A mixture of *Intermediate 31* (70% pure, 50 mg, 0.10 mmol), 2-bromo-5-iodo-
pyrazine (60 mg, 0.21 mmol) and 2M aqueous sodium carbonate solution (0.32 mL) in
20 DMSO (1 mL) was purged with nitrogen for 5 minutes. Tetrakis(triphenylphosphine)-
palladium(0) (12 mg, 0.01 mmol) was added, then the reaction mixture was heated at
110°C for 1 h. The reaction mixture was combined and partitioned between ethyl acetate
(20 mL) and water (10 mL). The aqueous layer was separated and extracted with ethyl
acetate (3 x 20 mL). The combined organic extracts were washed with brine (20 mL),
25 dried over sodium sulphate, filtered and evaporated. The crude residue was purified by
FCC, eluting with 25-100% ethyl acetate in heptane, then further purified by trituration
with dichloromethane/heptane, to afford the *title compound* (214 mg, 44%) as an off-
white solid. δ_{H} (500 MHz, CDCl₃) 8.68 (s, 1H), 8.65 (s, 1H), 8.57 (s, 1H), 7.75 (q, *J* 9.8
Hz, 2H), 7.28 (m, 1H), 7.17 (d, *J* 8.1 Hz, 1H), 7.09 (t, *J* 7.5 Hz, 1H), 6.96 (d, *J* 7.6 Hz,
30 1H), 6.67 (t, *J* 73.6 Hz, 1H), 4.35 (s, 2H), 2.55 (s, 3H). Method B HPLC-MS: MH⁺ *m/z*
535, RT 445/447 minutes.

INTERMEDIATE 165

Methyl 4-[5-(3-{[2-(difluoromethoxy)phenyl]methyl}-2-methylimidazo[1,2-*a*]pyridin-6-yl)pyrazin-2-yl]cyclohex-3-ene-1-carboxylate

- 5 A mixture of *Intermediate 164* (50 mg, 0.10 mmol), methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-ene-1-carboxylate (prepared in an analogous manner to *Intermediate 56*, 40 mg, 0.15 mmol) and 2M aqueous sodium carbonate solution (0.15 mL) in 1,4-dioxane (1 mL) was purged with nitrogen for 5 minutes. Tetrakis(triphenylphosphine)palladium(0) (6 mg, 0.005 mmol) was added and
- 10 the reaction mixture was heated at 120°C under microwave irradiation for 30 minutes. The reaction mixture was partitioned between ethyl acetate (20 mL) and water (10 mL). The aqueous layer was separated and extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried over sodium sulfate and evaporated. The resulting crude residue was purified by FCC, eluting with 25-100%
- 15 ethyl acetate in heptane followed by 1-10% methanol in ethyl acetate, to afford the *title compound* (120 mg) as a pale yellow solid. δ_H (500 MHz, DMSO- d_6) 9.15 (d, *J* 1.2 Hz, 1H), 8.88 (s, 1H), 8.86 (d, *J* 1.2 Hz, 1H), 7.92 (dd, *J* 9.4, 1.6 Hz, 1H), 7.60 (d, *J* 9.4 Hz, 1H), 7.47-7.10 (m, 4H), 7.04 (d, *J* 7.6 Hz, 1H), 6.89 (s, 1H), 4.40 (s, 2H), 3.65 (s, 3H), 2.69 (dd, *J* 16.5, 3.2 Hz, 2H), 2.55 (s, 1H), 2.44 (dd, *J* 18.0, 9.3 Hz, 2H), 2.33 (s, 3H),
- 20 2.14-2.06 (m, 1H), 1.83-1.67 (m, 1H).

INTERMEDIATES 166 & 167

- Methyl (1*R**,4*R**)-4-[5-(3-{[2-(difluoromethoxy)phenyl]methyl}-2-methylimidazo[1,2-*a*]pyridin-6-yl)pyrazin-2-yl]cyclohexane-1-carboxylate (*trans* isomer) and Methyl
- 25 (1*S**,4*S**)-4-[5-(3-{[2-(difluoromethoxy)phenyl]methyl}-2-methylimidazo[1,2-*a*]pyridin-6-yl)pyrazin-2-yl]cyclohexane-1-carboxylate (*cis* isomer)

- To a stirring solution of *Intermediate 165* (200 mg, 0.40 mmol) in ethyl acetate (10 mL) and triethylamine (55 μ L, 0.4 mmol), degassed and purged with nitrogen, was
- 30 added palladium on carbon (10%, 42 mg, 0.04 mmol). The reaction mixture was degassed and purged with nitrogen, then stirred under a hydrogen balloon at room temperature until the reduction was complete. The reaction mixture was filtered through celite and the solids were washed with excess 1:1 ethyl acetate/methanol. The filtrate was

evaporated. The resulting dark orange residue was purified by FCC, eluting with 50-100% ethyl acetate in heptane followed by 1-20% methanol in ethyl acetate. The material was then further purified to isomeric purity, using SFC (Cellulose-3 column; 10% MeOH /90% CO₂ eluent), to afford the *title compounds* as the *trans* isomer (25 mg, 12%) and the

5 *cis* isomer (74 mg, 36%).

Intermediate 166 (trans isomer): δ_{H} (500 MHz, CDCl₃) 8.82 (s, 1H), 8.61 (s, 1H), 8.49 (s, 1H), 7.98 (m, 2H), 7.29 (m, 1H), 7.18 (d, *J* 8.1 Hz, 1H), 7.12 (t, *J* 7.4 Hz, 1H), 6.98 (d, *J* 7.5 Hz, 1H), 6.68 (t, *J* 73.4 Hz, 1H), 4.35 (s, 2H), 3.71 (s, 3H), 2.82 (d, *J* 8.2 Hz, 1H), 2.42 (t, *J* 9.8 Hz, 1H), 2.18 (d, *J* 10.5 Hz, 2H), 2.06 (d, *J* 10.4 Hz, 2H), 1.65 (q, *J* 12.2 Hz, 4H). Method B HPLC-MS: MH⁺ *m/z* 507, RT 1.73 minutes.

10

Intermediate 167 (cis isomer): δ_{H} (500 MHz, CDCl₃) 8.79 (d, *J* 1.4 Hz, 1H), 8.53 (s, 1H), 8.48 (d, *J* 1.3 Hz, 1H), 7.91-7.79 (m, 2H), 7.28 (d, *J* 1.4 Hz, 1H), 7.18 (d, *J* 7.9 Hz, 1H), 7.09 (t, *J* 7.5 Hz, 1H), 6.94 (d, *J* 7.6 Hz, 1H), 6.68 (t, *J* 73.5 Hz, 1H), 4.35 (s, 2H), 3.72 (s, 3H), 2.93-2.85 (m, 1H), 2.74 (d, *J* 4.3 Hz, 1H), 2.54 (s, 3H), 2.28-2.22 (m, 2H), 1.87 (td, *J* 9.9, 8.8, 4.2 Hz, 4H), 1.71 (td, *J* 15.2, 14.4, 5.1 Hz, 2H). Method B HPLC-MS: MH⁺ *m/z* 507, RT 1.74 minutes.

15

INTERMEDIATE 168

20 **Methyl 3-(trifluoromethanesulfonyloxy)cyclopentene-1-carboxylate**

Methyl 3-oxocyclopentane-1-carboxylate (1.5 g, 10.55 mmol) was dissolved in anhydrous toluene (30 mL) under nitrogen, DIPEA (2.76 mL, 15.83 mmol) was added and the mixture was warmed to 45°C. Trifluoromethanesulfonic anhydride (2.66 mL, 15.83 mmol) was added dropwise and the reaction mixture was stirred at 45°C for a

25 further 20 minutes. The reaction mixture was treated with additional DIPEA (3 mL) and trifluoromethanesulfonic anhydride (2.5 mL), then stirred at 45°C for a further 20 minutes. The reaction mixture was diluted with ethyl acetate (150 mL), and washed with saturated aqueous sodium bicarbonate solution (60 mL), saturated aqueous ammonium chloride solution (60 mL) and brine (40 mL), then dried over sodium sulfate and

30 concentrated under vacuum. The resulting dark brown oil was purified by chromatography (Biotage 100g SNAP cartridge), eluting with constant gradient EtOAc: heptane 0:1 to 1:9, to afford the *title compound* (2.89 g, 38%) as a mixture of double bond isomers (~1:1 ratio) as a light brown oil. δ_{H} (500 MHz, CDCl₃) 5.71 (q, *J* 2.1 Hz, 0.5H),

5.59 (p, J 2.3 Hz, 0.5H), 3.73 (d, J 5.7 Hz, 3H), 3.62 (ddq, J 8.7, 5.6, 2.6 Hz, 0.5H), 3.33-3.24 (m, 0.5H), 3.02-2.94 (m, 0.5H), 2.87-2.67 (m, 2H), 2.62 (dddd, J 14.1, 9.0, 4.1, 2.1 Hz, 0.5H), 2.38-2.26 (m, 1H).

5

INTERMEDIATE 169Methyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopentene-1-carboxylate

A mixture of 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (833 mg, 3.28 mmol), *Intermediate 168* (1.20 g, 4.38 mmol),
 10 potassium acetate (0.43 g, 4.38 mmol), 1,1'-bis(diphenylphosphanyl)ferrocene (24 mg, 0.04 mmol) and 1,4-dioxane (12 mL) was degassed for 30 minutes. Pd(dppf)Cl₂ complex with dichloromethane (36 mg, 0.04 mmol) was added and the reaction mixture was sealed under nitrogen, then stirred at 90°C for 18 h. The reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate (100 mL). The organic layers were
 15 washed with water (20 mL), saturated aqueous sodium bicarbonate solution (20 mL) and brine (20 mL), then dried over sodium sulphate, filtered and concentrated under vacuum. The residue was purified by chromatography (Biotage SNAP 100g cartridge), eluting with heptane:ethyl acetate 1:0 to 1:1, to afford the *title compound* (223 mg, 40%) as a mixture of double bond isomers (~1:1 ratio) as a light brown oil. δ_H (500 MHz, CDCl₃)
 20 6.44 (tt, J 5.3, 2.7 Hz, 1H), 3.78-3.59 (m, 3.5H), 3.23-3.07 (m, 0.5H), 2.87-2.68 (m, 2H), 2.68-2.42 (m, 1H), 2.22-2.11 (m, 1H), 1.29 (d, J 3.5 Hz, 12H).

INTERMEDIATE 170

25 Methyl 3-[5-(3-{[2-(difluoromethoxy)phenyl]methyl}-2-methylimidazo[1,2-*a*]pyridin-6-yl)pyrimidin-2-yl]cyclopentene-1-carboxylate

Intermediate 29 (90%, 262 mg, 0.59 mmol) and *Intermediate 169* (178 mg, 0.71 mmol) were charged to a sealed tube with 2M aqueous potassium carbonate solution (1.18 mL) and 1,4-dioxane (5 mL). The mixture was degassed for 30 minutes. Tetrakis-
 30 (triphenylphosphine)palladium(0) (34 mg, 0.03 mmol) was added and the reaction mixture was sealed under nitrogen. The reaction mixture was stirred at 90°C for 18 h. Additional *Intermediate 168* (50 mg) was added, then the reaction mixture was degassed for 20 minutes and stirred at 90°C for 4 h. The reaction mixture was diluted with ethyl

acetate (80 mL), and washed with water (15 mL), saturated sodium bicarbonate solution (15 mL) and brine (15 mL), then dried over sodium sulfate, filtered and concentrated under vacuum. The residue was purified by flash chromatography (eluting with heptane: ethyl acetate 3:7 to 0:1) to afford the *title compound* (160 mg, 53%) as a mixture of double bond isomers (~1:1 ratio) as a brown solid. δ_{H} (500 MHz, CDCl_3) 8.75 (d, J 9.4 Hz, 2H), 7.91 (s, 1H), 7.66 (d, J 9.3 Hz, 1H), 7.31 (dd, J 9.3, 1.6 Hz, 1H), 7.29-7.22 (m, 1H), 7.16 (d, J 8.0 Hz, 1H), 7.08 (t, J 7.5 Hz, 1H), 6.94 (dq, J 18.6, 2.3 Hz, 1H), 6.91-6.46 (m, 2H), 4.31 (s, 2H), 3.84 (ddd, J 11.5, 5.8, 2.5 Hz, 0.54H), 3.72 (d, J 1.6 Hz, 3H), 3.40-3.30 (m, 0.44H), 3.20 (dd, J 5.4, 2.7 Hz, 1H), 3.10-2.83 (m, 2H), 2.53 (s, 3H), 2.46-2.32 (m, 1H).

INTERMEDIATE 171

Methyl 3-[5-(3-{[2-(difluoromethoxy)phenyl]methyl}-2-methylimidazo[1,2-*a*]pyridin-6-yl)pyrimidin-2-yl]cyclopentane-1-carboxylate

Intermediate 170 (96%, 160 mg, 0.31 mmol) was dissolved in ethanol (3 mL) and the solution was degassed with nitrogen. The mixture was added to palladium on carbon (10%, 35 mg, 0.03 mmol), then degassed with nitrogen and allowed to stir under a hydrogen balloon at room temperature for 3 h. The reaction mixture was filtered through celite which was washed with ethanol (150 mL). The filtrate was concentrated under vacuum. The residue was purified by flash chromatography (0-6% methanol in DCM) to afford the *title compound* (43 mg, 27%) as a red oil. δ_{H} (500 MHz, CDCl_3) 8.66 (s, 2H), 7.84 (s, 1H), 7.64 (d, J 9.2 Hz, 1H), 7.27 (dd, J 9.2, 1.7 Hz, 1H), 7.22-7.17 (m, 1H), 7.10 (d, J 8.0 Hz, 1H), 7.02 (t, J 7.5 Hz, 1H), 6.82 (d, J 7.6 Hz, 1H), 6.57 (t, J 73.6 Hz, 1H), 4.26 (s, 2H), 3.62 (s, 3H), 3.41 (td, J 8.1, 2.5 Hz, 1H), 2.94-2.86 (m, 1H), 2.48 (s, 3H), 2.42-2.35 (m, 1H), 2.25-2.17 (m, 1H), 2.13-1.94 (m, 4H). Method B HPLC-MS: MH^+ m/z 493, RT 1.72 minutes.

INTERMEDIATE 172

30

2-Methyl-4-oxocyclohexane-1-carboxylate

Ethyl 2-methyl-4-oxocyclohex-2-ene-1-carboxylate (5 g, 27.44 mmol) was dissolved in ethanol (50 mL) and palladium on carbon (10%, 1.46 g, 1.37 mmol) was

added. The suspension was degassed using vacuum/N₂/H₂ and the reaction mixture was stirred under H₂ at room temperature and atmospheric pressure for 18 h. The mixture was filtered through celite, concentrated and purified by column chromatography (eluting with 10-50% ethyl acetate in heptane), to afford the *title compound* (4.19 g, 80%) as a 93:7

5 *cis:trans* isomer mixture as a colourless liquid. δ_{H} (500 MHz, CDCl₃) 4.18 (qd, *J* 7.1, 4.4 Hz, 2H), 2.84 (dt, *J* 8.4, 4.2 Hz, 1H), 2.60-2.48 (m, 2H), 2.49-2.42 (m, 2H), 2.31 (ddd, *J* 14.6, 8.5, 6.2 Hz, 1H), 2.22-2.10 (m, 1H), 2.10-2.00 (m, 1H), 1.28 (t, *J* 7.1 Hz, 3H), 0.98 (d, *J* 6.8 Hz, 3H).

10

INTERMEDIATE 173

Ethyl 6-methyl-4-(trifluoromethanesulfonyloxy)cyclohexene-1-carboxylate

Intermediate 172 (3.2 g, 17.37 mmol) and DIPEA (12.1 ml, 69.48 mmol) were dissolved in toluene (5 mL) and heated at 45°C for 10 minutes. Trifluoromethanesulfonic anhydride in dichloromethane (1M, 70 mL) was added dropwise over 10 minutes and the mixture was heated for 2 h. The mixture was allowed to cool to room temperature, concentrated, diluted with water (150 mL) and extracted with ethyl acetate (2 x 100 mL). The organic layer was washed with saturated sodium bicarbonate solution (50 mL) and brine (50 mL), then dried over magnesium sulphate, filtered and concentrated. The resulting dark brown solid was purified by column chromatography, eluting with 20-50% ethyl acetate in heptane, to afford the *title compound* (4.8 g, 74%) as a mixture of double bond isomers (1.2:1) as a light reddish oil. δ_{H} (250 MHz, CDCl₃) 5.75 (d, *J* 5.4 Hz, 1H), 4.17 (qd, *J* 7.2, 2.2 Hz, 2H), 2.89-2.55 (m, 2H), 2.55-2.25 (m, 2H), 2.23-1.81 (m, 1H), 1.27 (m, 4H), 0.98 (dd, 3H). Method B HPLC-MS: MH⁺ *m/z* 317, RT 2.44 minutes.

25

INTERMEDIATE 174

Ethyl 6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohexene-1-carboxylate

30 *Intermediate 173* (85%, 2 g, 5.37 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (2.05 g, 8.06 mmol) and potassium acetate (1.58 g, 16.12 mmol) were suspended in 1,4-dioxane (20 mL). The reaction mixture was degassed for 10 minutes, then 1,1'-bis(diphenylphosphanyl)-

ferrocene (89 mg, 0.16 mmol) was added, followed by Pd(dppf)Cl₂ complex with dichloromethane (132 mg, 0.16 mmol). The mixture was heated at 90°C for 5 h. The mixture was cooled to room temperature, diluted with water (200 mL) and extracted with ethyl acetate (2 x 200 mL). The combined organic layers were washed with brine (100 mL), dried over magnesium sulphate, filtered and concentrated. The resulting brown oil was purified by chromatography on Biotage, eluting with 10-50% ethyl acetate in heptane, to afford the *title compound* (9:1 *cis:trans* ratio, 1.2:1 mixture of double bond isomers) (725 mg, 46%) as a pale yellow oil. δ_{H} (250 MHz, CDCl₃) 6.59-6.35 (m, 1H), 4.25-3.95 (m, 2H), 2.73-2.54 (m, 1H), 2.46-2.19 (m, 3H), 2.12-1.99 (m, 1H), 1.90-1.56 (m, 1H), 1.26 (d, *J* 2.9 Hz, 15H), 0.90 (dd, *J* 23.8, 7.0 Hz, 3H). Method B HPLC-MS: MH⁺ *m/z* 295, RT 2.48 minutes.

INTERMEDIATE 175

Ethyl 4-[5-(3-{[2-(difluoromethoxy)phenyl]methyl}-7-fluoro-2-methylimidazo[1,2-*a*]-pyridin-6-yl)pyrimidin-2-yl]-2-methylcyclohexene-1-carboxylate

A mixture of *Intermediate 152* (95%, 600 mg, 1.36 mmol), *Intermediate 174* (506 mg, 1.63 mmol) and 2M aqueous sodium carbonate solution (2.04 mL) in 1,4-dioxane (6 mL) was degassed with nitrogen for 5 minutes, then tetrakis(triphenylphosphine)-palladium(0) (79 mg, 0.07 mmol) was added and the mixture was heated at 120°C for 1 h under microwave irradiation. The reaction mixture were diluted with ethyl acetate (150 mL), then washed with water (25 mL) and brine (25 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated. The resulting crude material was purified twice by column chromatography, eluting with 70-100% ethyl acetate in heptane, to afford the *title compound* (541 mg, 72%) as a mixture of double bond isomers (1:1) as a light pink sticky oil. δ_{H} (500 MHz, CDCl₃) 8.78-8.57 (m, 2H), 7.80 (d, *J* 6.7 Hz, 1H), 7.55-7.39 (m, 1H), 7.38-7.27 (m, 2H), 7.17 (d, *J* 8.1 Hz, 1H), 7.12 (t, *J* 7.5 Hz, 1H), 6.92 (d, *J* 7.4 Hz, 1H), 6.62 (t, *J* 73.6 Hz, 1H), 4.29 (s, 2H), 4.24-4.15 (m, 2H), 4.12 (q, *J* 7.1 Hz, 1H), 3.01-2.84 (m, 1H), 2.81-2.71 (m, 1H), 2.70-2.61 (m, 1H), 2.54 (s, 3H), 2.12-2.05 (m, 1H), 1.95-1.81 (m, 1H), 1.31-1.27 (m, 3H), 1.03 (dd, *J* 36.2, 7.0 Hz, 3H). Method A HPLC-MS: MH⁺ *m/z* 551, RT 5.39 minutes.

INTERMEDIATE 176

Methyl 4-[5-(3-{[2-(difluoromethoxy)phenyl]methyl}-2,7-dimethylimidazo[1,2-a]-pyridin-6-yl)pyrimidin-2-yl]cyclohex-3-ene-1-carboxylate

- 5 *Intermediate 47* (50 mg, 0.12 mmol), methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-ene-1-carboxylate (38 mg, 0.15 mmol) and 2M aqueous potassium carbonate solution (0.19 mL) were added to 1,4-dioxane (1 mL) in a microwave tube, and the mixture was degassed for 10 minutes. Bedford's catalyst (13 mg, 0.01 mmol) was added and reaction mixture was heated under microwave irradiation
- 10 for 30 minutes at 120°C. The reaction mixture was further heated at 150°C for 30 minutes under microwave irradiation. Water (5 mL) was added, and the reaction mixture was extracted with ethyl acetate (50 mL). The organic phase was washed with brine (30 mL), dried with sodium sulphate, filtered and concentrated under vacuum. The resulting black oil was purified by chromatography on a Biotage, using 10g SNAP cartridge (eluent 80%
- 15 ethyl acetate in heptane to 100% EtOAc), to afford the *title compound* (110 mg, 41%) as a black oil. Method B HPLC-MS: MH+ *m/z* 519, RT 1.68 minutes.

INTERMEDIATE 177

- 20 Methyl 4-[5-(3-{[2-(difluoromethoxy)phenyl]methyl}-2,7-dimethylimidazo[1,2-a]-pyridin-6-yl)pyrimidin-2-yl]cyclohexane-1-carboxylate

- Intermediate 176* (76%, 110 mg, 0.16 mmol) and triethylamine (0.03 mL, 0.22 mmol) were dissolved in ethyl acetate (3 mL) and degassed with nitrogen. Palladium (10% on carbon, 18 mg, 0.02 mmol) was added and the reaction mixture was purged with
- 25 nitrogen (3 times) before replacing nitrogen by hydrogen gas. The reaction mixture was stirred under hydrogen for 3 h at room temperature. The reaction mixture was filtered through celite, washed with ethyl acetate (15 mL) and concentrated to ~3 mL under vacuum. Additional triethylamine (30 µL) and fresh palladium on carbon (10%, 17.67 mg, 0.02 mmol) were added, and the reaction mixture was stirred at room temperature
- 30 overnight under hydrogen. The reaction mixture was filtered through celite and washed with ethyl acetate (2 mL). The organic filtrate was washed with water (20 mL) and brine (20 mL), then dried with sodium sulphate, filtered and concentrated under vacuum. The resulting orange oil was purified, using the Biotage system on a 10g SNAP cartridge

(eluent: 25 to 100% EtOAc in heptane), to afford the *title compound* (45 mg, 53%) as a clear oil (69:31 mixture of *cis* and *trans* isomers). Method B HPLC-MS: MH⁺ *m/z* 521, RT 1.75 minutes.

5

INTERMEDIATE 178**Methyl 2-[4-(trifluoromethanesulfonyloxy)cyclohex-3-en-1-yl]acetate**

Methyl (4-oxocyclohexyl)acetate (900 mg, 5.29 mmol) was dissolved in anhydrous toluene (2 mL) under nitrogen, DIPEA (2.7 mL 15.5 mmol) was added and the mixture was warmed to 45°C. Trifluoromethanesulfonic anhydride (2.7 mL, 16.05 mmol) was added dropwise and the reaction mixture was stirred at 45°C for 1 h. The reaction mixture was diluted with EtOAc (15 mL), and washed with saturated aqueous sodium bicarbonate solution (10 mL), saturated aqueous ammonium chloride solution (10 mL) and brine (10 mL), then dried over sodium sulfate and concentrated under vacuum. The residue was purified by column chromatography on silica (0-25% ethyl acetate in heptane) to afford the *title compound* (682 mg, 48%) as a viscous clear yellow liquid. δ_{H} (500 MHz, CDCl₃) 5.76-5.66 (m, 1H), 3.68 (s, 3H), 2.48-2.25 (m, 5H), 2.22-2.04 (m, 1H), 1.92 (dtd, *J* 14.4, 6.1, 3.3 Hz, 2H), 1.59-1.43 (m, 1H).

20

INTERMEDIATE 179**Methyl 2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-en-1-yl]acetate**

Intermediate 178 (680 mg, 2.25 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane (855 mg, 3.37 mmol), potassium acetate (660 mg, 6.72 mmol) and 1,1'-bis(diphenylphosphanyl)ferrocene (65 mg, 0.12 mmol) were charged in a tube with anhydrous 1,4-dioxane (5 mL). The mixture was degassed by bubbling nitrogen for 30 minutes. Pd(dppf)Cl₂ complex with dichloromethane (90 mg, 0.11 mmol) was added and the mixture was sealed under nitrogen. The reaction mixture was stirred at 90°C for 18 h. The reaction mixture was allowed to cool to room temperature, then diluted with ethyl acetate (50 mL) and water (10 mL). The aqueous phase was separated and the organic phase was washed with saturated aqueous sodium bicarbonate solution (10 mL) and brine (10 mL), then dried over sodium sulphate, filtered and concentrated under vacuum. The crude residue was purified by column chromatography on silica (0 to 100% DCM in

heptane, followed by 0 to 2% methanol in DCM), to afford the *title compound* (259 mg, 29%) as a viscous light brown liquid. 6.46 (s, 1H), 3.65-3.58 (m, 3H), 2.26-2.12 (m, 4H), 2.11-1.96 (m, 2H), 1.81-1.65 (m, 2H), 1.38-1.24 (m, 1H), 1.25-1.14 (m, 12H).

5

INTERMEDIATE 180

Methyl 2-{4-[5-(3-{[2-(difluoromethoxy)phenyl]methyl}-7-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl]pyrimidin-2-yl]cyclohexyl}acetate

Intermediate 152 (250 mg, 0.6 mmol) and *Intermediate 179* (66%, 253 mg, 0.6 mmol) were dissolved in 1,4-dioxane (40 mL) and 2M aqueous sodium carbonate solution (0.90 mL) was added. The resulting mixture was degassed with nitrogen for 5 minutes, then tetrakis(triphenylphosphine)palladium(0) (70 mg, 0.06 mmol) was added and the reaction mixture was heated at 120°C for 2 h under microwave irradiation. Additional tetrakis(triphenylphosphine)palladium(0) (35 mg, 0.03 mmol) was added and the reaction mixture was heated at 120°C for a further 1 h under microwave irradiation. The mixture was diluted with ethyl acetate (15 mL), then washed with saturated sodium bicarbonate solution (10 mL), water (2 x 10 mL) and brine (10 mL). The organic layer was dried over sodium sulphate, filtered and concentrated under vacuum. The resulting bright yellow solid was purified by column chromatography on silica (0 to 10% methanol in DCM) to afford a yellow solid (300 mg), which was dissolved in ethyl acetate (3 mL). Triethylamine (60 µL, 0.43 mmol) was added and the mixture was degassed with nitrogen. Palladium on carbon (10%, 40 mg, 0.04 mmol) was added. The mixture was degassed with nitrogen and allowed to stir under a hydrogen balloon at room temperature for 17 h. The reaction mixture was filtered over a celite pad which was washed with ethyl acetate (200 mL). The filtrate was concentrated under vacuum, and the crude residue was purified by preparative HPLC (Method C), to afford the *title compound* (81 mg, 45%) as a yellow oil. δ_{H} (500 MHz, CD₃OD) 8.80 (d, *J* 9.2 Hz, 2H), 8.30 (t, *J* 6.7 Hz, 1H), 7.32 (d, *J* 10.8 Hz, 1H), 7.27 (t, *J* 7.7 Hz, 1H), 7.17 (d, *J* 8.2 Hz, 1H), 7.14-7.07 (m, 2H), 6.89 (td, *J* 74.0, 1.2 Hz, 1H), 4.37 (s, 2H), 3.65 (d, *J* 7.9 Hz, 3H), 3.06-2.79 (m, 1H), 2.39 (s, 3H), 2.36 (d, *J* 7.5 Hz, 1H), 2.26 (d, *J* 6.7 Hz, 1H), 2.19-1.61 (m, 7H), 1.58-1.48 (m, 1H), 1.17 (q, *J* 12.7 Hz, 1H).

INTERMEDIATE 181

Methyl 3-[5-(3-{[2-(difluoromethoxy)phenyl]methyl}-7-fluoro-2-methylimidazo[1,2-a]-pyridin-6-yl)pyrimidin-2-yl]cyclopentane-1-carboxylate

5 *Intermediate 152* (200 mg, 0.48 mmol) and *Intermediate 169* (150 mg, 0.59 mmol) were dissolved in 1,4-dioxane (2 mL) and 2M aqueous sodium carbonate solution (0.75 mL) was added. The resulting mixture was degassed with nitrogen for 5 minutes, then tetrakis(triphenylphosphine)palladium(0) (55 mg, 0.05 mmol) was added and the reaction mixture was heated at 120°C for 2 h under microwave irradiation. The reaction
10 mixture was diluted with dichloromethane (15 mL), then washed with saturated sodium bicarbonate solution (10 mL), water (2 x 10 mL) and brine (10 mL). The organic layer was dried over sodium sulphate, filtered and concentrated under vacuum. The resulting dark oil was purified by column chromatography (0-10% methanol in dichloromethane). The resulting material (150 mg) and triethylamine (0.05 mL, 0.36 mmol) were dissolved
15 in ethanol (3 mL) and the reaction mixture was degassed with nitrogen. The mixture was added to palladium on carbon (10%, 35 mg, 0.03 mmol) and the mixture was degassed with nitrogen, then allowed to stir under a hydrogen balloon at room temperature for 18 h. The reaction mixture was filtered through celite which was washed with ethanol (200 mL). The filtrate was concentrated under vacuum, and the resulting crude residue was
20 purified by preparative HPLC (Method C), to afford the *title compound* (84 mg, 57%) as a red oil. δ_{H} (500 MHz, CD₃OD) 8.79 (s, 2H), 8.29 (d, *J* 7.1 Hz, 1H), 7.32 (d, *J* 10.8 Hz, 1H), 7.25 (d, *J* 7.5 Hz, 1H), 7.16 (d, *J* 8.1 Hz, 1H), 7.13-7.07 (m, 2H), 6.89 (t, *J* 74.0 Hz, 1H), 4.37 (s, 2H), 3.66 (s, 3H), 3.46 (dd, *J* 10.9, 5.7 Hz, 1H), 3.03-2.94 (m, 1H), 2.38 (s, 4H), 2.28-2.17 (m, 1H), 2.17-2.00 (m, 4H).

25

INTERMEDIATE 182

Methyl 5-oxobicyclo[2.2.2]octane-2-carboxylate

To a cooled solution of diisopropylamine (7.72 mL, 54.62 mmol) in ether (40 mL)
30 at -78°C was added 2.5M *n*-butyllithium (21.8 mL) dropwise. The reaction mixture was allowed to warm to -11°C. A solution of cyclohex-2-en-1-one (5.04 mL, 52.01 mmol) in diethyl ether (60 mL) was added over 45 minutes. During the addition, the temperature was maintained between -11°C and -3°C. The mixture was stirred for an additional 25

minutes before a solution of methyl prop-2-enoate (4.68 mL, 52.01 mmol) in THF (40 mL) was added dropwise over 60 minutes. The reaction mixture was stirred at this temperature for 1 h and stored in a freezer overnight. The reaction mixture was poured into saturated ammonium chloride solution (200 mL) and stirred for 15 minutes. A brown sticky polymer was formed and removed using tweezers. The organic layer was separated and the aqueous layer was extracted with *tert*-butyl methyl ether (2 x 300 mL). The combined organic layers were dried over sodium sulfate and concentrated. The crude residue was purified by column chromatography (Biotage; 0-60% ethyl acetate in heptane) in 2 batches, to afford the *title compound* (2.98 g, 31%) as the *trans* isomer as a clear colourless liquid. δ_{H} (500 MHz, CDCl_3) 3.70 (s, 3H), 2.76 (ddt, J 10.6, 6.4, 1.8 Hz, 1H), 2.53-2.48 (m, 1H), 2.47-2.38 (m, 1H), 2.37-2.31 (m, 1H), 2.22 (ddt, J 14.2, 6.3, 2.5 Hz, 1H), 2.13 (ddd, J 19.1, 2.9, 1.8 Hz, 1H), 2.02 (ddd, J 14.3, 11.0, 3.5 Hz, 1H), 1.89-1.74 (m, 3H), 1.70-1.60 (m, 1H).

15

INTERMEDIATE 183Methyl 5-(trifluoromethanesulfonyloxy)bicyclo[2.2.2]oct-5-ene-2-carboxylate

Intermediate 182 (1 g, 5.49 mmol) was dissolved in toluene (10 mL), DIPEA (3.82 mL, 21.95 mmol) was added and the mixture was heated at 45°C. Trifluoromethanesulfonic anhydride (3.69 mL, 21.95 mmol) was added dropwise and the reaction mixture was stirred for 2 h at 45°C. The reaction mixture was allowed to cool and diluted with ethyl acetate (50 mL), then aqueous sodium bicarbonate solution (70 mL) was added. The phases were separated and the aqueous phase was extracted with ethyl acetate (2 x 30 mL). The organic extracts were washed with saturated aqueous ammonium chloride solution (20 mL), dried over sodium sulphate, filtered and concentrated. The crude residue was purified by chromatography (Biotage; 0-30% ethyl acetate in heptane) to afford the *title compound* (2.33 g, quantitative) as the *trans* isomer as a yellow liquid. δ_{H} (500 MHz, CDCl_3) 5.98 (dd, J 7.4, 2.5 Hz, 1H), 3.65 (s, 3H), 3.23-3.17 (m, 1H), 2.79 (q, J 2.7 Hz, 1H), 2.66 (ddd, J 10.0, 5.2, 2.3 Hz, 1H), 2.03-1.95 (m, 1H), 1.88 (ddd, J 12.9, 10.0, 2.7 Hz, 1H), 1.66-1.52 (m, 3H), 1.46-1.34 (m, 1H).

INTERMEDIATE 184

Methyl 5-[5-(3-{[2-(difluoromethoxy)phenyl]methyl}-7-fluoro-2-methylimidazo[1,2-a]-pyridin-6-yl)pyrimidin-2-yl]bicyclo[2.2.2]octane-2-carboxylate

- 5 *Intermediate 183* (1 g, 3.18 mmol) was dissolved in dry 1,4-dioxane (10 mL) and the mixture was degassed for 5 minutes with nitrogen. Bis(pinacolato)diboron (1.21 g, 4.77 mmol), potassium acetate (1 g, 10.19 mmol), 1,1'-bis(diphenylphosphanyl)ferrocene (90 mg, 0.16 mmol) and Pd(dppf)Cl₂ complex with dichloromethane (130 mg, 0.16 mmol) were added. The mixture was heated at 90°C and stirred for 2 h. The reaction
- 10 mixture was diluted with ethyl acetate (50 mL) and saturated aqueous sodium bicarbonate solution (50 mL) was added. The phases were separated. The aqueous phase was washed with ethyl acetate (50 mL), then the organic extracts were washed with brine (50 mL), dried over sodium sulphate, filtered and concentrated. The crude product was purified
- 15 twice by column chromatography (Biotage, 0-30% ethyl acetate in heptane; then Biotage, 0-100% dichloromethane in heptane). The material thus obtained was added to
- Intermediate 152* (240 mg, 0.57 mmol) in a microwave vial. Dry 1,4-dioxane (3 mL) and 2M aqueous sodium carbonate solution (900 µL) were added. The mixture was degassed with nitrogen for 2 minutes. Tetrakis(triphenylphosphine) palladium(0) (66 mg, 0.06 mmol) was added and the reaction mixture was heated for 45 minutes under microwave
- 20 irradiation at 120°C. The reaction mixture was quenched with water (20 mL) and extracted with ethyl acetate (2 x 25 mL), then dried over sodium sulphate, filtered and concentrated. The crude residue was purified by chromatography (0-3% methanol in dichloromethane). The residue (204 mg) was filtered through charcoal, eluting with ethyl acetate. The resulting solution was concentrated and re-dissolved in ethyl acetate (5 mL).
- 25 Triethylamine (51.32 µL, 0.37 mmol) and palladium on carbon (10%, 50 mg, 0.05 mmol) were added. The mixture was flushed with nitrogen (3 times) and hydrogen (3 times). The mixture was stirred under hydrogen for 20 h. The reaction mixture was filtered through celite and concentrated. The crude residue was purified by column chromatography (0-2% methanol in dichloromethane), to afford the *title compound* (139
- 30 mg, 75%) as a pink oil. Method B HPLC-MS: MH⁺ *m/z* 551, RT 1.80 minutes.

INTERMEDIATES 185 TO 189 [removed]

INTERMEDIATE 190

Ethyl (1*S*,5*S*,6*R*)-3-[5-(3-{[2-(difluoromethoxy)phenyl]methyl}-7-fluoro-2-methylimidazo[1,2-*a*]pyridin-6-yl)pyrimidin-2-yl]bicyclo[3.1.0]hex-2-ene-6-carboxylate

5 *Intermediate 152* (190 mg, 0.45 mmol) and *Intermediate 134* (75%, 185 mg, 0.5 mmol) were dissolved in 1,4-dioxane (3 mL). Aqueous potassium carbonate solution (2M, 0.7 mL) was added and the reaction mixture was degassed for 5 minutes using nitrogen. Tetrakis(triphenylphosphine)palladium(0) (52 mg, 0.05 mmol) was added and the mixture was heated under microwave irradiation for 2.5 h at 120°C. The phases were
10 separated and the aqueous phase was extracted with ethyl acetate (2 x 3 mL). The organic extracts were combined, dried over sodium sulphate, filtered and concentrated. The resulting crude residue was purified by preparative HPLC (Method C), to afford the *title compound* (120 mg, 45%) as a pink oily solid. Method D HPLC-MS: MH⁺ *m/z* 536, RT 2.65 minutes.

15

INTERMEDIATE 191

Ethyl 4-[5-(3-{[2-(difluoromethoxy)phenyl]methyl}-7-fluoro-2-methylimidazo[1,2-*a*]pyridin-6-yl)pyrimidin-2-yl]-1-methylcyclohex-3-ene-1-carboxylate

20 *Intermediate 68* (1.0 g, 2.60 mmol) and *Intermediate 221* (1.16 g, 3.12 mmol) were dissolved in 1,4-dioxane (20 mL). Aqueous sodium carbonate solution (2M, 4 mL) was added and the mixture was degassed with nitrogen for 15 minutes, then bis[3-(diphenylphosphanyl)cyclopenta-2,4-dien-1-yl]iron dichloropalladium dichloromethane complex (110 mg, 0.13 mmol) was added and the reaction mixture was heated at 100°C
25 under nitrogen for 4.5 h. The reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (30 mL). The organic layer was washed with brine (20 mL), dried over sodium sulphate, filtered and concentrated to dryness. The resulting residue was purified by flash chromatography (50g KP-silica cartridge, eluting with 60 to 100% ethyl acetate in heptane) to afford the *title compound* (820 mg, 57%) as a beige solid. δ_{H}
30 (500 MHz, CDCl₃) 8.70 (d, *J* 1.4 Hz, 2H), 7.76 (d, *J* 7.0 Hz, 1H), 7.40-7.32 (m, 2H), 7.30-7.27 (m, 1H), 7.16 (d, *J* 7.9 Hz, 1H), 7.13-7.06 (m, 1H), 6.96-6.84 (m, 1H), 6.61 (t, *J* 73.5 Hz, 1H), 4.29 (s, 2H), 4.21-4.06 (m, 2H), 2.93-2.83 (m, 1H), 2.73-2.61 (m, 2H), 2.51 (s, 3H), 2.28-2.18 (m, 1H), 2.18-2.10 (m, 1H), 1.83-1.74 (m, 1H), 1.28 (s, 3H), 1.25 (t, *J*

7.2 Hz, 3H). Method C HPLC-MS: MH⁺ *m/z* 551, RT 1.23 minutes.

INTERMEDIATE 192

5 4-[5-(3-{[2-(Difluoromethoxy)phenyl]methyl}-7-fluoro-2-methylimidazo[1,2-*a*]pyridin-6-yl)pyrimidin-2-yl]-1-methylcyclohex-3-ene-1-carboxylic acid

Intermediate 191 (275 mg, 0.5 mmol) was dissolved in 1,4-dioxane (3 mL) and water (1.5 mL), then a 2M solution of potassium hydroxide in water (1.5 mL) was added and the reaction mixture was heated at 85°C for 2 h. The reaction mixture was adjusted to
 10 pH 6 with 1M aqueous hydrogen chloride solution, and the solid that formed was collected by filtration, to afford the *title compound* (200 mg, 77%) as an off-white solid. The filtrate was acidified to pH 5 with 1M aqueous hydrogen chloride solution and the solid that formed was collected by filtration. A further crop was obtained from re-filtering the filtrate. The two crops were combined to afford an additional quantity of the *title*
 15 *compound* (40 mg, 15%) as a pale yellow solid. δ_{H} (500 MHz, DMSO-*d*₆) 8.92 (d, *J* 1.5 Hz, 2H), 8.54 (d, *J* 7.5 Hz, 1H), 7.53 (d, *J* 11.3 Hz, 1H), 7.42-7.10 (m, 5H), 7.04 (d, *J* 6.3 Hz, 1H), 4.36 (s, 2H), 2.81-2.68 (m, 1H), 2.61-2.55 (m, 2H), 2.28 (s, 3H), 2.16 (dd, *J* 18.6, 3.1 Hz, 1H), 2.05-1.96 (m, 1H), 1.74-1.62 (m, 1H), 1.20 (s, 3H). Method C HPLC-MS: MH⁺ *m/z* 523, RT 1.08 minutes.

20

INTERMEDIATE 193

Cyclohex-3-en-1-ol

A solution of 9-borabicyclo[3.3.1]nonane in tetrahydrofuran (0.5M, 80 mL, 40
 25 mmol) was added dropwise to cyclohexa-1,4-diene (3.2 g, 40 mmol). The solution was stirred overnight at room temperature. An aqueous solution of sodium hydroxide (3M, 12 mL) was added, followed by dropwise addition of hydrogen peroxide (30%, 12 mL). The resulting solution was heated at reflux for 1 h, then allowed to cool. The reaction mixture was poured into brine (200 mL) and extracted with diethyl ether (3 x 200 mL). The
 30 combined ethereal layers were dried over magnesium sulfate, filtered and concentrated. The residue was purified by chromatography, eluting with 0 to 100% ethyl acetate in heptane, then 0 to 50% methanol in ethyl acetate, to afford the *title compound* (1.25 g, 32%) as a clear oil. δ_{H} (250 MHz, CDCl₃) 5.82-5.45 (m, 1H), 4.03-3.74 (m, 1H), 2.60-

0.71 (m, 8H).

INTERMEDIATE 194

5 *tert*-Butyl(cyclohex-3-en-1-yloxy)dimethylsilane

To a solution of *Intermediate 193* (1.25 g, 12.74 mmol) and imidazole (1.75 g, 25.71 mmol) in dichloromethane (25 mL) was added *tert*-butyldimethylsilyl chloride (1M, 12.75 mL, 12.75 mmol) and the solution was stirred over 2 days at room temperature. The mixture was poured into water (50 mL) and extracted with diethyl ether (3 x 50 mL). The combined ethereal layers were dried over magnesium sulfate, filtered and concentrated. The resulting crude residue was purified by chromatography, eluting with 0 to 30% ethyl acetate in heptane, to afford the *title compound* (1.87 g, 69%) as a clear oil. δ_{H} (500 MHz, CDCl_3) 5.58-5.45 (m, 1H), 3.86-3.71 (m, 1H), 2.26-1.85 (m, 2H), 1.82-1.14 (m, 5H), 0.89-0.74 (m, 9H), 0.06-0.11 (m, 6H).

15

INTERMEDIATE 195

Ethyl-3-[(*tert*-butyldimethylsilyl)oxy]bicyclo[4.1.0]heptane-7-carboxylate

1-(2-Ethoxy-2-oxoethylidene)diazonium (1.1 mL, 8.77 mmol) in dichloromethane (2 mL) was added slowly via syringe pump over 6 h to a stirred solution of *Intermediate 194* (1.55 g, 7.30 mmol) and rhodium(II) acetate (1:2) (33 mg, 0.075 mmol) in dichloromethane (50 mL) under nitrogen at room temperature. The reaction mixture was stirred at room temperature overnight. The reaction mixture was filtered through celite and concentrated. The crude orange oil was purified by chromatography, eluting with 5-30% ethyl acetate in heptane, to afford the *title compound* (1.23 g, 56%) as a clear oil. δ_{H} (500 MHz, CDCl_3) 4.15-4.00 (m, 2H), 3.67-3.46 (m, 1H), 2.27-2.06 (m, 1H), 2.06-1.80 (m, 2H), 1.76 (dq, J 20.7, 7.7, 7.1 Hz, 1H), 1.68-1.38 (m, 4H), 1.35-1.17 (m, 3H), 1.11 (dtd, J 13.3, 10.2, 5.1 Hz, 1H), 0.92-0.76 (m, 9H), 0.01 (dq, J 4.5, 2.5 Hz, 6H).

30

INTERMEDIATE 196

Ethyl-3-hydroxybicyclo[4.1.0]heptane-7-carboxylate

TBAF (1M in tetrahydrofuran, 8.1 mL, 8.1 mmol) was added dropwise to a stirred

solution of *Intermediate 195* (1.2 g, 4.02 mmol) in tetrahydrofuran (25 mL) at room temperature and the reaction mixture was heated at 50°C for 1 h. The mixture was cooled to room temperature and concentrated under reduced pressure. The resulting light brownish oil was diluted with ethyl acetate (50 mL) and washed with water (2 x 20 mL) and brine (20 mL), then dried over magnesium sulphate, filtered and concentrated under reduced pressure. The crude residue was purified by chromatography, eluting with 20 to 100% ethyl acetate in heptane, to afford the *title compound* (0.49 g, 66%) as a clear oil. δ_{H} (500 MHz, CDCl_3) 4.01 (qd, J 7.1, 0.9 Hz, 2H), 3.53 (dtd, J 11.1, 6.4, 3.3 Hz, 1H), 2.31-2.06 (m, 1H), 1.95 (ddt, J 12.1, 9.5, 4.5 Hz, 1H), 1.90-1.68 (m, 1H), 1.66-1.25 (m, 6H), 1.24-1.11 (m, 4H).

INTERMEDIATE 197

Ethyl-3-oxobicyclo[4.1.0]heptane-7-carboxylate

Intermediate 196 (490 mg, 2.66 mmol) was dissolved in dichloromethane (10 mL) and Dess-Martin Periodinane (2.26 g, 5.33 mmol) was added. The mixture was stirred at room temperature overnight. The reaction mixture was diluted with dichloromethane (100 mL) and washed with saturated aqueous sodium bicarbonate solution (2 x 50 mL), water (50 mL) and brine (50 mL), then dried over sodium sulphate, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with 20 to 100% ethyl acetate in heptane, to afford the *title compound* (400 mg, 82%) as a yellow oil. δ_{H} (500 MHz, CDCl_3) 4.15 (q, J 7.1 Hz, 2H), 2.77-2.59 (m, 2H), 2.41-2.27 (m, 2H), 2.22-2.06 (m, 2H), 1.87 (s, 2H), 1.67 (t, J 4.1 Hz, 1H), 1.29 (t, J 7.2 Hz, 3H).

INTERMEDIATE 198

Ethyl 3-(trifluoromethanesulfonyloxy)bicyclo[4.1.0]heptene-7-carboxylate

Intermediate 197 (400 mg, 2.195 mmol) was dissolved in toluene (10 mL), then DIPEA (1.55 mL, 8.90 mmol) was added and the mixture was heated at 45°C for 10 minutes. 1M trifluoromethanesulfonic anhydride (8.8 mL, 8.8 mmol) was added dropwise and the mixture was heated for 1 h. The reaction mixture was allowed to cool to room temperature, diluted with water (50 mL) and extracted with dichloromethane (2 x

100 mL). The organic layer was washed with saturated aqueous sodium bicarbonate solution (50 mL) and brine (50 mL), then dried over magnesium sulfate and concentrated. The residue was purified by column chromatography, eluting with 10 to 100% ethyl acetate in heptane, to afford the *title compound* (0.40 g, 56%) as a mixture of double bond isomers as an orange oil. δ_{H} (500 MHz, CDCl_3) 5.86 (ddd, J 236.4, 5.6, 2.5 Hz, 1H), 4.16 (qd, J 7.1, 3.1 Hz, 2H), 2.95-1.47 (m, 7H), 1.37-1.21 (m, 3H). Method C HPLC-MS: MH⁺ m/z 315, RT 1.53 minutes.

INTERMEDIATE 199

10

Ethyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)bicyclo[4.1.0]heptene-7-carboxylate

Intermediate 198 (400 mg, 1.27 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (485 mg, 1.91 mmol), and potassium acetate (375 mg, 3.82 mmol) were suspended in dry 1,4-dioxane (10 mL) and the mixture was degassed for 10 minutes, then 1,1'-bis(diphenylphosphanyl)ferrocene (21 mg, 38 μmol) was added, followed by $\text{PdCl}_2(\text{dppf})$ complex with dichloromethane (31 mg, 38 μmol). The reaction mixture was heated at 90°C for 3 h in a microwave reactor. Additional 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane, 1,1'-bis(diphenylphosphanyl)ferrocene and $\text{PdCl}_2(\text{dppf})$ complex with dichloromethane were added and the mixture was heated at 90°C in a microwave reactor for a total of 7 h, then at 100°C for 2 h. The mixture was cooled to room temperature, diluted with water (50 mL) and extracted with ethyl acetate (2 x 100 mL). The combined organic layers were washed with brine (80 mL), dried over sodium sulphate, filtered and concentrated. The residue was purified by chromatography, eluting with 5 to 50% ethyl acetate in heptanes, to afford the *title compound* (418 mg, 47% yield at 41% purity) as a yellow solid. δ_{H} (500 MHz, CDCl_3) 6.87-6.23 (m, 1H), 4.22-3.95 (m, 2H), 2.62-1.40 (m, 7H), 1.18 (d, J 9.2 Hz, 15H). Method C HPLC-MS: MH⁺ m/z 293, RT 1.59 minutes.

INTERMEDIATE 200

30

Ethyl 3-[5-(3-{[2-(difluoromethoxy)phenyl]methyl}-7-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)pyrimidin-2-yl]bicyclo[4.1.0]hept-2-ene-7-carboxylate

A mixture of *Intermediate 152* (95%, 200 mg, 0.454 mmol), *Intermediate 199*

(355 mg, 0.499 mmol), and 2M aqueous sodium carbonate solution (0.69 mL) in 1,4-dioxane (3 mL) was purged with nitrogen for 10 minutes, then tetrakis(triphenylphosphine)palladium(0) (26 mg, 5 mol %) was added and the reaction mixture was heated at 120°C for 1 h under microwave irradiation. The reaction mixture was diluted with ethyl acetate (25 mL), then washed with water (5 mL) and brine (5 mL). The organic layer was dried over sodium sulfate, filtered and concentrated. The crude residue was purified by flash chromatography, eluting with 5 to 100% ethyl acetate in heptane, to afford the *title compound* (169 mg, 68%) as a brown oil. δ_{H} (500 MHz, CDCl_3) 8.70 (dd, J 5.2, 1.5 Hz, 2H), 7.77 (dd, J 7.0, 1.6 Hz, 1H), 7.73-7.63 (m, 1H), 7.35 (d, J 10.6 Hz, 1H), 7.28-7.14 (m, 2H), 7.11 (t, J 7.5 Hz, 1H), 6.91 (d, J 7.7 Hz, 1H), 6.63 (td, J 73.6, 0.7 Hz, 1H), 4.30 (s, 2H), 4.19-4.08 (m, 2H), 3.30-3.02 (m, 1H), 2.85-2.70 (m, 1H), 2.52 (s, 3H), 2.36-2.09 (m, 2H), 2.05 (s, 1H), 1.82 (ddq, J 19.4, 10.0, 3.4, 3.0 Hz, 1H), 1.69-1.58 (m, 1H), 1.26 (td, J 7.1, 2.4 Hz, 3H). Method A HPLC-MS: MH^+ m/z 549, RT 3.67 minutes.

INTERMEDIATE 201

Ethyl 3-[5-(3-{[2-(difluoromethoxy)phenyl]methyl}-7-fluoro-2-methylimidazo[1,2-*a*]pyridin-6-yl)pyrimidin-2-yl]bicyclo[4.1.0]heptane-7-carboxylate

Intermediate 200 (145 mg, 0.243 mmol) was dissolved in ethyl acetate (5 mL) and palladium on carbon (10%, 26 mg, 10 mol %) and triethylamine (34 μL , 0.243 mmol) were added. The suspension was degassed using vacuum/nitrogen/hydrogen and the reaction mixture was stirred under hydrogen at room temperature for 2 h. The mixture was filtered through celite, then concentrated under reduced pressure. The residue was treated several times as described above until starting material was consumed. The reaction mixture was filtered through celite and concentrated to afford a crude yellow oil. The crude residues obtained from batches 1 and 2 were combined and purified by preparative HPLC (basic method), to afford the *title compound* (12.4 mg, 8%) as a pink oil. δ_{H} (250 MHz, CDCl_3) 8.69 (dd, J 4.8, 1.6 Hz, 2H), 7.76 (d, J 7.0 Hz, 1H), 7.36 (d, J 10.6 Hz, 1H), 7.32-7.23 (m, 1H), 7.21-7.05 (m, 2H), 6.95-6.30 (m, 2H), 4.29 (s, 2H), 4.12 (q, J 7.1 Hz, 2H), 2.96-2.68 (m, 1H), 2.51 (s, 4H), 2.27-2.09 (m, 1H), 2.09-1.98 (m, 1H), 1.97-1.81 (m, 2H), 1.79-1.64 (m, 2H), 1.55 (t, J 4.4 Hz, 1H), 1.41 (td, J 12.9, 4.7 Hz, 1H), 1.27 (t, J 7.1 Hz, 3H).

INTERMEDIATE 202

5 2-Chloro-5-(3-{[2-(difluoromethoxy)phenyl]methyl}-7-fluoro-2-methylimidazo[1,2-a]-pyridin-6-yl)pyridine

Intermediate 68 (1 g, 2.6 mmol) and (6-chloropyridin-3-yl)boronic acid (368 mg, 2.34 mmol) were dissolved in 1,4-dioxane (6 mL) and 2M aqueous potassium carbonate solution (3.9 mL). The mixture was added to a sealed tube and degassed for 10 minutes with nitrogen. Pd(dppf)Cl₂ complex with dichloromethane (106 mg, 0.13 mmol) was added and the mixture was heated at 80°C for 1.5 h. Additional (6-chloropyridin-3-yl)-boronic acid (123 mg, 0.78 mmol) was added, and the reaction mixture was degassed for 10 minutes. Pd(dppf)Cl₂ complex with dichloromethane (106 mg, 0.13 mmol) was added and the mixture was heated at 80°C overnight. The mixture was extracted with ethyl acetate (2 x 25 mL). The organic phase was washed with brine (2 x 25 mL), dried with sodium sulphate, filtered and concentrated under vacuum. The resulting black oily residue was purified by chromatography using Biotage (100g SNAP cartridge), eluting with 100% ethyl acetate, then further purified by trituration in ethyl acetate (4 mL), to afford the *title compound* (173 mg, 15%) as a white solid. Further solid in the filtrate was trituated with ethyl acetate (4 mL) and filtered, to afford an additional quantity of the *title compound* (145 mg, 13%) as a white solid. Method B HPLC-MS: MH⁺ *m/z* 417, RT 1.60 minutes.

INTERMEDIATE 203

25 Ethyl (1*s*,5*s*,6*r*)-3-[5-(3-{[2-(difluoromethoxy)phenyl]methyl}-7-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl)pyridin-2-yl]bicyclo[3.1.0]hex-2-ene-6-carboxylate

Intermediate 202 (350 mg, 0.84 mmol) and *Intermediate 134* (75%, 372 mg, 1.00 mmol) were dissolved in 1,4-dioxane (4 mL), then 2M aqueous potassium carbonate solution (1.3 mL) was added and the reaction mixture was degassed for 10 minutes before addition of tetrakis(triphenylphosphine)palladium(0) (484 mg, 0.42 mmol). The reaction mixture was stirred at 120°C under microwave irradiation for 1.5 h. The reaction mixture was extracted with ethyl acetate (30 mL), and the organic phase was washed with water (2 x 20 mL) and brine (25 mL). The solid present in the organic phase was filtered and

discarded. The organic phase was dried over sodium sulphate, filtered and concentrated under vacuum. The resulting orange residue was purified on the Biotage system (100g SNAP cartridge used, eluting with 25 to 100% ethyl acetate in heptane), to afford the *title compound* (92 mg, 20%) as a yellow gum. Method B HPLC-MS: MH⁺ *m/z* 534, RT 1.76, 1.87 minutes.

INTERMEDIATE 204

Ethyl (1*R*,5*s*,6*r*)-3-[5-(3-{[2-(difluoromethoxy)phenyl]methyl}-7-fluoro-2-methyl-imidazo[1,2-*a*]pyridin-6-yl)pyridin-2-yl]bicyclo[3.1.0]hexane-6-carboxylate

Intermediate 203 (192 mg, 0.17 mmol) was dissolved in ethyl acetate (2 mL), then triethylamine (30 μ L, 0.21 mmol) and palladium on carbon (10%, 183 mg, 0.17 mmol) were added. The reaction mixture was purged with nitrogen, then evacuated (3 times), filled with hydrogen and evacuated (3 times). The reaction mixture was stirred at room temperature for 2.5 h under hydrogen. The reaction mixture was filtered through celite and washed with ethyl acetate (25 mL), then the filtrate was concentrated under vacuum. The residue was purified by preparative HPLC (Method C) to afford the *title compound* (47 mg, 51%) as an orange gum. Method B HPLC-MS: MH⁺ *m/z* 536, RT 1.78 minutes.

INTERMEDIATE 205

7-Benzyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-one

To a solution of tetrahydro-4*H*-pyran-4-one (6 g, 60 mmol) and powdered paraformaldehyde (4.50 g, 150 mmol) in isopropanol (150 mL) at 65°C was added a solution of benzylamine (7.2 mL, 66 mmol) and acetic acid (3.77 mL, 66 mmol) in isopropanol (150 mL) dropwise over 1.5 h. The reaction mixture was stirred at 65°C for 1.5 h. Upon cooling, the solvent was removed *in vacuo*. The residue was diluted with water (250 mL) and 1M hydrogen chloride solution (22.5 mL), and extracted with *tert*-butyl methyl ether (2 x 100 mL). The aqueous phase was basified to pH 13 with 1M aqueous sodium hydroxide solution and extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated. The residue was purified by flash column chromatography (Biotage Isolera 4, SNAP 100 g), eluting with 0 to 100% ethyl acetate in heptanes, to afford the *title compound* 6 g, 37%) as

a yellow oil. δ_{H} (500 MHz, DMSO- d_6) 7.40-7.18 (m, 5H), 4.09 (d, J 10.9 Hz, 2H), 3.73 (dd, J 11.2, 2.8 Hz, 2H), 3.52 (s, 2H), 2.97 (dd, J 11.1, 2.9 Hz, 2H), 2.89 (dd, J 11.1, 6.8 Hz, 2H), 2.49-2.44 (m, 2H). Method E HPLC-MS: MH^+ m/z 232, RT 4.10 minutes.

5

INTERMEDIATE 206

7-Benzyl-3-oxa-7-azabicyclo[3.3.1]nonane-9-carbonitrile

To a solution of *Intermediate 205* (85%, 6 g, 22.05 mmol) and 1-[(isocyano-methyl)sulfonyl]-4-methylbenzene (10.33 g, 52.92 mmol) in 1,2-dimethoxyethane (73 mL) and ethanol (2 mL) at 0°C was added potassium *tert*-butoxide (5.94 g, 52.92 mmol) portionwise over 20 minutes. The reaction mixture was stirred at 0°C for 1.5 h, then at 40°C for 1 h. Upon cooling, the mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was dissolved in ethyl acetate (200 mL), and washed with water (100 mL) and brine (100 mL), then dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (Biotage Isolera 4, SNAP 100 g), eluting with 0 to 10% methanol in dichloromethane, to afford the *title compound* (4.1 g 58%) as an orange-brown gum. δ_{H} (500 MHz, DMSO- d_6) 7.45-7.18 (m, 5H), 3.85 (d, J 12.1 Hz, 1H), 3.77 (t, J 13.0 Hz, 2H), 3.65 (d, J 11.8 Hz, 1H), 3.45 (d, J 18.1 Hz, 2H), 2.86 (dd, J 26.6, 10.9 Hz, 2H), 2.54 (d, J 11.8 Hz, 1H), 2.44-2.26 (m, 2H), 2.00 (s, 2H). Method E HPLC-MS: MH^+ m/z 243, RT 4.25 minutes.

INTERMEDIATE 207

Methyl 7-benzyl-3-oxa-7-azabicyclo[3.3.1]nonane-9-carboxylate

Intermediate 206 (75%, 4.1 g, 12.69 mmol) in a 12N hydrogen chloride solution in water (50 mL) was heated at reflux for 12 h. The solvent was removed *in vacuo*, then the residue was dissolved in methanol (100 mL) and concentrated sulphuric acid (2 mL) was added. The mixture was heated at reflux for 20 h. Upon cooling, the reaction mixture was concentrated *in vacuo* and partitioned between saturated aqueous sodium bicarbonate solution (200 mL) and ethyl acetate (300 mL). The aqueous layer was extracted with ethyl acetate (2 x 200 mL). The combined organic layers were washed with brine (200 mL), dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (Biotage Isolera 4, SNAP 100 g),

cluting with 0 to 100% methanol in dichloromethane, to afford the *title compound* (1.67 g, 47%) as a red-brown oil. δ_{H} (250 MHz, CDCl_3) 7.46-7.10 (m, 5H), 4.15-3.77 (m, 2H), 3.73 (d, J 1.9 Hz, 3H), 3.69-3.49 (m, 3H), 3.48-3.34 (m, 1H), 2.95-2.74 (m, 2H), 2.56-2.09 (m, 5H). Method B HPLC-MS: MH^+ m/z 276, RT 1.03 minutes.

5

INTERMEDIATE 208

Methyl 3-oxa-7-azabicyclo[3.3.1]nonane-9-carboxylate hydrochloride

Intermediate 207 (98%, 1.3 g, 4.63 mmol) was dissolved in ethyl acetate (15 mL) and the solution was degassed with nitrogen. Palladium on carbon (10%, 500 mg, 0.47 mmol) was added and the mixture was degassed with nitrogen. The reaction mixture was allowed to stir under hydrogen at room temperature for 18 h. Additional palladium on carbon (10%, 250 mg, 0.23 mmol) was added and the mixture was degassed with nitrogen. The reaction mixture was allowed to stir under hydrogen at room temperature for 18 h. Additional palladium on carbon (10%, 250 mg, 0.23 mmol) and 1M hydrogen chloride in ethyl acetate (5 mL) were added and the mixture was degassed with nitrogen. The reaction mixture was allowed to stir under hydrogen at room temperature for 18 h. The reaction mixture was filtered through celite which was washed excessively with ethyl acetate (200 mL) followed by dichloromethane (200 mL). The filtrate was concentrated under vacuum to afford the *title compound* (1.03 g, 98%) as an orange solid. δ_{H} (500 MHz, CD_3OD) 4.19 (d, J 11.6 Hz, 1H), 4.01 (d, J 12.0 Hz, 1H), 3.79 (dd, J 25.6, 2.6 Hz, 5H), 3.65 (d, J 12.7 Hz, 1H), 3.49 (d, J 13.3 Hz, 1H), 3.42 (d, J 12.7 Hz, 1H), 3.35-3.31 (m, 1H), 3.09 (s, 1H), 2.36 (d, J 13.3 Hz, 2H).

25

INTERMEDIATE 209

Methyl 7-[5-(3-{[2-(difluoromethoxy)phenyl]methyl}-7-fluoro-2-methylimidazo[1,2-a]-pyridin-6-yl)pyrimidin-2-yl]-3-oxa-7-azabicyclo[3.3.1]nonane-9-carboxylate

Intermediate 152 (95%, 200 mg, 0.45 mmol), *Intermediate 208* (150 mg, 0.68 mmol) and a 1M solution of potassium carbonate in water (1.4 mL) were suspended in 1-methylpyrrolidin-2-one (3 mL) and the reaction mixture was heated at 120°C under microwave irradiation for 1 h. The reaction mixture was concentrated under vacuum. The residue was diluted with dichloromethane (25 mL) and saturated aqueous sodium

bicarbonate solution (25 mL). The organic phase was separated, washed with brine, dried over sodium sulfate, filtered and concentrated under vacuum. The residue was purified by flash column chromatography, eluting with 0 to 10% methanol in dichloromethane, and further purified by preparative HPLC (Method C), to afford the *title compound* (210 mg, 82%) as an orange gum. δ_{H} (500 MHz, CD_3OD) 8.34 (d, J 5.3 Hz, 2H), 8.05 (d, J 5.1 Hz, 1H), 7.31-7.22 (m, 2H), 7.17 (d, J 8.1 Hz, 1H), 7.12 (s, 1H), 7.08-6.73 (m, 2H), 5.00 (d, J 13.3 Hz, 1H), 4.62 (d, J 13.8 Hz, 1H), 4.34 (s, 2H), 3.99 (d, J 11.3 Hz, 1H), 3.81 (d, J 11.6 Hz, 1H), 3.78-3.69 (m, 5H), 3.47 (d, J 13.6 Hz, 1H), 3.24 (d, J 13.2 Hz, 1H), 2.92 (s, 1H), 2.39 (s, 3H), 2.29 (s, 2H).

INTERMEDIATE 210

1-tert-Butyl 2-methyl 5-oxopiperidine-1,2-dicarboxylate

1-(*tert*-Butoxycarbonyl)-5-oxopiperidine-2-carboxylic acid (2.0 g, 8.22 mmol) was dissolved in DMF (20 mL) under nitrogen and potassium carbonate (1.7 g, 12.33 mmol) was added, followed by iodomethane (620 μL , 9.95 mmol). The reaction mixture was stirred at room temperature under nitrogen for 23 h. Additional methyl iodide (256 μL , 4.11 mmol) was added and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was diluted with ethyl acetate (100 mL) and washed with saturated aqueous sodium bicarbonate solution (2 x 25 mL) and brine (2 x 25 mL), then dried over sodium sulfate and concentrated to dryness. The crude residue was purified by flash column chromatography (Biotage), eluting with 0 to 100% ethyl acetate in heptanes, to afford the *title compound* (2.42 g, 53%) as a pale yellow oil. δ_{H} (250 MHz, CDCl_3) 4.70 (dt, J 59.4, 6.3 Hz, 1H), 4.35 (dd, J 27.3, 19.0 Hz, 1H), 3.90 (dd, J 19.0, 12.4 Hz, 1H), 3.77 (s, 3H), 2.56-1.95 (m, 4H), 1.45 (s, 9H).

INTERMEDIATE 211

1-tert-Butyl 2-methyl 5-(trifluoromethanesulfonyloxy)-1,2,3,6-tetrahydropyridine-1,2-dicarboxylate and 1-tert-Butyl 2-methyl 5-(trifluoromethanesulfonyloxy)-1,2,3,4-tetrahydropyridine-1,2-dicarboxylate

To a stirred solution of *Intermediate 210* (1.05 g, 4.08 mmol) in tetrahydrofuran (70 mL) cooled to -78°C was added dropwise 1M lithium 1,1,1,3,3,3-hexamethyl-

disilazan-2-ide in tetrahydrofuran (4.29 mL). The reaction mixture was stirred at -78°C for 1 h prior to the addition of 1,1,1-trifluoro-*N*-phenyl-*N*-[(trifluoromethyl)sulfonyl]-methanesulfonamide (1.53 g, 4.29 mmol) in tetrahydrofuran (30 mL). The reaction mixture was stirred at -78°C for 30 minutes, then allowed to warm to room temperature, and stirred at room temperature over 2 days. The reaction mixture was quenched with aqueous sodium hydrogensulphate solution (50 mL) and extracted with ethyl acetate (70 mL). The organic layer was washed with 0.5M aqueous sodium hydroxide solution (70 mL), saturated aqueous ammonium chloride solution (70 mL) and brine (70 mL), then dried over sodium sulphate, filtered and concentrated under vacuum. The resulting crude yellow oil was purified twice by column chromatography (Biotage Isolera 4, 50 g cartridge), eluting with 0% to 100% *tert*-butyl methyl ether in heptane for the first column and 0 to 50% *tert*-butyl methyl ether in heptane for the second column, to afford the *title compounds* (597 mg, 32%) as a colourless oil. Method B HPLC-MS: [M-BOC]⁺ *m/z* 290, RT 2.25 minutes.

INTERMEDIATE 212

1-*tert*-Butyl 2-methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine-1,2-dicarboxylate and 1-*tert*-Butyl 2-methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4-tetrahydropyridine-1,2-dicarboxylate

Intermediate 211 (595 mg, 1.33 mmol), bis(pinacolato)diborane (508 mg, 2.00 mmol) and potassium acetate (393 mg, 4.00 mmol) were suspended in 1,4-dioxane (12 mL) and the mixture was degassed with nitrogen for 5 minutes. 1,1'-Bis(diphenylphosphanyl)ferrocene (22 mg, 0.04 mmol) and Pd(dppf)Cl₂ complex with dichloromethane (33 mg, 0.04 mmol) were added and the mixture was heated in a sealed tube at 90°C for 3 h. The cooled reaction mixture was diluted with ethyl acetate (30 mL) and washed with saturated aqueous sodium bicarbonate solution (15 mL). The aqueous layer was further extracted with ethyl acetate (2 x 30 mL). The combined organic layers were washed with brine, dried over sodium sulphate, filtered and concentrated. The resulting dark residue was purified by column chromatography (Biotage Isolera 4, 50 g cartridge), eluting with 0% to 50% ethyl acetate in heptane, to afford the *title compounds* (296 mg, 60%) as a pale yellow oil. Method B HPLC-MS: [M-BOC]⁺ *m/z* 268, RT 2.24, 2.29 minutes.

INTERMEDIATE 213

1-*tert*-Butyl 2-methyl 5-[5-(3-{[2-(difluoromethoxy)phenyl]methyl}-7-fluoro-2-methyl-
imidazo[1,2-*a*]pyridin-6-yl)pyrimidin-2-yl]-1,2,3,6-tetrahydropyridine-1,2-dicarboxylate
and 1-*tert*-Butyl 2-methyl 5-[5-(3-{[2-(difluoromethoxy)phenyl]methyl}-7-fluoro-2-
methylimidazo[1,2-*a*]pyridin-6-yl)pyrimidin-2-yl]-1,2,3,4-tetrahydropyridine-1,2-
dicarboxylate

A mixture of *Intermediate 152* (280 mg, 0.70 mmol), *Intermediate 212* (294 mg,
0.80 mmol) and 2M aqueous sodium carbonate solution (1.0 mL) in 1,4-dioxane (5.0 mL)
was purged with nitrogen for 5 minutes. Tetrakis(triphenylphosphine)palladium(0) (38
mg, 0.03 mmol) was then added and the reaction mixture was heated at 120°C under
microwave irradiation for 1 h. The cooled reaction mixture was partitioned between ethyl
acetate (20 mL) and water (10 mL). The aqueous layer was separated and extracted into
ethyl acetate (3 x 20 mL). The combined organic extracts were washed with brine (20
mL), dried over sodium sulphate, filtered and evaporated. The resulting crude residue
was successively purified by column chromatography (Biotage Isolera, 25 g cartridge),
eluting with 40% to 100% ethyl acetate in heptane, and by preparative chromatography
(Method C), to afford the *title compounds* (205 mg, 49%) as a pale brown solid. Method
B HPLC-MS: MH⁺ *m/z* 624, RT 1.92 minutes.

INTERMEDIATE 214

1-*tert*-Butyl 2-methyl 5-[5-(3-{[2-(difluoromethoxy)phenyl]methyl}-7-fluoro-2-methyl-
imidazo[1,2-*a*]pyridin-6-yl)pyrimidin-2-yl]piperidine-1,2-dicarboxylate

To a stirring solution of *Intermediate 213* (200 mg, 0.32 mmol) in ethyl acetate (5
mL), dichloromethane (5 mL) and triethylamine (45 µl, 0.32 mmol), degassed and purged
with nitrogen, was added palladium on carbon (10%, 34 mg, 0.03 mmol). The reaction
mixture was stirred under hydrogen at room temperature until the reaction was complete.
The reaction mixture was filtered through celite and the solids were washed with excess
ethyl acetate. The filtrate was evaporated to give a pale residue which was successively
purified by column chromatography (Biotage Isolera 4, 25 g cartridge), eluting with 20%
to 100% ethyl acetate in heptanes, and by preparative HPLC (Method C), to afford the

title compound (52 mg, 26%) as a pale crystallising oil (55:45 mixture of diastereoisomers). δ_{H} (500 MHz, CDCl_3) 8.71 (d, J 1.5 Hz, 2H), 7.76 (dd, J 7.0, 3.0 Hz, 1H), 7.36 (d, J 10.6 Hz, 1H), 7.28 (m, 1H), 7.16 (d, J 8.2 Hz, 1H), 7.10 (t, J 7.5 Hz, 1H), 6.89 (t, J 8.5 Hz, 1H), 6.62 (t, J 73.6 Hz, 1H), 5.09-4.32 (m, 2H), 4.28 (s, 2H), 3.76 (d, J 4.9 Hz, 3H), 3.58-2.96 (m, 2H), 2.50 (s, 3H), 2.41 (t, J 11.2 Hz, 1H), 2.14-2.06 (m, 2H), 1.88 (ddd, J 13.9, 10.7, 5.4 Hz, 1H), 1.43 (d, J 50.8 Hz, 9H). Method B HPLC-MS: MH^+ m/z 626, RT 1.74, 1.78 minutes.

INTERMEDIATE 215

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Methyl 5-[5-(3-{[2-(difluoromethoxy)phenyl]methyl}-7-fluoro-2-methylimidazo[1,2-*a*]-pyridin-6-yl)pyrimidin-2-yl]piperidine-2-carboxylate

To a stirred solution of *Intermediate 214* (50 mg, 0.08 mmol) in dichloromethane (2 mL) was added trifluoroacetic acid (0.6 mL). The reaction mixture was stirred at room temperature for 4.5 h. The reaction mixture was loaded onto a 1 g SCX cartridge and eluted with methanol, followed by 7N ammonia in methanol, to afford the *title compound* (25 mg, 59%) as a pale crystallising oil (mixture of diastereoisomers). δ_{H} (500 MHz, CDCl_3) 8.71 (dd, J 7.2, 1.3 Hz, 2H), 7.75 (dd, J 6.8, 5.2 Hz, 1H), 7.37-7.30 (m, 1H), 7.29-7.26 (m, 1H), 7.16 (d, J 8.1 Hz, 1H), 7.09 (t, J 7.5 Hz, 1H), 6.88 (d, J 7.5 Hz, 1H), 6.62 (td, J 73.6, 4.6 Hz, 1H), 4.28 (s, 2H), 3.75 (d, J 7.2 Hz, 3H), 3.56-3.38 (m, 2H), 3.27-2.90 (m, 2H), 2.50 (s, 3H), 2.35-2.13 (m, 2H), 1.96-1.61 (m, 2H). Method B HPLC-MS: MH^+ m/z 526, RT 1.22 minutes.

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INTERMEDIATE 216 [removed]

GENERAL METHOD C

Formation of Functionalised Pyrimidine Boronic Acids

To a suspension of (2-chloropyrimidin-5-yl)boronic acid (1.0 eq) in ethanol is added the appropriate amine (0.95 eq). Triethylamine (2.5 eq) is added and the mixture stirred at either ambient temperature or 80°C until the reaction is complete by TLC or LCMS. If the product precipitates the desired compound is isolated by filtration. For soluble products the reaction mixture is concentrated *in vacuo* and the crude product

mixture is partitioned between aqueous medium and ethyl acetate. The aqueous layer is separated and re-extracted with ethyl acetate. The organic layers are combined and washed with brine, then dried (Na₂SO₄), filtered and concentrated *in vacuo*. The product can be further purified if required by column chromatography on silica gel or preparative mass-directed HPLC.

INTERMEDIATE 217

4-(5-Boronopyrimidin-2-yl)-1,4-oxazepane-7-carboxylic acid

The *title compound* was prepared from 1,4-oxazepane-7-carboxylic acid and (2-chloropyrimidin-5-yl)boronic acid in accordance with *General Method C*.

INTERMEDIATE 218

(2R)-4-(5-Boronopyrimidin-2-yl)morpholine-2-carboxylic acid

The *title compound* was prepared from (2R)-morpholine-2-carboxylic acid and (2-chloropyrimidin-5-yl)boronic acid in accordance with *General Method C*.

INTERMEDIATE 219

[2-(7-oxo-3,6-diazabicyclo[3.2.2]nonan-3-yl)pyrimidin-5-yl]boronic acid

The *title compound* was prepared from 3,6-diazabicyclo[3.2.2]nonan-7-one and (2-chloropyrimidin-5-yl)boronic acid in accordance with *General Method C*.

INTERMEDIATE 220

Ethyl 4-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidin-2-yl]cyclohex-3-ene-1-carboxylate

The *title compound* was synthesised from *Intermediate 56* in accordance with the method outlined for *Intermediate 221*.

INTERMEDIATE 221

Ethyl 1-methyl-4-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidin-2-yl]cyclohex-3-ene-1-carboxylate

- 5 A stirred mixture of ethyl 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enecarboxylate (prepared in an analogous manner to *Intermediate 273*; 70 g, 190 mmol, 80%), 5-bromo-2-iodopyrimidine (54.2 g, 190 mmol) and sodium carbonate (60.5 g, 571 mmol) in 1,2-dimethoxyethane (750 mL) and water (250 mL) was flushed with argon. 1,1'-Bis(diphenylphosphino)ferrocenepalladium(II) dichloride (4.66 g, 5.71
- 10 mmol) was added and the resulting mixture was stirred at 100°C until the reaction was complete by LCMS or TLC. The reaction mixture was quenched into aqueous NaCl solution (~10 wt %, 1000 mL) and EtOAc (200 mL) with stirring. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 200 mL). The combined extracts were dried with Na₂SO₄ and concentrated *in vacuo*. The resulting brown-black
- 15 tar (95 g) was triturated in diisopropyl ether/heptane (1:1, 400 mL) under slight heating for 1 h. The whole was filtered over kieselguhr and rinsed with diisopropyl ether/heptane (1:1). Upon concentration *in vacuo* the residue was triturated in warm heptane (1 L) together with Norit® activated charcoal. The whole was again filtered over kieselguhr and concentrated *in vacuo*. The resulting clear yellow-orange oil (69 g), which solidified
- 20 upon standing, was purified by gravity column chromatography. The resulting white solid (27 g, 83 mmol) was stirred with bis(pinacolato)diboron (21.08 g, 83 mmol) and potassium acetate (24.4 g, 249 mmol) in 1,4-dioxane (anhydrous, 300 mL) and flushed with argon (3 vacuum-argon cycles) for 5 minutes. 1,1'-Bis(diphenylphosphino)-ferrocenepalladium(II) dichloride (2.034 g, 2.491 mmol) was added, and the resulting
- 25 mixture was stirred at 90°C for 3 h. The reaction mixture was cooled to ~40°C and filtered over a pad of kieselguhr, which was rinsed with EtOAc (300 mL). The filtrate was concentrated *in vacuo*. The resulting dark brown solid (51 g) was triturated in heptane/diisopropyl ether (1:1, 400 mL) at ~50°C, and some scoops of Norit® activated charcoal were added. After 30 minutes the insoluble materials were removed by filtration
- 30 over kieselguhr. The residue was rinsed with heptane/diisopropyl ether (1:1, 500 mL) at ~50°C. More insoluble material (sticky dark gum) precipitated from the filtrate. Norit® activated charcoal was added and the resulting suspension was stirred for 30 minutes at room temperature. The residue was filtered over a new pad of kieselguhr and rinsed with

warm heptane/diisopropyl ether (1:1, 500 mL). Concentration of the filtrate *in vacuo* yielded the *title compound* (38 g) as a beige solid.

GENERAL METHOD B

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Pyrimidine Displacements

The appropriate 2-chloropyrimidine (e.g. *Intermediate 29* or *Intermediate 152*; 1 eq), the appropriate amine (1 eq) and triethylamine (1 eq) are dissolved in ethanol and heated at 80°C until the reaction is complete by TLC or LCMS analysis. The ethanol is removed under vacuum and water added. Depending on solubility, the product is isolated by filtration or extracted into ethyl acetate. Ethyl acetate solutions are subsequently dried over sodium sulphate, filtered and concentrated *in vacuo*. The crude residue thus obtained is purified by an appropriate technique, typically column chromatography on silica gel or preparative mass-directed HPLC.

15

INTERMEDIATE 222

1-[5-Bromo-4-(trifluoromethyl)pyrimidin-2-yl]-1,4-diazepan-5-one

Synthesised from 5-bromo-2-chloro-4-(trifluoromethyl)pyrimidine (1.14 g, 4.35 mmol) and 1,4-diazepan-5-one (490 mg, 4.30 mmol) in accordance with *General Method B*, giving the *title compound* (1.20 g, 81%) as a white solid. δ_H (300 MHz, DMSO- d_6) 8.79 (s, 1H), 7.71 (t, J 4.8 Hz, 1H), 3.90 (m, 4H), 3.21 (m, 2H), 2.54 (m, 2H). LC-MS (pH 3) MH^+ m/z 339.0, RT 1.93 minutes. LC-MS (pH 10) MH^+ m/z 339.0, RT 1.91 minutes.

25

INTERMEDIATE 223

{2-[4-Ethoxycarbonyl-4-(hydroxymethyl)piperidin-1-yl]pyrimidin-5-yl}boronic acid

A solution of 1-*tert*-butyl 4-ethyl piperidine-1,4-dicarboxylate (1g, 3.89 mmol) in THF (5 mL) was stirred at -78°C and lithium bis(trimethylsilyl)amide (1M in toluene, 5.8 mL, 29 mmol) was added dropwise, then stirred for 1 h. Paraformaldehyde (0.7370 g, 7.773 mmol) was added and the mixture was stirred for 16 h, allowing the temperature to rise slowly to ambient. The reaction mixture was quenched using saturated aqueous

ammonium chloride solution, then partitioned between EtOAc and brine. The aqueous layer was further extracted using EtOAc. The combined organic extracts were dried (MgSO₄) and the solvent was removed under vacuum. The resulting material was dissolved and stirred for 1 h in TFA (10 mL), then rotary evaporated to dryness. The crude residue (theoretical 0.7 g, 3.891 mmol) was dissolved in ethanol (12 mL), then sodium carbonate (1.03 g, 9.72 mmol) and (2-chloropyrimidin-5-yl)boronic acid (0.68 g, 4.3 mmol) were added and the reaction mixture was stirred at 60°C for 2 h. LC/MS showed completion of reaction. The mixture was cooled to ambient temperature and filtered through celite. The solvent was removed to give the crude *title compound* (1 g, 83%) as a cream solid, which was used without further purification. LCMS (pH 10) MH⁺ 310, RT 0.95 minutes.

INTERMEDIATE 224

[2-(1-Ethoxycarbonyl-3-azabicyclo[4.1.0]heptan-3-yl)pyrimidin-5-yl]boronic acid

The *title compound* was synthesized from *Intermediate 91* in accordance with *General Method C*.

INTERMEDIATE 225

{2-[4-Ethoxycarbonyl-4-(trifluoromethyl)piperidin-1-yl]pyrimidin-5-yl}boronic acid

TFA (5 mL) was added to 1-*tert*-butyl 4-ethyl 4-(trifluoromethyl)piperidine-1,4-dicarboxylate (0.42 g, 1.29 mmol). The mixture was stirred for 30 minutes, then rotary evaporated to dryness and left on a high vacuum line for 1 h. The residual syrup was dissolved in ethanol (4 mL), anhydrous sodium carbonate (0.35 g, 3.3 mmol) was added, and the mixture was stirred for 10 minutes. (2-Chloropyrimidin-5-yl)boronic acid (0.23 g, 1.4 mmol) was added and the reaction mixture was stirred at 60°C for 6 h. The mixture was filtered through celite and concentrated to give the *title compound* (0.4 g, 89%) as an off-white foam, which was used without further purification. LCMS (pH 10) MH⁺ 348, RT 1.31 minutes.

INTERMEDIATE 226**[2-(4-Ethoxycarbonyl-4-fluoropiperidin-1-yl)pyrimidin-5-yl]boronic acid**

A mixture of ethyl 4-fluoropiperidine-4-carboxylate hydrochloride (2 g, 9.4491 mmol), (2-chloropyrimidin-5-yl)boronic acid (1.5426 g, 9.4493 mmol) and sodium carbonate decahydrate (2.53 g, 23.6 mmol) in ethanol (15 mL) was stirred at 60°C for 12 h. The reaction mixture was filtered through celite, the solvent was evaporated and the residue was dried under vacuum to give the *title compound* (2.7 g, 97%) as a pale yellow gum, which was used without further purification. LCMS (pH 10) MH⁺ 298, RT 1.19 minutes.

INTERMEDIATE 227**{2-[4-Methoxy-4-(methoxycarbonyl)piperidin-1-yl]pyrimidin-5-yl} boronic acid**

A 2% solution of HCl in MeOH was prepared by adding acetyl chloride (1.1 mL) to MeOH (25 mL). To this solution was added 1-[(*tert*-butoxy)carbonyl]-4-methoxy-piperidine-4-carboxylic acid (1 g, 3.6637 mmol) and the solution was heated under reflux for 6 h. The reaction mixture was evaporated to dryness and left on a vacuum line for 30 minutes. The material thus obtained was dissolved in ethanol (8 mL) and stirred with sodium carbonate (0.96 g, 9.1 mmol) for 10 minutes, then (2-chloropyrimidin-5-yl)-boronic acid (0.57g, 3.61mmol) was added and the mixture was stirred at 60°C for 6 h. The reaction mixture was filtered through celite and the solvents removed *in vacuo* to give the *title compound* (0.8 g, 71%) as a white foam, which was used without further purification. LCMS (pH 10) MH⁺ 296, RT 0.86 minutes.

INTERMEDIATE 228**{2-[4-Ethyl-4-(methoxycarbonyl)piperidin-1-yl]pyrimidin-5-yl} boronic acid**

TFA (8 mL) was added to a stirred solution of 1-*tert*-butyl 4-methyl 4-ethyl-piperidine-1,4-dicarboxylate (0.61 g, 2.25 mmol) in 1,4-dioxane (2 mL). The reaction mixture was stirred for 2 h, then the volatiles were removed by rotary evaporation and the residue was left on a high vacuum line for 1 h. The syrupy material thus obtained was dissolved in ethanol (8 mL), anhydrous sodium carbonate (0.72 g, 6.79 mmol) was added

and the mixture was stirred for 10 minutes. (2-Chloropyrimidin-5-yl)boronic acid (0.37 g, 2.3 mmol) was added and the mixture was stirred at 80°C for 7 h. The reaction mixture was filtered through celite, then the solvent was removed under vacuum, and water was added. The mixture was decanted and washed again with water, then the residual gum was freeze-dried, to give the *title compound* (0.4 g, 60%) as a pale yellow lyophilised solid, which was used without further purification. LCMS (pH 10) MH⁺ 294, RT 1.15 minutes.

INTERMEDIATE 229

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{2-[(1R,5S)-8-(Methoxycarbonyl)-3-azabicyclo[3.2.1]octan-3-yl]pyrimidin-5-yl}boronic acid

Prepared from methyl 3-azabicyclo[3.2.1]octane-8-carboxylate hydrochloride (0.57 g, 2.8 mmol) and (2-chloropyrimidin-5-yl)boronic acid (0.45 g, 2.8 mmol) in accordance with *General Method C* to afford the *title compound* (1 g) as an off-white gum. LCMS (pH 3) MH⁺ 292, RT 0.79 minutes.

INTERMEDIATE 230

20 {2-[(1R,5S,8S)-8-(Methoxycarbonyl)-3-azabicyclo[3.2.1]octan-3-yl]pyrimidin-5-yl}-boronic acid

(1R,5S)-3-*tert*-Butoxycarbonyl-3-azabicyclo[3.2.1]octane-8-carboxylic acid (9.0 g, 35.3 mmol) was suspended in HCl solution (2.25M in MeOH) and the reaction mixture was heated at reflux for 4 h. The reaction mixture was allowed to cool to r.t., then concentrated *in vacuo*. To the resulting white solid was added (2-chloropyrimidin-5-yl)boronic acid (5.58 g, 35.2 mmol) and the mixture was suspended in EtOH (130 mL). Triethylamine (9.90 mL, 70.5 mmol) was added and the reaction mixture was heated at 80°C for 5 h. The reaction mixture was allowed to cool to r.t., then water (30 mL) was added. The reaction mixture was concentrated to around one-third volume, then more water (100 mL) was added. The resulting off-white solid precipitate was filtered and washed with water (2 x 30 mL), to afford the *title compound* (8.9 g, 86%) as an off-white powder. δ_H (300 MHz, DMSO-d₆) 8.59 (2H, s), 8.02 (2H, s), 4.45 (2H, dd, *J* 13.1, 3.4

Hz), 3.62 (3H, s), 2.98 (2H, br d, J 12.4 Hz), 2.77 (1H, s), 2.59 (2H, br s), 1.66-1.63 (2H, m), 1.38-1.33 (2H, m). HPLC-MS (pH 10): MH^+ m/z 292, RT 0.97 minutes.

INTERMEDIATE 231

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{2-[(1*S*,6*R* or 1*R*,6*S*)-6-(Methoxycarbonyl)-3-azabicyclo[4.1.0]heptan-3-yl]pyrimidin-5-yl}boronic acid

Prepared from *Intermediate 116* (301 mg, 1.57 mmol) and (2-chloropyrimidin-5-yl)boronic acid (249 mg, 1.57 mmol) in accordance with *General Method C* to give the
10 *title compound* (306 mg, 70%) as an off-white foam. δ_H (DMSO- d_6) 8.60 (s, 1H), 8.03 (s, 1H), 4.19-4.30 (m, 1H), 3.81-3.92 (m, 1H), 3.70-3.80 (m, 1H), 3.60 (s, 3H), 3.33-3.43 (m, 2H), 1.70-1.83 (m, 2H), 1.29 (dd, 1H, J 9.1, 4.4 Hz), 0.75-0.82 (m, 1H). LCMS (ES+) 278 ($M+H$)⁺, RT 0.79 minutes.

15

INTERMEDIATE 232

{2-[(1*R*,5*R* or 1*S*,5*S*)-5-(Methoxycarbonyl)-3-azabicyclo[3.1.0]hexan-3-yl]pyrimidin-5-yl}boronic acid

Prepared from *Intermediate 144* (300 mg, 1.69 mmol) and (2-chloropyrimidin-5-yl)boronic acid (267 mg, 1.57 mmol) in accordance with *General Method C* to give the
20 *title compound* (269 mg, 60%). δ_H (DMSO- d_6) 8.60 (s, 2H), 8.05 (s, 2H), 3.78-3.96 (m, 2H), 3.66 (s, 3H), 3.55 (dd, 1H, J 11.3, 4.4 Hz), 3.04-3.14 (m, 1H), 2.18-2.28 (m, 1H), 1.50-1.57 (m, 1H), 0.92 (t, 1H, J 5.0 Hz). LCMS (ES+) 264 ($M+H$)⁺, RT 0.49 minutes.

25

INTERMEDIATE 233

Methyl 3-azabicyclo[3.1.0]hexane-1-carboxylate hydrochloride (*Enantiomer B*)

Intermediate 143 (5 g, 20 mmol) was separated using chiral preparative HPLC (Chiracel OJ column, 20 x 250 mm, 5 μ m; 100% acetonitrile eluent; 20 mL/minute flow
30 rate) and the first-eluting diastereomer was isolated (1.87 g, 7.62 mmol). This was dissolved in methanol (55 mL) and the mixture was degassed with nitrogen, then palladium on carbon (10%, 195 mg, 0.18 mmol) was added. The reaction mixture was

stirred under a hydrogen balloon at room temperature for 5 h. The reaction mixture was filtered through celite and the solids were washed with excess methanol. The filtrate was concentrated by evaporation. To the residue was added 4M hydrochloric acid in diethyl ether (10 mL), and the mixture was stirred at room temperature for 10 minutes. The resulting precipitate was filtered, washed with diethyl ether and dried, to afford the *title compound* as an off-white solid. δ_{H} (500 MHz, CD_3OD) 3.83 (dd, J 11.8, 1.3 Hz, 1H), 3.75 (s, 3H), 3.59-3.52 (m, 2H), 3.44 (d, J 11.7 Hz, 1H), 2.40-2.30 (m, 1H), 1.76-1.69 (m, 1H), 1.17 (t, J 5.9 Hz, 1H).

10

INTERMEDIATE 234

{2-[(1R,6S or 1S,6R)-6-(Methoxycarbonyl)-3-azabicyclo[4.1.0]heptan-3-yl]pyrimidin-5-yl}boronic acid (*Enantiomer B*)

Prepared from *Intermediate 117* (299 mg, 1.56 mmol) and (2-chloropyrimidin-5-yl)boronic acid (250 mg, 1.58 mmol) in accordance with *General Method C* to give the *title compound* (232 mg, 54%) as a white solid. δ_{H} (DMSO-d_6) 8.53 (s, 2 H), 7.96 (s, 2H), 4.16 (dd, 1H, J 13.9, 2.3 Hz), 3.79 (dd, 1H, J 13.8, 4.7 Hz), 3.62-3.72 (m, 1H), 3.53 (s, 3H), 3.25-3.36 (m, 1H), 2.35-2.43 (m, 1H), 1.64-1.82 (m, 2H), 1.23 (dd, 1H, J 9.2, 4.4 Hz), 0.71 (dd, 1H, J 6.2, 4.5 Hz). LCMS (ES+) 278 ($\text{M}+\text{H}$)⁺, RT 0.79 minutes.

20

INTERMEDIATE 235

{2-[(1R,6S or 1S,6R)-6-(Ethoxycarbonyl)-4-azabicyclo[4.1.0]heptan-4-yl]pyrimidin-5-yl}boronic acid (*Enantiomer B*)

Prepared from *Intermediate 120* (237 mg, 1.15 mmol) and 2-chloropyrimidin-5-yl)boronic acid (152 mg, 0.96 mmol) in accordance with *General Method C* to give the *title compound* (241 mg, 86%) as a pale yellow solid. δ_{H} (DMSO-d_6) 8.67 (s, 2H), 4.24-4.34 (m, 1H), 4.07 (q, 2H, J 7.1 Hz), 3.98-4.06 (m, 1H), 3.64-3.77 (m, 1H), 3.32-3.45 (m, 1H), 1.94-2.16 (m, 1H), 1.60-1.85 (m, 2H), 1.21-1.33 (m, 1H), 1.18 (t, 3H, J 7.1 Hz), 0.78-0.81 (m, 1H). LCMS (ES+) 292 ($\text{M}+\text{H}$)⁺, RT 1.14 minutes.

30

INTERMEDIATE 236**Ethyl 3-(trifluoromethylsulfonyloxy)cyclohex-2-ene-1-carboxylate**

To a stirred solution of ethyl 3-oxocyclohexanecarboxylate (0.47 mL, 2.9 mmol) in THF (2.5 mL, 100 mass %) at -78°C was added lithium bis(trimethylsilyl)amide (3.10 mL, 1M in THF) dropwise. The reaction mixture stirred at -78°C for 1 h, after which time *N*-phenyltrifluoromethanesulfonimide (1.10 g, 3.08 mmol) in THF (2.5 mL, 100 mass %) was added to the mixture. The reaction mixture was stirred at -78°C for a further 1.5 h, after which time the reaction mixture allowed to warm to room temperature and stirred overnight. The reaction mixture was quenched with aqueous sodium hydrogensulphate solution (~10 mL) and diluted with ethyl acetate (50 mL). The layers were separated and organic layers were washed with 5% aqueous NaOH solution (2 x 30 mL), saturated aqueous ammonium chloride solution (20 mL) and brine (20 mL), then dried (MgSO₄), filtered and concentrated *in vacuo*, to give the *title compound* (932 mg, quantitative) as a yellow oil. δ_{H} (DMSO-*d*₆) 5.89-5.95 (m, 1H), 4.00-4.15 (m, 2H), 2.77-2.91 (m, 1H), 2.16-2.35 (m, 2H), 1.51-1.97 (m, 4H), 1.12-1.24 (m, 3H).

INTERMEDIATE 237**Ethyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-2-ene-1-carboxylate**

To a stirred solution of *Intermediate 236* (888 mg, 2.9 mmol) in 1,4-dioxane (20 mL) were added bis(pinacolato)diboron (1.18 g, 4.63 mmol), potassium acetate (913 mg, 9.30 mmol), 1,1'-bis(diphenylphosphino)ferrocene (62 mg, 0.11 mmol) and [1,1'-bis-(diphenylphosphino)ferrocene]dichloropalladium(II)-DCM adduct (91 mg, 0.11 mmol), and the mixture was stirred at 90°C for 18 h. The reaction mixture was cooled to room temperature, filtered through celite, washed with EtOAc and concentrated *in vacuo*. The crude material was purified by column chromatography (SiO₂, 5-100% EtOAc in hexane and 0-10% MeOH in EtOAc) to give the *title compound* (412 mg, 50%) as a yellow oil. δ_{H} (DMSO-*d*₆) 6.37-6.45 (m, 1H), 3.98-4.14 (m, 2H), 2.20-2.32 (m, 1H), 2.04-2.17 (m, 2H), 1.41-2.03 (m, 4H), 1.11-1.24 (m, 15H).

INTERMEDIATE 238

Ethyl 3-[5-(3-{[2-(difluoromethoxy)phenyl]methyl}-2-methylimidazo[1,2-a]pyridin-6-yl)pyrimidin-2-yl]cyclohex-2-ene-1-carboxylate

- 5 To a stirred solution of *Intermediate 29* (480 mg, 1.20 mmol) and *Intermediate 237* (400 mg, 1.43 mmol) in 1,4-dioxane (15 mL) was added 2M aqueous potassium carbonate solution (2.40 mL). The reaction mixture was degassed, then [1,1'-bis-(diphenylphosphino)ferrocene]dichloropalladium(II) DCM adduct (51 mg, 0.062 mmol) was added and the reaction mixture was heated under nitrogen at 100°C for 18 h. The
- 10 reaction mixture was cooled to room temperature, diluted with water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine (30 mL), then dried (MgSO₄), filtered and concentrated *in vacuo*. The crude material was purified by column chromatography (SiO₂, 25-100% EtOAc in hexane) to give the *title compound* (353 mg, 57%) as a brown oil. δ_{H} (DMSO-d₆) 9.09 (s, 1H), 8.65 (s, 1H), 7.54-7.66 (s, 3H), 7.29-7.33 (m, 1H), 7.29 (t, 1H, *J* 73.9 Hz), 7.25-7.29 (m, 1H), 7.05-7.22 (m, 3H), 4.37-4.44 (m, 2H), 4.07-4.17 (m, 2H), 2.86-2.89 (m, 1H), 2.66-2.75 (m, 1H), 2.54 (s, 1H), 2.33-2.42 (m, 2H), 2.32 (s, 3H), 2.00-2.08 (m, 1H), 1.57-1.73 (m, 1H), 1.22 (t, 3H, *J* 7.1 Hz). LCMS (ES⁺) 519 (M+H)⁺, RT 2.51 minutes.
- 15

20

INTERMEDIATE 239

Ethyl 3-[5-(3-{[2-(difluoromethoxy)phenyl]methyl}-2-methylimidazo[1,2-a]pyridin-6-yl)pyrimidin-2-yl]cyclohexanecarboxylate

- 25 To a stirred solution of *Intermediate 238* (350 mg, 0.68 mmol) in EtOH (25 mL) was added 10% palladium on carbon (16 mg, 0.15 mmol) and the reaction mixture was stirred under an atmosphere of hydrogen for 72 h. The reaction mixture was filtered through celite, washed with EtOH and MeOH, and concentrated *in vacuo*, to give the *title compound* (300 mg, 85%) as a yellow oil. LCMS (ES⁺) 521 (M+H)⁺, RT 2.41, 2.46 minutes.

30

INTERMEDIATE 240

{2-[4-(*tert*-Butoxycarbonylamino)-4-(methoxycarbonyl)piperidin-1-yl]pyrimidin-5-yl}-boronic acid

5 The *title compound* was synthesised from methyl 4-(*tert*-butoxycarbonylamino)-piperidine-4-carboxylate and (2-chloropyrimidin-5-yl)boronic acid in accordance with *General Method C*.

INTERMEDIATE 241

10

Methyl 4-(*tert*-butoxycarbonylamino)-1-[5-(3-{[2-(difluoromethoxy)phenyl]methyl}-7-fluoro-2-methylimidazo[1,2-*a*]pyridin-6-yl)pyrimidin-2-yl]piperidine-4-carboxylate

Intermediate 68 (0.50 g, 1.30 mmol) and *Intermediate 240* (0.642 g, 1.69 mmol) were dissolved in 1,4-dioxane (30 mL). Tetrakis(triphenylphosphine)palladium(0) (45 mg, 0.039 mmol) and 2M aqueous sodium carbonate solution (6 mL, 12 mmol) were
15 added, and the mixture was heated at reflux for 4 h. The mixture was diluted with ethyl acetate (100mL) and washed with water (100mL). The organic phase was dried (Na₂SO₄), filtered and concentrated *in vacuo*. The residue was purified by chromatography (silica, EtOAc, 50g, R_f 0.35) to give the *title compound* (720 mg, 86.6%)
20 as a foamy white solid. δ_{H} (DMSO-*d*₆) 8.50 (d, 2H, *J* 1.5 Hz), 8.35 (d, 1H, *J* 7.5 Hz), 7.52-6.90 (m, 6H), 4.33 (s, 2H), 4.32-4.28 (m, 2H), 3.61 (s, 3H), 3.40-3.30 (m, 2H), 2.28 (s, 3H), 2.05-1.95 (m, 2H), 1.90-1.82 (m, 2H), 1.39 (s, 9H). LCMS (pH10): MH⁺ (641.8), RT 2.73 minutes.

25

INTERMEDIATE 242

Methyl 4-amino-1-[5-(3-{[2-(difluoromethoxy)phenyl]methyl}-7-fluoro-2-methylimidazo[1,2-*a*]pyridin-6-yl)pyrimidin-2-yl]piperidine-4-carboxylate

Intermediate 241 (250 mg, 0.390 mmol) was dissolved in 4.0M hydrochloric acid
30 (10 mL, 40 mmol) in 1,4-dioxane. The mixture was stirred under nitrogen for 4 h, then concentrated *in vacuo*. The residue was redissolved in methanol/ethyl acetate and concentrated to dryness, then dried under high vacuum for 30 minutes, to give the *title compound* (210 mg, 88%) as a white solid. δ_{H} (DMSO-*d*₆) 8.87 (br s, 3H, NH₃⁺), 8.62 (d,

2H, *J* 2.2 Hz), 8.10 (d, 1H, *J* 9.4 Hz), 7.40-7.15 (m, 6H), 4.48 (s, 3H), 4.28-4.20 (m, 2H), 3.97-3.80 (m, 2H), 3.80 (s, 3H), 2.41 (s, 3H), 2.20-2.10 (m, 2H), 1.99-1.91 (m, 2H).
LCMS (pH10): MH^+ (541.8), RT 2.21 minutes.

5

INTERMEDIATE 243

[2-(3-oxo-8-azabicyclo[3.2.1]octan-8-yl)pyrimidin-5-yl]boronic acid

Prepared from nortropan-3-one (2.00 g, 16.0 mmol) and (2-chloropyrimidin-5-yl)-
boronic acid (2.53 g, 16.0 mmol) in accordance with *General Method C* to give the *title*
10 *compound* (1.90 g, 48%) as a pale orange oil. δ_H (DMSO- d_6) 8.93 (s, 2H), 8.70 (s, 2H),
4.95-4.90 (m, 2H), 3.68-3.60 (m, 2H), 2.65-2.59 (m, 2H), 2.35-2.26 (m, 2H), 2.12-2.07
(m, 2H), 1.75-1.68 (m, 2H). LCMS (pH 3): MH^+ (248.8), RT 0.87 minutes.

INTERMEDIATE 244

15

2-(Bromomethyl)-3-{[2-(difluoromethoxy)phenyl]methyl}-7-fluoro-6-[4-(methyl)-
sulfonyl]phenyl]imidazo[1,2-*a*]pyridine

Example 226 (180 mg, 0.3778 mmol) was dissolved in tetrahydrofuran (3 mL) at
0°C and phosphorous tribromide (10% solution in THF, 38 μ L, 0.3966 mmol) was added
20 dropwise. After 30 minutes, the reaction mixture was quenched with water, extracted
with DCM and washed with water, then dried over $NaSO_4$, filtered, evaporated onto silica
and purified by column chromatography, to give a white foam-like solid, which was used
without further purification. LCMS (pH 3): (M+H)⁺ 539.6, RT 2.46 minutes. LCMS
(pH 10): (M+H)⁺ 541.6, RT 2.35 minutes.

25

INTERMEDIATE 245

6-Bromo-2-(chloromethyl)-3-{[2-(difluoromethoxy)phenyl]methyl}-7-fluoroimidazo[1,2-
a]pyridine

30 *Intermediate 54* (1.0 g, 2.5 mmol) was cooled (iced bath) and thionyl chloride (10
mL, 137 mmol) was added with stirring. The reaction mixture was stirred for 1 h. The
volatiles were removed *in vacuo* and the residue was separated between DCM and sodium
bicarbonate solution. The organic layer was passed through a phase separator, then

evaporated *in vacuo*, to give the *title compound* (1.0 g, 96%) as an off white solid. LCMS (ES+) 421 (M+H)⁺, RT 2.5 minutes.

INTERMEDIATE 246

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3-{3-[(6-Bromo-3-{[2-(difluoromethoxy)phenyl]methyl}-7-fluoroimidazo[1,2-*a*]pyridin-2-yl)methoxy]phenyl}oxazolidin-2-one

Intermediate 245 (300 mg, 0.72 mmol), potassium carbonate (148 mg, 1.07 mmol) and 3-(3-hydroxyphenyl)oxazolidin-2-one (141 mg, 0.79 mmol) were stirred together in DMF (5 mL) for 2 h. Further potassium carbonate (148 mg, 1.07 mmol) was added, and the reaction mixture was stirred for a further 4 h. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was dried over sodium sulphate, filtered, and evaporated *in vacuo*. The residue was purified by column chromatography (SiO₂, 10 to 100% ethyl acetate in hexanes) to give the *title compound* (100 mg, 24%) as a white powder. δ_H (300 MHz, DMSO-*d*₆) 8.67 (d, 1H, *J* 6.7 Hz), 7.70 (d, 1H, *J* 9.6 Hz), 7.22 (m, 6H), 7.07 (td, 1H, *J* 7.5, 1.2 Hz), 6.93 (dd, 1H, *J* 7.7, 1.5 Hz), 6.75 (m, 1H), 5.14 (s, 2H), 4.42 (m, 4H), 4.01 (m, 2H). LCMS (ES+) 564 (M+H)⁺, RT 2.50 minutes.

15

INTERMEDIATE 247

20

1-*tert*-Butyl 4-methyl 4-isopropylpiperidine-1,4-dicarboxylate

A solution of 1-*tert*-butyl 4-methyl piperidine-1,4-dicarboxylate (0.55 g, 2.26 mmol) and 2-iodopropane (0.32 mL, 3.2 mmol) in THF (2.5 mL) was stirred at -78°C. Lithium hexamethyldisilazane (3.2 mL, 3.2 mmol) was added, then the reaction mixture was allowed to warm to ambient temperature and stirred for 18 h. The reaction mixture was partitioned between diethyl ether and brine. The ether extract was dried (MgSO₄), filtered and concentrated *in vacuo*, to give the *title compound* (0.54 g, 84%) as a pale yellow syrup, which was used without further purification. δ_H (400 MHz, DMSO-*d*₆) 3.86 (m, 2H), 3.68 (m, 3H), 2.69 (m, 2H), 1.99 (m, 2H), 1.68 (m, 1H), 1.53 (m, 1H), 1.36 (s, 9H), 1.28 (m, 1H), 0.80 (d, *J* 6.9 Hz, 6H).

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30

INTERMEDIATE 248**{2-[4-Isopropyl-4-(methoxycarbonyl)piperidin-1-yl]pyrimidin-5-yl}boronic acid**

TFA (10 mL) was added to a stirred solution of *Intermediate 247* (0.54 g, 1.90 mmol) in 1,4-dioxane (2 mL). The mixture was stirred for 2 h, then the solvent was removed by rotary evaporation and the residue was dried under vacuum for 1 h. The residual syrup was dissolved in ethanol (10 mL), then sodium carbonate (0.5 g, 4.72 mmol) and (2-chloropyrimidin-5-yl)boronic acid (0.37 g, 2.3 mmol) were added and the reaction mixture was stirred at 80°C for 5 h. The cooled reaction mixture was filtered through celite and concentrated to dryness, to give the *title compound* as a foam, which was used without further purification. LCMS (pH 10): MH⁺ 308, RT 1.23 minutes.

INTERMEDIATE 249**Methyl 4-hydroxypiperidine-4-carboxylate**

4-Hydroxy-4-piperidinecarboxylic acid hydrochloride salt (1 g, 5.1 mmol) was added to a 2% hydrochloric acid solution in methanol (25 mL) and the mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure to give the *title compound* as the hydrochloride salt (1 g, 92%) as a white solid. δ_H (400 MHz, DMSO-d₆) 9.06 (broad, 2H), 5.89 (broad, 1H), 3.68 (m, 3H), 3.14 (m, 2H), 3.02 (m, 2H), 2.07 (m, 2H), 1.79 (m, 2H).

INTERMEDIATE 250**{2-[4-Hydroxy-4-(methoxycarbonyl)piperidin-1-yl]pyrimidin-5-yl}boronic acid**

Prepared from *Intermediate 249* in accordance with *General Method C* to give the *title compound* (1.5 g) as an off white solid, which was used without further purification. LCMS (pH 10): MH⁺ 282, RT 0.23 minutes.

INTERMEDIATE 251**5-Bromo-4-chloropyridin-2-amine**

To a stirred solution of 2-amino-4-chloropyridine (1 g) in acetonitrile (8 mL) was
5 added dropwise a solution of *N*-bromosuccinimide (1.5 g) in acetonitrile (2 mL). The
reaction mixture was stirred at 25-28°C for 1 h. The solvent was evaporated, then the
residue was suspended in water and extracted with dichloromethane (2 x 20 mL). The
organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under
vacuum. The resulting crude material was purified by column chromatography, using
10 100-200 mesh size silica and 10-25% EtOAc in hexane as eluent, to give the *title*
compound (1 g) as a yellow solid. δ_{H} (400 MHz, CDCl_3) 8.16 (s, 1H), 6.62 (s, 1H), 4.55
(br s, 2H). LCMS: m/z 208.9, RT 2.19 minutes.

INTERMEDIATE 252

15

***N'*-(5-Bromo-4-chloropyridin-2-yl)-*N,N*-dimethylacetimidamide**

To a stirred solution of *Intermediate 251* (0.1 g) in ethanol (5 mL) was added *N,N*-
dimethylacetamide dimethyl acetal (0.064 g) and the reaction mixture was heated at 90°C
for 1 h. The solvent was evaporated, then the residue was suspended in water and
20 extracted with dichloromethane (3 x 10 mL). The organic layer was dried over anhydrous
sodium sulphate, filtered and concentrated *in vacuo*. The resulting crude material was
purified by column chromatography, using 100-200 mesh size silica and 10-25% EtOAc
in hexane as eluent, to give the *title compound* (0.08 g) as a yellow oil. δ_{H} (400 MHz,
 CDCl_3) 8.39 (s, 1H), 6.86 (s, 1H), 3.06 (s, 1H), 3.06 (s, 6H), 2.02 (s, 3H). LCMS m/z
25 277.95, RT 2.4 minutes.

INTERMEDIATE 253

(6-Bromo-7-chloro-2-methylimidazo[1,2-*a*]pyridin-3-yl)[2-(difluoromethoxy)phenyl]-
30 **methanone**

A solution of *Intermediate 252* (16 g) and *Intermediate 4* (15.3 g, 0.0577 mol) in
ethanol (30 mL) was heated at 100°C for 2 h. The solvent was evaporated, then the
residue was suspended in water and extracted with dichloromethane (3 x 25 mL). The

organic layer was dried over anhydrous sodium sulphate, then filtered and concentrated *in vacuo*. The crude material was purified by column chromatography, using 100-200 mesh size silica and 10-25% EtOAc in hexane as eluent, to give the *title compound* (10.6 g) as an off-white solid. δ_{H} (400 MHz, DMSO- d_6) 9.88 (s, 1H), 8.23 (s, 1H), 7.68-7.63 (m, 1H), 7.53 (dd, J 6.0, 1.6 Hz, 1H), 7.44-7.41 (m, 2H), 7.26 (t, J 73.2 Hz, 1H), 1.89 (s, 3H). LCMS: m/z 417.1, RT 3.00 minutes.

INTERMEDIATE 254

10 (6-Bromo-7-chloro-2-methylimidazo[1,2-*a*]pyridin-3-yl)[2-(difluoromethoxy)phenyl]-methanol

Sodium borohydride (1.15 g, 0.0305 mol) was added in one portion to a stirred solution of *Intermediate 253* (10.6 g, 0.0254 mol) in ethanol (30 mL) at 25-28°C. The reaction mixture was quenched with aqueous ammonium chloride solution (20 mL) and
15 further concentrated under vacuum. The residue was suspended in water and extracted with dichloromethane (3 x 20 mL). The combined organic layer was dried over anhydrous sodium sulphate and filtered, then concentrated under vacuum and washed with diethyl ether (2 x 20 mL), to obtain the *title compound* (10.6 g) as a yellow solid. δ_{H} (400 MHz, DMSO- d_6) 8.76 (s, 1H), 7.90 (dd, J 4.8, 2.0 Hz, 1H), 7.85 (s, 1H), 7.40-6.91
20 (m, 4H), 6.40 (s, 1H), 2.10 (s, 3H). LCMS m/z 219.1, RT 2.59 minutes.

INTERMEDIATE 255

6-Bromo-7-chloro-3-[2-(difluoromethoxy)benzyl]-2-methylimidazo[1,2-*a*]pyridine
25 A mixture of *Intermediate 254* (10.6 g) and sodium iodide (37.9 g) in acetonitrile (40 mL) was heated at 80°C under nitrogen for 2 h. Chlorotrimethylsilane (8.27 g) was added dropwise over 1 h, and the mixture was stirred for an additional 1 h at 80°C. The reaction mixture was concentrated under vacuum. The residue was suspended in water, extracted with dichloromethane (3 x 20 mL) and washed with a saturated aqueous
30 solution of sodium bicarbonate (~20 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under vacuum. The crude material was purified by column chromatography, using 100-200 mesh size silica gel and 10-25%

EtOAc in hexane as eluent, to give the *title compound* (5.2 g) as a brown solid. δ_{H} (400 MHz, DMSO- d_6) 8.67 (s, 1H), 7.87 (s, 1H), 7.43-6.99 (m, 5H), 4.32 (s, 2H), 2.27 (s, 3H).

INTERMEDIATE 256

5

{2-[4-(Methylsulfonyl)piperazin-1-yl]pyrimidin-5-yl}boronic acid

The *title compound* was synthesised from 1-(methylsulfonyl)piperazine in accordance with *General Method C*. MS: m/z 403.05, RT 3.20 minutes.

10

INTERMEDIATE 257

Ethyl 3-(2,5-dimethylbenzyl)imidazo[1,2-*a*]pyridine-2-carboxylate

A mixture of ethyl imidazo[1,2-*a*]pyridine-2-carboxylate (0.48 g, 2.5 mmol), 2-(chloromethyl)-1,4-dimethylbenzene (0.6 mL, 3.75 mmol), palladium pivalate (15 mg, 0.05 mmol), 2-(diphenylphosphino)-2'-(*N,N*-dimethylamino)biphenyl (38 mg, 0.1 mmol),
15 pivalic acid (51 mg, 0.5 mmol) and cesium carbonate (1.22 g, 3.75 mmol) in toluene (5 mL) was degassed and flushed with N_2 three times. The reaction mixture was heated with stirring at 110°C until TLC or LCMS analysis indicated that the reaction was complete. The reaction mixture was allowed to cool to room temperature and evaporated *in vacuo*.
20 The crude residue was suspended in EtOAc (30 mL) and washed with water. The aqueous phases were extracted with further EtOAc (4 x 30 mL), then the combined organic layers were dried (MgSO_4), filtered and concentrated *in vacuo*. The crude material was purified by chromatography (SiO_2 ; 2-60% EtOAc in DCM) to afford the *title compound* (420 mg, 55%) as a pale orange solid. δ_{H} (400 MHz, CDCl_3) 7.74 (d, J 9.2 Hz, 1H), 7.66 (d, J 7.0 Hz, 1H), 7.20-7.26 (m, 1H), 7.11 (d, J 7.7 Hz, 1H), 6.94 (d, J 7.6 Hz, 1H), 6.75 (t, J 6.9 Hz, 1H), 6.39 (s, 1H), 4.70 (s, 2H), 4.50 (q, J 7.1 Hz, 2H), 2.41 (s, 3H), 2.12 (s, 3H), 1.44 (t, J 7.1 Hz, 3H). LCMS (ES+) ($\text{M}+\text{H}$)⁺ 308, RT 2.31 minutes.
25

INTERMEDIATE 258

30

{3-[(2,5-Dimethylphenyl)methyl]imidazo[1,2-*a*]pyridin-2-yl}methanol

To a solution of *Intermediate 257* (0.8 g, 0.025 mmol) in THF (10 mL) was added a 2M solution of borane dimethyl sulphide in THF (1.2 mL) at 0°C. The mixture was

stirred at r.t. for 30 minutes and heated under reflux for 2 h, then cooled to ambient temperature and hydrolyzed with methanol (3 mL). To the mixture was added 2M aqueous sodium hydroxide solution until pH >8 was reached. The aqueous phases were extracted with EtOAc (4 x 30 mL), then the combined organic layers were dried (MgSO₄), filtered and concentrated *in vacuo*. The crude product was used without further purification.

INTERMEDIATE 259

10 {2-[4-(Hydroxymethyl)-4-methylpiperidin-1-yl]pyrimidin-5-yl}boronic acid
(4-Methylpiperidin-4-yl)methanol hydrochloride (2.09 g, 12.63 mmol), (2-chloropyrimidin-5-yl)boronic acid (2 g, 12.63 mmol) and triethylamine (1.8 mL, 12.630 mmol) in ethanol (15 mL) was stirred at 80°C overnight. The reaction mixture was cooled to r.t. and concentrated *in vacuo* to give the *title compound* as an orange semi-
15 solid. This material was used without any further purification. HPLC-MS: MH⁺ *m/z* 252.2, RT 0.34 minutes.

INTERMEDIATE 260

20 {2-[4-(Sulfamoyl)piperidin-1-yl]pyrimidin-5-yl}boronic acid
Prepared from piperidine-4-sulfonamide hydrochloride (1.27 g, 6.315 mmol) and (2-chloropyrimidin-5-yl)boronic acid (1 g, 6.32 mmol) in accordance with *General Method C* to give the *title compound* as an off-white semi-solid. HPLC-MS: *m/z* (M-H)⁺ 285.1, RT 0.14 minutes.

25

INTERMEDIATE 261

{2-[4-(Methylsulfonyl)piperidin-1-yl]pyrimidin-5-yl}boronic acid
Prepared from 4-(methylsulfonyl)piperidine (0.515 g, 3.16 mmol) and (2-chloropyrimidin-5-yl)boronic acid (0.5 g, 3.16 mmol) in accordance with *General Method C* to give the *title compound* as an off-white semi-solid. HPLC-MS: *m/z* MH⁺ 286.2, RT 0.17 minutes.

30

INTERMEDIATE 262

{2-[4-(5-Hydroxy-1,3,4-oxadiazol-2-yl)piperidin-1-yl]pyrimidin-5-yl}boronic acid

Prepared from 5-(piperidin-4-yl)-1,3,4-oxadiazol-2-ol hydrochloride (1.30 g, 6.32 mmol) and (2-chloropyrimidin-5-yl)boronic acid (1 g, 6.32 mmol) in accordance with
5 *General Method C* to give the *title compound* as an off-white semi-solid. HPLC-MS: *m/z* (M-H)⁺ 290.2, RT 0.17 minutes.

INTERMEDIATE 263

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6-Bromo-3-{1-[2-(difluoromethoxy)phenyl]ethyl}-7-fluoro-2-methylimidazo[1,2-*a*]-pyridine

A solution of *Intermediate 68* (15.5 g, 40.2 mmol) and methyl iodide (5.71 g, 40.2 mmol, 2.52 mL) in anhydrous tetrahydrofuran (200 mL) was cooled to between -110°C
15 and -100°C under N₂ and potassium bis(trimethylsilyl)amide solution (1M in THF, 47 mL, 47 mmol) was added dropwise. The reaction mixture was stirred at approximately -110°C for 1.5 h. The reaction mixture was treated with water (200 mL) and stirred overnight at 5°C. EtOAc (300 mL) was added and the layers were separated. The
20 aqueous layer was extracted twice with EtOAc and the combined organic layers were washed with brine, then dried over Na₂SO₄, filtered and concentrated *in vacuo*. The resulting crude brown oil (17.8 g) was triturated with a 1:1 mixture of heptane and Et₂O. The resulting powder was further triturated with diisopropyl ether to give the *title compound* (8.9 g, 55%) as a pale brown solid. HPLC-MS (pH 3): *m/z* 399.0 [M+H]⁺, RT 1.77 minutes.

25

INTERMEDIATE 264

6-Bromo-3-{[2-(difluoromethoxy)phenyl]methyl}-7-fluoroimidazo[1,2-*a*]pyridine-2-carbaldehyde

30 The *title compound* can be synthesised from *Intermediate 54* by treatment with a suitable oxidant such as Dess Martin Periodinane in dichloromethane and subsequent purification by column chromatography on silica gel.

INTERMEDIATES 265 TO 269

The following compounds were prepared by reaction of (2-chloropyrimidin-5-yl)boronic acid with the appropriate amine according to *General Method C*.

5

Intermediate	Name	m/z
265	[2-(4-Cyano-4-methylpiperidin-1-yl)pyrimidin-5-yl]boronic acid	247.2
266	[2-(1,1,3-Trioxo-3a,4,6,7-tetrahydro-[1,2,5]thiadiazolo[2,3- <i>a</i>]-pyrazin-5-yl)pyrimidin-5-yl]boronic acid	314.2
267	[2-(2-Methyl-5-oxo-1,4-diazepan-1-yl)pyrimidin-5-yl]boronic acid	251.2
268	[2-(7-Methyl-5-oxo-1,4-diazepan-1-yl)pyrimidin-5-yl]boronic acid	251.2
269	[2-[4-(2 <i>H</i> -Tetrazol-5-yl)piperidin-1-yl]pyrimidin-5-yl]boronic acid	276.8

INTERMEDIATE 270

2-{1-[7-Fluoro-2-methyl-6-(1-methyl-1*H*-pyrazol-4-yl)imidazo[1,2-*a*]pyridin-3-yl]-ethyl}phenol

10

A suspension of *Example 259* (3.7 g, 7.12 mmol) in DCM (100 mL) was cooled to 0°C and treated with 1M boron tribromide in DCM (21.35 mL, 21.35 mmol). The resulting solution was allowed to warm to room temperature and was stirred for 16 h. The reaction mixture was cooled in an ice bath and quenched by careful addition of MeOH (8 mL). Saturated aqueous NaHCO₃ solution (50 mL) was added and the layers were separated. The aqueous layer was extracted with DCM. The combined organic layers were washed with 1M aqueous NaOH solution (80 mL) and brine (80 mL), then dried over Na₂SO₄ and concentrated *in vacuo*. The resulting crude brown foam was coated onto C18-silica gel (8g) and purified in 3 batches by C18-reversed phase column chromatography (120g, eluent: water to 100% acetonitrile + 0.1% formic acid). The fractions containing the product were combined and neutralised (pH 7-8) by addition of saturated aqueous NaHCO₃ solution. The aqueous layer was extracted with DCM (3 x 75 ml), and the combined DCM layers were concentrated *in vacuo*, to afford the *title*

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compound (1.0 g, 35%) as a brown foam. LCMS (pH 10): m/z 351 $[M+H]^+$, RT 2.09 minutes.

INTERMEDIATE 271

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1-(*tert*-Butoxycarbonyl)-4-[5-(3-{[2-(difluoromethoxy)phenyl]methyl}-2-methylimidazo-[1,2-*a*]pyridin-6-yl)pyrimidin-2-yl]piperazine-2-carboxylic acid

Prepared from 1-(*tert*-butoxycarbonyl)piperazine-2-carboxylic acid and *Intermediate 29* in accordance with *General Method B* to give the *title compound* (80 mg, 58%) as a solid. HPLC-MS (pH 10): m/z 595.8 $[M+H]^+$, RT 2.09 minutes.

10

INTERMEDIATE 272

Methyl 1-methyl-4-(trifluoromethylsulfonyloxy)cyclohex-3-ene-1-carboxylate

To a stirred solution of 1-methyl-4-oxocyclohexanecarboxylic acid methyl ester (1.05 g, 6.15 mmol) in THF (5 mL) at -78°C was added lithium bis(trimethylsilyl)amide (6.25 mL, 1M in THF). The reaction mixture was stirred at -78°C for 30 minutes, after which time *N*-phenyltrifluoromethanesulfonimide (2.20 g, 6.17 mmol) in THF (5 mL) was added and the reaction mixture was allowed to warm slowly to room temperature, then stirred for 18 h. The reaction mixture was quenched with aqueous sodium hydrogen-sulphate solution (15 mL) and diluted with ethyl acetate (50 mL). The layers were separated. The organic layers were washed with 5% aqueous NaOH solution (2 x 30 mL), saturated aqueous ammonium chloride solution (20 mL) and brine (20 mL), then dried over MgSO₄, filtered and concentrated *in vacuo*, to give the *title compound* (2.79 g, quantitative) as a yellow oil. δ_H (300 MHz, DMSO-*d*₆) 5.83-5.89 (m, 1H), 3.61 (s, 3H), 2.54-2.66 (m, 1H), 2.29-2.38 (m, 2H), 2.11 (dq, 1H, *J* 17.8, 3.1 Hz), 1.96-2.06 (m, 1H), 1.67-1.78 (m, 1H), 1.17 (s, 3H).

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INTERMEDIATE 273

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Methyl 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-ene-1-carboxylate

To a stirred solution of *Intermediate 272* (1.77 g, 5.86 mmol) in 1,4-dioxane (50

mL) were added bis(pinacolato)diboron (4.46 g, 17.6 mmol), potassium acetate (3.46 g, 35.3 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)-DCM adduct (338 mg, 0.41 mmol). The mixture was stirred at 90°C for 18 h. The reaction mixture was cooled to room temperature, filtered through celite, washed with EtOAc and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluting with hexane:EtOAc, a gradient from 1:0 to 9:1), to afford the *title compound* (0.9 g, 55%) as a pale gum.

INTERMEDIATE 274

10

Methyl 4-[5-(3-{[2-(difluoromethoxy)phenyl]methyl}-7-fluoro-2-methylimidazo[1,2-a]-pyridin-6-yl)pyrimidin-2-yl]-1-methylcyclohex-3-ene-1-carboxylate

A solution of *Intermediate 273* (340 mg, 1.2 mmol) and *Intermediate 152* (335 mg, 0.8 mmol) in 1,4-dioxane (10 mL) was treated with 2N aqueous K₂CO₃ solution (2.5 mL) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (30 mg, 0.04 mmol) and heated at 100°C under N₂ for 1.5 h. The reaction mixture was diluted with water (40 mL) and extracted with EtOAc (3 x 40 mL). The combined organic extracts were washed with water (40 mL) and brine (50 mL), dried over MgSO₄, filtered and concentrated *in vacuo*. The resulting crude brown gum was purified by FCC on silica gel (eluting with DCM/EtOAc, a gradient from 1:0 to 0.1) to give the *title compound* (300 mg, 70%) as a white powder. HPLC-MS (pH 10): *m/z* 537.2 [M+H]⁺, RT 1.20 minutes.

GENERAL METHOD A

Palladium-Catalysed Suzuki Coupling

Aryl bromide (e.g. *Intermediate 7* or *Intermediate 68*) (1 eq), boronic acid or ester (1.2 eq) and 2M aqueous sodium carbonate solution (3 eq) are dissolved in 1,4-dioxane. The mixture is degassed with three cycles of vacuum and nitrogen prior to the addition of [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (5 mol %). The reaction mixture is heated for sufficient time (typically 3-5 h) at 100°C until TLC or LCMS indicates that the reaction is complete. After being allowed to cool to room temperature the solution is filtered through celite, diluted with water and extracted with ethyl acetate. The combined organic phases are dried over sodium sulphate and filtered, and the

volatiles are removed *in vacuo*. The crude residue thus obtained is purified by an appropriate technique, typically column chromatography on silica gel or preparative mass-directed HPLC.

5

INTERMEDIATE 275

Methyl (1*R*,5*S*)-3-[5-(3-{[2-(difluoromethoxy)phenyl]methyl}-7-fluoro-2-(hydroxymethyl)imidazo[1,2-*a*]pyridin-6-yl)pyrimidin-2-yl]-3-azabicyclo[3.2.1]octane-8-carboxylate

10 Prepared from *Intermediate 54* and *Intermediate 230* in accordance with *General Method A* to give the *title compound* (200 mg, 40%) as a pale solid. LCMS (pH 10) *m/z* 568.3 [M+H]⁺, RT 2.08 minutes.

INTERMEDIATE 276

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(3*R*)-1-(5-Boronopyrimidin-2-yl)piperidine-3-carboxylic acid

The *title compound* was synthesised from (2-chloropyrimidin-5-yl)boronic acid and (3*R*)-piperidine-3-carboxylic acid in accordance with *General Method C*.

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INTERMEDIATE 277

(3*S*)-1-(5-Boronopyrimidin-2-yl)piperidine-3-carboxylic acid

The *title compound* was synthesised from (2-chloropyrimidin-5-yl)boronic acid and (3*S*)-piperidine-3-carboxylic acid in accordance with *General Method C*.

25

INTERMEDIATE 278

(2*S*)-4-(5-Boronopyrimidin-2-yl)morpholine-2-carboxylic acid; triethylammonium; dichloride

30 Prepared from (2-chloropyrimidin-5-yl)boronic acid and (2*S*)-morpholine-2-carboxylic acid in accordance with *General Method C* to give the *title compound* as a yellow gum. LCMS (pH 10) MH⁺ (253.5), RT 0.2 minutes.

INTERMEDIATE 279

(2R)-4-(5-Boronopyrimidin-2-yl)morpholine-2-carboxylic acid; triethylammonium; dichloride

- 5 The *title compound* was synthesised from (2-chloropyrimidin-5-yl)boronic acid and (2R)-morpholine-2-carboxylic acid in accordance with *General Method C*.

INTERMEDIATE 280

- 10 N-{{(6-Bromo-2-methylimidazo[1,2-a]pyridin-3-yl)[2-(difluoromethoxy)phenyl]methyl}}-acetamide

- To a suspension of *Intermediate 6* (0.1 g, 0.26 mmol) in acetonitrile (1 mL) at room temperature was added concentrated sulphuric acid (4 drops) and the mixture was heated to 60°C for 1 h. The reaction mixture was diluted with EtOAc (5 mL) and basified
15 with saturated aqueous NaHCO₃ solution. The organic layers were separated, dried (Na₂SO₄), filtered and concentrated *in vacuo*, to give the *title compound* (89 mg, 80%) as a white solid. δ_{H} (400 MHz, DMSO-d₆) 9.00 (d, 1H, *J* 8.2 Hz), 8.28 (s, 1H), 7.58 (m, 1H), 7.48 (m, 1H), 7.44 (m, 1H), 7.34 (m, 2H), 7.20 (d, 1H, *J* 8.1 Hz), 7.13 (t, 1H, *J* 78 Hz), 6.73 (d, 1H, *J* 8.2 Hz), 2.01 (s, 3H), 1.96 (s, 3H). LCMS (pH 3): 426.6 MH⁺, RT
20 1.32 minutes.

INTERMEDIATE 281

(6-Bromo-2-methylimidazo[1,2-a]pyridin-3-yl)[2-(difluoromethoxy)phenyl]methanamine

- 25 A mixture of *Intermediate 280* (3.24 g, 7.64 mmol), 6N aqueous HCl solution (30 mL) and MeOH (30 mL) was heated at 100°C for 7 h. The mixture was allowed to cool to room temperature, then concentrated under reduced pressure. The aqueous residue was treated until alkaline with 1N aqueous NaOH solution, and extracted with EtOAc (3 times). The combined organic extracts were washed with brine, dried over Na₂SO₄,
30 filtered and concentrated under reduced pressure. The resulting off-white solid was triturated with diisopropyl ether and filtered, to afford the *title compound* (2.30 g, 79%) as an off-white solid. δ_{H} (300 MHz, DMSO-d₆) 8.71 (dd, 1H, *J* 1.8, 0.6 Hz), 7.93 (m, 1H), 7.40 (dd, 1H, *J* 9.4, 0.6 Hz), 7.34 (m, 2H), 7.24 (dd, 1H, *J* 9.5, 1.9 Hz), 7.11 (m, 2H), 5.80

(s, 1H), 2.42 (s, 2H), 2.14 (s, 3H). LCMS (pH 3): 382.6 MH⁺, RT 0.88 minutes.

INTERMEDIATE 282

5 *tert*-Butyl 2-{(6-bromo-2-methylimidazo[1,2-*a*]pyridin-3-yl)[2-(difluoromethoxy)-phenyl]methoxy}acetate

To a solution of *Intermediate 6* (0.65 g, 1.7 mmol) in THF (15 mL) at room temperature was added sodium hydride (0.075 g, 1.9 mmol). The mixture was stirred for 15 minutes prior to the addition of *tert*-butyl bromoacetate (0.36 g, 1.8 mmol, 0.27 mL).
10 After stirring for 30 minutes, the mixture was diluted with EtOAc (50 mL) and water (25 mL). The organic layers were separated, washed with brine (20 mL) and concentrated *in vacuo*. The resulting crude product was subjected to column chromatography (eluent: hexane to 35% EtOAc in hexane). The resulting clear oil solidified on standing to give the *title compound* (0.64 g, 76%) as a white solid. δ_{H} (400 MHz, CDCl₃) 8.57 (s, 1H),
15 7.80 (d, 1H, *J* 7.5 Hz), 7.35 (m, 3H), 7.21 (d, 1H, *J* 9.4 Hz), 7.10 (d, 1H, *J* 7.8 Hz), 6.35 (s, 1H), 3.98 (s, 2H), 2.34 (s, 3H), 1.45 (s, 9H). LCMS (pH 10): MH⁺, 499.0 (Br isotope), RT 1.62 minutes.

INTERMEDIATE 283

20 *tert*-Butyl 2-([2-(difluoromethoxy)phenyl]{2-methyl-6-[2-(morpholin-4-yl)pyrimidin-5-yl]imidazo[1,2-*a*]pyridin-3-yl}methoxy)acetate

Prepared from *Intermediate 282* (0.6 g, 1.21 mmol) and *Intermediate 38* (0.33 g, 1.56 mmol) in accordance with *General Method A* to provide the *title compound* (0.542 g,
25 77.2%) as an off-white foam. δ_{H} (400 MHz, DMSO-*d*₆) 8.71 (s, 1H), 8.67 (s, 2H), 7.92 (m, 1H), 7.56 (s, 2H), 7.43 (m, 2H), 7.20 (d, 1H, *J* 7.8 Hz), 7.15 (s, 1H), 6.40 (s, 1H), 4.08 (m, 2H), 3.73 (m, 8H), 2.12 (s, 3H), 1.34 (s, 9H). LCMS (pH 10): MH⁺ 582.2, RT 1.59 minutes.

30 **INTERMEDIATE 284**

6-Bromo-3-{1-[2-(difluoromethoxy)phenyl]ethyl}-2-methylimidazo[1,2-*a*]pyridine

To a degassed, cold (-78°C) solution of *Intermediate 7* (1.00 g, 2.72 mmol) in

THF (10 mL) was added methyl iodide (0.427 g, 2.99 mmol, 0.187 mL). To the mixture was added dropwise a solution of potassium hexamethyldisilylazide (0.5M in toluene, 5.7 mL, 2.9 mmol). The mixture was stirred at this temperature for 1 h. Additional methyl iodide (0.05 mL) and potassium hexamethyldisilylazide (0.5M in toluene, 1mL) were
5 added at -78°C, and stirring was continued for a further 1 h. The mixture was quenched at -78°C by the addition of saturated aqueous ammonium chloride solution (5 mL), warmed to room temperature, diluted with EtOAc (20 mL), washed with water (10 mL) and brine (10 mL), then dried (Na₂SO₄), filtered and concentrated *in vacuo*. The resulting crude brown oil was purified by column chromatography (eluent: hexane to 70% EtOAc in
10 hexane) to give the *title compound* (0.94 g, 91%) as a pale solid.

INTERMEDIATE 285

15 6-Bromo-3-{[2-(difluoromethoxy)phenyl](methoxy)methyl}-2-methylimidazo[1,2-a]-pyridine

To a solution of *Intermediate 6* (0.5 g, 1.30 mmol) in methanol (10 mL) at room temperature was added concentrated sulphuric acid (0.1 g, 0.9 mmol, 0.05 mL). The mixture was heated at 60°C overnight. The reaction mixture was concentrated *in vacuo*, diluted with EtOAc (30 mL) and basified by the addition of saturated aqueous Na₂CO₃
20 solution (~5 mL). The organic layers were separated and washed with brine (5 mL), then dried (Na₂SO₄), filtered and concentrated *in vacuo*. The resulting crude material was purified by column chromatography (eluent: hexane to 50% EtOAc in hexane) to give the *title compound* (0.418 g, 81%) as a clear colourless oil. δ_H (400 MHz, DMSO-d₆) 8.63 (s, 1H), 7.75 (m, 1H), 7.55 (m, 1H), 7.44 (m, 2H), 7.36 (m, 1H), 7.18 (d, 1H, *J* 8.0 Hz), 7.13
25 (t, 1H, *J* 78 Hz), 6.14 (s, 1H), 3.34 (s, 3H), 2.23 (s, 3H). LCMS (pH 10): MH⁺ 397.0 (bromine pattern), RT 1.32 minutes.

INTERMEDIATE 286

30 Benzyl 2-(6-bromo-2-methylimidazo[1,2-a]pyridin-3-yl)-2-[2-(difluoromethoxy)phenyl]-acetate

To a cold (-78°C) solution of *Intermediate 7* (0.6 g, 1.64 mmol) in THF (10 mL) was added benzyl chloroformate (0.58 g, 3.43 mmol, 0.48 mL), followed by KHMDS

DEMANDES OU BREVETS VOLUMINEUX

**LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS
COMPREND PLUS D'UN TOME.**

CECI EST LE TOME __1__ DE __2__

NOTE: Pour les tomes additionels, veuillez contacter le Bureau Canadien des Brevets.

JUMBO APPLICATIONS / PATENTS

**THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE
THAN ONE VOLUME.**

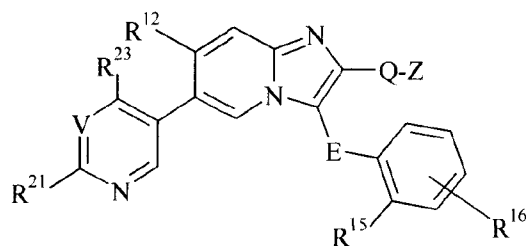
THIS IS VOLUME __1__ OF __2__

NOTE: For additional volumes please contact the Canadian Patent Office.

Claims

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

5



(IIB)

wherein

E represents -N(R⁵)-, -CH₂-, -CH(OH)-, -CH(OCH₃)-, -CH(OCH₂CO₂H)-,
10 -CH(NH₂)-, -CH(NHCOCH₃)-, -CH(CO₂H)-, -CH(CO₂benzyl)-, -CH(CH₃)- or
-C(CH₃)(OH)-;

Q represents -CH₂-, -CH(CN)-, -CH(OH)-, -CH(OCH₃)-, -CH₂O-, -CH₂N(R⁶)- or
-CH₂OCH₂-;

Z represents hydrogen, fluoro, trifluoromethyl, methyl, ethyl, *n*-propyl, isopropyl,
15 isobutyl, *tert*-butyl, cyclopropyl, cyclopentyl, cyclohexyl, oxocyclohexyl, phenyl, bromo-
phenyl, cyanophenyl, nitrophenyl, methoxyphenyl, difluoromethoxyphenyl, trifluoro-
methoxyphenyl, methylenedioxyphenyl, methylsulfonylphenyl, dimethylaminophenyl,
acetylaminophenyl, methylsulfonylaminophenyl, carboxyphenyl, aminocarbonylphenyl,
methylaminocarbonylphenyl, dimethylaminocarbonylphenyl, aminocarbonylamino-
20 phenyl, tetrahydrofuranyl, oxopyrrolidinyl, dimethylaminopyrrolidinyl, *tert*-butoxy-
carbonylpyrrolidinyl, indolyl, tetrahydropyranyl, piperidinyl, ethylpiperidinyl, *tert*-
butoxycarbonylpiperidinyl, aminocarbonylpiperidinyl, 2-oxo-3,4-dihydroquinolyl,
morpholyl, azocanyl, oxothiazolyl, furyl, hydroxymethylfuryl, thienyl, methyl-
pyrazolyl, dimethylpyrazolyl, 4,5,6,7-tetrahydroindazolyl, benzoxazolyl, methyl-
25 isoxazolyl, dimethylisoxazolyl, methylthiazolyl, aminothiazolyl, benzothiazolyl,
methylbenzothiazolyl, aminobenzothiazolyl, imidazolyl, methylimidazolyl, methyl-
benzimidazolyl, dimethyl[1,2,4]triazolo[1,5-*a*]pyrimidinyl, dimethylaminoethyltetrazolyl,
pyridinyl, fluoropyridinyl, chloropyridinyl, cyanopyridinyl, methylpyridinyl, (cyano)-

(methyl)pyridinyl, trifluoromethylpyridinyl, oxopyridinyl, methoxypyridinyl, dimethylaminomethylpyridinyl, acetaminopyridinyl, carboxypyridinyl, methoxycarbonylpyridinyl, aminocarbonylpyridinyl, (aminocarbonyl)(fluoro)pyridinyl, methylaminocarbonylpyridinyl, dimethylaminocarbonylpyridinyl, hydrazinocarbonylpyridinyl, 5 quinolinyl, isoquinolinyl, (methyl)(oxo)phthalazinyl, pyrimidinyl, pyrazinyl, oxopyrrolidinylphenyl, dioxopyrrolidinylphenyl, (hydroxy)(oxo)pyrrolidinylphenyl, (amino)(oxo)pyrrolidinylphenyl, (oxo)oxazolidinylphenyl, oxoimidazolidinylphenyl, imidazolylphenyl, methylthiazolylphenyl, formylthiazolylphenyl, imidazolylphenyl, tetrazolylphenyl, phenylpyrrolidinyl, hydroxyphenylpiperazinyl, (methyl)(phenyl)- 10 pyrazolyl, oxoimidazolidinylthiazolyl, hydroxyphenyltriazolyl, morpholinyltetrazolyl, oxopyrrolidinylpyridinyl, (oxo)oxazolidinylpyridinyl, oxoimidazolidinylpyridinyl, pyridinylthiazolyl, pyridinyltetrazolyl, morpholinylcarbonylphenyl or methylsulfonylpyridinyl;

V represents C-R²² or N;

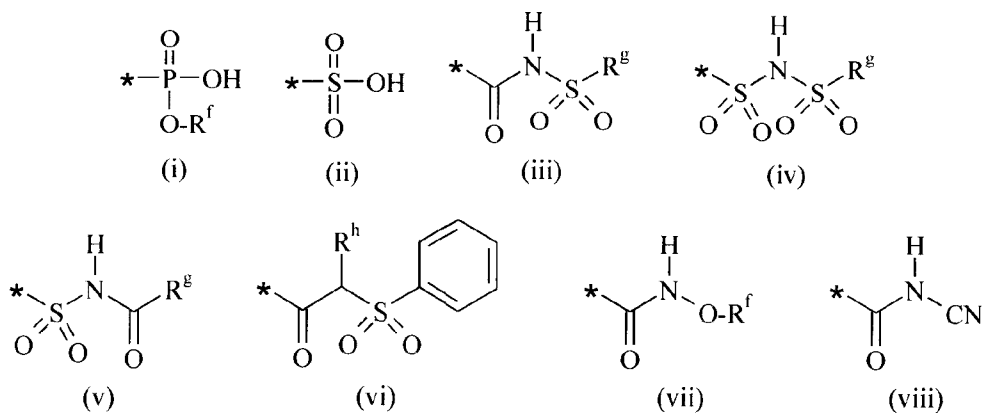
15 R⁵ and R⁶ independently represent hydrogen or C₁₋₆ alkyl;

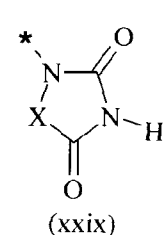
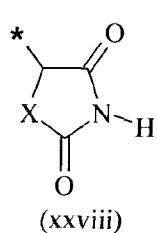
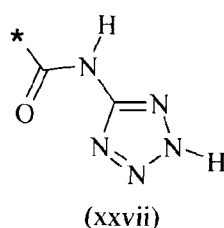
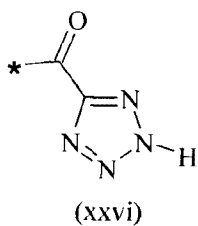
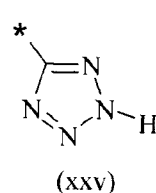
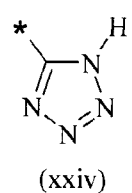
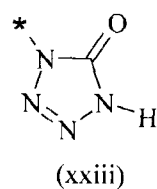
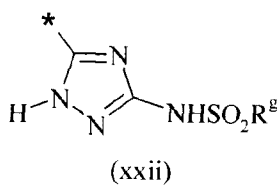
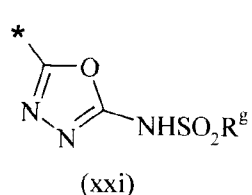
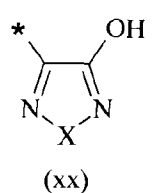
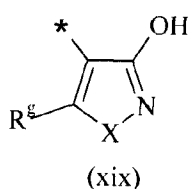
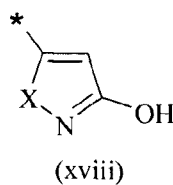
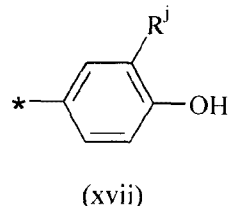
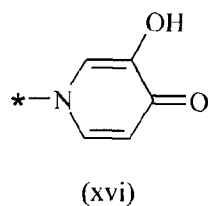
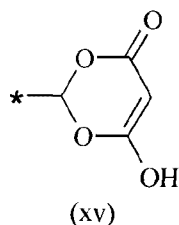
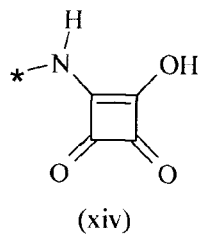
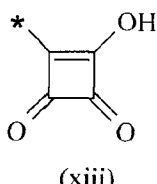
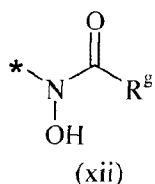
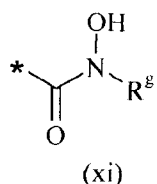
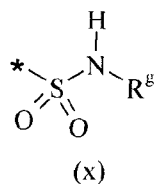
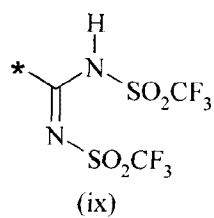
R¹² represents hydrogen, fluoro, chloro, trifluoromethyl, methyl or ethoxycarbonylethyl;

R¹⁵ and R¹⁶ independently represent hydrogen, halogen, cyano, nitro, C₁₋₆ alkyl, trifluoromethyl, hydroxy, C₁₋₆ alkoxy, difluoromethoxy, trifluoromethoxy, C₁₋₆ alkylthio, 20 C₁₋₆ alkylsulfinyl, C₁₋₆ alkylsulfonyl, amino, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino, phenylamino, C₂₋₆ alkylcarbonylamino, C₁₋₆ alkylsulfonylamino, formyl, C₂₋₆ alkylcarbonyl, C₃₋₆ cycloalkylcarbonyl, C₃₋₆ heterocycloalkylcarbonyl, carboxy, C₂₋₆ alkoxycarbonyl, aminocarbonyl, C₁₋₆ alkylaminocarbonyl, di(C₁₋₆)alkylaminocarbonyl, aminosulfonyl, C₁₋₆ alkylaminosulfonyl or di(C₁₋₆)alkylaminosulfonyl;

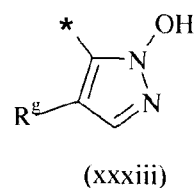
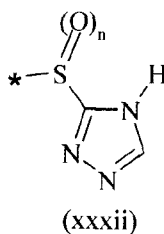
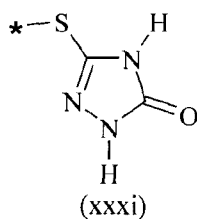
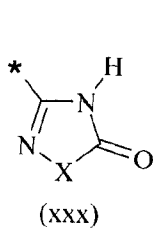
25 R²¹ represents hydrogen, halogen, halo(C₁₋₆)alkyl, cyano, C₁₋₆ alkyl, trifluoromethyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, hydroxy, hydroxy(C₁₋₆)alkyl, C₁₋₆ alkoxy, (C₁₋₆)alkoxy-(C₁₋₆)alkyl, difluoromethoxy, trifluoromethoxy, trifluoroethoxy, carboxy(C₃₋₇)cycloalkyloxy, C₁₋₆ alkylthio, C₁₋₆ alkylsulphonyl, (C₁₋₆)alkylsulphonyl(C₁₋₆)alkyl, amino, amino-(C₁₋₆)alkyl, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino, (C₁₋₆)alkoxy(C₁₋₆)alkylamino, *N*-[(C₁₋₆)- 30 alkyl]-*N*-[hydroxy(C₁₋₆)alkyl]amino, C₂₋₆ alkylcarbonylamino, (C₂₋₆)alkylcarbonylamino-(C₁₋₆)alkyl, C₂₋₆ alkoxycarbonylamino, *N*-[(C₁₋₆)alkyl]-*N*-[carboxy(C₁₋₆)alkyl]amino, carboxy(C₃₋₇)cycloalkylamino, carboxy(C₃₋₇)cycloalkyl(C₁₋₆)alkylamino, C₁₋₆ alkylsulphonylamino, C₁₋₆ alkylsulphonylamino(C₁₋₆)alkyl, formyl, C₂₋₆ alkylcarbonyl,

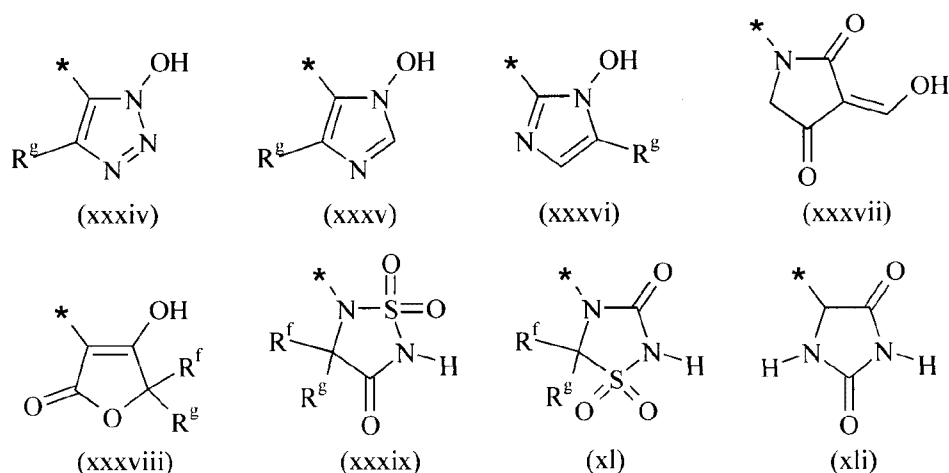
- (C₂₋₆)alkylcarbonyloxy(C₁₋₆)alkyl, carboxy, carboxy(C₁₋₆)alkyl, C₂₋₆ alkoxy carbonyl, morpholinyl(C₁₋₆)alkoxy carbonyl, C₂₋₆ alkoxy carbonyl(C₁₋₆)alkyl, C₂₋₆ alkoxy carbonyl-methylidenyl, aminocarbonyl, C₁₋₆ alkylaminocarbonyl, di(C₁₋₆)alkylaminocarbonyl, aminosulphonyl, C₁₋₆ alkylaminosulphonyl or di(C₁₋₆)alkylaminosulphonyl; or R²¹
- 5 represents (C₃₋₇)cycloalkyl, (C₃₋₇)cycloalkyl(C₁₋₆)alkyl, (C₄₋₇)cycloalkenyl, (C₄₋₉)bicycloalkyl, (C₃₋₇)heterocycloalkyl, (C₃₋₇)heterocycloalkenyl, (C₄₋₉)heterobicycloalkyl or (C₄₋₉)spiroheterocycloalkyl, any of which groups may be optionally substituted by one or more substituents independently selected from the group consisting of halogen, cyano, cyano(C₁₋₆)alkyl, C₁₋₆ alkyl, trifluoromethyl, trifluoroethyl,
- 10 C₂₋₆ alkenyl, hydroxy, C₁₋₆ alkoxy, difluoromethoxy, trifluoromethoxy, trifluoroethoxy, C₁₋₆ alkylthio, C₁₋₆ alkylsulphonyl, (C₁₋₆)alkyl-sulphonyl(C₁₋₆)alkyl, oxo, amino, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino, C₂₋₆ alkylcarbonyl-amino, C₂₋₆ alkoxy carbonylamino, C₁₋₆ alkylsulphonylamino, formyl, C₂₋₆ alkylcarbonyl, carboxy, carboxy(C₁₋₆)alkyl, C₂₋₆ alkoxy carbonyl, C₂₋₆ alkoxy carbonyl(C₁₋₆)alkyl, a carboxylic acid isostere or prodrug
- 15 moiety Ω as defined below, aminocarbonyl, C₁₋₆ alkyl-aminocarbonyl, di(C₁₋₆)alkylaminocarbonyl, aminosulphonyl, di(C₁₋₆)alkylamino-sulphonyl, -(C₁₋₆)alkyl- Ω , halo(C₁₋₆)alkyl, nitro(C₁₋₆)alkyl, hydroxy(C₁₋₆)alkyl, (C₂₋₆)alkylcarbonylamino(C₁₋₆)alkyl, morpholinyl(C₁₋₆)alkoxy carbonyl, C₂₋₆ alkoxy-carbonylmethylidenyl and C₁₋₆ alkoxyaminocarbonyl;
- 20 R²² represents hydrogen, halogen or C₁₋₆ alkyl; and
R²³ represents hydrogen, C₁₋₆ alkyl, trifluoromethyl or C₁₋₆ alkoxy;
where Ω represents one of the following groups (i)-(xli):





5





wherein

the asterisk (*) represents the site of attachment to the remainder of the molecule;

5 n is zero, 1 or 2;

X represents oxygen or sulphur;

R^f represents hydrogen, C₁₋₆ alkyl or -CH₂CH(OH)CH₂OH;

R^g represents C₁₋₆ alkyl, trifluoromethyl, -CH₂CH₂F, -CH₂CHF₂, -CH₂CF₃ or -CF₂CF₃;

10 R^h represents hydrogen, cyano or -CO₂R^d, in which R^d is hydrogen, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, aryl, C₃₋₇heterocycloalkyl or heteroaryl any of which groups may be optionally substituted by one or more substituents selected from the group consisting of halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, oxo, C₂₋₆ alkylcarbonyloxy and di(C₁₋₆)alkylamino; and

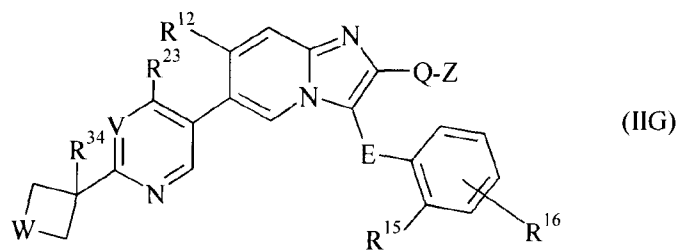
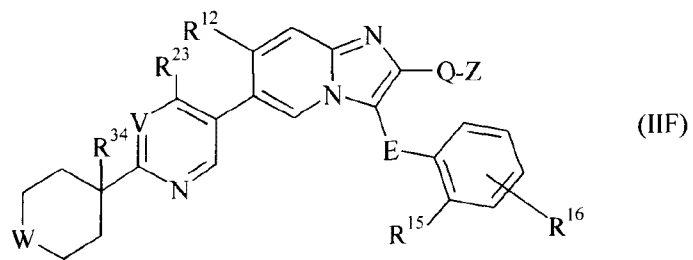
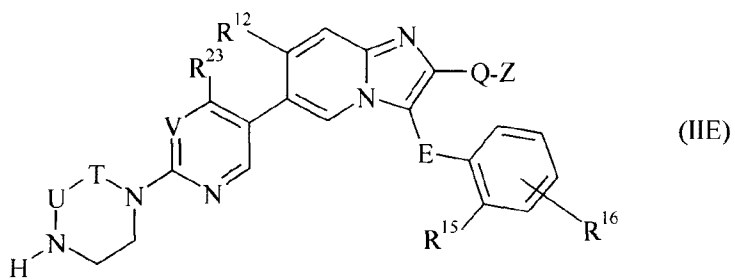
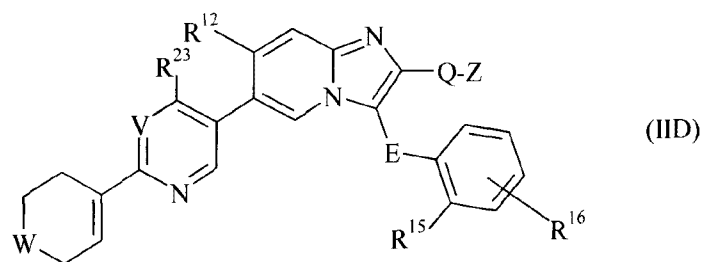
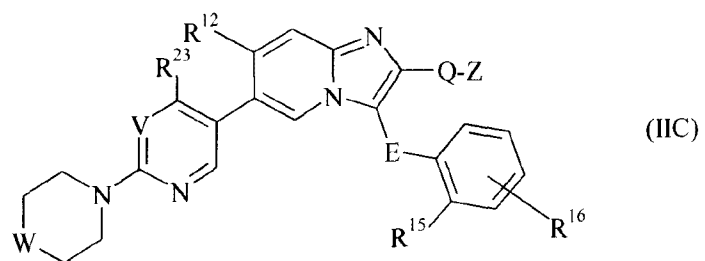
R^j represents hydrogen or halogen.

15

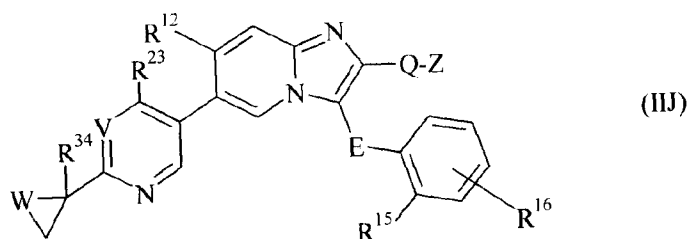
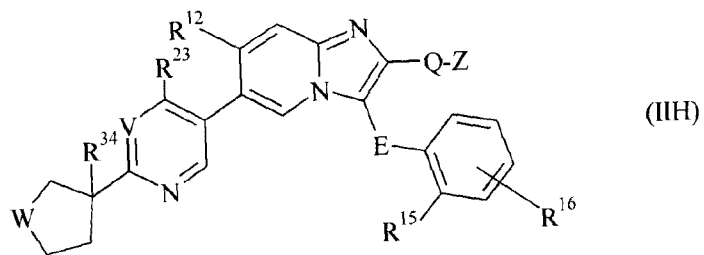
2. A compound as claimed in claim 1 wherein R²¹ represents hydroxy(C₁₋₆)alkyl.

3. A compound as claimed in claim 2 wherein R²¹ represents 2-hydroxyprop-2-yl.

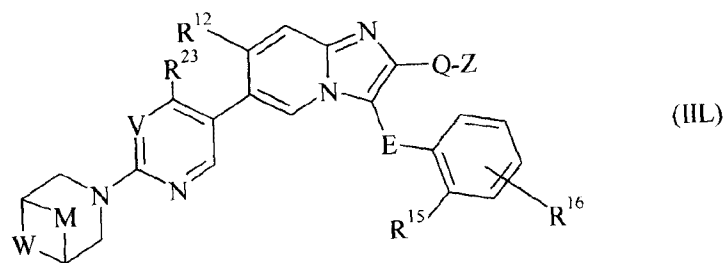
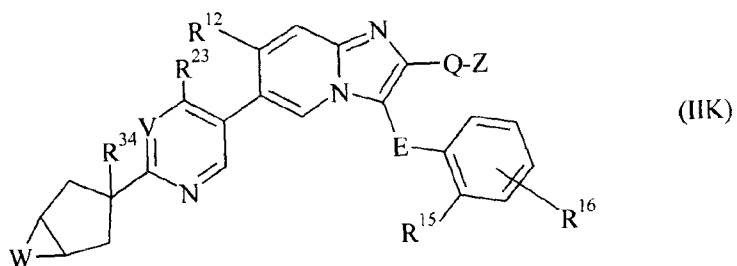
20 4. A compound as claimed in claim 1 represented by formula (IIC), (IID), (IIE), (IIF), (IIG), (IIH), (IIJ), (IIK) or (IIL) or an *N*-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof, or a co-crystal thereof:



5



5



10 wherein

T represents $-CH_2-$ or $-CH_2CH_2-$;

U represents $C(O)$ or $S(O)_2$;

W represents O, S, $S(O)$, $S(O)_2$, $N(R^{31})$ or $C(R^{32})(R^{33})$;

-M- represents $-CH_2-$ or $-CH_2CH_2-$;

R³¹ represents hydrogen, cyano(C₁₋₆)alkyl, C₁₋₆ alkyl, trifluoromethyl, trifluoroethyl, C₁₋₆ alkylsulphonyl, (C₁₋₆)alkylsulphonyl(C₁₋₆)alkyl, formyl, C₂₋₆ alkylcarbonyl, carboxy, carboxy(C₁₋₆)alkyl, C₂₋₆ alkoxycarbonyl, C₂₋₆ alkoxycarbonyl(C₁₋₆)alkyl, a carboxylic acid isostere or prodrug moiety Ω , -(C₁₋₆)alkyl- Ω , aminocarbonyl, C₁₋₆ alkylaminocarbonyl, di(C₁₋₆)alkylaminocarbonyl, aminosulphonyl or di(C₁₋₆)alkylaminosulphonyl;

R³² represents hydrogen, halogen, cyano, hydroxy, hydroxy(C₁₋₆)alkyl, C₁₋₆ alkylsulphonyl, formyl, C₂₋₆ alkylcarbonyl, carboxy, carboxy(C₁₋₆)alkyl, C₂₋₆ alkoxycarbonyl, C₂₋₆ alkoxycarbonyl(C₁₋₆)alkyl, aminosulphonyl, a carboxylic acid isostere or prodrug moiety Ω , or -(C₁₋₆)alkyl- Ω ;

R³³ represents hydrogen, halogen, C₁₋₆ alkyl, trifluoromethyl, hydroxy, hydroxy-(C₁₋₆)alkyl, C₁₋₆ alkoxy, amino or carboxy;

R³⁴ represents hydrogen, halogen, halo(C₁₋₆)alkyl, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ alkylsulphinyl, C₁₋₆ alkylsulphonyl, amino, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino, (C₂₋₆)alkylcarbonylamino, (C₂₋₆)alkylcarbonylamino(C₁₋₆)alkyl, (C₁₋₆)alkylsulphonylamino, or (C₁₋₆)alkylsulphonylamino(C₁₋₆)alkyl; and E, Q, Z, V, R¹², R¹⁵, R¹⁶, R²³ and Ω are as defined in claim 1.

5. A compound as claimed in claim 4 wherein R³⁴ represents hydrogen or hydroxy.

6. A compound as claimed in any one of claims 1 to 5 wherein E represents -CH₂- or -CH(CH₃)-.

7. A compound as claimed in any one of claims 1 to 6 wherein R¹² represents hydrogen or fluoro.

8. A compound as claimed in any one of claims 1 to 7 wherein R¹⁵ represents hydrogen, halogen, C₁₋₆ alkyl, trifluoromethyl, C₁₋₆ alkoxy, difluoromethoxy or trifluoromethoxy.

9. A compound as claimed in claim 8 wherein R¹⁵ represents difluoromethoxy.

10. A compound as claimed in any one of claims 1 to 9 wherein R¹⁶ represents hydrogen, halogen, C₁₋₆ alkyl, trifluoromethyl, difluoromethoxy or amino.

11. A compound as claimed in claim 10 wherein R¹⁶ represents hydrogen.

5

12. A compound of formula (IIB) as defined in any one of claims 1 to 11 or an *N*-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof, or a co-crystal thereof, for use in the treatment and/or prevention of disorders for which the administration of a modulator of TNF α function is indicated.

10

13. A compound of formula (IIB) as defined in any one of claims 1 to 11 or an *N*-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof, or a co-crystal thereof, for use in the treatment and/or prevention of an inflammatory or autoimmune disorder, a neurological or neurodegenerative disorder, pain or a nociceptive disorder, a cardiovascular disorder, a metabolic disorder, an ocular disorder, or an oncological disorder.

15

14. Use of a compound of formula (IIB) as defined in any one of claims 1 to 11 or an *N*-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof, or a co-crystal thereof, in the treatment and/or prevention of disorders for which the administration of a modulator of TNF α function is indicated.

20

15. Use of a compound of formula (IIB) as defined in any one of claims 1 to 11 or an *N*-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof, or a co-crystal thereof, in the treatment and/or prevention of an inflammatory or autoimmune disorder, a neurological or neurodegenerative disorder, pain or a nociceptive disorder, a cardiovascular disorder, a metabolic disorder, an ocular disorder, or an oncological disorder.

25

16. Use of a compound of formula (IIB) as defined in any one of claims 1 to 11 or an *N*-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof, or a co-crystal thereof, in the manufacture of a medicament for the treatment and/or prevention of disorders for which the administration of a modulator of TNF α function is indicated.

30

17. Use of a compound of formula (IIB) as defined in any one of claims 1 to 11 or an *N*-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof, or a co-crystal thereof, in the manufacture of a medicament for the treatment and/or prevention of
5 an inflammatory or autoimmune disorder, a neurological or neurodegenerative disorder, pain or a nociceptive disorder, a cardiovascular disorder, a metabolic disorder, an ocular disorder, or an oncological disorder.

18. A pharmaceutical composition comprising a compound of formula (IIB) as
10 defined in any one of claims 1 to 11 or an *N*-oxide thereof, or a pharmaceutically acceptable salt or solvate thereof, or a co-crystal thereof, in association with a pharmaceutically acceptable carrier.

19. A pharmaceutical composition as claimed in claim 18 further comprising an
15 additional pharmaceutically active ingredient.

