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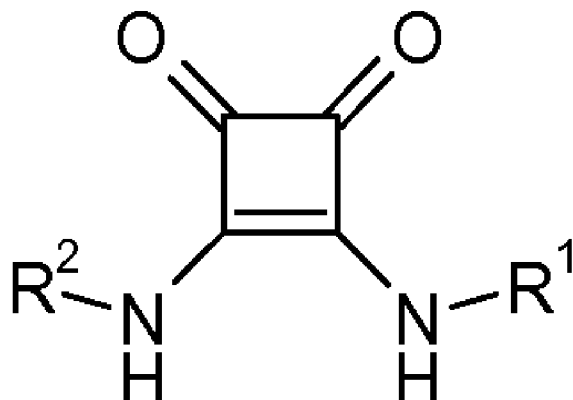
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[Continued on next page]

(54) Title: CYCLOBUTENEDIONE DERIVATIVES



(I)

(57) **Abstract:** The present invention relates to compounds of the formula (I): to pharmaceutically acceptable salts therefore and to pharmaceutically acceptable solvates of said compounds and salts, wherein the substituents are defined herein; to compositions containing such compounds; and to the uses of such compounds in the treatment of various diseases, particularly inflammatory conditions.



DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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CYCLOBUTENEDIONE DERIVATIVES

The present invention relates to cyclobutenedione derivatives, pharmaceutical compositions comprising such derivatives and their use as medicaments. More particularly, the present invention provides 4-heteroarylaminocyclobut-3-ene-1,2-dione derivatives which are antagonists of the CXCR-2 receptor and useful for the treatment of inflammatory conditions, including inflammatory conditions of the airways, such as asthma, chronic obstructive pulmonary disease and cystic fibrosis. The compounds are also useful in the treatment of other inflammatory conditions such as rheumatoid arthritis and psoriasis and in the treatment of non-inflammatory conditions such as cancer.

Cytokines are signaling molecules that play an important role in intercellular communication. In particular, cytokines play an important role in the functioning of the immune system, being secreted by a wide variety of cells in response to a pathogen challenge in order to recruit further immune cells to the site of infection or in response to tumour growth. Chemokines (chemotactic cytokines) are a class of cytokines that mediate such attraction between cells. They are small peptidic molecules (generally 8-10 kilodaltons in size) with a characteristic three-dimensional shape determined by cysteine residues which form disulphide bridges. Chemokines are involved in the inflammatory response and act as chemical attractants, encouraging the migration of cells including monocytes, macrophages, T-lymphocytes, eosinophils, basophils and neutrophils from the blood to sites of infection or tissue damage to protect tissues and promote healing.

Chemokines can be divided into certain classes based on sequence homology, particularly according to the distribution of cysteine residues. The members of one class, known as the CXC chemokines, have two N-terminal cysteine residues (C) separated by one amino acid (X). Examples include interleukin-8 (IL-8), neutrophil activating protein 1 (NAP-1), neutrophil activating protein 2 (NAP-2), GRO α , GRO β , GRO γ , ENA-78, GCP-2, IP-10, MIG and PF-4. Such CXC chemokines can further be divided on the basis of whether or not they contain a glutamic acid-leucine-arginine (E-L-R) motif immediately before the first cysteine of the CXC sequence. Those that share this E-L-R motif are responsible for inducing the migration of neutrophils by activating two cell-surface chemokine receptors CXCR1 and CXCR2. An important CXC chemokine of this kind is interleukin-8 (IL-8) which binds to both CXCR1 and CXCR2 receptors on the surface of neutrophils and induces them to migrate from the blood stream into surrounding tissues. Tissues release these chemokines in response to bacterial, fungal or viral infection and in response to other factors as well. For example, exposure of lung

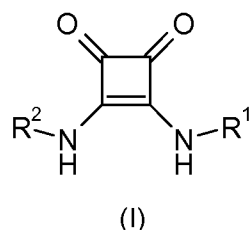
tissue to cigarette smoke, dust, pollutants and noxious gas (e.g. ozone) is known to cause the release of chemokines and to result in an inflammatory response.

The CXCR2 receptor, sometimes referred to as the interleukin 8 receptor beta (IL8RB), is a G-protein coupled receptor which binds all ELR+ chemokines (CXCL1-8) with high affinity and is activated by several of them including interleukin-8. Convincing evidence exists that the activation of the CXCR2 receptor by interleukin-8 plays an important role in the development of several inflammatory diseases such as rheumatoid arthritis, septic shock, asthma, cystic fibrosis and psoriasis (see, for example, *FEBS Lett.*, 1992, **307**, 97; *Crit. Rev. Immunol.*, 1992, **12**, 17; *Annual Rev. Immunol.*, 1991, **9**, 617; *J. Clin. Invest.*, 1991, **87**, 463; *Am. Rev. Respir. Dis.*, 1992, **146**, 427; and *Lancet*, 1993, **341**, 643). Monoclonal antibodies to interleukin-8, which block its ability to bind to CXCR-2 receptors and mediate neutrophil recruitment, are able to prevent tissue damage in the rabbit lung which normally results from lung ischemia/reperfusion (*Nature*, 1993, **365**, 654). Another study demonstrated that antibodies to interleukin-8 have a beneficial effect in an endotoxin-induced model of pleurisy in rabbits (*J. Immunol.*, 1994, **152**, 2960). The physiological role of this receptor in mediating neutrophil recruitment has been defined in man and a range of other species (including non-human primates, rodents and rabbits) using a range of pharmacological tools (see, for example, *Eur. Respir. J.*, 2007, **30** (supplement 1), 209s; *J. Pharmacol. Exp. Ther.*, 2007, **322**, 486; *J. Immunol.*, 1999, **163**, 2829; *Immunobiology*, 2004, **209**, 225; *J. Exp. Med.*, 2004, **200**, 935; *J. Leukocyte Biol.*, 2005, **78**, 1265; *Am. J. Physiol. Lung Cell Mol. Physiol.*, 2005, **289**, L322; *J. Immunol.*, 2002, **169**, 6435; *Lab. Invest.*, 2002, **82**, 1297). Mice deficient in the CXCR-2 receptor have been generated and show a pronounced peripheral neutrophilia, altered leukocyte rolling capabilities and impaired PMN recruitment into the inflamed lung (see, for example, *Science*, 1994, **265**, 682; *Microvasc. Res.*, 1997, **54**, 199; *J. Clin. Invest.*, 2006, **116**, 695; *Am. J. Physiol. Lung Cell Mol. Physiol.*, 2005, **288**, L61). Further, because of an involvement in tumour growth and angiogenesis, CXCR-2 antagonists are potentially useful for the treatment of cancer.

All the available evidence therefore suggests that interleukin-8 is an important inflammatory mediator and that an antagonist of the CXCR-2 receptor should have a beneficial effect in the treatment of inflammatory conditions by diminishing the recruitment of neutrophils and other leukocytes to the sites of inflammatory mediator release. There is therefore a need to provide new CXCR-2 receptor antagonists that are suitable as drug candidates. Such compounds should be potent, selective for CXCR-2 with respect to other physiologically important receptors (or selective for CXCR-1 and CXCR-2) and have appropriate oral bioavailability, tissue penetration, metabolic stability and pharmacokinetic properties.

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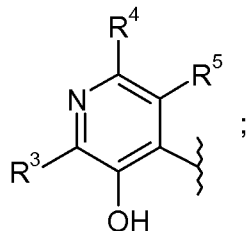
The invention therefore provides, as embodiment E1, a compound of formula (I):



or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of said compound or salt, wherein:

R^1 is C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, C_6 - C_{12} bicycloalkyl, Aryl¹, Aryl², Het¹, Het², Het³ or Het⁴, said C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl and C_6 - C_{12} bicycloalkyl being optionally substituted by 1 to 3 substituents independently selected from -CN, halo, -NH₂, -SH, -SO₂NH₂, -OCONH₂ and -X-R^a, with the proviso that the R^1 moiety may not be attached through a methylene (-CH₂-) group;

R^2 is



X is a bond, C_1 - C_6 alkylene, -CO-, -O-, -O-(C_1 - C_6 alkylene)-, -NR⁶-, -S-, -SO-, -SO₂-, -COO-, -OCO-, -NR⁶SO₂-, -SO₂NR⁶-, -NR⁶CONR⁶-, -NR⁶COO- or -OCONR⁶-;

R^a is C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, Aryl¹, Aryl², Het¹, Het², Het³ or Het⁴, said C_3 - C_8 cycloalkyl and C_6 - C_{12} bicycloalkyl being optionally substituted by one or more C_1 - C_6 alkyl, -OH or C_1 - C_6 alkoxy groups;

R^3 and R^4 are each independently H, -CN, halo, -OH, -NH₂, -SH, -CONH₂, -SO₂NH₂, -NR⁶CONH₂, -OCONH₂ or -Y-R^b;

or, alternatively, where R^3 and R^4 are attached to adjacent carbon atoms, R^3 and R^4 , taken together with the carbon atoms to which they are attached, form a 5 or 6-membered ring which may be aromatic or partially saturated and which may be carbocyclic or contain up to two

heteroatoms selected from N, S and O, said ring being optionally substituted by 1-3 substituents selected from C₁-C₆ alkyl, C₃-C₈ cycloalkyl, halo, -CN, -OR⁶, -NR⁷R⁸, -SR⁶, -SOR⁹, -SO₂R⁹, -COR⁶, -OCOR⁶, -COOR⁶, -NR⁶COR⁶, -CONR⁷R⁸, -NR⁶SO₂R⁹, -SO₂NR⁷R⁸, -NR⁶CONR⁷R⁸, -NR⁶COOR⁹ and -NR⁶SO₂NR⁷R⁸;

R⁵ is H, -CN, halo, -OH, -NH₂, -SH, -CONH₂, -SO₂NH₂, -NR⁶CONH₂, -OCONH₂ or -Y-R^b;

Y is a bond, C₁-C₆ alkylene, -CO-, -O-, -NR⁶-, -S-, -SO-, -SO₂-, -CONR⁶-, -COO-, -OCO-, -NR⁶CO-, -NR⁶SO₂-, -SO₂NR⁶-, -NR⁶CONR⁶-, -NR⁶COO- or -OCONR⁶-;

R^b is C₁-C₆ alkyl, C₃-C₈ cycloalkyl, C₆-C₁₂ bicycloalkyl, Aryl¹, Aryl², Het¹, Het², Het³ or Het⁴, said C₁-C₆ alkyl, C₃-C₈ cycloalkyl and C₆-C₁₂ bicycloalkyl being optionally substituted by 1-5 substituents selected from R⁹, -CN, -OR⁶, -NR⁷R⁸, -SR⁶, -SOR⁹, -SO₂R⁹, -COR⁶, -OCOR⁶, -COOR⁶, -NR⁶COR⁶, -CONR⁷R⁸, -NR⁶SO₂R⁹, -SO₂NR⁷R⁸, -NR⁶CONR⁷R⁸, -NR⁶COOR⁹ and -NR⁶SO₂NR⁷R⁸ and optionally substituted by 1 substituent R^d;

Aryl¹ is phenyl or naphthyl, said phenyl and naphthyl being optionally substituted by 1 substituent -Z-R^d and 1-4 substituents each independently selected from -Z-R^e;

Aryl² is a 3 to 8-membered monocyclic or 6 to 12-membered bicyclic carbocycle which is partially unsaturated, said carbocycle being optionally substituted by 1 substituent -Z-R^d and 1-4 substituents each independently selected from -Z-R^f;

Het¹ is a 3 to 8-membered saturated or partially unsaturated monocyclic heterocycle, containing 1 or 2 heteroatoms selected from O and N, said heterocycle being optionally substituted by 1 substituent -Z-R^d and 1-4 substituents each independently selected from -Z-R^f;

Het² is a 6 to 12-membered saturated or partially unsaturated multicyclic heterocycle containing 1-3 heteroatoms selected from O, S and N, said heterocycle being optionally substituted by 1 substituent -Z-R^d and 1-4 substituents each independently selected from -Z-R^f;

Het³ is (i) a 6-membered aromatic heterocycle containing 1-3 N atoms or (ii) a 5-membered aromatic heterocycle containing either (a) 1-4 N atoms or (b) 1 O or S atom and 0-3 N atoms, said heterocycle being optionally substituted by 1 substituent -Z-R^d and 1-4 substituents each independently selected from -Z-R^e;

Het⁴ is (i) a 10-membered bicyclic aromatic heterocycle containing 1-4 N atoms or (ii) a 9-membered bicyclic aromatic heterocycle containing either (a) 1-4 N atoms or (b) 1 O or S atom and 0-3 N atoms or (iii) an 8-membered bicyclic aromatic heterocycle containing (a) 1-4 N atoms or (b) 1 O or S atom and 1-3 N atoms or (c) 2 O or S atoms and 0-2 N atoms, said heterocycle being optionally substituted by 1 substituent -Z-R^d and 1-4 substituents each independently selected from -Z-R^e;

Z is a bond, -CO- or C₁-C₆ alkylene;

R^d is Aryl³, Aryl⁴, Het⁵, Het⁶, Het⁷ or Het⁸;

R^e is C₁-C₆ alkyl, C₃-C₈ cycloalkyl, halo, -CN, -OR⁶, -NR⁷R⁸, -SR⁶, -SOR⁹, -SO₂R⁹, -COR⁶, -OCOR⁶, -COOR⁶, -NR⁶COR⁶, -CONR⁷R⁸, -NR⁶SO₂R⁹, -SO₂NR⁷R⁸, -NR⁶CONR⁷R⁸, -NR⁶COOR⁹ or -NR⁶SO₂NR⁷R⁸;

R^f is C₁-C₆ alkyl, C₃-C₈ cycloalkyl, halo, oxo, -OR⁶, -NR⁷R⁸, -SR⁶, -SOR⁹, -SO₂R⁹, -COR⁶, -OCOR⁶, -COOR⁶, -NR⁶COR⁶, -CONR⁷R⁸, -NR⁶SO₂R⁹, -SO₂NR⁷R⁸, -NR⁶CONR⁷R⁸, -NR⁶COOR⁹ or -NR⁶SO₂NR⁷R⁸;

Aryl³ is phenyl or naphthyl, said phenyl and naphthyl being optionally substituted with 1-5 substituents selected from C₁-C₆ alkyl, C₃-C₈ cycloalkyl, halo, -CN, -OR⁶, -NR⁷R⁸, -SR⁶, -SOR⁹, -SO₂R⁹, -COR⁶, -OCOR⁶, -COOR⁶, -NR⁶COR⁶, -CONR⁷R⁸, -NR⁶SO₂R⁹, -SO₂NR⁷R⁸, -NR⁶CONR⁷R⁸, -NR⁶COOR⁹ and -NR⁶SO₂NR⁷R⁸;

Aryl⁴ is a 3 to 8-membered monocyclic or 6 to 12-membered bicyclic carbocycle which is partially unsaturated, said carbocycle being optionally substituted by 1-5 substituents selected from C₁-C₆ alkyl, C₃-C₈ cycloalkyl, halo, oxo, -OR⁶, -NR⁷R⁸, -SR⁶, -SOR⁹, -SO₂R⁹, -COR⁶, -OCOR⁶, -COOR⁶, -NR⁶COR⁶, -CONR⁷R⁸, -NR⁶SO₂R⁹, -SO₂NR⁷R⁸, -NR⁶CONR⁷R⁸, -NR⁶COOR⁹ and -NR⁶SO₂NR⁷R⁸;

Het⁵ is a 3 to 8-membered saturated or partially unsaturated monocyclic heterocycle, containing 1 or 2 heteroatoms selected from O and N, said heterocycle being optionally substituted by 1-5 substituents selected from C₁-C₆ alkyl, C₃-C₈ cycloalkyl, halo, oxo, -OR⁶, -NR⁷R⁸, -SR⁶, -SOR⁹, -SO₂R⁹, -COR⁶, -OCOR⁶, -COOR⁶, -NR⁶COR⁶, -CONR⁷R⁸, -NR⁶SO₂R⁹, -SO₂NR⁷R⁸, -NR⁶CONR⁷R⁸, -NR⁶COOR⁹ and -NR⁶SO₂NR⁷R⁸;

Het⁶ is a 6 to 12-membered saturated or partially unsaturated multicyclic heterocycle containing 1-3 heteroatoms selected from O, S and N, said heterocycle being optionally substituted by 1-5 substituents selected from C₁-C₆ alkyl, C₃-C₈ cycloalkyl, halo, oxo, -OR⁶, -NR⁷R⁸, -SR⁶, -SOR⁹, -SO₂R⁹, -COR⁶, -OCOR⁶, -COOR⁶, -NR⁶COR⁶, -CONR⁷R⁸, -NR⁶SO₂R⁹, -SO₂NR⁷R⁸, -NR⁶CONR⁷R⁸, -NR⁶COOR⁹ and -NR⁶SO₂NR⁷R⁸;

Het⁷ is (i) a 6-membered aromatic heterocycle containing 1-3 N atoms or (ii) a 5-membered aromatic heterocycle containing either (a) 1-4 N atoms or (b) 1 O or S atom and 0-3 N atoms, said heterocycle being optionally substituted with 1-4 substituents selected from C₁-C₆ alkyl, C₃-C₈ cycloalkyl, halo, -CN, -OR⁶, -NR⁷R⁸, -SR⁶, -SOR⁹, -SO₂R⁹, -COR⁶, -OCOR⁶, -COOR⁶, -NR⁶COR⁶, -CONR⁷R⁸, -NR⁶SO₂R⁹, -SO₂NR⁷R⁸, -NR⁶CONR⁷R⁸, -NR⁶COOR⁹ and -NR⁶SO₂NR⁷R⁸;

Het⁸ is (i) a 10-membered bicyclic aromatic heterocycle containing 1-4 N atoms or (ii) a 9-membered bicyclic aromatic heterocycle containing either (a) 1-4 N atoms or (b) 1 O or S atom and 0-3 N atoms, or (iii) an 8-membered bicyclic aromatic heterocycle containing (a) 1-4 N atoms or (b) 1 O or S atom and 1-3 N atoms or (c) 2 O or S atoms and 0-2 N atoms, said heterocycle being optionally substituted with 1-5 substituents selected from C₁-C₆ alkyl, C₃-C₈ cycloalkyl, halo, -CN, -OR⁶, -NR⁷R⁸, -SR⁶, -SOR⁹, -SO₂R⁹, -COR⁶, -OCOR⁶, -COOR⁶, -NR⁶COR⁶, -CONR⁷R⁸, -NR⁶SO₂R⁹, -SO₂NR⁷R⁸, -NR⁶CONR⁷R⁸, -NR⁶COOR⁹ and -NR⁶SO₂NR⁷R⁸;

R⁶ is H, C₁-C₆ alkyl or C₃-C₈ cycloalkyl, said C₁-C₆ alkyl and C₃-C₈ cycloalkyl being optionally substituted by -OH or C₁-C₆ alkoxy;

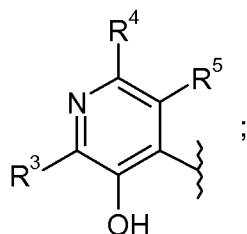
R⁷ and R⁸ are each independently H, C₁-C₆ alkyl or C₃-C₈ cycloalkyl or are taken together with the nitrogen atom to which they are attached to form a 4-, 5- or 6-membered saturated heterocyclic ring containing 1-2 nitrogen atoms or 1 nitrogen and 1 oxygen atom, said heterocyclic ring being optionally substituted by one or more C₁-C₆ alkyl or C₃-C₈ cycloalkyl groups; and

R⁹ is C₁-C₆ alkyl or C₃-C₈ cycloalkyl, said C₁-C₆ alkyl and C₃-C₈ cycloalkyl being optionally substituted by -OH or C₁-C₆ alkoxy;

wherein, in each instance, said C₁-C₆ alkyl, C₁-C₆ alkylene, C₃-C₈ cycloalkyl and C₆-C₁₂ bicycloalkyl may have one or more hydrogen atoms replaced with a fluorine atom.

In the preferred embodiments set out below, any group not specifically defined has the meaning assigned to it in embodiment E1 above.

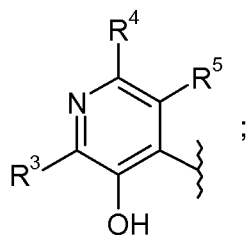
The invention also provides, as preferred embodiment E2, a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of said compound or salt, wherein R² is:



wherein R³, R⁴ and R⁵ are each independently H, -CN, halo, C₁-C₆ alkyl, C₃-C₈ cycloalkyl, -(C₁-C₆ alkylene)-(Aryl¹), -NR⁶SO₂-(C₁-C₆ alkyl), -NR⁶-(C₁-C₆ alkyl), -NR⁶CONR⁶-(C₁-C₆ alkyl), -NR⁶CO-(C₃-C₈ cycloalkyl), -NR⁶CO-(C₁-C₆ alkyl), -SO-(C₁-C₆ alkyl), -S-(C₁-C₆ alkyl), -SO₂-(C₁-C₆ alkyl), -SO₂-(Aryl¹), -SO₂-(Het¹), -SO₂NR⁶-(C₁-C₆ alkyl), -SO₂-(C₃-C₈ cycloalkyl), -O-(C₁-C₆ alkyl), -CONH₂, -CONR⁶-(C₁-C₆ alkyl), -CONR⁶-(C₁-C₆ alkylene)-(C₃-C₈ cycloalkyl), -CONR⁶-(Het¹), -CONR⁶-(Het²), -CO-(Het¹), Aryl¹, Het³, -CO-(Het²), -CONR⁶-(C₃-C₈ cycloalkyl), -CONR⁶-(C₁-C₆ alkylene)-(Aryl¹), -CONR⁶-(C₁-C₆ alkylene)-(Het¹), -CONR⁶-(C₁-C₆ alkylene)-(Het³) or -CONR⁶-(Het³), said C₁-C₆ alkyl and C₃-C₈ cycloalkyl, in each case, being optionally substituted by 1-5 substituents selected from -CN, -OR⁶, -NR⁷R⁸, -SR⁶, -SOR⁹, -SO₂R⁹, -COR⁶, -OCOR⁶, -COOR⁶, -NR⁶COR⁶, -CONR⁷R⁸, -NR⁶SO₂R⁹, -SO₂NR⁷R⁸, -NR⁶CONR⁷R⁸, -NR⁶COOR⁹ and -NR⁶SO₂NR⁷R⁸;

wherein, in each instance, said C₁-C₆ alkyl, C₁-C₆ alkylene and C₃-C₈ cycloalkyl may have one or more hydrogen atoms replaced with a fluorine atom.

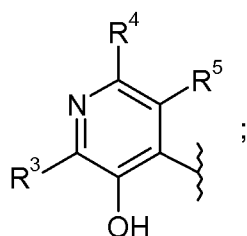
The invention also provides, as preferred embodiment E3, a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of said compound or salt, wherein R² is:



wherein R^3 , R^4 and R^5 are each independently H, -CN, halo, C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, $-(C_1-C_6 \text{ alkylene})-(Aryl^1)$, $-NR^6SO_2-(C_1-C_6 \text{ alkyl})$, $-NR^6-(C_1-C_6 \text{ alkyl})$, $-NR^6CONR^6-(C_1-C_6 \text{ alkyl})$, $-NR^6CO-(C_3-C_8 \text{ cycloalkyl})$, $-NR^6CO-(C_1-C_6 \text{ alkyl})$, $-SO-(C_1-C_6 \text{ alkyl})$, $-S-(C_1-C_6 \text{ alkyl})$, $-SO_2-(C_1-C_6 \text{ alkyl})$, $-SO_2-(Aryl^1)$, $-SO_2-(Het^1)$, $-SO_2NR^6-(C_1-C_6 \text{ alkyl})$, $-SO_2-(C_3-C_8 \text{ cycloalkyl})$, $-O-(C_1-C_6 \text{ alkyl})$, $-CONH_2$, $-CONR^6-(C_1-C_6 \text{ alkyl})$, $-CONR^6-(C_1-C_6 \text{ alkylene})-(C_3-C_8 \text{ cycloalkyl})$, $-CONR^6-(Het^1)$, $-CONR^6-(Het^2)$, $-CO-(Het^1)$, $Aryl^1$ or Het^3 , said C_1 - C_6 alkyl and C_3 - C_8 cycloalkyl, in each case, being optionally substituted by 1-5 substituents selected from -CN, $-OR^6$, $-CONR^7R^8$, $-NR^7R^8$ and $-COOR^6$;

wherein, in each instance, said C_1 - C_6 alkyl, C_1 - C_6 alkylene and C_3 - C_8 cycloalkyl may have one or more hydrogen atoms replaced with a fluorine atom.

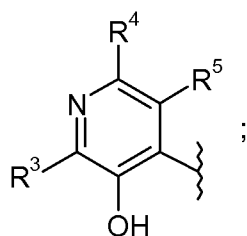
The invention also provides, as preferred embodiment E4, a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of said compound or salt, wherein R^2 is:



wherein R^3 , R^4 and R^5 are each independently H, -CN, halo, C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, $-(C_1-C_6 \text{ alkylene})-(Aryl^1)$, $-NR^6SO_2-(C_1-C_6 \text{ alkyl})$, $-NR^6-(C_1-C_6 \text{ alkyl})$, $-NR^6CONR^6-(C_1-C_6 \text{ alkyl})$, $-NR^6CO-(C_3-C_8 \text{ cycloalkyl})$, $-NR^6CO-(C_1-C_6 \text{ alkyl})$, $-SO-(C_1-C_6 \text{ alkyl})$, $-S-(C_1-C_6 \text{ alkyl})$, $-SO_2-(C_1-C_6 \text{ alkyl})$, $-SO_2-(Aryl^1)$, $-SO_2-(Het^1)$, $-SO_2NR^6-(C_1-C_6 \text{ alkyl})$, $-SO_2-(C_3-C_8 \text{ cycloalkyl})$, $-O-(C_1-C_6 \text{ alkyl})$, $-CONH_2$, $-CONR^6-(C_1-C_6 \text{ alkyl})$, $-CONR^6-(C_1-C_6 \text{ alkylene})-(C_3-C_8 \text{ cycloalkyl})$, $-CONR^6-(Het^1)$, $-CONR^6-(Het^2)$, $-CO-(Het^1)$, $Aryl^1$ or Het^3 , said C_1 - C_6 alkyl and C_3 - C_8 cycloalkyl, in each case, being optionally substituted by 1-5 substituents selected from -CN, $-OR^6$, $-CONR^7R^8$, $-NR^7R^8$ and $-COOR^6$;

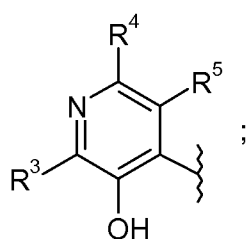
wherein, in each instance, said C₁-C₆ alkyl, C₁-C₆ alkylene and C₃-C₈ cycloalkyl may have one or more hydrogen atoms replaced with a fluorine atom.

The invention also provides, as preferred embodiment E5, a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of said compound or salt, wherein R² is:



wherein R³, R⁴ and R⁵ are each independently H, C₁-C₆ alkyl, -CONR⁶-(C₁-C₆ alkyl), -CO(Het¹), or -SO₂NR⁶-(C₁-C₆ alkyl).

The invention also provides, as preferred embodiment E6, a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of said compound or salt, wherein R² is:

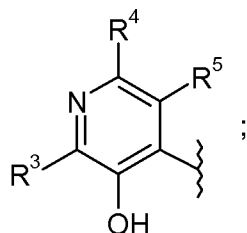


wherein R³ is H, C₁-C₆ alkyl, -CONR⁶-(C₁-C₆ alkyl), -CO(Het¹), or -SO₂NR⁶-(C₁-C₆ alkyl);

R⁴ is H; and

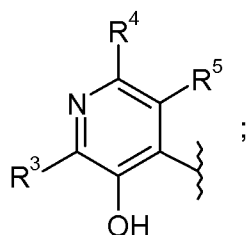
R⁵ is H.

The invention also provides, as preferred embodiment E7, a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of said compound or salt, wherein R² is:



wherein R^3 , R^4 and R^5 are each independently H, methyl, $-\text{CON}(\text{CH}_3)_2$, (carboxypyrrolidinyl)carbonyl, (hydroxypiperidinyl)carbonyl or (methylpiperazinyl)carbonyl.

The invention also provides, as preferred embodiment E8, a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of said compound or salt, wherein R^2 is:



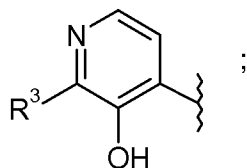
wherein R^3 is H, methyl, $-\text{CON}(\text{CH}_3)_2$, (carboxypyrrolidinyl)carbonyl, (hydroxypyrrolidinyl)carbonyl or (methylpiperazinyl)carbonyl;

R^4 is H; and

R^5 is H.

The invention also provides, as preferred embodiment E9, a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of said compound or salt, wherein R^2 is 2-(dimethylaminocarbonyl)-3-hydroxypyrid-4-yl, 2-((2-carboxypyrrolidin-1-yl)carbonyl)-3-hydroxypyrid-4-yl, 2-((3-hydroxypyrrolidin-1-yl)carbonyl)-3-hydroxypyrid-4-yl, 2-((4-methylpiperazin-1-yl)carbonyl)-3-hydroxypyrid-4-yl or 2-dimethylaminosulphonyl-3-hydroxypyrid-4-yl.

The invention also provides, as preferred embodiment E10, a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of said compound or salt, wherein R^2 is:



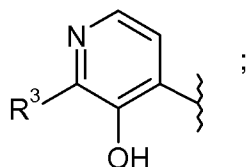
R^3 is $-\text{CONR}^6\text{-R}^b$, $-\text{COR}^b$, $-\text{SO}_2\text{NR}^5\text{-R}^b$ or $\text{C}_1\text{-C}_6$ alkyl;

R^6 is H, $\text{C}_1\text{-C}_6$ alkyl or $\text{C}_3\text{-C}_8$ cycloalkyl; and

R^b is $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_3\text{-C}_8$ cycloalkyl, Het^1 , Het^2 or Het^3 , said $\text{C}_1\text{-C}_6$ alkyl being optionally substituted by 1 substituent Aryl^3 or Het^7 ;

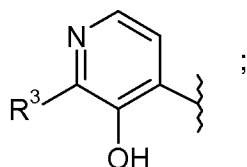
wherein, in each instance, said $\text{C}_1\text{-C}_6$ alkyl and $\text{C}_3\text{-C}_8$ cycloalkyl may have one or more hydrogen atoms replaced with a fluorine atom.

The invention also provides, as preferred embodiment E11, a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of said compound or salt, wherein R^2 is:



wherein R^3 is $-\text{CONH}(\text{C}_1\text{-C}_6 \text{ alkyl})$, $-\text{CONH}(\text{C}_3\text{-C}_8 \text{ cycloalkyl})$, $-\text{CON}(\text{C}_1\text{-C}_6 \text{ alkyl})(\text{C}_1\text{-C}_6 \text{ alkyl})$, $-\text{CON}(\text{C}_1\text{-C}_6 \text{ alkyl})(\text{C}_3\text{-C}_8 \text{ cycloalkyl})$, $-\text{CON}(\text{C}_3\text{-C}_8 \text{ cycloalkyl})(\text{C}_3\text{-C}_8 \text{ cycloalkyl})$, $-\text{CON}(\text{C}_1\text{-C}_6 \text{ alkyl})(\text{Het}^1)$, $-\text{CON}(\text{C}_1\text{-C}_6 \text{ alkyl})(\text{Het}^3)$, $-\text{CON}(\text{C}_1\text{-C}_6 \text{ alkyl})(\text{CH}_2\text{Ph})$, $-\text{CON}(\text{C}_1\text{-C}_6 \text{ alkyl})(\text{CH}_2\text{Het}^3)$, $\text{C}_1\text{-C}_6 \text{ alkyl}$, $-\text{SO}_2\text{N}(\text{C}_1\text{-C}_6 \text{ alkyl})(\text{C}_1\text{-C}_6 \text{ alkyl})$, $-\text{COHet}^1$ or $-\text{COHet}^2$; wherein, in each instance, said $\text{C}_1\text{-C}_6$ alkyl and $\text{C}_3\text{-C}_8$ cycloalkyl may have one or more hydrogen atoms replaced with a fluorine atom.

The invention also provides, as preferred embodiment E12, a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of said compound or salt, wherein R^2 is:



wherein R³ is -CON(CH₃)₂, -CO(carboxypyrrolidinyl), -CO(hydroxypyrrolidinyl), -CO(methylpiperazinyl), -SO₂N(CH₃)₂, -CO(pyrrolo[3,4-b]pyrazinyl), -CO(isoindolinyl), -CO(methylpyrrolidinyl), -CON(CH₃)(CH₂CH₂CH₃), -CON(CH₃)(CH₂CH₃), -CON(CH₂CH₃)(CH₂CH₃), -CO(dimethylaminopyrrolidinyl), -CO(methyl-3,8-diazabicyclo[3.2.1]octanyl), -CO(methyl-2,5-diazabicyclo[2.2.1]heptanyl), -CO(methylaminocarbonylpyrrolidinyl), -CO(methylaminocarbonylpiperidinyl), -CON(CH₃)(cyclobutyl), -CON(CH₃)(methylpyrrolidinyl), -CON(CH₃)(methylpiperidinyl), -CON(CH₃)(CH₂CF₃), -CON(CH₃)(CH₂Ph), -CON(CH₃)(pyridylmethyl), -CO(methoxypyrrolidinyl), -CO(difluoropyrrolidinyl), -CO(fluoropyrrolidinyl), -CO(difluoropiperidinyl), -CO(aminocarbonylpiperidinyl), -CO(1,4-oxazepanyl), -CO(pyrimidinylazetidiny), -CO(pyridazinylazetidiny), -CON(CH₃)(cyclopentyl), -CO(dimethylaminoazetidiny), -CO(2-oxa-6-azaspiro[3.3]heptanyl), -CO(acetyl piperazinyl), -CONH(isopropyl), -CO(methyl-1,4-diazepanyl), -CO(ethylpiperazinyl), -CO(morpholinyl), -CON(CH₃)(t-butyl), -CO(pyrrolidinyl), -CON(CH₃)(isopropyl), -CO(hydroxymethylpyrrolidinyl), -CON(CH₃)(pyridyl), -CO(2-azabicyclo[2.2.1]heptanyl), -CO(2-azabicyclo[2.2.2]octanyl), -CO(3-azabicyclo[3.2.0]heptanyl), -CO(piperidinyl), -CO(1,4-diazabicyclo[3.2.2]nonanyl), -CO(2,3-dihydro-1H-pyrrolo[3,4-c]pyridinyl), -CO(6,7-dihydro-5H-pyrrolo[3,4-b]pyridinyl), -CO(6,7-dihydro-5H-pyrrolo[3,4-b]pyrazinyl), -CO(methylpyrrolidinyl), -CO(methyl-3-oxopiperazinyl), -CO(azetidiny), -CO(fluoroazetidiny) or methyl.

The invention also provides, as preferred embodiment E13, a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of said compound or salt, wherein R² is as defined in any one of embodiments E1, E2, E3, E4, E5, E6, E7, E8, E9, E10, E11 and E12 and R¹ is C₁-C₆ alkyl, C₃-C₈ cycloalkyl, Aryl¹, Aryl², Het¹, Het², -CO-(Aryl¹) or -SO₂-(Aryl¹), said C₁-C₆ alkyl and C₃-C₈ cycloalkyl being optionally substituted by 1 to 3 substituents independently selected from -CN, halo, -NH₂, -SH, -CONH₂, -SO₂NH₂, -NR⁶CONH₂, -OCONH₂ and -X-R^a; wherein, in each instance, said C₁-C₆ alkyl and C₃-C₈ cycloalkyl may have one or more hydrogen atoms replaced with a fluorine atom.

The invention also provides, as preferred embodiment E14, a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of said compound or salt, wherein R² is as defined in any one of embodiments E1, E2, E3, E4, E5, E6, E7, E8, E9, E10, E11 and E12 and R¹ is C₁-C₆ alkyl, C₃-C₈ cycloalkyl, Aryl¹, Aryl², Het¹, Het²,

-CO-(Aryl¹) or -SO₂-(Aryl¹), said C₁-C₆ alkyl and C₃-C₈ cycloalkyl being optionally substituted by 1 to 3 substituents independently selected from -NH₂, -NR⁶-(C₁-C₆ alkyl), -O-(C₁-C₆ alkyl), C₃-C₈ cycloalkyl, Aryl¹, Het¹, Het², Het³, Het⁴, -SO₂-(Het¹), -(C₁-C₆ alkylene)-(Het¹), -(C₁-C₆ alkylene)-(Aryl¹), -O-(C₁-C₆ alkylene)-(Aryl¹) and hydroxyl(C₃-C₈ cycloalkyl); wherein, in each instance, said C₁-C₆ alkyl and C₃-C₈ cycloalkyl may have one or more hydrogen atoms replaced with a fluorine atom.

The invention also provides, as preferred embodiment E15, a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of said compound or salt, wherein R² is as defined in any one of embodiments E1, E2, E3, E4, E5, E6, E7, E8, E9, E10, E11 and E12 and R¹ is C₁-C₆ alkyl optionally substituted by 1 to 3 substituents independently selected from -NH₂, -NR⁶-(C₁-C₆ alkyl), -O-(C₁-C₆ alkyl), C₃-C₈ cycloalkyl, Aryl¹, Het¹, Het², Het³, Het⁴, -SO₂-(Het¹), -(C₁-C₆ alkylene)-(Het¹), -(C₁-C₆ alkylene)-(Aryl¹), -O-(C₁-C₆ alkylene)-(Aryl¹) and hydroxyl(C₃-C₈ cycloalkyl); wherein, in each instance, said C₁-C₆ alkyl and C₃-C₈ cycloalkyl may have one or more hydrogen atoms replaced with a fluorine atom.

The invention also provides, as preferred embodiment E16, a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of said compound or salt, wherein R² is as defined in any one of embodiments E1, E2, E3, E4, E5, E6, E7, E8, E9, E10, E11 and E12 and R¹ is C₁-C₆ alkyl optionally substituted by 1 to 3 substituents independently selected from Aryl¹, Het³ and Het⁴.

The invention also provides, as preferred embodiment E17, a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of said compound or salt, wherein R² is as defined in any one of embodiments E1, E2, E3, E4, E5, E6, E7, E8, E9, E10, E11 and E12 and R¹ is C₁-C₃ alkyl substituted by 1 substituent selected from Aryl¹, Het³, Het⁴ and C₁-C₃ alkyl.

The invention also provides, as preferred embodiment E18, a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of said compound or salt, wherein R² is as defined in any one of embodiments E1, E2, E3, E4, E5, E6, E7, E8, E9, E10, E11 and E12 and R¹ is C₁-C₃ alkyl optionally substituted by 1 substituent selected from furanyl, imidazo[2,1-b][1,3]thiazolyl, phenyl, pyridinyl, C₁-C₃ alkyl and pyrimidinyl, said furanyl, imidazo[2,1-b][1,3]thiazolyl, phenyl, pyridinyl and pyrimidinyl being optionally substituted by methyl.

The invention also provides, as preferred embodiment E19, a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of said compound or salt, wherein R^2 is as defined in any one of embodiments E1, E2, E3, E4, E5, E6, E7, E8, E9, E10, E11 and E12 and R^1 is (methylfuranyl)propyl, (imidazo[2,1-b][1,3]thiazolyl)propyl, (phenyl)propyl, pyridinylpropyl, methylbutyl or pyrimidinylpropyl

The invention also provides, as preferred embodiment E20, a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of said compound or salt, wherein R^2 is as defined in any one of embodiments E1, E2, E3, E4, E5, E6, E7, E8, E9, E10, E11 and E12 and R^1 is 1-(5-methylfuran-2-yl)propyl, 1-(imidazo[2,1-b][1,3]thiazol-6-yl)propyl, 1-(phenyl)propyl, 1-(pyridin-2-yl)propyl, 3-methylbut-2-yl or 1-(pyrimidin-3-yl)propyl.

The invention also provides, as preferred embodiment E21, a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of said compound or salt, wherein R^2 is as defined in any one of embodiments E1, E2, E3, E4, E5, E6, E7, E8, E9, E10, E11 and E12 and R^1 is (a) $-\text{CHR}^x\text{R}^y$, wherein R^x is $\text{C}_1\text{-C}_5$ alkyl or $\text{C}_3\text{-C}_8$ cycloalkyl, said $\text{C}_1\text{-C}_5$ alkyl being optionally substituted by methoxy and R^y is Het^3 , Het^4 , phenyl, $-\text{CH}_2\text{OCH}_2\text{Ph}$ or $\text{C}_3\text{-C}_8$ cycloalkyl, said Het^3 , Het^4 and phenyl being optionally substituted by $\text{C}_1\text{-C}_6$ alkyl, halo, $\text{C}_1\text{-C}_6$ alkoxy, $-\text{CN}$ or $\text{C}_3\text{-C}_8$ cycloalkyl; or (b) $\text{C}_3\text{-C}_8$ cycloalkyl optionally substituted by phenyl or benzyl, said phenyl or benzyl being optionally substituted by halo; or (c) t-butyl, 3-methylbut-2-yl, isopropyl or pent-3-yl; wherein, in each instance, said $\text{C}_1\text{-C}_5$ alkyl, $\text{C}_1\text{-C}_6$ alkyl and $\text{C}_3\text{-C}_8$ cycloalkyl may have one or more hydrogen atoms replaced with a fluorine atom.

The invention also provides, as preferred embodiment E22, a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of said compound or salt, wherein R^2 is as defined in any one of embodiments E1, E2, E3, E4, E5, E6, E7, E8, E9, E10, E11 and E12 and R^1 is (a) $-\text{CHR}^x\text{R}^y$, wherein R^x is methyl, ethyl, isopropyl, methoxymethyl or cyclopropyl and R^y is $-\text{CH}_2\text{OCH}_2\text{Ph}$, cyclopropyl, phenyl, pyrimidinyl, furanyl, imidazo[2,1-b]thiazolyl, thiazolyl, pyridyl or pyrimidinyl, said phenyl, pyrimidinyl, furanyl, imidazo[2,1-b]thiazolyl, thiazolyl, pyridyl and pyrimidinyl being optionally substituted by $\text{C}_1\text{-C}_6$ alkyl, halo, $\text{C}_1\text{-C}_6$ alkoxy, $-\text{CN}$ or $\text{C}_3\text{-C}_8$ cycloalkyl; or (b) cyclobutyl, cyclopentyl or cyclohexyl, each being optionally substituted by phenyl, fluorophenyl or benzyl; or (c) t-butyl, 3-methylbut-2-yl, isopropyl or pent-3-yl; wherein said $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_3\text{-C}_8$ cycloalkyl, methyl, ethyl, isopropyl, methoxymethyl and cyclopropyl may have one or more hydrogen atoms replaced with a fluorine atom.

The invention also provides, as preferred embodiment E23, a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of said compound or salt, wherein R² is as defined in any one of embodiments E1, E2, E3, E4, E5, E6, E7, E8, E9, E10, E11 and E12 and R¹ is 1-phenylprop-1-yl, 1-pyridylprop-1-yl, 1-pyrazinylprop-1-yl, 3-methylbut-2-yl, 1-pyrimidinylprop-1-yl, 1-(methylphenyl)prop-1-yl, 1-(trifluoromethylphenyl)prop-1-yl, 1-(methoxyphenyl)prop-1-yl, 1-(dimethylphenyl)prop-1-yl, 1-(methylfuranyl)prop-1-yl, 1-((methyl)(isopropyl)furanyl)prop-1-yl, 1-phenylbut-1-yl, 1-(isopropylfuranyl)prop-1-yl, (fluorophenyl)(isopropyl)methyl, (trifluoromethyl)(furanyl)methyl, *tert*-butyl, (trifluoromethyl)(methoxyphenyl)methyl, 1-phenylbut-1-yl, (chloromethyl)(methyl)methyl, (chlorophenylmethyl)cyclopropyl, 1-(imidazo[2,1-*b*]thiazolyl)prop-1-yl, (trifluoromethyl)(phenyl)methyl, 1-(trifluoromethylphenyl)prop-1-yl, 1-(fluorophenyl)prop-1-yl, 1-(cyclopropylphenyl)prop-1-yl, 1-phenyl-2-methoxyprop-1-yl, difluorophenylcyclopentyl, phenylcyclopentyl, isopropyl, 1-thiazolylprop-1-yl, 1-(difluorophenyl)prop-1-yl, pent-3-yl, cyclopentyl, cyclohexyl, benzylcyclobutyl, 1-thiazolylprop-1-yl (phenyl)(isopropyl)methyl, (methyl)(methylisoxazolyl)methyl, (isopropyl)(triazolyl)methyl, phenylcyclopentyl, (methyl)((difluoro)(methyl)phenyl)methyl, (methyl)(pyridyl)methyl, fluorophenylcyclopentyl, 1-(difluorophenyl)prop-1-yl, dicyclopropylmethyl, 1-(fluorophenyl)prop-1-yl, 2-methyl-3-phenylprop-3-yl, (phenyl)(cyclopropyl)methyl, (methyl)((difluoro)(methyl)phenyl)methyl, 1-((fluoro)(methyl)phenyl)prop-1-yl, (isopropyl)(methoxyphenyl)methyl, 1-pyrimidinylprop-1-yl, 1-(dimethylphenyl)prop-1-yl, 1-(methylphenyl)prop-1-yl, 1-((fluoro)(methoxy)phenyl)prop-1-yl, 1-((fluoro)(trifluoromethyl)prop-1-yl, (cyclopropyl)(difluorophenyl)methyl, 1-chlorophenylprop-1-yl, 1-cyanophenylprop-1-yl, 1-(benzyloxymethyl)prop-1-yl, ((methyl)(chloro)phenyl)(methyl)methyl or 1-methoxyphenylprop-1-yl.

The present invention also provides: a method of treating a disease or condition mediated at least in part by activation of the CXCR-2 receptor, in a subject in need of such treatment, comprising administering to the subject a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of said compound or salt; the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of said compound or salt, for the manufacture of a medicament for treating a disease or condition mediated at least in part by activation of the CXCR-2 receptor; a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of said compound or salt, for use as a medicament; a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of said compound or salt, for use in the treatment of a disease or condition mediated at least in part by activation of the CXCR-2 receptor; a

pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of said compound or salt, and a pharmaceutically acceptable excipient; a pharmaceutical composition for the treatment of a disease or condition mediated at least in part by activation of the CXCR-2 receptor comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of said compound or salt.

The disease or condition mediated at least in part by activation of the CXCR-2 receptor is preferably an inflammatory disease, particularly an inflammatory respiratory condition such as allergic rhinitis, nasal congestion, rhinorrhea, perennial rhinitis, nasal inflammation, asthma of all types, chronic obstructive pulmonary disease (COPD), acute COPD exacerbations, chronic or acute bronchoconstriction, chronic bronchitis, small airways obstruction, emphysema, chronic eosinophilic pneumonia, acute respiratory distress syndrome (ARDS), exacerbation of airways hyper-reactivity consequent to other drug therapy, airways disease that is associated with pulmonary hypertension, acute lung injury (ALI), bronchiectasis, cystic fibrosis, idiopathic pulmonary fibrosis, bronchiolitis obliterans syndrome, bronchopulmonary dysplasia or sinusitis, most particularly asthma or chronic obstructive pulmonary disease.

Types of asthma include atopic asthma, non-atopic asthma, allergic asthma, atopic bronchial IgE-mediated asthma, bronchial asthma, essential asthma, true asthma, intrinsic asthma caused by pathophysiologic disturbances, extrinsic asthma caused by environmental factors, essential asthma of unknown or inapparent cause, bronchitic asthma, emphysematous asthma, exercise-induced asthma, allergen induced asthma, cold air induced asthma, occupational asthma, infective asthma caused by bacterial, fungal, protozoal, or viral infection, non-allergic asthma, incipient asthma, wheezy infant syndrome and bronchiolitis.

The treatment of asthma includes palliative treatment for the symptoms and conditions of asthma such as wheezing, coughing, shortness of breath, tightness in the chest, shallow or fast breathing, nasal flaring (nostril size increases with breathing), retractions (neck area and between or below the ribs moves inward with breathing), cyanosis (gray or bluish tint to skin, beginning around the mouth), runny or stuffy nose, and headache.

Other diseases and conditions of interest include rheumatoid arthritis, osteoarthritis, systemic lupus erythematosus, psoriasis, allergic conjunctivitis, atopic dermatitis, pruritus, cancer, endometriosis, inflammatory bowel disease (including Crohn's disease and ulcerative colitis), gastric ulceration, septic shock, endotoxic shock, sepsis, toxic shock syndrome, meningitis, stroke, cardiac and renal reperfusion injury, glomerulo-nephritis, glomerulo-thrombosis,

atherosclerosis, Alzheimer's disease, graft versus host reaction, allograft rejection, wound healing, spinal cord injury, multiple sclerosis, acute inflammatory pain, chronic inflammatory pain, acute neuropathic pain, chronic neuropathic pain and HIV infection.

The present invention also provides any of the uses, methods or compositions as defined above wherein the compound of formula (I), or pharmaceutically acceptable salt thereof, or pharmaceutically acceptable solvate of said compound or salt, is used in combination with another pharmacologically active compound, particularly one of the functionally-defined classes or specific compounds listed below. Generally, the compounds of the combination will be administered together as a formulation in association with one or more pharmaceutically acceptable excipients.

Suitable agents for use in combination therapy with a compound of formula (I), or pharmaceutically acceptable salt thereof, or pharmaceutically acceptable solvate of said compound or salt, particularly in the treatment of respiratory disease include:

- a 5-lipoxygenase activating protein (FLAP) antagonist;
- a leukotriene antagonist (LTRA) such as an antagonist of LTB₄, LTC₄, LTD₄, LTE₄, CysLT₁ or CysLT₂, e.g. montelukast or zafirlukast;
- a histamine receptor antagonist, such as a histamine type 1 receptor antagonist or a histamine type 2 receptor antagonist, e.g. loratidine, fexofenadine, desloratidine, levocetirizine, methapyrilene or cetirizine;
- an α 1-adrenoceptor agonist or an α 2-adrenoceptor agonist, e.g. phenylephrine, methoxamine, oxymetazoline or methylnorephrine;
- a muscarinic M3 receptor antagonist, e.g. tiotropium or ipratropium;
- a PDE inhibitor, such as a PDE3 inhibitor, a PDE4 inhibitor or a PDE5 inhibitor, e.g. theophylline, sildenafil, vardenafil, tadalafil, ibudilast, cilomilast or roflumilast;
- sodium cromoglycate or sodium nedocromil;
- a cyclooxygenase (COX) inhibitor, such as a non-selective inhibitor (e.g. aspirin or ibuprofen) or a selective COX-2 inhibitor (e.g. celecoxib or valdecoxib);
- a glucocorticosteroid, e.g. fluticasone, mometasone, dexamethasone, prednisolone, budesonide, ciclesonide or beclamethasone;
- an anti-inflammatory monoclonal antibody, e.g. infliximab, adalimumab, tanezumab, ranibizumab, bevacizumab or mepolizumab;
- a β 2 agonist, e.g. salmeterol, albuterol, salbutamol, fenoterol or formoterol, particularly a long-acting β 2 agonist;
- an integrin antagonist, e.g. natalizumab;
- an adhesion molecule inhibitor, such as a VLA-4 antagonist;

- a kinin B₁ or B₂ receptor antagonist;
- an immunosuppressive agent, such as an inhibitor of the IgE pathway (e.g. omalizumab) or cyclosporine;
- a matrix metalloprotease (MMP) inhibitor, such as an inhibitor of MMP-9 or MMP-12;
- a tachykinin NK₁, NK₂ or NK₃ receptor antagonist;
- a protease inhibitor, such as an inhibitor of elastase, chymase or cathepsin G;
- an adenosine A_{2a} receptor agonist;
- an adenosine A_{2b} receptor antagonist;
- a urokinase inhibitor;
- a dopamine receptor agonist (e.g. ropinirole), particularly a dopamine D2 receptor agonist (e.g. bromocriptine);
- a modulator of the NFκB pathway, such as an IKK inhibitor;
- a modulator of a cytokine signalling pathway such as an inhibitor of syk kinase, JAK kinase, p38 kinase, SPHK-1 kinase, Rho kinase, EGF-R or MK-2;
- a mucolytic, mucokinetic or anti-tussive agent
- an antibiotic;
- an antiviral agent;
- a vaccine;
- a chemokine;
- an epithelial sodium channel (ENaC) blocker or Epithelial sodium channel (ENaC) inhibitor;
- a nucleotide receptor agonist, such as a P2Y2 agonist;
- a thromboxane inhibitor;
- niacin;
- a 5-lipoxygenase (5-LO) inhibitor, e.g. Zileuton;
- an adhesion factor, such as VLAM, ICAM or ELAM;
- a CRTH2 receptor (DP₂) antagonist;
- a prostaglandin D₂ receptor (DP₁) antagonist;
- a haematopoietic prostaglandin D2 synthase (HPGDS) inhibitor;
- interferon-β;
- a soluble human TNF receptor, e.g. Etanercept;
- a HDAC inhibitor;
- a phosphoinositide 3-kinase gamma (PI3K_γ) inhibitor;
- a phosphoinositide 3-kinase delta (PI3KTM) inhibitor; and
- a CXCR-1 receptor antagonist;

including the pharmaceutically acceptable salts of the specifically named compounds and the pharmaceutically acceptable solvates of said specifically named compounds and their salts.

Besides being useful for human treatment, compounds of formula (I) are also useful for veterinary treatment of companion animals, exotic animals and farm animals.

When used in the present application, the following abbreviations have the meanings set out below:

APCI (in relation to mass spectrometry) is atmospheric pressure chemical ionization;
BOP is (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate;
Calc is calculated;
CDCl₃ is deuteriochloroform;
CO₂Et is ethyl carboxylate;
DCC is N,N'-dicyclohexylcarbodiimide;
DCM is dichloromethane;
DEA is diethylamine;
DIPEA is N,N-diisopropylethylamine;
DMA is N,N-dimethylacetamide;
DMF is dimethylformamide;
DMSO-d₆ is fully deuterated dimethyl sulphoxide;
EDC/EDCI is N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride;
ES (in relation to mass spectrometry) is electrospray;
Et is ethyl;
h is hour(s);
HATU is N,N,N',N'-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate;
HBTU is N,N,N',N'-tetramethyl-O-(1H-benzotriazol-1-yl)uronium hexafluorophosphate;
HCl is hydrochloric acid;
¹H NMR or ¹H NMR is proton nuclear magnetic resonance;
HOAt is 1-hydroxy-7-azabenzotriazole;
HOBt is 1-hydroxybenzotriazole;
HPLC is high performance liquid chromatography;
H₂SO₄ is sulphuric acid;
IPA is isopropyl alcohol;
iPr is isopropyl;
K₂CO₃ is potassium carbonate;
KMnO₄ is potassium permanganate;

LCMS is liquid chromatography mass spectrometry;

LRMS is low resolution mass spectrometry;

NMM is 4-methylmorpholine;

Me is methyl;

MeCN is acetonitrile;

MeOD-d₄ is fully deuterated methanol;

MgSO₄ is magnesium sulfate;

min is minute(s);

MS is mass spectroscopy;

NaCl is sodium chloride;

Obs is observed;

Pd(OAc)₂ is palladium(II)acetate

RT is retention time;

TBTU is O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate;

TEA is triethylamine;

TFA is trifluoroacetic acid;

THF is tetrahydrofuran.

Unless otherwise defined herein, scientific and technical terms used in connection with the present invention have the meanings that are commonly understood by those of ordinary skill in the art.

The phrase "therapeutically effective" is intended to qualify the amount of compound or pharmaceutical composition, or the combined amount of active ingredients in the case of combination therapy. This amount or combined amount will achieve the goal of treating the relevant condition.

The term "treatment," as used herein to describe the present invention and unless otherwise qualified, means administration of the compound, pharmaceutical composition or combination to effect preventative, palliative, supportive, restorative or curative treatment. The term treatment encompasses any objective or subjective improvement in a subject with respect to a relevant condition or disease.

The term "preventive treatment," as used herein to describe the present invention, means that the compound, pharmaceutical composition or combination is administered to a subject to inhibit or stop the relevant condition from occurring in a subject, particularly in a subject or member of a population that is significantly predisposed to the relevant condition.

The term “palliative treatment,” as used herein to describe the present invention, means that the compound, pharmaceutical composition or combination is administered to a subject to remedy signs and/or symptoms of a condition, without necessarily modifying the progression of, or underlying etiology of, the relevant condition.

The term “supportive treatment,” as used herein to describe the present invention, means that the compound, pharmaceutical composition or combination is administered to a subject as a part of a regimen of therapy, but that such therapy is not limited to administration of the compound, pharmaceutical composition or combination. Unless otherwise expressly stated, supportive treatment may embrace preventive, palliative, restorative or curative treatment, particularly when the compounds or pharmaceutical compositions are combined with another component of supportive therapy.

The term “restorative treatment,” as used herein to describe the present invention, means that the compound, pharmaceutical composition or combination is administered to a subject to modify the underlying progression or etiology of a condition. Non-limiting examples include an increase in forced expiratory volume in one second (FEV₁) for lung disorders, decreased rate of a decline in lung function over time, inhibition of progressive nerve destruction, reduction of biomarkers associated and correlated with diseases or disorders, a reduction in relapses, improvement in quality of life, reduced time spent in hospital during an acute exacerbation event and the like.

The term “curative treatment,” as used herein to describe the present invention, means that compound, pharmaceutical composition or combination is administered to a subject for the purpose of bringing the disease or disorder into complete remission, or that the disease or disorder is undetectable after such treatment.

The term “selective”, when used to describe a functionally-defined receptor ligand or enzyme inhibitor means selective for the defined receptor or enzyme subtype as compared with other receptor or enzyme subtypes in the same family. For instance, a selective PDE5 inhibitor is a compound which inhibits the PDE5 enzyme subtype more potently than any other PDE enzyme subtype. Such selectivity is preferably at least 2 fold (as measured using conventional binding assays), more preferably at least 10 fold, most preferably at least 100 fold.

The term “alkyl”, alone or in combination, means an acyclic, saturated hydrocarbon group of the formula C_nH_{2n+1} which may be linear or branched. Examples of such groups include methyl,

ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl and hexyl. Unless otherwise specified, an alkyl group comprises from 1 to 6 carbon atoms.

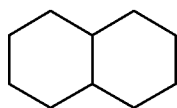
The term "alkylene" means a bivalent acyclic, saturated hydrocarbon group of the formula C_nH_{2n} which may be linear or branched. Example of such groups include $-CH_2-$, $-CH(CH_3)-$, $-CH_2CH_2-$, $-CH(CH_3)CH_2-$, $-CH(CH_3)CH(CH_3)-$ and $-CH_2CH_2CH_2-$. Unless otherwise specified, an alkylene group comprises from 1 to 6 carbon atoms.

The carbon atom content of alkyl and various other hydrocarbon-containing moieties is indicated by a prefix designating a lower and upper number of carbon atoms in the moiety, that is, the prefix C_i-C_j indicates a moiety of the integer "i" to the integer "j" carbon atoms, inclusive. Thus, for example, C_1-C_6 alkyl refers to alkyl of one to six carbon atoms, inclusive.

The term "hydroxy," as used herein, means an OH radical.

Het¹ and Het⁵ are saturated or partially saturated (i.e. non aromatic) heterocycles and may be attached via a ring nitrogen atom (when the heterocycle is attached to a carbon atom) or a ring carbon atom (in all cases). Equally, when substituted, the substituent may be located on a ring nitrogen atom (if the substituent is joined through a carbon atom) or a ring carbon atom (in all cases). Specific examples include oxiranyl, aziridinyl, oxetanyl, azetidiny, tetrahydrofuranyl, pyrrolidinyl, tetrahydropyranyl, piperidinyl, 1,4-dioxanyl, morpholinyl, piperazinyl, azepanyl, oxepanyl, oxazepanyl and diazepinyl.

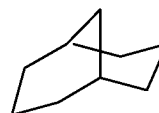
Het² and Het⁶ are saturated or partially saturated heterocycles and may be attached via a ring nitrogen atom (when the heterocycle is attached to a carbon atom) or a ring carbon atom (in all cases). Equally, when substituted, the substituent may be located on a ring nitrogen atom (if the substituent is joined through a carbon atom) or a ring carbon atom (in all cases). Het² and Het⁶ are multicyclic heterocyclic groups, containing two or more rings. Such rings may be joined so as to create a bridged, fused or spirofused ring system, as illustrated with two six-membered rings below (heteroatoms not shown):



fused



spirofused



bridged

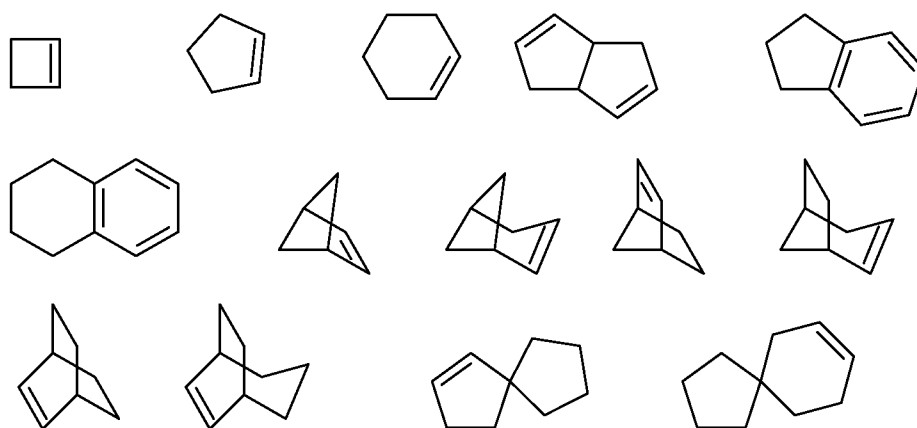
Het² and Het⁶ may be fully saturated or partially unsaturated, i.e. they may have one or more degrees of unsaturation but may not be fully aromatic. In the case of a fused ring system, one of the rings may be aromatic but not both of them. An example of Het² is tropanyl (azabicyclo[3.2.1]octanyl).

Het³ and Het⁷ are aromatic heterocycles and may be attached via a ring carbon atom (in all cases) or a ring nitrogen atom with an appropriate valency (when the heterocycle is attached to a carbon atom). Equally, when substituted, the substituent may be located on a ring carbon atom (in all cases) or a ring nitrogen atom with an appropriate valency (if the substituent is joined through a carbon atom). Specific examples include thienyl, furanyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridyl, pyridaziny, pyrimidinyl and pyrazinyl.

Het⁴ and Het⁸ are aromatic heterocycles and may be attached via a ring carbon atom (in all cases) or a ring nitrogen atom with an appropriate valency (when the heterocycle is attached to a carbon atom). Equally, when substituted, the substituent may be located on a ring carbon atom (in all cases) or a ring nitrogen atom with an appropriate valency (if the substituent is joined through a carbon atom). Het⁴ and Het⁸ are aromatic and are therefore necessarily fused bicycles. Specific examples include imidazo[2,1-b][1,3]thiazolyl, benzofuranyl, benzothienyl, indolyl, benzimidazolyl, indazolyl, benzotriazolyl, pyrrolo[2,3-b]pyridyl, pyrrolo[2,3-c]pyridyl, pyrrolo[3,2-c]pyridyl, pyrrolo[3,2-b]pyridyl, imidazo[4,5-b]pyridyl, imidazo[4,5-c]pyridyl, pyrazolo[4,3-d]pyridyl, pyrazolo[4,3-c]pyridyl, pyrazolo[3,4-c]pyridyl, pyrazolo[3,4-b]pyridyl, isoindolyl, indazolyl, purinyl, indoliziny, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, pyrazolo[1,5-a]pyridyl, pyrrolo[1,2-b]pyridaziny, imidazo[1,2-c]pyrimidinyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, 1,6-naphthyridinyl, 1,7-naphthyridinyl, 1,8-naphthyridinyl, 1,5-naphthyridinyl, 2,6-naphthyridinyl, 2,7-naphthyridinyl, pyrido[3,2-d]pyrimidinyl, pyrido[4,3-d]pyrimidinyl, pyrido[3,4-d]pyrimidinyl, pyrido[2,3-d]pyrimidinyl, pyrido[2,3-d]pyrazinyl, pyrido[3,4-b]pyrazinyl, pyrimido[5,4-d]pyrimidinyl, pyrazino[2,3-b]pyrazinyl and pyrimido[4,5-d]pyrimidine.

Aryl² and Aryl⁴ are each a 3 to 8-membered monocyclic or a 6 to 12-membered bicyclic carbocycle which is partially unsaturated. The 6 to 12-membered bicyclic carbocycle may be fused, spirofused or bridged (see above). In this context, partially unsaturated means that the carbocycle includes at least one double bond but is not, as a whole, aromatic. A 6-membered monocyclic carbocycle with three double bonds would therefore not fall within the definition since it would amount to a phenyl group. Nor would a 10-membered bicyclic carbocycle with two fused six-membered rings and five double bonds fall within the definition since it would amount

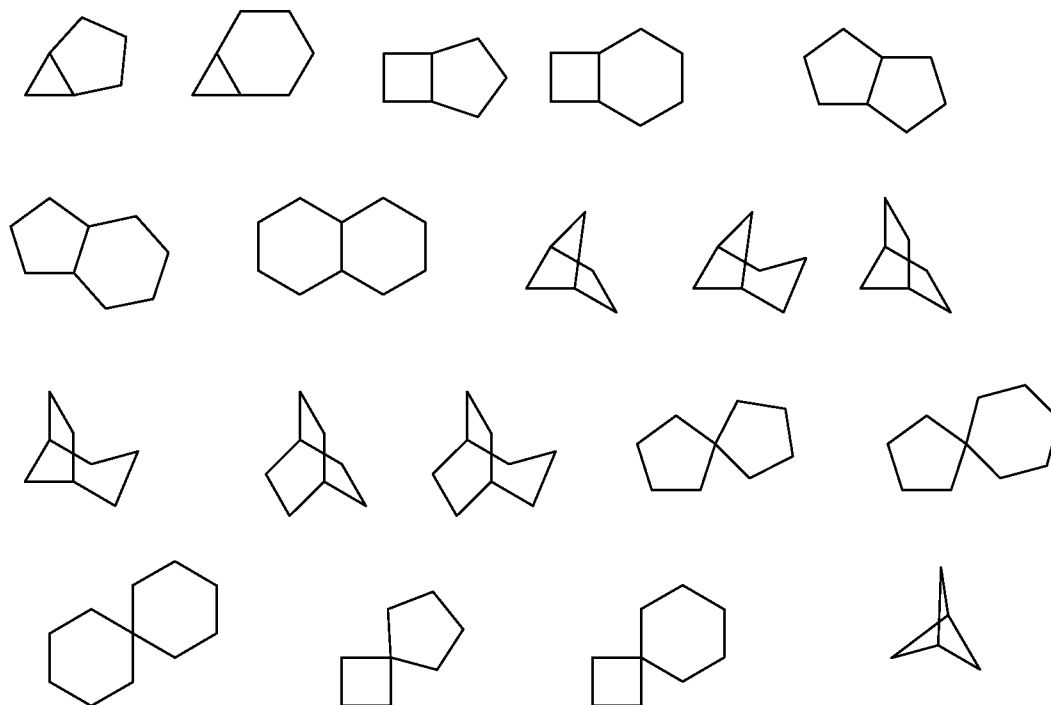
to a naphthyl group. In the case of a fused bicyclic carbocycle, however, it is possible for one of the rings to be aromatic. The carbocycle may be attached through a fully saturated or an unsaturated carbon atom. Some examples of Aryl² and Aryl⁴ are as follows:



The term "cycloalkyl" means a means a monocyclic, saturated hydrocarbon group of the formula C_nH_{2n-1} . Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl. Unless otherwise specified, a cycloalkyl group comprises from 3 to 8 carbon atoms.

The term bicycloalkyl means a bicyclic, saturated hydrocarbon group of the formula C_nH_{2n-3} in which the two rings are joined in a fused, spiro-fused or bridged manner (see above). The following groups are illustrative of C_5 - C_{12} bicycloalkyl (note that as drawn, these groups have an extra hydrogen atom where the linking bond would be):

25



The moieties C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, C_1 - C_6 alkylene and C_6 - C_{12} bicycloalkyl, whether these groups are named individually or as part of a composite group, may have one or more hydrogen atoms replaced by a fluorine atom. Thus, for example, the C_1 alkyl group methyl may be substituted with 1-3 fluorine atoms to form $-CH_2F$, $-CHF_2$ or CF_3 .

The term “oxo” means a doubly bonded oxygen.

The term “alkoxy” means a radical comprising an alkyl radical that is bonded to an oxygen atom, such as a methoxy radical. Examples of such radicals include methoxy, ethoxy, propoxy, isopropoxy, butoxy and tert-butoxy.

As used herein, the terms “co-administration”, “co-administered” and “in combination with”, referring to a combination of a compound of formula (I) and one or more other therapeutic agents, includes the following:

- simultaneous administration of such a combination of a compound of formula (I) and a further therapeutic agent to a patient in need of treatment, when such components are formulated together into a single dosage form which releases said components at substantially the same time to said patient,

- substantially simultaneous administration of such a combination of a compound of formula(I) and a further therapeutic agent to a patient in need of treatment, when such components are formulated apart from each other into separate dosage forms which are taken at substantially the same time by said patient, whereupon said components are released at substantially the same time to said patient,
- sequential administration of such a combination of a compound of formula (I) and a further therapeutic agent to a patient in need of treatment, when such components are formulated apart from each other into separate dosage forms which are taken at consecutive times by said patient with a significant time interval between each administration, whereupon said components are released at substantially different times to said patient; and
- sequential administration of such a combination of a compound of formula (I) and a further therapeutic agent to a patient in need of treatment, when such components are formulated together into a single dosage form which releases said components in a controlled manner.

The term 'excipient' is used herein to describe any ingredient other than a compound of formula (I). The choice of excipient will to a large extent depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form. The term "excipient" encompasses diluent, carrier or adjuvant.

One way of carrying out the invention is to administer a compound of formula (I) in the form of a prodrug. Thus, certain derivatives of a compound of formula (I) which may have little or no pharmacological activity themselves can, when administered into or onto the body, be converted into a compound of formula (I) having the desired activity, for example by hydrolytic cleavage, particularly hydrolytic cleavage promoted by an esterase or peptidase enzyme. Such derivatives are referred to as 'prodrugs'. Further information on the use of prodrugs may be found in 'Prodrugs as Novel Delivery Systems', Vol. 14, *ACS Symposium Series* (T. Higuchi and W. Stella) and 'Bioreversible Carriers in Drug Design', Pergamon Press, 1987 (Ed. E. B. Roche, American Pharmaceutical Association). Reference can also be made to *Nature Reviews/Drug Discovery*, 2008, **7**, 355 and *Current Opinion in Drug Discovery and Development*, 2007, **10**, 550.

Prodrugs in accordance with the invention can, for example, be produced by replacing appropriate functionalities present in the compounds of formula (I) with certain moieties known to those skilled in the art as 'pro-moieties' as described, for example, in 'Design of Prodrugs' by H. Bundgaard (Elsevier, 1985).

Thus, a prodrug in accordance with the invention is (a) an ester or amide derivative of a carboxylic acid in a compound of formula (I); (b) an ester, carbonate, carbamate, phosphate or ether derivative of a hydroxyl group in a compound of formula (I); (c) an amide, imine, carbamate or amine derivative of an amino group in a compound of formula (I); (d) a thioester, thiocarbonate, thiocarbamate or sulphide derivatives of a thiol group in a compound of formula (I); or (e) an oxime or imine derivative of a carbonyl group in a compound of formula (I).

Some specific examples of prodrugs in accordance with the invention include:

- (i) where the compound of formula (I) contains a carboxylic acid functionality (-COOH), an ester thereof, such as a compound wherein the hydrogen of the carboxylic acid functionality of the compound of formula (I) is replaced by C₁-C₈ alkyl (e.g. ethyl) or (C₁-C₈ alkyl)C(=O)OCH₂- (e.g. ^tBuC(=O)OCH₂-);
- (ii) where the compound of formula (I) contains an alcohol functionality (-OH), an ester thereof, such as a compound wherein the hydrogen of the alcohol functionality of the compound of formula (I) is replaced by -CO(C₁-C₈ alkyl) (e.g. methylcarbonyl) or the alcohol is esterified with an amino acid;
- (iii) where the compound of formula (I) contains an alcohol functionality (-OH), an ether thereof, such as a compound wherein the hydrogen of the alcohol functionality of the compound of formula (I) is replaced by (C₁-C₈ alkyl)C(=O)OCH₂- or -CH₂OP(=O)(OH)₂;
- (iv) where the compound of formula (I) contains an alcohol functionality (-OH), a phosphate thereof, such as a compound wherein the hydrogen of the alcohol functionality of the compound of formula (I) is replaced by -P(=O)(OH)₂ or -P(=O)(ONa)₂ or -P(=O)(O⁻)₂Ca²⁺;
- (v) where the compound of formula (I) contains a primary or secondary amino functionality (-NH₂ or -NHR where R ≠ H), an amide thereof, for example, a compound wherein, as the case may be, one or both hydrogens of the amino functionality of the compound of formula (I) is/are replaced by (C₁-C₁₀)alkanoyl, -COCH₂NH₂ or the amino group is derivatised with an amino acid;
- (vi) where the compound of formula (I) contains a primary or secondary amino functionality (-NH₂ or -NHR where R ≠ H), an amine thereof, for example, a compound wherein, as

the case may be, one or both hydrogens of the amino functionality of the compound of formula (I) is/are replaced by $-\text{CH}_2\text{OP}(=\text{O})(\text{OH})_2$.

Certain compounds of formula (I) may themselves act as prodrugs of other compounds of formula (I). It is also possible for two compounds of formula (I) to be joined together in the form of a prodrug. In certain circumstances, a prodrug of a compound of formula (I) may be created by internally linking two functional groups in a compound of formula (I), for instance by forming a lactone.

References below to compounds of formula (I) are taken to include the compounds themselves and prodrugs thereof. The invention includes such compounds of formula (I) as well as pharmaceutically acceptable salts of such compounds and pharmaceutically acceptable solvates of said compounds and salts.

Pharmaceutically acceptable salts of the compounds of formula (I) include acid addition and base salts.

Suitable acid addition salts are formed from acids which form non-toxic salts. Examples include the acetate, adipate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulfate/sulfate, borate, camsylate, citrate, cyclamate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulfate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, pyroglutamate, saccharate, stearate, succinate, tannate, tartrate, tosylate, trifluoroacetate, naphthalene-1,5-disulfonic acid and xinofoate salts.

Suitable base salts are formed from bases which form non-toxic salts. Examples include the aluminium, arginine, benzathine, calcium, choline, diethylamine, diolamine, glycine, lysine, magnesium, meglumine, olamine, potassium, sodium, tromethamine and zinc salts.

Hemisalts of acids and bases may also be formed, for example, hemisulfate and hemicalcium salts. For a review on suitable salts, see Handbook of Pharmaceutical Salts: Properties, Selection, and Use by Stahl and Wermuth (Wiley-VCH, 2002).

Pharmaceutically acceptable salts of compounds of formula (I) may be prepared by one or more of three methods:

- (i) by reacting the compound of formula (I) with the desired acid or base;
- (ii) by removing an acid- or base-labile protecting group from a suitable precursor of the compound of formula (I) or by ring-opening a suitable cyclic precursor, for example, a lactone or lactam, using the desired acid or base; or
- (iii) by converting one salt of the compound of formula (I) to another by reaction with an appropriate acid or base or by means of a suitable ion exchange column.

All three reactions are typically carried out in solution. The resulting salt may precipitate out and be collected by filtration or may be recovered by evaporation of the solvent. The degree of ionisation in the resulting salt may vary from completely ionised to almost non-ionised.

The compounds of formula (I), and pharmaceutically acceptable salts thereof, may exist in unsolvated and solvated forms. The term 'solvate' is used herein to describe a molecular complex comprising the compound of formula (I), or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable solvent molecules, for example, ethanol. The term 'hydrate' is employed when said solvent is water.

A currently accepted classification system for organic hydrates is one that defines isolated site, channel, or metal-ion coordinated hydrates - see Polymorphism in Pharmaceutical Solids by K. R. Morris (Ed. H. G. Brittain, Marcel Dekker, 1995). Isolated site hydrates are ones in which the water molecules are isolated from direct contact with each other by intervening organic molecules. In channel hydrates, the water molecules lie in lattice channels where they are next to other water molecules. In metal-ion coordinated hydrates, the water molecules are bonded to the metal ion.

When the solvent or water is tightly bound, the complex will have a well-defined stoichiometry independent of humidity. When, however, the solvent or water is weakly bound, as in channel solvates and hygroscopic compounds, the water/solvent content will be dependent on humidity and drying conditions. In such cases, non-stoichiometry will be the norm.

Also included within the scope of the invention are multi-component complexes (other than salts and solvates) wherein the drug and at least one other component are present in stoichiometric or non-stoichiometric amounts. Complexes of this type include clathrates (drug-host inclusion complexes) and co-crystals. The latter are typically defined as crystalline complexes of neutral molecular constituents which are bound together through non-covalent interactions, but could also be a complex of a neutral molecule with a salt. Co-crystals may be prepared by melt

crystallisation, by recrystallisation from solvents, or by physically grinding the components together - see Chem Commun, 17, 1889-1896, by O. Almarsson and M. J. Zaworotko (2004). For a general review of multi-component complexes, see J Pharm Sci, 64 (8), 1269-1288, by Halebian (August 1975).

The compounds of the invention may exist in a continuum of solid states ranging from fully amorphous to fully crystalline. The term 'amorphous' refers to a state in which the material lacks long range order at the molecular level and, depending upon temperature, may exhibit the physical properties of a solid or a liquid. Typically such materials do not give distinctive X-ray diffraction patterns and, while exhibiting the properties of a solid, are more formally described as a liquid. Upon heating, a change from solid to liquid properties occurs which is characterised by a change of state, typically second order ('glass transition'). The term 'crystalline' refers to a solid phase in which the material has a regular ordered internal structure at the molecular level and gives a distinctive X-ray diffraction pattern with defined peaks. Such materials when heated sufficiently will also exhibit the properties of a liquid, but the change from solid to liquid is characterised by a phase change, typically first order ('melting point').

The compounds of formula (I) may also exist in a mesomorphic state (mesophase or liquid crystal) when subjected to suitable conditions. The mesomorphic state is intermediate between the true crystalline state and the true liquid state (either melt or solution). Mesomorphism arising as the result of a change in temperature is described as 'thermotropic' and that resulting from the addition of a second component, such as water or another solvent, is described as 'lyotropic'. Compounds that have the potential to form lyotropic mesophases are described as 'amphiphilic' and consist of molecules which possess an ionic (such as $\text{-COO}^-\text{Na}^+$, $\text{-COO}^-\text{K}^+$, or $\text{-SO}_3^-\text{Na}^+$) or non-ionic (such as $\text{-N}^+\text{N}(\text{CH}_3)_3$) polar head group. For more information, see Crystals and the Polarizing Microscope by N. H. Hartshorne and A. Stuart, 4th Edition (Edward Arnold, 1970).

Hereinafter all references to compounds of formula (I) include references to pharmaceutically acceptable salts, solvates, multi-component complexes and liquid crystals thereof and to solvates, multi-component complexes and liquid crystals of pharmaceutically acceptable salts thereof.

The compounds of formula (I) may exhibit polymorphism and/or one or more kinds of isomerism (e.g. optical, geometric, anisotropic or tautomeric isomerism). The compounds of formula (I) may also be isotopically labelled. Such variation is implicit to the compounds of formula (I)

defined as they are by reference to their structural features and therefore within the scope of the invention.

Compounds of formula (I) containing one or more asymmetric carbon atoms can exist as two or more stereoisomers. Where a compound of formula (I) contains an alkenyl or alkenylene group, geometric cis/trans (or Z/E) isomers are possible. Where structural isomers are interconvertible via a low energy barrier, tautomeric isomerism ('tautomerism') can occur. This can take the form of proton tautomerism in compounds of formula (I) containing, for example, an imino, keto, or oxime group, or so-called valence tautomerism in compounds which contain an aromatic moiety. It follows that a single compound may exhibit more than one type of isomerism.

The pharmaceutically acceptable salts of compounds of formula (I) may also contain a counterion which is optically active (e.g. d-lactate or l-lysine) or racemic (e.g. dl-tartrate or dl-arginine).

Cis/trans isomers may be separated by conventional techniques well known to those skilled in the art, for example, chromatography and fractional crystallisation.

Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC). Alternatively, the racemate (or a racemic precursor) may be reacted with a suitable optically active compound, for example, an alcohol, or, in the case where the compound of formula (I) contains an acidic or basic moiety, a base or acid such as 1-phenylethylamine or tartaric acid. The resulting diastereomeric mixture may be separated by chromatography and/or fractional crystallization and one or both of the diastereoisomers converted to the corresponding pure enantiomer(s) by means well known to a skilled person. Chiral compounds of formula (I) (and chiral precursors thereof) may be obtained in enantiomerically-enriched form using chromatography, typically HPLC, on an asymmetric resin with a mobile phase consisting of a hydrocarbon, typically heptane or hexane, containing from 0 to 50% by volume of isopropanol, typically from 2% to 20%, and from 0 to 5% by volume of an alkylamine, typically 0.1% diethylamine. Concentration of the eluate affords the enriched mixture. Chiral chromatography using sub- and supercritical fluids may be employed. Methods for chiral chromatography useful in some embodiments of the present invention are known in the art (see, for example, Smith, Roger M., Loughborough University, Loughborough, UK; *Chromatographic Science Series* (1998), 75 (Supercritical Fluid Chromatography with Packed Columns), pp. 223-249 and references cited therein). In some relevant examples herein, columns were obtained from

Chiral Technologies, Inc, West Chester, Pennsylvania, USA, a subsidiary of Daicel[®] Chemical Industries, Ltd., Tokyo, Japan.

When any racemate crystallises, crystals of two different types are possible. The first type is the racemic compound (true racemate) referred to above wherein one homogeneous form of crystal is produced containing both enantiomers in equimolar amounts. The second type is the racemic mixture or conglomerate wherein two forms of crystal are produced in equimolar amounts each comprising a single enantiomer. While both of the crystal forms present in a racemic mixture have identical physical properties, they may have different physical properties compared to the true racemate. Racemic mixtures may be separated by conventional techniques known to those skilled in the art - see, for example, Stereochemistry of Organic Compounds by E. L. Eliel and S. H. Wilen (Wiley, 1994).

The present invention includes all pharmaceutically acceptable isotopically-labelled compounds of formula (I) wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number which predominates in nature. Isotopically-labelled compounds of formula (I) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labelled reagent in place of the non-labelled reagent previously employed. In particular, hydrogen atoms may be replaced by deuterium atoms since such deuterated compounds are sometimes more resistant to metabolism.

Also included within the scope of the invention are active metabolites of compounds of formula (I), that is, compounds formed in vivo upon administration of the drug, often by oxidation or dealkylation. Some examples of metabolites in accordance with the invention include

- (i) where the compound of formula (I) contains a methyl group, an hydroxymethyl derivative thereof ($-\text{CH}_3 \rightarrow -\text{CH}_2\text{OH}$);
- (ii) where the compound of formula (I) contains an alkoxy group, an hydroxy derivative thereof ($-\text{OR} \rightarrow -\text{OH}$);
- (iii) where the compound of formula (I) contains a tertiary amino group, a secondary amino derivative thereof ($-\text{NRR}' \rightarrow -\text{NHR}$ or $-\text{NHR}'$);

- (iv) where the compound of formula (I) contains a secondary amino group, a primary derivative thereof (-NHR -> -NH₂);
- (v) where the compound of formula (I) contains a phenyl moiety, a phenol derivative thereof (-Ph -> -PhOH); and
- (vi) where the compound of formula (I) contains an amide group, a carboxylic acid derivative thereof (-CONH₂ -> COOH).

For administration to human patients, the total daily dose of a compound of formula (I) is typically in the range of 0.01mg to 500mg depending, of course, on the mode of administration. In another embodiment of the present invention, the total daily dose of a compound of formula (I) is typically in the range of 0.1 mg to 300mg. In yet another embodiment of the present invention, the total daily dose of a compound of formula (I) is typically in the range of 1mg to 30mg. The total daily dose may be administered in single or divided doses and may, at the physician's discretion, fall outside of the typical range given herein. These dosages are based on an average human subject having a weight of about 65kg to 70kg. The physician will readily be able to determine doses for subjects whose weight falls outside this range, such as infants and the elderly.

In the case of dry powder inhalers and aerosols, the dosage unit is determined by means of a prefilled capsule, blister or pocket or by a system that utilises a gravimetrically fed dosing chamber. Units in accordance with the invention are typically arranged to administer a metered dose or "puff" containing from 1 to 5000 µg of drug. The overall daily dose will typically be in the range 1µg to 20mg which may be administered in a single dose or, more usually, as divided doses throughout the day.

A compound of formula (I) can be administered per se, or in the form of a pharmaceutical composition, which, as active constituent contains an efficacious dose of at least one compound of the invention, in addition to customary pharmaceutically innocuous excipients and/or additives.

Pharmaceutical compositions suitable for the delivery of compounds of the present invention and methods for their preparation will be readily apparent to those skilled in the art. Such compositions and methods for their preparation may be found, for example, in Remington's Pharmaceutical Sciences, 19th Edition (Mack Publishing Company, 1995).

Compounds of formula (I) are preferably administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, or buccal or sublingual administration may be employed by which the compound enters the blood stream directly from the mouth. Formulations suitable for oral administration include solid formulations such as tablets, capsules containing particulates, liquids, or powders, lozenges (including liquid-filled), chews, multi- and nano-particulates, gels, solid solution, liposome, films, ovules, sprays and liquid formulations.

In respect of the present invention, in all its embodiments, oral administration is preferred. Oral administration in the form of a tablet or capsule is particularly preferred.

Liquid formulations include suspensions, solutions, syrups and elixirs. Such formulations may be employed as fillers in soft or hard capsules and typically comprise a carrier, for example, water, ethanol, polyethylene glycol, propylene glycol, methylcellulose, or a suitable oil, and one or more emulsifying agents and/or suspending agents. Liquid formulations may also be prepared by the reconstitution of a solid, for example, from a sachet.

Compounds of formula (I) may also be used in fast-dissolving, fast-disintegrating dosage forms such as those described in Expert Opinion in Therapeutic Patents, 11 (6), 981-986, by Liang and Chen (2001).

For tablet dosage forms, depending on dose, the drug may make up from 1 weight % to 80 weight % of the dosage form, more typically from 5 weight % to 60 weight % of the dosage form. In addition to the drug, tablets generally contain a disintegrant. Examples of disintegrants include sodium starch glycolate, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, croscarmellose sodium, crospovidone, polyvinylpyrrolidone, methyl cellulose, microcrystalline cellulose, lower alkyl-substituted hydroxypropyl cellulose, starch, pregelatinised starch and sodium alginate. Generally, the disintegrant will comprise from 1 weight % to 25 weight %. In one embodiment of the present invention, the disintegrant will comprise from 5 weight % to 20 weight % of the dosage form. Binders are generally used to impart cohesive qualities to a tablet formulation. Suitable binders include microcrystalline cellulose, gelatin, sugars, polyethylene glycol, natural and synthetic gums, polyvinylpyrrolidone, pregelatinised starch, hydroxypropyl cellulose and hydroxypropyl methylcellulose. Tablets may also contain diluents, such as lactose (monohydrate, spray-dried monohydrate, anhydrous and the like), mannitol, xylitol, dextrose, sucrose, sorbitol, microcrystalline cellulose, starch and dibasic calcium phosphate dihydrate. Tablets may also optionally comprise surface active agents, such as sodium lauryl sulfate and polysorbate 80, and glidants such as silicon dioxide and talc. When

present, surface active agents may comprise from 0.2 weight % to 5 weight % of the tablet, and glidants may comprise from 0.2 weight % to 1 weight % of the tablet. Tablets also generally contain lubricants such as magnesium stearate, calcium stearate, zinc stearate, sodium stearyl fumarate, and mixtures of magnesium stearate with sodium lauryl sulfate. Lubricants generally comprise from 0.25 weight % to 10 weight %. In one embodiment of the present invention, lubricants comprise from 0.5 weight % to 3 weight % of the tablet. Other possible ingredients include anti-oxidants, colourants, flavouring agents, preservatives and taste-masking agents.

Exemplary tablets contain up to about 80% drug, from about 10 weight % to about 90 weight % binder, from about 0 weight % to about 85 weight % diluent, from about 2 weight % to about 10 weight % disintegrant, and from about 0.25 weight % to about 10 weight % lubricant.

Tablet blends may be compressed directly or by roller to form tablets. Tablet blends or portions of blends may alternatively be wet-, dry-, or melt-granulated, melt congealed, or extruded before tableting. The final formulation may comprise one or more layers and may be coated or uncoated; it may even be encapsulated. Formulations of tablets are discussed in *Pharmaceutical Dosage Forms: Tablets*, Vol. 1, by H. Lieberman and L. Lachman (Marcel Dekker, New York, 1980).

Consumable oral films for human or veterinary use are typically pliable water-soluble or water-swellaable thin film dosage forms which may be rapidly dissolving or mucoadhesive and typically comprise a compound of formula (I), a film-forming polymer, a binder, a solvent, a humectant, a plasticiser, a stabiliser or emulsifier, a viscosity-modifying agent and a solvent. Some components of the formulation may perform more than one function. The film-forming polymer may be selected from natural polysaccharides, proteins, or synthetic hydrocolloids and is typically present in the range 0.01 to 99 weight %, more typically in the range 30 to 80 weight %. Other possible ingredients include anti-oxidants, colorants, flavourings and flavour enhancers, preservatives, salivary stimulating agents, cooling agents, co-solvents (including oils), emollients, bulking agents, anti-foaming agents, surfactants and taste-masking agents. Films in accordance with the invention are typically prepared by evaporative drying of thin aqueous films coated onto a peelable backing support or paper. This may be done in a drying oven or tunnel, typically a combined coater dryer, or by freeze-drying or vacuuming.

Solid formulations for oral administration may be formulated to be immediate and/or modified release. Modified release includes delayed, sustained, pulsed, controlled, targeted and programmed release. Suitable modified release formulations for the purposes of the invention are described in US Patent No. 6,106,864. Details of other suitable release technologies such

as high energy dispersions and osmotic and coated particles are to be found in Pharmaceutical Technology On-line, 25(2), 1-14, by Verma et al (2001). The use of chewing gum to achieve controlled release is described in WO-A-00/35298.

Compounds of formula (I) may also be administered directly into the blood stream, into muscle, or into an internal organ. Such parenteral administration includes intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular and subcutaneous administration. Suitable devices for parenteral administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques.

Compounds of the invention may also be administered topically to the skin or mucosa, that is, dermally or transdermally.

The compounds of formula (I) can also be administered intranasally or by inhalation, typically in the form of a dry powder (either alone, as a mixture, for example, in a dry blend with lactose, or as a mixed component particle, for example, mixed with phospholipids, such as phosphatidylcholine) from a dry powder inhaler, as an aerosol spray from a pressurised container, pump, spray, atomiser (preferably an atomiser using electrohydrodynamics to produce a fine mist), or nebuliser, with or without the use of a suitable propellant, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane, or as nasal drops. For intranasal use, the powder may comprise a bioadhesive agent, for example, chitosan or cyclodextrin.

The pressurised container, pump, spray, atomizer, or nebuliser contains a solution or suspension of the compound of formula (I) comprising, for example, ethanol, aqueous ethanol, or a suitable alternative agent for dispersing, solubilising, or extending release of the compound, a propellant as solvent and an optional surfactant, such as sorbitan trioleate, oleic acid, or an oligolactic acid.

Prior to use in a dry powder or suspension formulation, the drug product is micronised to a size suitable for delivery by inhalation (typically less than 5 microns). This may be achieved by any appropriate comminuting method, such as spiral jet milling, fluid bed jet milling, supercritical fluid processing to form nanoparticles, high pressure homogenisation, or spray drying.

Capsules (made, for example, from gelatin or hydroxypropylmethylcellulose), blisters and cartridges for use in an inhaler or insufflator may be formulated to contain a powder mix of the compound of the invention, a suitable powder base such as lactose or starch and a performance modifier such as L-leucine, mannitol, or magnesium stearate. The lactose may be

anhydrous or in the form of the monohydrate, preferably the latter. Other suitable excipients include dextran, glucose, maltose, sorbitol, xylitol, fructose, sucrose and trehalose.

A suitable solution formulation for use in an atomiser using electrohydrodynamics to produce a fine mist may contain from 1µg to 20mg of the compound of the invention per actuation and the actuation volume may vary from 1µl to 100µl. A typical formulation may comprise a compound of formula (I), propylene glycol, sterile water, ethanol and sodium chloride. Alternative solvents which may be used instead of propylene glycol include glycerol and polyethylene glycol.

Suitable flavours, such as menthol and levomenthol, or sweeteners, such as saccharin or saccharin sodium, may be added to those formulations of the invention intended for intranasal administration. Formulations for intranasal administration may be formulated to be immediate and/or modified release using, for example, PGLA. Modified release includes delayed, sustained, pulsed, controlled, targeted and programmed release.

Compounds of formula (I) may also be administered directly to the eye or ear, typically in the form of drops of a micronised suspension or solution in isotonic, pH-adjusted, sterile saline.

Compounds of formula (I) may be combined with soluble macromolecular entities, such as cyclodextrin and suitable derivatives thereof or polyethylene glycol-containing polymers, in order to improve their solubility, dissolution rate, taste, bioavailability and/or stability when using any of the aforementioned modes of administration. Drug-cyclodextrin complexes, for example, are found to be generally useful for most dosage forms and administration routes. Both inclusion and non-inclusion complexes may be used. As an alternative to direct complexation with the drug, the cyclodextrin may be used as an auxiliary additive, i.e. as a carrier, diluent, or solubiliser. Most commonly used for these purposes are alpha-, beta- and gamma-cyclodextrins, examples of which may be found in international patent publications WO-A-91/11172, WO-A-94/02518 and WO-A-98/55148.

Inasmuch as it may be desirable to administer a combination of active compounds, for example, for the purpose of treating a particular disease or condition, it is within the scope of the present invention that two or more pharmaceutical compositions, at least one of which contains a compound of formula (I), may conveniently be combined in the form of a kit suitable for coadministration of the compositions. Thus, a kit of the invention comprises two or more separate pharmaceutical compositions, at least one of which contains a compound of formula (I), and means for separately retaining said compositions, such as a container, divided bottle, or divided foil packet. An example of such a kit is the familiar blister pack used for the packaging of

tablets, capsules and the like. Such a kit is particularly suitable for administering different dosage forms, for example, oral and parenteral, for administering separate compositions at different dosage intervals, or for titrating the separate compositions against one another. To assist compliance, the kit typically comprises directions for administration and may be provided with a so-called memory aid.

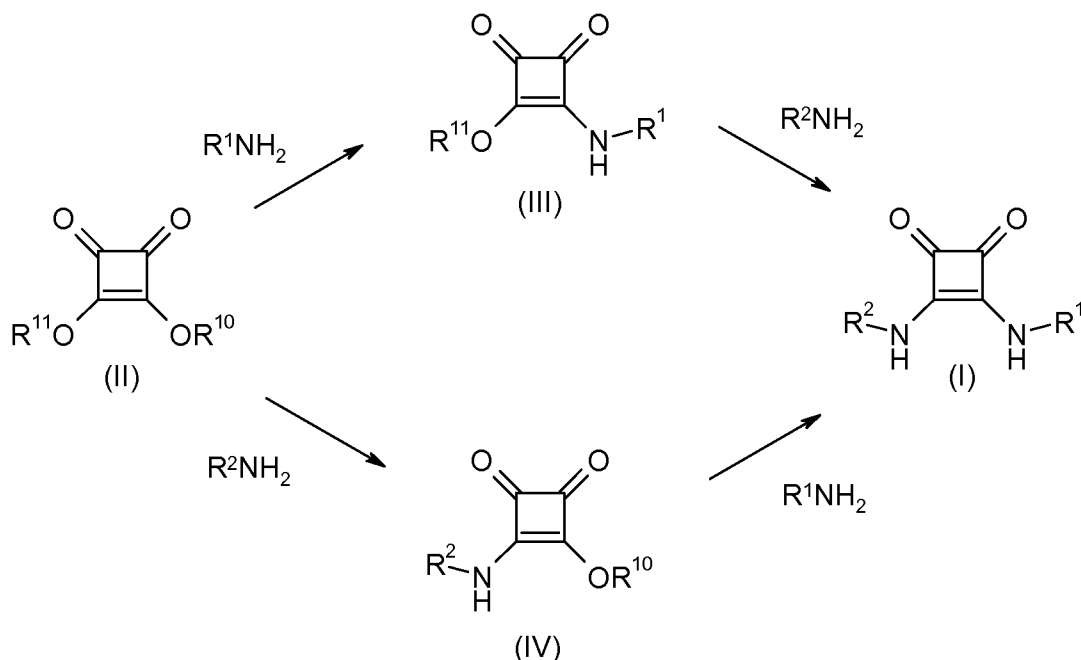
All the compound of formula (I) can be made by the specific and general experimental procedures described below in combination with the common general knowledge of one skilled in the art (see, for example, *Comprehensive Organic Chemistry*, Ed. Barton and Ollis, Elsevier; *Comprehensive Organic Transformations: A Guide to Functional Group Preparations*, Larock, John Wiley and Sons). In the general methods that follow, R^1 and R^2 have the meanings given in embodiment E1 described above unless otherwise stated.

A compound of formula (I) may be prepared as shown in Scheme 1 by reacting an amine of formula R^2NH_2 with a compound of formula (III) or by reacting an amine of formula R^1NH_2 with a compound of formula (IV). In compounds of formula (III) and (IV), R^{10} and R^{11} are each C_1-C_6 alkyl, preferably ethyl. In either case, the reaction is typically carried out in the presence of an inert solvent or mixture of inert solvents (e.g. ethanol, dimethyl sulphoxide, toluene, *N,N*-dimethylformamide, propionitrile, acetonitrile), optionally in the presence of a suitable base (e.g. triethylamine, diisopropylethylamine, potassium carbonate, potassium hydrogen carbonate, sodium hydrogen carbonate) at an elevated temperature (e.g. between 80°C and 120°C). The reaction typically takes 12 to 48 hours to reach completion. In a preferred procedure, a solution of the two starting materials in ethanol is treated with diisopropylamine and, where necessary, heated (e.g. at reflux).

Compounds of formula (III) and (IV) may be prepared by reacting an amine of formula R^1NH_2 or R^2NH_2 , respectively, with a compound of formula (II). Typically, the reaction is carried out in the presence of a suitable inert solvent or mixture of inert solvents (e.g. ethanol, dimethyl sulphoxide, toluene, *N,N*-dimethylformamide, propionitrile, acetonitrile). Optionally, a base such as triethylamine, diisopropylethylamine, potassium carbonate, potassium hydrogen carbonate or sodium hydrogen carbonate may be added and the reaction may be accelerated by the application of heat. In a preferred procedure, the reaction is carried out in ethanol at room temperature.

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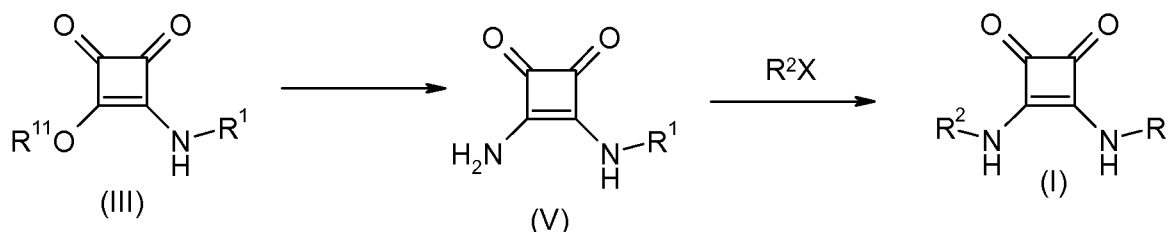
Scheme 1



Alternatively compounds of formula (I) may be prepared as shown in Scheme 2 by reacting an amide of formula (V) with a heteroaryl halide of formula R^2X , where X is chloride, bromide or iodide (for instance, a compound of formula (XII) or (XIV) – see below). The reaction is typically carried out in the presence of a suitable palladium catalyst (e.g. tris(dibenzylideneacetone)dipalladium/2-dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl of formula $Pd_2(dba)_3/\{DavePhos\}_2$) in the presence of a solvent or mixture of solvents (e.g. tetrahydrofuran, toluene, acetonitrile, hexane) and in the presence of a base (e.g. triethylamine, diisopropylethylamine, potassium carbonate, potassium hydrogen carbonate, cesium carbonate). Preferably, the reaction is carried out at a temperature of from 70°C to 110°C for 4 to 16 hours. In the case where R^2X contains a potentially reactive moiety such as a hydroxyl or amino group, this group is preferably protected using a suitable protecting group (see, for example, 'Protective Groups in Organic Synthesis' by Theorora Greene and Peter Wuts, third edition, 1999, John Wiley and Sons) which may be later removed.

The amide of formula (V) may be prepared by reaction of a compound of formula (III) with ammonia. Typically, the reaction is carried out in the presence of a suitable inert solvent or mixture of inert solvents (e.g. ethanol, dimethyl sulfoxide, toluene, N,N-dimethylformamide, propionitrile, acetonitrile) and the reaction may be accelerated by the application of heat. In a preferred procedure, the reaction is carried out in ethanol at room temperature.

Scheme 2

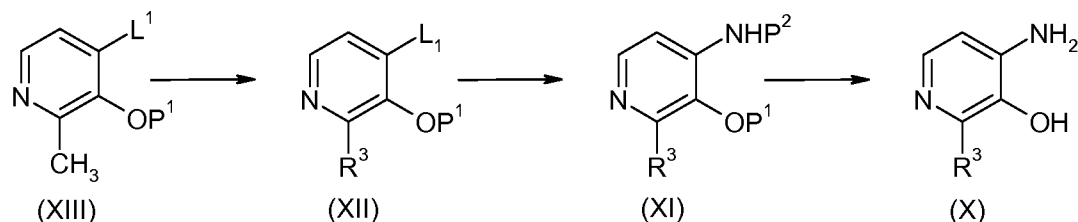


Where the compound R^2NH_2 is of formula (X), wherein R_3 is an amide group of formula $-CONH_2$ or $-CONR^6R^b$, it may be prepared as shown in Scheme 3 by deprotection of a compound of formula (XI). The groups P^1 and P^2 represent suitable alcohol and amino protecting groups, respectively, and both the choice of protecting group and suitable conditions for its removal are within the scope of the skilled person's common general knowledge (see, for example, 'Protective Groups in Organic Synthesis' by Theorora Greene and Peter Wuts, third edition, 1999, John Wiley and Sons). Preferably, P^1 is methyl or benzyl and P^2 is acyl. In a typical reaction, where P^1 is methyl and P^2 is acyl, a solution of the compound of formula (XI) in aqueous ammonia is kept at a temperature of from $0^\circ C$ to room temperature for 12 to 24 hours in order to remove the amine protecting group and the product of this reaction is then dissolved in dichloromethane and treated with boron tribromide at a temperature of from $0^\circ C$ to $40^\circ C$ for 0.5 to 6 hours.

A compound of formula (XI) may be prepared by reacting a compound of formula (XII), wherein L^1 is a suitable leaving group such as a halide, with a suitably protected amine H_2NP^2 . In a typical procedure, the compound of formula (XII) and the amine H_2NP^2 are reacted together in the presence of a suitable palladium catalyst (e.g. palladium acetate/Xanthphos) in the presence of a solvent or mixture of solvents (e.g. toluene, 1,4-dioxane or hexane) and in the presence of a base (e.g. triethylamine, diisopropylethylamine, potassium carbonate or potassium hydrogen carbonate). Preferably, the reaction is carried out at a temperature of from $70^\circ C$ to $110^\circ C$ for 4 to 16 hours.

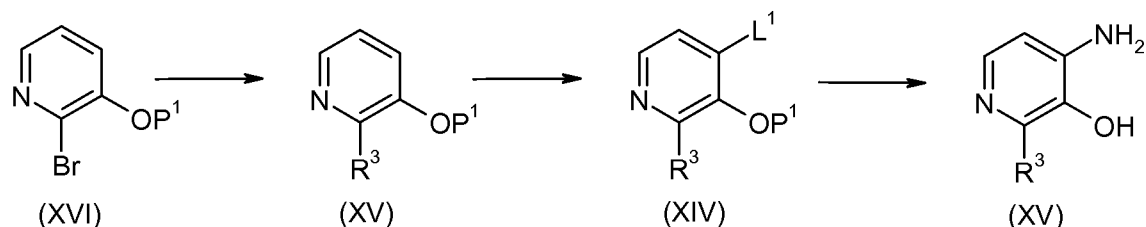
A compound of formula (XII) may be prepared from a compound of formula (XIII) by oxidation with a suitable oxidizing agent followed by formation of the amide bond by standard methodology well known to the skilled person - see, for example, 'Comprehensive Organic Transformations' by Richard Larock (1999, VCH Publishers Inc.). In a preferred procedure, a compound of formula (XIII) in water is treated with $KMnO_4$ at a temperature of from room temperature to $100^\circ C$ for 4 to 16 hours. The resulting carboxylate intermediate is then dissolved in dichloromethane and treated with oxalylchloride and DMF at a temperature of from $0^\circ C$ to

room temperature for 1 to 4 hours. The resulting acyl chloride is then quenched with ammonia or a suitable primary or secondary amine of formula HNR^6R^b at a temperature ranging from 0°C to room temperature for 4 to 16 hours.

Scheme 3

Where the compound R^2NH_2 is of formula (XV), wherein R_3 is a sulfonamide group of formula $-\text{SO}_2\text{NH}_2$ or $-\text{SO}_2\text{NR}_6\text{R}_b$, it may be prepared as shown in Scheme 4 from a compound of formula (XIV) in an analogous manner to the preparation of a compound of formula (X) from a compound of formula (XII), as described above. A compound of formula (XIV) may be prepared by halogenation of a compound of formula (XV). In a typical procedure, a solution of the compound of formula (XV) in THF is treated with a suitable base (e.g. lithium 2,2,6,6-tetramethylpiperidine) at a temperature of from -78°C to -40°C for 0.5 to 2 hours and quenched with a suitable halogen source (e.g. iodine) at a temperature of from -50°C to room temperature for 1 to 4 hours.

A compound of formula (XV) may be prepared by sulphonylation of a compound of formula (XVI). In a typical procedure, a solution of the compound of formula (XVI) in THF is treated with a suitable base (e.g. *n*-butyl lithium or isopropylmagnesium chloride) at room temperature for 0.5 to 2 hours. This resulting deprotonated intermediate is then treated with sulfonyl chloride followed by ammonia or an appropriate primary or secondary amine, at a temperature ranging from 0°C to room temperature, for 1 to 4 hours.

Scheme 4

Compounds of formula (II), R^1NH_2 , R^2NH_2 , (III), R^2X , (XIII) and (XVI) are either commercially available or can easily be prepared by the skilled person from commercially available starting

materials using common functional group transformation known in the common general knowledge and described in text books of synthetic organic chemistry such as 'Comprehensive Organic Transformations' by Richard Larock (1999, VCH Publishers Inc.).

The skilled person will appreciate that the individual steps of the general methods described above can be reversed in many instances to provide alternative routes to compounds of formula (I). For example, in Scheme 4, a compound of formula (XIV) could be used to arylate a compound of formula (V) prior to deprotection of P¹. Compounds of formula (I) can likewise be interconverted (e.g. from a compound of formula (I) in which R³ is an ester to a compound of formula (I) in which R³ is an amide). Such a transformation of ester/acid to amide can also be effected in compounds of formula (XII) and (XI) above.

The following experimental details illustrate specifically how certain compounds of formula (I) may be prepared. All Examples are compounds of formula (I). Preparations are intermediates useful in the synthesis of compounds of formula (I).

General methods used

One or more of the following nine general preparative methods were used in the experiments described below.

Method (i): A carboxylic acid (e.g. Preparation 32 or 35, 130μmol) was dissolved in dimethylformamide (800uL). HATU (130μmol) and DIPEA (300μmol) were added and the reaction mixture was stirred at 25°C for 30 minutes. A solution of an amine reactant (0.5M in dimethylformamide, 200uL, 100μmol) was added and the reaction mixture was heated to 50°C for 16 hours. The reaction mixture was concentrated *in vacuo* then purified by preparative HPLC.

Method (ii): A 0.15M solution of compound of formula (IV) (e.g. Preparation 38) in dimethylsulfoxide (0.5mL, 75μmol) was added to an amine of formula R¹NH₂ (75μmol). DIPEA (150μmol) was added and the reaction mixture was sealed and heated at 60°C for 2 hours. The reaction mixture was purified preparative HPLC.

Method (iii): A 0.1M solution of compound of formula (IV) (e.g. Preparation 1) in ethanol (1.0mL, 100μmol) was added to amine of formula R¹NH₂ (100μmol). Cesium fluoride (200μmol) was added and the reaction mixture was sealed and heated at 80°C for 16 hours. The reaction mixture was concentrated *in vacuo* and then purified by preparative HPLC.

Method (iv): A 0.1M solution of a compound of formula (IV) (e.g. Preparation 1) in ethanol (750uL, 75μmol) was added to an amine of formula R¹NH₂ (200μmol). DIPEA (39uL, 225μmol) was added and the reaction mixture was sealed and heated at 30°C for 48 hours. The reaction mixture was concentrated *in vacuo* and then purified by preparative HPLC.

Method (v): A compound of formula (IV) (e.g. Preparation 1, 33mg, 100 μ mol) dissolved in 533 μ L of ethanol was added to an amine of formula R¹NH₂ (100 μ mol). DIPEA (133 μ L) was added and the reaction mixture was sealed and heated at 30°C for 48 hours. The reaction mixture was concentrated *in vacuo* and then purified by preparative HPLC.

Method (vi): A solution of a compound of formula (IV) (e.g. Preparation 38, 100 μ mol) in dimethylsulfoxide was added to an amine of formula R¹NH₂ (100 μ mol). Cesium fluoride (30mg, 200 μ mol) was added and the reaction mixture was sealed and heated under microwave radiation for 30 minutes at 100°C. The reaction mixture was filtered, concentrated *in vacuo* and then purified by preparative HPLC.

Method (vii): A compound of formula (IV) (e.g. Preparation 38) (100 μ mol) in dimethylsulfoxide was added to an amine of formula R¹NH₂ (100 μ mol). Cesium fluoride (30mg, 200 μ mol) was added and the reaction mixture was sealed and heated at 80°C for 16 hours. The reaction mixture was filtered, concentrated *in vacuo* and then purified by preparative HPLC.

Method (viii): A solution of a compound of formula (IV) (e.g. Preparation 38, 100 μ mol) in dimethylsulfoxide was added to an amine of formula R¹NH₂ (100 μ mol). Potassium hydroxide (11mg, 200 μ mol) was added and the reaction mixture was sealed and heated under microwave radiation for 40 minutes at 170°C. The reaction mixture was filtered, concentrated *in vacuo* and then purified by preparative HPLC.

Method (ix): 4-(2-Ethoxy-3,4-dioxocyclobut-1-enylamino)-3-hydroxy-*N,N*-dimethyl picolinamide (Preparation 16, 100mg, 0.328mmol) and an amine of formula R¹NH₂ (0.393mmol, 1.2eq) were combined with ethanol (1.5mL) with or without DIPEA (126.9mg, 0.983mmol) and the reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was concentrated *in vacuo* and purified by preparative HPLC, trituration with an appropriate solvent or preparative thin layer chromatography on silica.

Analytical HPLC

One or more of the following analytical HPLC Methods were used in the experiments described below.

HPLC conditions	HPLC-MS Method A (analytical)	HPLC-MS Method B (analytical)
Column	Restek C18 30 x 2.1mm 3 micron	Welch XB-C18 2.1 x 50mm 5 μ m
Injection Volume	3 μ L	2 μ L
Flow rate	1.5mL/min	0.8mL/min

Mobile Phase	Solvent A: 0.05% Formic acid in water Solvent B: Acetonitrile		Solvent A: 0.05% NH ₄ OH in water. Solvent B: 100% Acetonitrile	
Gradient	Time (min)	%B	Time (min)	%B
	0	2	0.00	5
	0.75	2	0.50	5
	1.00	10	3.40	100
	2.00	98	4.20	100
	2.25	98	4.21	5
	2.90	2	4.70	5
	3.00	2		

HPLC conditions	HPLC-MS Method C (analytical)		HPLC-MS Method D (analytical)	
Column	Welch XB-C18 2.1 x 50mm 5µm		Welch XB-C18 2.1 x 50mm 5µm	
Injection Volume	2µL		2µL	
Flow rate	0.8mL/min		0.8mL/min	
Mobile Phase	Solvent A: 0.0375% trifluoroacetic acid in water Solvent B: 0.01875% trifluoroacetic acid in acetonitrile.		Solvent A: 0.0375% trifluoroacetic acid in water Solvent B: 0.01875% trifluoroacetic acid in acetonitrile.	
Gradient	Time (min)	%B	Time (min)	%B
	0	1	0	10
	0.6	5	0.5	10
	4.0	100	4.0	100
	4.3	1	4.3	10
	4.7	1	4.7	10

HPLC conditions	HPLC-MS Method E (analytical)		HPLC-MS Method F (analytical)	
Column	SunFire C18, 5um 4.6 x 50mm. Ambient temperature		XTerra C18, 5um 4.6 x 50mm Ambient temperature	
Detection	UV 225nm- ELSD -MS		UV 225nm- ELSD -MS	
Injection Volume	5µL		5µL	
Flow rate	1.5mL/min		1.5mL/min	
Mobile Phase	Solvent A: Water +0.1% formic acid Solvent B: Acetonitrile + 0.1% formic acid		Solvent A: Water + 0.1% Ammonia Solvent B: Acetonitrile + 0.1% Ammonia	
Gradient	Time (min)	%B	Time (min)	%B
	0	5	0	5
	3.0	95	3.0	95
	4.0	95	4.0	95
	4.1	5	4.1	5
	5.0	5	5.0	5

Preparative HPLC

One or more of the following preparative HPLC Methods were used in the experiments described below.

HPLC conditions	HPLC-MS Method 1 (preparative)	HPLC-MS Method 2 (preparative)
Column	SunFire C18, 5um 19 x 100mm. Ambient temperature	XTerra C18, 5um 19 x 100mm Ambient temperature
Detection	ELSD -MS	ELSD -MS
Injection Volume	1000µL	1000µL

Flow rate	18mL/min		18mL/min	
Mobile Phase	Solvent A: Water +0.1% formic acid Solvent B: Acetonitrile + 0.1% formic acid		Solvent A: Water + 0.1% diethylamine Solvent B: Acetonitrile + 0.1% diethylamine	
Gradient	Time (min)	%B	Time (min)	%B
	0-1	5	0-1	5
	1-7	98	1-7	98
	7-9	98	7-9	98
	9-9.1	98-5	9-9.1	98-5
	9.1-10	5	9.1-10	5

HPLC conditions	HPLC-MS Method 3 (preparative)	
Column	Xbridge C18 50 x 19mm, 5 micron	
Flow rate	20 mL/ min	
Mobile Phase	Solvent A: 0.05% formic acid in water Solvent B: Acetonitrile (100%)	
Gradient	Time (min)	%B
	0	10
	1	10
	7	80
	7.5	95
	8.5	95
	9	10
	10	10

HPLC conditions	HPLC-MS Method 4 (preparative)	HPLC-MS Method 5 (preparative)
Column	Phenomenex Luna C18 100 x 21.2mm x 5um	Grace Vydac C18 250 x 20mm x 5um
Flow rate	25 to 30 mL/min	25 to 30 mL/min
Mobile Phase	Solvent A: Water +0.1% trifluoroacetic acid Solvent B: Acetonitrile	Solvent A: Water +0.1% trifluoroacetic acid Solvent B: Acetonitrile

HPLC conditions	HPLC-MS Method 6 (preparative)	HPLC-MS Method 7 (preparative)
Column	YMC-pack ODS-AQ 75 x 30mm x 5um	Agelia Venusil ASB C18 150 x 21.2mm x 5um 250 x 20mm x 5um
Flow rate	25 mL/min	25 to 30 mL/min
Mobile Phase	Solvent A: Water +0.1% trifluoroacetic acid Solvent B: Acetonitrile	Solvent A: Water +0.1% trifluoroacetic acid Solvent B: Acetonitrile

HPLC conditions	HPLC-MS Method 8 (preparative)	HPLC-MS Method 9 (preparative)
Column	Waters Xbridge C18 150 x 20mm x 5um	Boston Symmetrix C18 ODS-H 150 x 30.0mm x 5um
Flow rate	25 mL/min	25 to 30 mL/min
Mobile Phase	Solvent A: Ammonium hydroxide (pH10) Solvent B: Acetonitrile	Solvent A: Water +0.1% trifluoroacetic acid Solvent B: Acetonitrile

Preparative HPLC Method 10

Column: Sunfire Prep C18 (100mm x 30 mm, 5 µm)

System: Waters Auto purification system

Detector: Photo Diode Array

Time (min)	Flow (mL/min)	Acetonitrile (%)	0.05% Formic acid in water (%)	Waters curve
-	24	10	90	-
1	24	10	90	6
16	24	50	50	8
18	24	100	0	6
22	24	100	0	6
23	24	10	90	6
25	24	10	90	6

Preparative HPLC Method 11

Column: Sunfire Prep C18 (100mm x 30 mm, 5 µm)

System: Waters Auto purification system

Detector: Photo Diode Array and MS

Time (min)	Flow (mL/min)	Acetonitrile (%)	0.05% Formic acid in water (%)	Waters curve
-	24	10	90	-
18	24	90	10	6
19	24	100	0	6
20	24	100	0	6
21	24	10	90	6
25	24	10	90	6

Preparative HPLC Method 12

Column: Sunfire Prep C18 (100mm x 30 mm, 5 µm)

System: Waters Auto purification system

Detector: Photo Diode Array

Time (min)	Flow (mL/min)	Acetonitrile (%)	0.05% Formic acid in water (%)	Waters curve
-	24	10	90	-
18	24	90	10	6
20	24	100	0	6
21	24	100	0	6

22	24	10	90	6
25	24	10	90	6

Preparative HPLC Method 13Column: Sunfire Prep C18 (100mm x 30 mm, 5 μ)

System: Waters Auto purification system

Detector: Photo Diode Array and MS

Time (min)	Flow (mL/min)	Acetonitrile (%)	0.05% Formic acid in water (%)	Waters curve
-	24	10	90	-
18	24	90	10	6
19	24	100	0	6
20	24	100	0	6
21	24	10	90	6
25	24	10	90	6

Preparative HPLC Method 14Column: Sunfire Prep C18 (100mm x 30 mm, 5 μ)

System: Waters Auto purification system

Detector: Photo Diode Array

Time (min)	Flow (mL/min)	Acetonitrile (%)	0.05% Formic acid in water (%)	Waters curve
-	24	10	90	-
3	24	30	70	6
18	24	30	70	6
19	24	100	0	6
20	24	100	0	6
21	24	10	90	8
25	24	10	90	8

Preparative HPLC Method 15Column: Sunfire Prep C18 (100mm x 30 mm, 5 μ)

System: Waters Auto purification system

Detector: Photo Diode Array

Time (min)	Flow (mL/min)	Acetonitrile (%)	0.05% Formic acid in water (%)	Waters curve
-	24	10	90	-

50

16	24	60	40	6
18	24	100	0	6
20	24	100	0	6
21	24	10	90	6
25	24	10	90	6

Preparative HPLC Method 16Column: Sunfire Prep C18 (100mm x 30 mm, 5 μ)

System: Waters Auto purification system

Detector: Photo Diode Array and MS

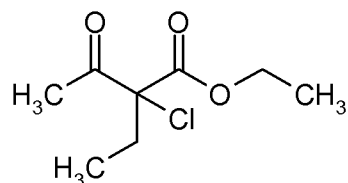
Time (min)	Flow (mL/min)	Acetonitrile (%)	0.05% Formic acid in water (%)	Waters curve
-	24	10	90	-
3	24	20	80	6
7	24	20	80	6
10	24	30	70	6
17	24	60	40	8
19	24	90	10	8
20	24	100	0	6
21	24	10	90	6
25	24	10	90	6

Preparative HPLC Method 17Column: Sunfire Prep C18 (100mm x 30 mm, 5 μ)

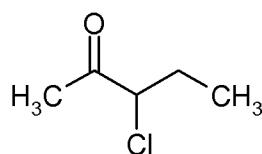
System: Waters Auto purification system

Detector: Photo Diode Array

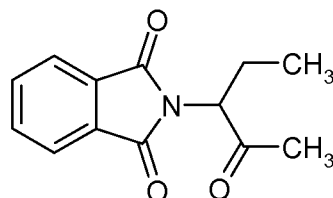
Time (min)	Flow (mL/min)	Acetonitrile(%)	0.05% Formic acid in water (%)	Waters curve
-	24	10	90	-
18	24	100	0	6
22	24	100	0	6
23	24	10	90	6
25	24	10	90	6

Preparation 1Ethyl 2-chloro-2-ethyl-3-oxobutanoate

Sulfuryl chloride (69g, 0.51mol) was added at room temperature to a stirred solution of ethyl 2-ethylacetoacetate (79g, 0.5mol) in dichloromethane (400mL). The mixture was stirred for 1 hour and poured into water. The organic layer was washed with saturated aqueous sodium chloride solution and dried over magnesium sulfate, and the solvent was removed *in vacuo*. The residual oil was distilled under a water-jet pump vacuum at b.p. 105–110°C/15mmHg to yield the title compound as a colorless oil, 72g.

Preparation 23-Chloropentan-2-one

A mixture of ethyl 2-chloro-2-ethyl-3-oxobutanoate (Preparation 1, 72g, 0.6mol), concentrated H₂SO₄ (290g, 3mol) and water (290mL) was refluxed with vigorous stirring for a total of 24 hours. The reaction mixture was then diluted with water (2L) and subjected to extraction with chloroform (3×150mL). The combined organic phases were washed with water (300mL) and saturated aqueous sodium chloride solution (300mL) and dried over magnesium sulfate. The solvent was removed *in vacuo*, and the residue was distilled at b.p. 130–134°C to give the title compound as a colourless oil, 52g.

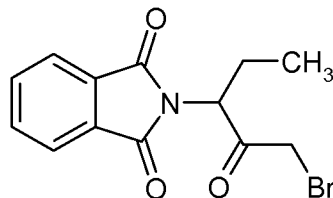
Preparation 32-(2-Oxopentan-3-yl)isoindoline-1,3-dione

A mixture of 3-chloropentan-2-one (Preparation 2, 120g, 1mol) and potassium phthalimide (185g, 1mol) in DMF (500mL) was stirred in a flask immersed in a boiling water bath for 6 hours.

The mixture was cooled and poured into water (3L). The precipitate that formed was separated by filtration and air-dried to give the title compound as fine, light-yellow crystals, 193g.

Preparation 4

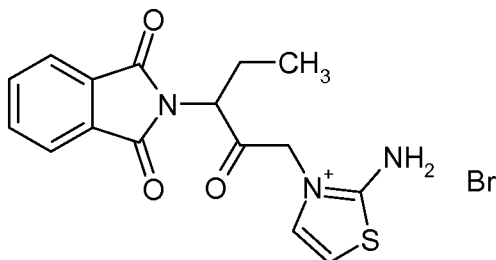
2-(1-Bromo-2-oxopentan-3-yl)isoindoline-1,3-dione



Bromine (130g, 0.8mol) was added dropwise at room temperature to a stirred solution of 2-(2-oxopentan-3-yl)isoindoline-1,3-dione (Preparation 3, 185g, 0.8mol) in chloroform (1L). The mixture was stirred at room temperature for 3 hours and the resultant solution was then concentrated to dryness *in vacuo*. The solid formed was suspended in water (400ml), filtered and washed with further water until washings were neutral. The solid was then crystallised from ethanol (400ml) to yield the title compound as white crystals, 195g.

Preparation 5

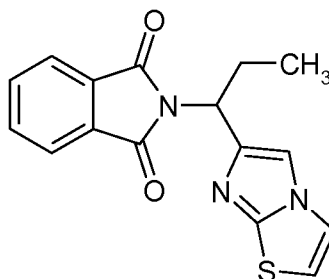
2-Amino-3-[3-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-2-oxopentyl]-1,3-thiazol-3-ium bromide



2-Aminothiazole (52g, 0.52mol) was added to a solution of 2-(1-bromo-2-oxopentan-3-yl)isoindoline-1,3-dione (Preparation 4, 150g, 0.49mol) in acetone (1L). The solution was left overnight and then filtered to give the title compound as white crystals, 163g.

Preparation 6

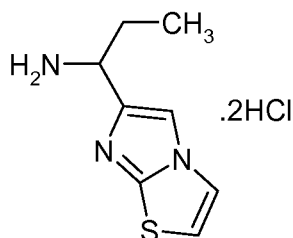
2-(1-(Imidazo[2,1-b]thiazol-6-yl)propyl)-isoindoline-1,3-dione



A mixture of 2-amino-3-[3-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-2-oxopentyl]-1,3-thiazol-3-ium bromide (Preparation 5, 163g, 0.4mol) and DMF (300mL) was stirred at 110°C for 1.5 hours and then poured into water (3L). Solid potassium carbonate was added to the resulting mixture until a pH of 9–10 was reached. The precipitate which formed was filtered, washed with water until washings were neutral and then air-dried to give the title compound as light-yellow crystals, 105 g.

Preparation 7

1-(Imidazo[2,1-b]thiazol-6-yl)propan-1-amine dihydrochloride



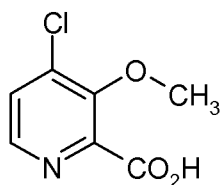
Hydrazine hydrate (17mL, 0.34mol) was added to a suspension of 2-(1-(imidazo[2,1-b]thiazol-6-yl)propyl)-1H-isoindoline-1,3-dione (Preparation 6, 105g, 0.34mol) in ethanol (400mL). The mixture was stirred under reflux for 2 hours and then cooled. Concentrated aqueous HCl (130mL) was added and the mixture was refluxed for a further 2 hours. Then the mixture was cooled and filtered and the precipitate was washed on the filter with water (200 mL). The combined filtrates were concentrated to dryness in vacuo, and the residue was dissolved in water (300mL). Charcoal (15–20g) was added, and the mixture was refluxed for 1 hour and filtered. The aqueous solution was evaporated in vacuo, and the residue was crystallized from 90% ethanol to give the title compound as yellow crystals, 54g.

¹H NMR (400MHz, d₆-DMSO): δ = 0.88 (3H, t), 1.90-2.15 (2H, m), 4.35 (1H, m), 7.46 (1H, d), 8.07 (1H, s), 8.13 (1H, d), 8.75 (3H, s) ppm.

LRMS (ES) : m/z 265 [M-NH₂]⁺.

Preparation 8

4-Chloro-3-methoxy-pyridine-2-carboxylic acid



A suspension of 4-chloro-3-methoxy-2-methyl-pyridine (prepared as described in Journal of Medicinal Chemistry, 1992, pages 1049-1057; 8g, 51mmol) in water (300mL) was treated with potassium permanganate (9.6g, 61mmol) and heated at reflux. Two more batches of potassium

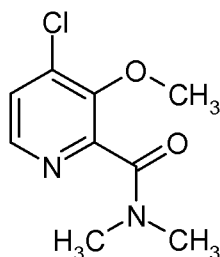
permanganate (2 x 9.6g, 2 x 61mol) were added to the reaction mixture at 1.5 hour intervals and the reaction mixture was then refluxed for another 16 hours. The reaction mixture was filtered through a short bed of Celite® and the filtrate was extracted with dichloromethane (3 x 50mL). The aqueous layer was acidified with citric acid and then extracted with a mix of methanol:dichloromethane (1:9) (10 x 100mL). Combined organic phases were washed with saturated aqueous sodium chloride solution (1 x 200mL), dried (sodium sulfate), and then evaporated *in vacuo* to furnish the product as a white solid, 4.6g.

^1H NMR (400MHz, DMSO- d_6): τ^m = 3.88 (3H, s), 7.75 (1H, d), 8.33 (1H, d), 13.70 (1H, bs) ppm.

LRMS: 188 $[\text{M}+\text{H}]^+$.

Preparation 9

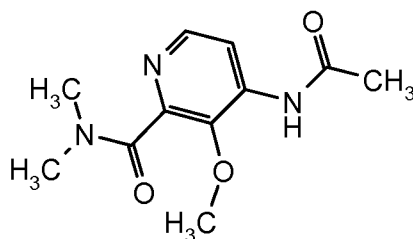
4-Chloro-3-methoxy-pyridine-2-carboxylic acid dimethylamide



To a stirred solution of 4-chloro-3-methoxy-pyridine-2-carboxylic acid (Preparation 8, 4.8g, 26mmol) in dichloromethane (100mL), oxalylchloride (4.3mL, 51mmol) was added drop-wise at 0°C. Dimethylformamide (5 drops) was then added, and the reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated *in vacuo*, and the residue was then re-dissolved in dichloromethane (100mL). A 2M solution of dimethyl amine in THF (15.5mL, 31mmol) and triethyl amine (10.8mL, 77mmol) were added dropwise to this solution at 0°C. The reaction mixture was then allowed to warm to room temperature and stirring was continued for 16 hours. The reaction mixture was washed with water (30mL) and saturated aqueous sodium chloride solution (30mL) and then dried (sodium sulfate) and the solvent was removed *in vacuo* to furnish dark brown gum. Column chromatographic purification on silica gel eluting with methanol:dichloromethane (1:39) afforded the title compound as brown solid, 4.5g.

^1H NMR (400MHz, CDCl_3): τ^m = 2.85 (3H, s), 3.14 (3H, s), 3.94 (3H, s), 7.35 (1H, d), 8.24 (1H, d) ppm.

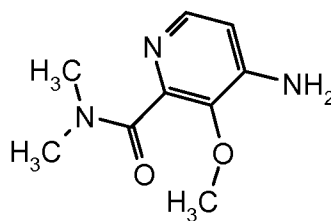
LRMS (ES): m/z 214 $[\text{M}+\text{H}]^+$.

Preparation 10**4-Acetamido-3-methoxy-*N,N*-dimethylpicolinamide**

4-Chloro-3-methoxy-pyridine-2-carboxylic acid dimethylamide (Preparation 9, 11.5g, 53.7mmol), acetamide (4.12g, 69.9mmol) and potassium carbonate (14.8g, 107.5mmol) were dissolved in 1,4-dioxane (200mL) and the resulting solution was purged with argon for 30 minutes. Palladium(II)acetate (601mg, 2.69mmol) and Xanthphos (3.109g, 5.373mmol) were added and the reaction mixture was heated at reflux for 16 hours. The reaction mixture was filtered and concentrated *in vacuo*. Column chromatographic purification on silica gel, using 2% methanol in dichloromethane, furnished the title compound as a white solid, 7.00g.

^1H NMR (400MHz, $\text{DMSO}-d_6$): δ =2.19 (3H, s), 2.76 (3H, s), 3.01 (3H, s), 3.73 (3H, s), 8.19 (2H, m), 9.76(1H, s) ppm.

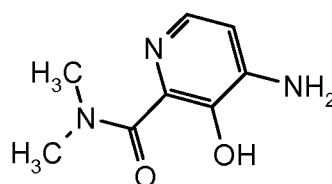
LRMS (ES): m/z 238 $[\text{M}+\text{H}]^+$.

Preparation 11**4-Amino-3-methoxy-*N,N*-dimethylpicolinamide**

4-Acetamido-3-methoxy-*N,N*-dimethylpicolinamide (Preparation 10, 1.00g, 4.20mmol) and concentrated aqueous ammonia solution (15.0mL) were stirred at 0°C for 16 hours in a sealed tube. The reaction mixture was concentrated *in vacuo* and purified by column chromatography on silica gel eluting with 3% methanol in dichloromethane to furnish the title compound as a white solid (670mg).

^1H NMR (400MHz, $\text{DMSO}-d_6$): δ = 2.73 (3H, s), 2.96 (3H, s), 3.61 (3H, s), 6.06 (2H, bs), 6.60 (1H, d), 7.77 (1H, d) ppm.

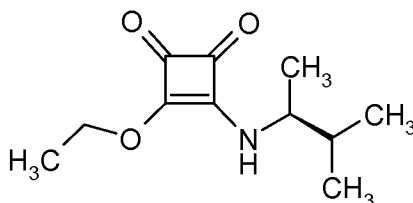
LRMS (ES): m/z 196 $[\text{M}+\text{H}]^+$.

Preparation 124-Amino-3-hydroxy-N,N-dimethylpicolinamide

4-Amino-3-methoxy-*N,N*-dimethylpicolinamide (Preparation 11, 10.0g, 51.2mmol) was dissolved in dichloromethane (200mL). Tetrabutylammonium iodide (12.3g, 33.3mmol) was added and the reaction mixture was cooled to 0°C. Boron tribromide solution (1.0M in dichloromethane, 307mL, 307mmol) was added dropwise. The resulting solution was allowed to warm to room temperature, stirred for 4 hours and quenched with saturated aqueous sodium hydrogen carbonate solution. The product was extracted into dichloromethane (2 × 100mL) and the combined organic phases were concentrated *in vacuo*. Purification by column chromatography on silica gel, eluting with dichloromethane:methanol (gradient elution, 99:1 to 92:8 by volume), gave a yellow solid. Trituration with diethyl ether and filtration furnished the title compound as a white solid (9.0g).

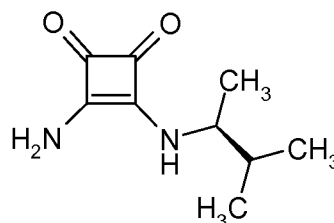
¹H NMR (400MHz, CD₃OD): δ = 3.09 (6H, s), 6.63 (1H, d), 7.43 (1H, d) ppm.

LRMS (ES): m/z 182 [M+H]⁺.

Preparation 13(S)-3-Ethoxy-4-(3-methylbutan-2-ylamino)cyclobut-3-ene-1,2-dione

To a stirred solution of 3,4-diethoxycyclobut-3-ene-1,2-dione (1.85mL, 12.6mmol) in absolute ethanol (35.0mL) was added (S)-3-methylbutan-2-amine (1.34 mL, 11.5 mmol). The reaction mixture was stirred at room temperature for 1.5 hours and then concentrated *in vacuo* to give a yellow solid. Recrystallisation from ethyl acetate/ heptane furnished the title compound as an off-white solid, 1.93g.

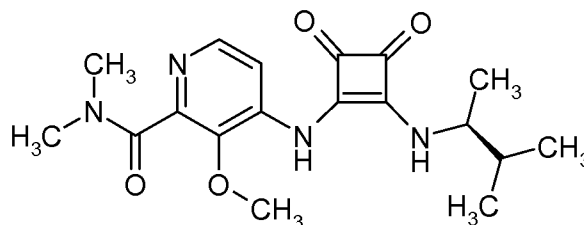
¹H NMR (400MHz, CDCl₃): δ = 0.93 (6H, d), 1.22 (3H, d), 1.46 (3H, t), 1.75 (1H, m), 3.6 (1H, m), 4.8 (2H, m), 6.00 (1H, m) ppm.

Preparation 14(S)-3-Amino-4-(3-methylbutan-2-ylamino)cyclobut-3-ene-1,2-dione

(S)-3-Ethoxy-4-(3-methylbutan-2-ylamino)cyclobut-3-ene-1,2-dione (Preparation 13, 250mg, 1.18mmol) was dissolved in 2.0mL of absolute ethanol. Ammonia solution (2M solution in ethanol, 2.37mL, 4.73mmol) was added. The reaction mixture was stirred at room temperature for 4 days. The reaction mixture was filtered and the resultant solid was dried to give the title compound as a white solid, 215mg.

^1H NMR (400MHz, $\text{DMSO}-d_6$): δ = 0.86 (6H, m), 1.12 (3H, d), 1.69 (1H, m), 3.86 (1H, bs), 7.08-7.54(2H, m) ppm.

LRMS (ES): m/z 181 $[\text{M}-\text{H}]^-$.

Preparation 15(S)-3-Methoxy-*N,N*-dimethyl-4-(2-(3-methylbutan-2-ylamino)-3,4-dioxocyclobut-1-enylamino)picolinamide

2-Methylbutan-2-ol (2.0mL) was added to a mixture of tris(dibenzylideneacetone)dipalladium(0) (43mg, 0.047mmol), 4-chloro-3-methoxy-*N,N*-dimethylpicolinamide, (Preparation 9, 100mg, 0.466 mmol), (S)-3-amino-4-(3-methylbutan-2-ylamino)cyclobut-3-ene-1,2-dione (Preparation 14, 106mg, 0.583mmol), Bippyphos® (47.1mg, 0.0930mmol) and caesium carbonate (228mg, 0.699mmol) and the reaction mixture was heated in a sealed tube at 80°C for 16 hours. The cooled reaction mixture was then diluted with ethyl acetate, washed with saturated aqueous ammonium chloride solution, dried using anhydrous sodium sulfate, filtered and concentrated *in vacuo* to give an orange-coloured oil. Column chromatographic purification on silica gel eluting with dichloromethane:methanol:ammonia (gradient elution, 100:0:0 to 90:10:1) afforded the title compound as a brown gum, 42mg.

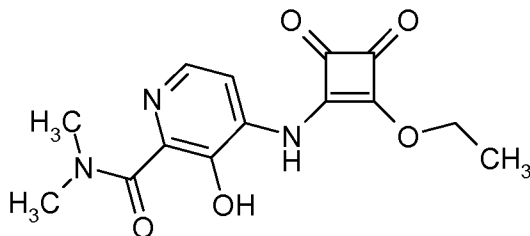
58

^1H NMR (400MHz, CD_3OD): δ = 1.00 (6H, m), 1.28 (3H, d), 1.83 (1H, m), 2.92 (3H, s), 3.15 (3H, s), 3.89(3H, s), 4.16 (1H, m), 8.17 (1H, d), 8.24 (1H, d) ppm.

LRMS (ES): m/z 359 $[\text{M}+\text{H}]^+$.

Preparation 16

4-(2-Ethoxy-3,4-dioxocyclobut-1-enylamino)-3-hydroxy-*N,N*-dimethylpicolinamide



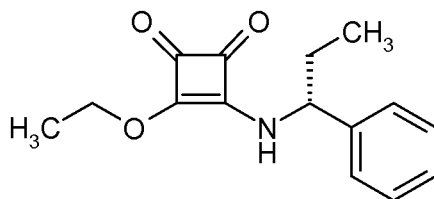
4-Amino-3-hydroxy-*N,N*-dimethylpicolinamide (Preparation 12, 100mg, 0.55mmol) and 3,4-diethoxycyclobut-3-ene-1,2-dione (113mg, 0.66mmol) were dissolved in 1.0mL of absolute ethanol. *N,N*-Diisopropylethylamine (71mg, 0.552mmol) was added and the reaction was heated in a sealed tube at 55°C for 3.5 days. The reaction mixture was concentrated *in vacuo* and purified by column chromatography on silica gel eluting with dichloromethane:methanol (gradient elution, 100:0 to 90:10 by volume) to afford the title compound as a yellow oil (100mg). The product contained approximately 0.25 equivalents *N,N*-diisopropylethylamine and was used without further purification in subsequent experiments.

^1H NMR (400MHz, CD_3OD): δ = 1.5(3H, t), 3.16(6H, m), 4.8(2H, m), 7.75(1H, d), 7.85(1H, d) ppm.

LRMS (ES): m/z 306 $[\text{M}+\text{H}]^+$.

Preparation 17

(*R*)-3-Ethoxy-4-(1-phenylpropylamino)cyclobut-3-ene-1,2-dione



To a stirred solution of 3,4-diethoxycyclobut-3-ene-1,2-dione (2.32g, 13.7mmol) in absolute ethanol (40 mL), at room temperature, was added, in a single portion, (*R*)-1-phenylpropan-1-amine (1.85g, 13.7mmol). The resulting solution was stirred at room temperature for 16 hours and then concentrated *in vacuo* to give a colourless oil. The oil was dissolved in ethyl acetate and the resulting solution was washed with 10% aqueous citric acid solution and water. The organic phase was further washed with saturated aqueous sodium hydrogen carbonate, then water and finally saturated aqueous sodium chloride solution. The organic phase was then dried

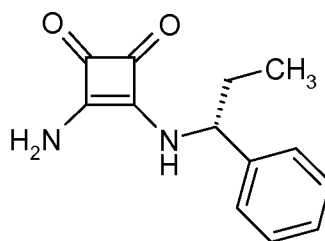
59

over magnesium sulfate and concentrated *in vacuo* to furnish the title compound as a clear oil, 3.22g.

^1H NMR (400MHz, CDCl_3): δ = 0.95 (3H, t), 1.40 (3H, t), 1.87-2.03 (2H, m), 4.58 (1H, bs), 4.73 (2H, q), 6.69 (1H, bs), 7.25-7.37 (5H, m) ppm.

Preparation 18

3-Amino-4-(1-phenyl-propylamino)-cyclobut-3-ene-1,2-dione



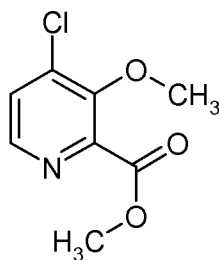
(*R*)-3-Ethoxy-4-(1-phenylpropylamino)cyclobut-3-ene-1,2-dione (Preparation 17, 580mg, 2.24mmol) was dissolved in absolute ethanol (10mL). Ammonia solution (7M in methanol, 0.8mL, 5.59mmol) was added and the reaction mixture was stirred at room temperature overnight. A precipitate had formed which was filtered and washed with methanol (2 x 20mL) to furnish the title compound as a solid, 260mg.

^1H NMR (400MHz, $\text{DMSO}-d_6$): δ = 0.88 (3H, t), 1.86 (2H, m), 4.94 (1H, m), 7.24-7.40 (5H, m), 7.44 (1H m), 7.77 (1H m) ppm.

LRMS (ES): m/z 229 $[\text{M}-\text{H}]^-$.

Preparation 19

Methyl 4-chloro-3-methoxypicolinate

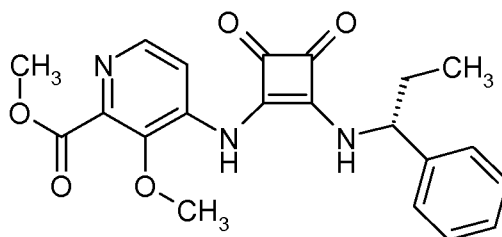


A mixture of 4-chloro-3-methoxypicolinic acid (Preparation 8, 5.0g, 26.6mmol), potassium carbonate (5.50g, 39.9mmol) and dimethylformamide (50mL) was stirred at room temperature for 30 minutes. Methyl iodide (2.5ml, 39.9mmol) was added and the reaction mixture was stirred at room temperature for 2 hours. The mixture was diluted with water and extracted with ethyl acetate. The organic layer was separated, washed with further water, dried and concentrated *in vacuo* to give the product as a light yellow liquid, 4.95g.

^1H NMR (400MHz, $\text{DMSO}-d_6$): δ = 3.88 (3H, s), 3.90 (3H, s), 7.81 (1H, d), 8.35 (1H, d) ppm.

Preparation 20

(R)-Methyl 4-(3,4-dioxo-2-(1-phenylpropylamino)cyclobut-1-enylamino)-3-methoxypicolinate

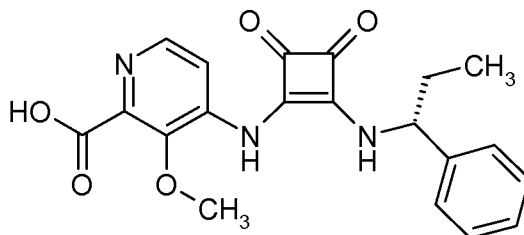


A mixture of (R)-3-amino-4-(1-phenylpropylamino)cyclobut-3-ene-1,2-dione (Preparation 18, 1.00g, 4.96mmol), methyl 4-chloro-3-methoxypicolinate (Preparation 19, 1.43g, 6.2mmol), cesium carbonate (2.42g, 7.44mmol) and 2-methylbutan-2-ol (25mL) was de-gassed with argon. Tris(dibenzylideneacetone) dipalladium(0) (227mg (0.248mmol) and Bippyphos® (251mg, 0.496mmol) were added and the reaction mixture was heated in a sealed tube at 80°C for 16 hours. The reaction mixture was filtered through a small bed of Celite® and the filtrate was diluted with water (100mL) and extracted with ethyl acetate (3 × 100mL). The combined organic layers were dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with dichloromethane:methanol (gradient elution, 99:1 to 95:5 by volume) to furnish the title compound as a brown solid, 750mg.

^1H NMR (400MHz, $\text{DMSO}-d_6$): δ = 0.88 (3H, t), 1.94 (2H, m), 3.81 (3H, s), 3.87 (3H, s), 5.09 (1H, q), 7.31 (1H, m), 7.38 (4H, m), 8.10 (1H, d), 8.22 (1H, d), 8.81 (1H, d), 9.69 (1H, s) ppm.

Preparation 21

(R)-4-(3,4-Dioxo-2-(1-phenylpropylamino)cyclobut-1-enylamino)-3-methoxypicolinic acid



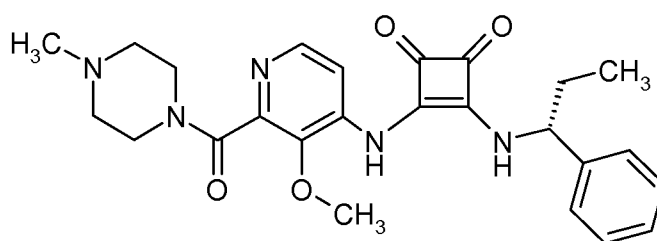
To a stirred solution of (R)-methyl 4-(3,4-dioxo-2-(1-phenylpropylamino)cyclobut-1-enylamino)-3-methoxypicolinate (Preparation 20, 750mg, 1.89mmol) in THF (8mL) was added a solution of lithium hydroxide monohydrate (119mg, 2.84mmol) in water (2ml) at 0°C. The reaction mixture was allowed to warm to room temperature and stirred for 2 hours. The reaction mixture was diluted with water (50mL) and washed with ethyl acetate (2 × 20mL). The aqueous was then acidified with hydrochloric acid (2N) to pH 4-5 and the resulting precipitate was filtered, triturated

with diethyl ether (3 × 10mL) and dried under vacuum to give the title compound as a brown solid, 400mg.

¹H NMR (400MHz, DMSO-*d*₆): δ = 0.91 (3H, t), 1.96 (2H, m), 3.85 (3H, s), 5.11 (1H, q), 7.32 (1H, m), 7.40 (4H, m), 8.09 (1H, d), 8.21 (1H, d), 8.89 (1H, d), 9.72 (1H, bs) ppm.

Preparation 22

(R)-3-(3-Methoxy-2-(1-methylpiperazine-4-carbonyl)pyridin-4-ylamino)-4-(1-phenylpropylamino)cyclobut-3-ene-1,2-dione

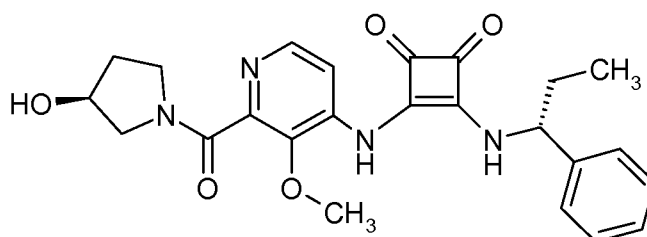


To a stirred solution of (*R*)-4-(3,4-dioxo-2-(1-phenylpropylamino)cyclobut-1-enylamino)-3-methoxypicolinic acid (Preparation 21, 150mg, 0.393mmol), 1-methylpiperazine (118mg, 1.18mmol) and HATU (225mg, 0.589mmol) in dimethylformamide (2mL) was added *N,N*-diisopropylethylamine (0.195mL, 1.18mmol) and the resulting mixture was stirred at room temperature for 16 hours. The reaction mixture was diluted with water (20mL) and extracted with ethyl acetate (4 × 20mL). The combined organic layers were dried over sodium sulfate and concentrated *in vacuo*. The residue was azeotroped with toluene (2 × 5mL) and triturated with diethyl ether (3 × 5mL) to furnish the title compound as a brown solid, 100mg.

LRMS (ES): *m/z* 464 [M+H]⁺.

Preparation 23

3-(2-((S)-3-Hydroxypyrrolidine-1-carbonyl)-3-methoxypyridin-4-ylamino)-4-((R)-1-phenylpropylamino)cyclobut-3-ene-1,2-dione



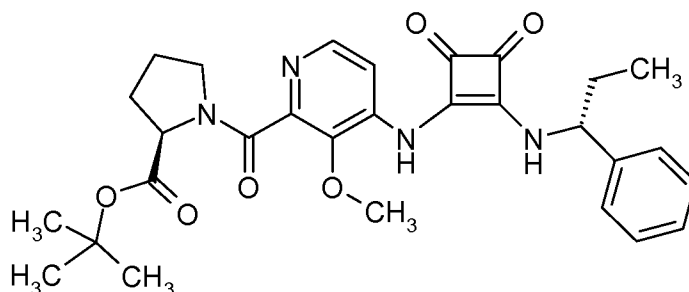
To a stirred solution of (*R*)-4-(3,4-dioxo-2-(1-phenylpropylamino)cyclobut-1-enylamino)-3-methoxypicolinic acid (Preparation 21, 100mg, 0.262mmol), (*S*)-pyrrolidin-3-ol (69mg, 0.787mmol) and HATU (150mg, 0.393mmol) in dimethylformamide (1.3mL) was added *N,N*-diisopropylethylamine (0.130mL, 0.787mmol). The reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was diluted with water (10mL) and extracted

with ethyl acetate (4 × 10mL). The combined organic layers were dried using sodium sulfate and concentrated *in vacuo*. The residue was triturated with diethyl ether (2 × 5ml) and dried to furnish the title compound as a brown solid, 150mg.

LRMS (ES): m/z 451 $[M+H]^+$.

Preparation 24

(R)-Tert-butyl 1-(4-(3,4-dioxo-2-((R)-1-phenylpropylamino)cyclobut-1-enylamino)-3-methoxypicolinoyl)pyrrolidine-2-carboxylate

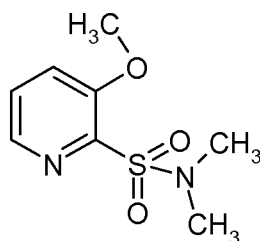


To a stirred solution of (R)-4-(3,4-dioxo-2-(1-phenylpropylamino)cyclobut-1-enylamino)-3-methoxypicolinic acid (Preparation 21, 100mg, 0.262mmol), (R)-tert-butyl pyrrolidine-2-carboxylate (135mg, 0.787mmol) and HATU (150mg, 0.393mmol) in dimethylformamide (1.3mL) was added *N,N*-diisopropylethylamine (0.130mL, 0.787mmol) and the resulting mixture was stirred at room temperature for 16 hours. The reaction mixture was diluted with ethyl acetate (100mL) and washed with water (5 × 20mL) and saturated aqueous sodium chloride solution. The organic layer was dried over sodium sulfate and concentrated *in vacuo*. The crude compound was triturated with diethyl ether (3 × 10mL) to furnish the title compound as a brown solid, 150mg.

LRMS (ES): m/z 535 $[M+H]^+$.

Preparation 25

3-Methoxy-*N,N*-dimethylpyridine-2-sulfonamide



Isopropylmagnesium chloride solution (2M in tetrahydrofuran, 9.77mL, 19.5mmol) was added dropwise via syringe to a stirred solution of 2-bromo-3-methoxypyridine (3.5g, 18.6mmol) in tetrahydrofuran (9.3mL), under nitrogen, at room temperature, to give an orange-red solution. After stirring for 1 hour at room temperature the reaction mixture was cooled to 0°C, sulfur

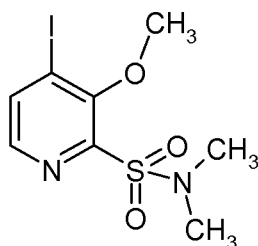
dioxide gas was bubbled through for 5 minutes and the reaction mixture was stirred at room temperature for 30 minutes. The reaction mixture was cooled to 0°C, treated with sulfonyl chloride (18.6mmol, 1.51mL), allowed to warm to room temperature and diluted with dimethylamine solution in THF (2M, 46.5mL, 93mmol). The reaction mixture was stirred at room temperature for 2 hours and quenched with water (20mL). Half the solvent was evaporated and the remaining mixture was basified with saturated aqueous sodium hydrogen carbonate solution. The product was extracted into dichloromethane. The combined organic phases were dried over magnesium sulfate and then concentrated *in vacuo* to leave a yellow oil which was purified by column chromatography on silica gel eluting with heptane:ethyl acetate (gradient elution, 100:0 to 0:100 by volume) to furnish the title compound as a white solid, 2.0g.

¹H NMR (400MHz, CDCl₃): δ = 3.09 (6H, s), 3.96 (3H, s), 7.36-7.42 (2H, m), 8.13 (1H, dd) ppm.

LRMS (ES): m/z 217 [M+H]⁺.

Preparation 26

4-Iodo-3-methoxy-N,N-dimethylpyridine-2-sulfonamide



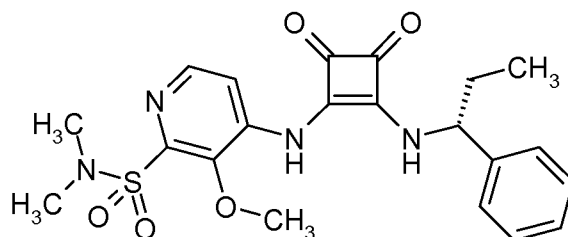
n-Butyl lithium (1.6M in hexane, 0.971mL, 1.55mmol) was added to a stirred solution of 2,2,6,6-tetramethylpiperidine (0.275mL, 1.63mmol) in tetrahydrofuran (1.5 mL) at -78°C under nitrogen and the reaction was stirred at this temperature for 30 minutes. A solution of 3-methoxy-N,N-dimethylpyridine-2-sulfonamide (Preparation 25, 320mg, 1.48mmol) in tetrahydrofuran (2.5 mL) was added dropwise to the reaction mixture which was then stirred at -78°C for 50 minutes to give a dark brown solution. A solution of iodine (1.78mmol, 451mg) in tetrahydrofuran (2.5 mL) was added quickly at -50°C and the reaction mixture was allowed to warm to room temperature for 1 hour, quenched with water (10mL) and basified with saturated aqueous sodium hydrogen carbonate solution. The product was extracted into dichloromethane and the combined organic phases were washed with saturated aqueous sodium thiosulfate solution, dried over magnesium sulfate then concentrated *in vacuo*. The resulting yellow oil was purified by column chromatography on silica gel eluting with heptane:ethyl acetate (gradient elution, 100:0 to 30:70 by volume) to furnish the title compound as a clear oil, 169mg.

¹H NMR (400MHz, CDCl₃): δ = 3.06 (6H, s), 4.03 (3H, s), 7.90 (2H, m) ppm.

LRMS (ES): m/z 343 [M+H]⁺.

Preparation 27

(R)-4-(3,4-Dioxo-2-(1-phenylpropylamino)cyclobut-1-enylamino)-3-methoxy-N,N-dimethylpyridine-2-sulfonamide



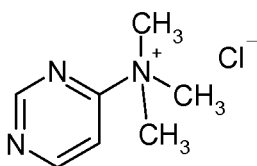
To a mixture of (*R*)-3-amino-4-(1-phenylpropylamino)cyclobut-3-ene-1,2-dione (Preparation 18, 40mg, 0.175mmol), 4-iodo-3-methoxy-N,N-dimethylpyridine-2-sulfonamide (Preparation 26, 60mg, 0.175mmol) and potassium carbonate (157mg, 1.14mmol) in a mixture of toluene (4mL), dioxan (0.4mL) and DMF (0.4mL) was added palladium(II) acetate (2.0mg, 0.009mmol) and xanthphos (5.2mg, 0.009mmol). The mixture was de-gassed with nitrogen and stirred in a sealed tube at 130°C in the microwave for 35 minutes. The cooled reaction mixture was diluted with ethyl acetate and washed with water and saturated aqueous ammonium chloride. The organic layer was further washed with saturated aqueous sodium chloride, dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with heptane:ethyl acetate (gradient elution, 95:5 to 0:100 by volume) to furnish the title compound as a yellow solid, 39mg.

¹H NMR (400MHz, CD₃OD): δ = 0.99 (3H, t), 1.96-2.08 (2H, m), 3.04 (6H, s), 3.97 (3H, s), 5.19 (1H, t), 7.28-7.43 (5H, m), 8.20 (1H, m), 8.26 (1H, m) ppm.

LRMS (ES): m/z 445 [M+H]⁺.

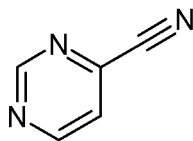
Preparation 28

N,N,N-Trimethylpyrimidin-4-aminium chloride



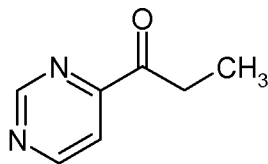
To a solution of trimethylamine (957mmol) in toluene (330mL) at 0°C was added a solution of 4-chloropyrimidine (19.0g, 165.9mmol) in toluene at 0°C. The mixture was allowed to warm to room temperature and stirred overnight. The precipitate which formed was filtered, washed with diethyl ether (2 × 50mL) and dried *in vacuo* to furnish the title compound as a solid, 13.5g.

¹H NMR (400MHz, DMSO-*d*₆): δ = 3.60 (9H, s), 8.28 (1H, d), 9.30 (1H, d), 9.42 (1H, s) ppm.

Preparation 29Pyrimidine-4-carbonitrile

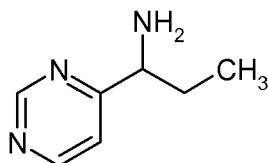
To a suspension of *N,N,N*-trimethylpyrimidin-4-aminium chloride (Preparation 28, 13.3g, 76.6mmol) in dichloromethane (76mL), at 0°C, was added dropwise a solution of tetraethylammonium cyanide (13.2g, 84.2mmol) in dichloromethane (76mL). The mixture was allowed to warm to room temperature and stirred for 1 hour. Water (100mL) was added, the organic phase was separated and the aqueous phase was extracted with dichloromethane (2 × 100mL). The combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to give a crude residue. Purification by column chromatography on silica gel eluting with 10-20% ethyl acetate in hexane gave the title compound as a liquid (7.0 g).

¹H NMR (400MHz, CDCl₃): δ = 7.66 (1H, d), 8.99 (1H, d), 9.36 (1H, s) ppm.

Preparation 301-(Pyrimidine-4-yl)propan-1-one

Ethyl magnesium bromide (3.0M in diethyl ether, 19mL) was added slowly by dropwise addition to a solution of pyrimidine-4-carbonitrile (Preparation 29, 6g, 57.1mmol) in diethyl ether at 0°C. The reaction mixture was allowed to warm to room temperature and stirred for 2 hours. The reaction mixture was treated with hydrochloric acid solution (2N, 60mL) and stirred for 0.5 hours at room temperature. The reaction was neutralised with saturated aqueous sodium hydrogen carbonate solution and extracted with diethyl ether (3 × 50 mL). The organic extracts were combined, washed with saturated aqueous sodium chloride solution, dried over sodium sulfate and concentrated *in vacuo* to give a crude residue. Purification by column chromatography on silica gel, eluting with 1% to 10% ethyl acetate in hexane, gave the title compound as a liquid, 2.5g.

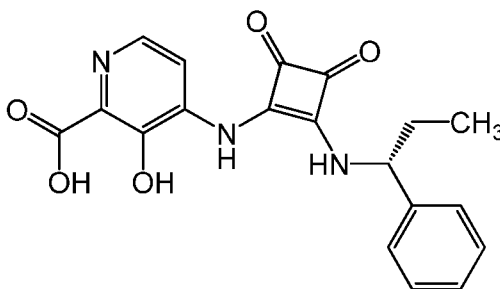
¹H NMR (400MHz, CDCl₃): δ= 1.20 (3H, t), 3.20 (2H, q), 7.87 (1H, d), 8.96 (1H, d), 9.33 (1H, s) ppm.

Preparation 311-(Pyrimidine-4-yl)propan-1-amine

To a solution of 1-(pyrimidine-4-yl)propan-1-one (Preparation 30, 2.5g, 18.4mmol) in methanol (144mL) was added ammonium acetate (21.2g, 275mmol) and the mixture was stirred for 2 hours at room temperature. The reaction mixture was cooled to 0°C and sodium cyanoborohydride (8.65g, 137mmol) was added portionwise. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was concentrated *in vacuo*, diluted with water, basified to pH 13-14 by the addition of 5% aqueous sodium hydroxide solution and extracted with dichloromethane (6 × 50mL). The combined organic extracts were dried over sodium sulfate and concentrated *in vacuo* and the crude residue was purified by column chromatography on silica gel eluting first with a mixture of dichloromethane and ammonia (1-2%) then dichloromethane, ammonia and 1-5% methanol to give the free amine 1-(pyrimidine-4-yl)propan-1-amine, 1.2g.

¹H NMR (400MHz, DMSO-*d*₆): δ= 0.85 (3H, t), 1.50-1.75 (2H, m), 3.75 (1H, m), 7.56 (1H, d), 8.71 (1H, d), 9.06 (1H, s) ppm.

LRMS (ES): *m/z* 138 [M+H]⁺.

Preparation 32(R)-4-(3,4-Dioxo-2-(1-phenylpropylamino)cyclobut-1-enylamino)-3-hydroxypyridine-5-carboxylic acid

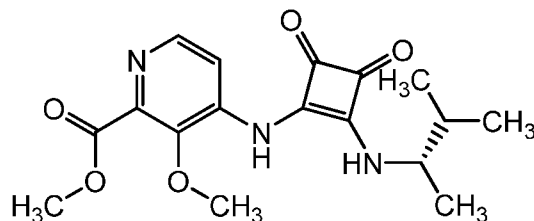
(*R*)-4-(3,4-Dioxo-2-(1-phenylpropylamino)cyclobut-1-enylamino)-3-methoxypyridine-5-carboxylic acid (Preparation 21, 1.0g, 2.6mmol) was suspended in dichloromethane (10.5mL) and cooled to 0°C. A solution of boron tribromide in dichloromethane (1.0M, 2.09mL, 20.9mmol) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 3 hours. The reaction was poured onto a mixture of dichloromethane and ice water (1:1) and stirred for 15 minutes. The organic phase was separated, dried over anhydrous sodium sulfate and concentrated *in vacuo* to afford the title compound as a solid (850mg, 88%).

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^1H NMR (400MHz, $\text{DMSO}-d_6$): δ = 0.90 (m, 3H), 1.92 (m, 2H), 5.10 (m, 1H), 7.31-7.41 (m, 5H), 7.90 (m, 1H), 8.30 (m, 1H), 9.34 (m, 1H), 10.38 (s, 1H) ppm, 2 exchangeables not observed.

Preparation 33

(S)-Methyl 3-methoxy-4-(2-(3-methylbutan-2-ylamino)-3,4-dioxocyclobut-1-enylamino)picolinate

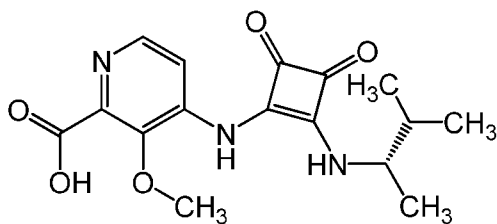


Methyl 4-chloro-3-methoxypicolinate (Preparation 19, 6.0g, 29.76mmol) and (S)-3-ethoxy-4-(3-methylbutan-2-ylamino)cyclobut-3-ene-1,2-dione (Preparation 13, 6.78g, 37.20mmol) were combined and suspended in 2-methyl-2-butanol (75mL). Cesium carbonate (14.5g, 44.64mmol), 5-(di-tert-butylphosphino)-1',3',5'-triphenyl-1'H-1,4'-bipyrazole (1.5g, 2.96mmol) and bis(dibenzylideneacetone)palladium(0) (1.36g, 1.49mmol) were added. The reaction vessel was degassed with Argon and heated at 90°C for 14 hours. The reaction mixture was filtered through Celite and washed with ethanol. Solvent was removed *in vacuo* and column chromatographic purification on silica gel eluting with 2% methanol in dichloromethane afforded the title compound as a solid (3.1g, 30%).

^1H NMR (400MHz, $\text{DMSO}-d_6$): δ = 0.91 (m, 6H), 1.20-1.22 (m, 3H), 1.76-1.78 (m, 1H), 3.84 (s, 3H), 3.89 (s, 3H), 4.04 (m, 1H), 8.14 (m, 1H), 8.24(m, 1H), 8.38-8.40 (m, 1H), 9.67 (m, 1H) ppm.

Preparation 34

(S)-3-Methoxy-4-(2-(3-methylbutan-2-ylamino)-3,4-dioxocyclobut-1-enylamino)picolinic acid



(S)-Methyl-3-methoxy-4-(2-(3-methylbutan-2-ylamino)-3,4-dioxocyclobut-1-enylamino)picolinate (Preparation 33, 9.1g, 26.22mmol) was dissolved in tetrahydrofuran (105mL) and the resulting solution was cooled to 0°C. A solution of lithium hydroxide (1.66g, 39.62mmol) in water (26.4mL) was added and the reaction was stirred at room temperature for 4 hours. Ethyl acetate and water were added and the layers were separated. The aqueous phase was acidified to pH6 using aqueous 2N HCl and a precipitate was formed which was collected by

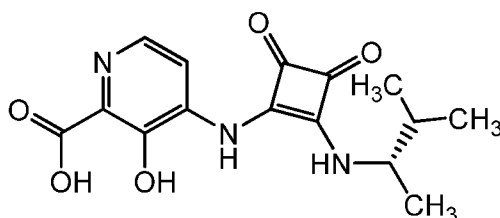
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filtration and washed with diethyl ether to afford the title compound as a yellow solid (8.5g, 97%).

^1H NMR (400MHz, $\text{DMSO}-d_6$): δ = 0.90 (m, 6H), 1.20-1.22 (m, 3H), 1.77 (m, 1H), 3.9 (s, 3H), 4.04 (m, 1H), 8.13 (m, 1H), 8.22 (m, 1H), 8.49 (m, 1H), 9.72 (s, 1H) ppm, 1 exchangeable not observed.

Preparation 35

(S)-3-Hydroxy-4-(2-(3-methylbutan-2-ylamino)-3,4-dioxocyclobut-1-enylamino)picolinic acid

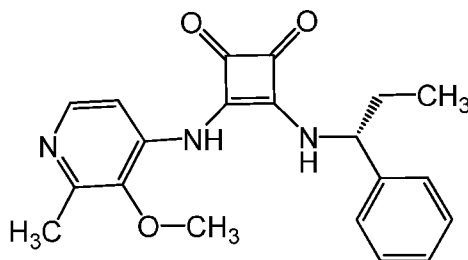


(S)-3-Methoxy-4-(2-(3-methylbutan-2-ylamino)-3,4-dioxocyclobut-1-enylamino)picolinic acid (Preparation 34, 2.0g, 6.0mmol) was dissolved in dichloromethane (24mL) and cooled to 0°C. A solution of boron tribromide in dichloromethane (1.0M, 24.04mL) was added and the reaction mixture was stirred at room temperature for 4.5 hours. The reaction mixture was quenched with cold aqueous sodium bicarbonate solution, forming a precipitate that was filtered off and washed with ether to afford the title compound as a solid (1.3g, 68%).

^1H NMR (400MHz, $\text{DMSO}-d_6$): δ = 0.90 (m, 6H), 1.17 (m, 3H), 1.75 (m, 1H), 4.01-4.10 (m, 1H), 7.66 (m, 1H), 7.92 (m, 1H), 8.49 (m, 1H), 9.50 (s, 1H) ppm, 2 exchangeables not observed.

Preparation 36

(R)-3-(3-Methoxy-2-methylpyridin-4-ylamino)-4-(1-phenylpropylamino)cyclobut-3-ene-1,2-dione



4-Chloro-3-methoxy-2-methylpyridine (see Journal of Medicinal Chemistry, 1992, 35(6), 1049; 200mg, 1.27mmol), (R)-3-amino-4-(1-phenyl-propylamino)-cyclobut-3-ene-1,2-dione (Preparation 18, 583.8mg, 2.538mmol) and potassium carbonate (350.3mg, 2.538mmol) were mixed with 1,4-dioxane (30 mL) and the reaction mixture was purged with Argon. Palladium (II) acetate (14.2mg, 0.063mmol) and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xanthphos) (73.4mg, 0.126mmol) were added and the reaction mixture was heated at reflux for 16 hours. The reaction mixture was filtered and the filtrate was purified by column

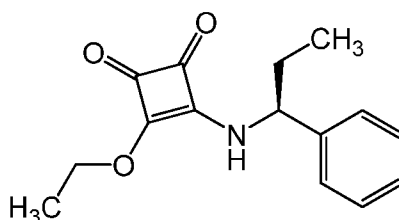
chromatography on silica gel eluting with 2% methanol in dichloromethane to afford a yellow solid (32mg).

^1H NMR (400MHz, $\text{DMSO}-d_6$): δ = 0.91 (t, 3H), 1.95 (m, 2H), 2.41 (s, 3H), 3.75 (s, 3H), 5.10 (m, 1H), 7.32-7.42 (m, 5H), 7.86 (s, 1H), 8.06 (d, 1H), 8.79 (d, 1H), 9.54 (s, 1H) ppm.

LRMS m/z 352.4 $[\text{M}+\text{H}]^+$.

Preparation 37

(S)-3-Ethoxy-4-(1-phenylpropylamino)cyclobut-3-ene-1,2-dione

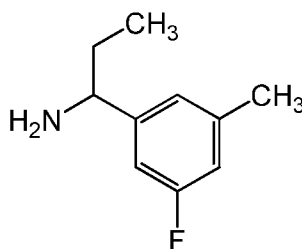


To a stirred solution of 3,4-diethoxycyclobut-3-ene-1,2-dione (5.46g, 32.1mmol) in absolute ethanol (80 mL), at room temperature, was added dropwise (S)-1-phenylpropan-1-amine (3.95, 29.2mmol) over 5 minutes. The resultant solution was stirred at room temperature for 3 hours and then concentrated *in vacuo* to give a brown oil. The crude product was purified by column chromatography on silica gel eluting with a gradient of from 25% to 100% 2-methoxy-2-methylpropane in heptane to afford a yellow oil. This oil was dissolved in ethyl acetate and pentane added to give a white precipitate which was filtered and dried to afford the title compound as a white solid (4.30g, 57%).

^1H NMR (400MHz, CDCl_3): δ = 0.95 (t, 3H), 1.40 (t, 3H), 1.87-2.03 (m, 2H), 4.58 (bs, 1H), 4.73 (q, 2H), 6.50 (bs, 1H), 7.25-7.37 (m, 5H) ppm.

Preparation 38

1-(3-Fluoro-5-methylphenyl)propylamine



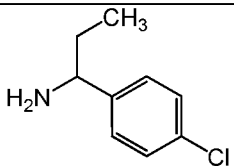
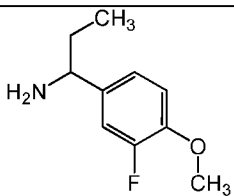
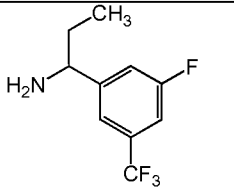
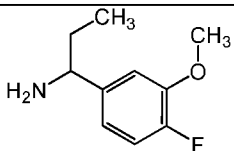
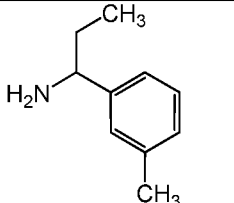
Step A: To a stirred solution of 3-fluoro-5-methylbenzoic acid (7.5g, 32.43mmol) in dichloromethane (50mL) was added oxalyl chloride (7.86mL, 97.31mmol), at 0°C, followed by a few drops of dimethylformamide and the reaction mixture was stirred at room temperature for 2 hours. The solvent was removed *in vacuo* and the residue was dried for a further 30 minutes

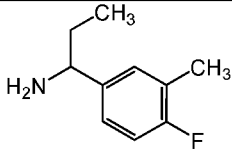
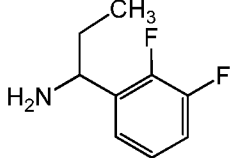
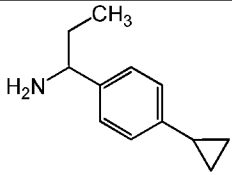
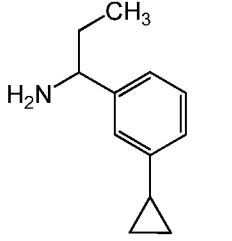
under vacuum. The material thus obtained was dissolved in dichloromethane (50mL). O,N-Dimethylhydroxylamine hydrochloride (4.74g, 48.64mmol) was added along with DIPEA (14.12mL, 81.09mmol) and the reaction was stirred at room temperature overnight. The mixture was diluted with dichloromethane and water, the phases were separated and the organic phase was washed with water (twice) and brine, dried using anhydrous sodium sulfate and concentrated *in vacuo*. Purification by silica column chromatography eluting with 15% ethyl acetate in hexane gave 5.6g of 3-fluoro-N-methoxy-5,N-dimethylbenzamide. LRMS: m/z 198 [M+H].

Step B: Ethyl magnesium bromide (3.0M in diethyl ether, 38mL, 113.70mmol) was added dropwise at 0°C to a solution of the product of Step A (5.6g, 28.42mmol) in tetrahydrofuran (100mL) and the reaction mixture was stirred at room temperature for 30 minutes. The reaction was quenched with aqueous ammonium chloride and then extracted with ethyl acetate. The ethyl acetate extract was washed with brine, dried over magnesium sulfate and concentrated *in vacuo*. Purification by silica column chromatography eluting with 5% ethyl acetate in hexane gave 3.5g of 1-(3-fluoro-5-methylphenyl)propan-1-one. ¹H-NMR (400MHz, CDCl₃): δ = 1.19-1.22 (t, 3H), 2.3 (s, 3H), 2.92-2.97 (m, 3H), 7.07 (d, 1H), 7.42 (d, 1H), 7.5 (s, 1H) ppm.

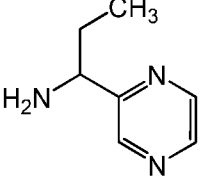
Step C: A mixture of the product of step B (3.5g, 21.08mmol), titanium(IV) isopropoxide (17.4, 63.25mmol) and 7M ammonia in methanol (15.05mL, 10.54mmol) was stirred at room temperature for 6 hours, sodium borohydride (1.196g, 31.62mmol) was added at 0°C (caution: effervescence) and the resulting mixture was stirred at room temperature overnight. The almost solid mixture was diluted with aqueous ammonia solution (60mL), stirred for 15 minutes, filtered and washed with ethyl acetate. The two phase filtrate was separated and the aqueous phase was washed with further ethyl acetate. The combined organic extracts were washed with 2N HCl. The aqueous phase was basified with saturated aqueous sodium carbonate and then re-extracted with ethyl acetate. The ethyl acetate extract was washed with brine, dried using magnesium sulfate and concentrated *in vacuo* to afford the title compound (1.5g). ¹H-NMR (400MHz, DMSO-*d*₆): δ = 0.7-0.8 (t, 3H), 1.4-1.5 (m, 2H), 2.29 (s, 3H), 3.65-3.68 (m, 1H), 6.8-6.9 (m, 3H) ppm, 2 exchangeables not observed.

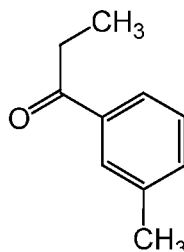
The following compounds were prepared using the method of Preparation 38 from starting materials as described in the table.

Preparation Number	Structure	Name	Preparation and Characterisation
39		1-(4-Chlorophenyl)propylamine	Prepared in an analogous manner to Preparation 38 step C starting with 1-(4-chlorophenyl)propan-1-one. ¹ H NMR (400MHz, CDCl ₃): δ = 0.85 (t, 3H), 1.60-1.73 (m, 4H), 3.79 (m, 1H), 7.23-7.30 (m, 4H) ppm.
40		1-(3-Fluoro-4-methoxyphenyl)propylamine	Prepared in an analogous manner to Preparation 38 starting with 3-fluoro-4-methoxybenzoic acid. ¹ H NMR (400MHz, DMSO- <i>d</i> ₆): δ = 0.73 (t, 3H), 1.73-1.80 (m, 1H), 1.91-1.96 (m, 1H), 3.8 (t, 3H), 4.0 (m, 1H), 7.1-7.2 (m, 2H), 7.3-7.4 (d, 1H), 8.4 (bs, 2H) ppm.
41		1-(3-Fluoro-5-trifluoromethylphenyl)propylamine	Prepared in an analogous manner to Preparation 38 starting with 3-fluoro-5-(trifluoromethyl)benzoic acid. ¹ H NMR (400MHz, DMSO- <i>d</i> ₆): δ = 0.75-0.78 (t, 3H), 1.81-1.99 (m, 2H), 4.2-4.3 (m, 1H), 7.71-7.80 (m, 3H), 8.4 (s, 2H) ppm.
42		1-(4-Fluoro-3-methoxyphenyl)propylamine	Prepared in an analogous fashion to Preparation 38, starting with 4-fluoro-3-methoxybenzoic acid. ¹ H NMR (400MHz, DMSO- <i>d</i> ₆): δ = 0.72-0.76 (t, 3H), 1.40-1.50 (m, 2H), 3.30 (m, 1H), 3.7 (s, 3H), 7.00-7.10 (m, 3H) ppm, 2 exchangeables not observed.
43		1-(3-Methylphenyl)-propylamine	Prepared in an analogous fashion to Preparation 38 step C starting with 1-(3-methylphenyl)propan-1-one (Preparation 49). ¹ H NMR (400MHz, DMSO- <i>d</i> ₆): δ = 0.73-0.76 (t, 3H), 1.74-1.81 (m, 1H), 1.92-1.97 (m, 1H), 2.30 (s, 3H), 4.00 (m, 1H), 7.1-7.4 (m, 4H) 8.4 (bs, 2H) ppm.

44		1-(4-Fluoro-3-methylphenyl)-propylamine	Prepared in an analogous fashion to Preparation 38 starting with 4-fluoro-3-methylbenzoic acid. ¹ H NMR (400MHz, DMSO- <i>d</i> ₆): δ = 0.73-0.80 (t, 3H), 1.40-1.60 (m, 2H), 2.21 (s, 3H), 3.65-3.68 (m, 1H), 7.0-7.20 (m, 3H) ppm, 2 exchangeables not observed. LRMS m/z [M+H] 202.
45		1-(2,3-Difluorophenyl)propylamine	Prepared in an analogous manner to Preparation 38 step C starting with 2,3 difluoropropiophenone. ¹ H NMR (400MHz, CDCl ₃): δ = 0.82-0.90 (t, 3H), 1.68-1.75 (m, 2H), 4.12 (t, 1H), 7.00 (m, 2H), 7.11 (m, 1H) ppm.
46		1-(4-Cyclopropylphenyl)propylamine	Prepared in an analogous fashion to Preparation 38 step C starting with 1-(4-cyclopropylphenyl)propan-1-one (Preparation 50). ¹ H NMR (400MHz, DMSO- <i>d</i> ₆): δ = 0.62 (m, 2H), 0.72-0.76 (t, 3H), 0.89-0.91(m, 2H), 1.50-1.57 (m, 2H), 1.86 (m, 1H), 3.65(m, 1H), 6.99 (d, 2H), 7.18 (d, 2H) ppm, 2 exchangeables not observed.
47		1-(3-Cyclopropylphenyl)propylamine	Prepared in an analogous fashion to Preparation 38 step C starting with 1-(3-cyclopropylphenyl)propan-1-one (Preparation 51). ¹ H NMR (400MHz, DMSO- <i>d</i> ₆): δ = 0.62 (m, 2H), 0.74-0.77 (t, 3H), 0.90-0.92 (m, 2H), 1.50-1.55 (m, 2H), 1.87-1.89 (m, 1H), 3.61-3.64 (m, 1H), 6.87 (d, 1H), 7.03-7.06 (d, 2H), 7.12-7.16 (m, 1H) ppm, 2 exchangeables not observed.

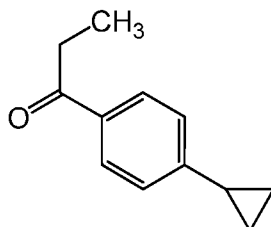
73

48		1-Pyrazin-2-yl propylamine	Prepared in an analogous manner to Preparation 38 step C starting with 1-pyrazine-2-ylpropan-1-one (Journal of Heterocyclic Chemistry, 1986, 23(2), 497). ¹ H NMR (400MHz, CDCl ₃): δ = 0.81 (t, 3H), 1.55-1.75 (m, 2H), 2.03 (bs, 2H), 3.80 (m, 1H), 8.51 (d, 2H), 8.69 (s, 1H) ppm.
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Preparation 491-(3-Methylphenyl)propan-1-one

A mixture of 1-(3-bromophenyl)propan-1-one (8.0g, 37.55mmol), trimethylboroxine (4.71g, 37.55mmol), potassium carbonate (15.65g, 112.65mmol), 1,4-dioxane (18.0mL) and water (18.0mL) was degassed and purged with argon for 30 minutes. (1,1'-Bis(diphenylphosphino)ferrocene)dichloropalladium(II) complex with dichloromethane (3.06g, 3.755mmol) was added and the resulting mixture was heated at reflux overnight. The reaction was cooled and filtered through Celite. The filtrate was diluted with ethyl acetate, washed with water and brine, dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was purified by silica column chromatography eluting with 1.5% ethyl acetate in hexane to afford the title compound (5.0g).

¹H NMR (400MHz, CDCl₃): δ = 1.19-1.22 (t, 3H), 2.4 (s, 3H), 2.95-3.00 (m, 2H), 7.30 (m, 2H), 7.70 (d, 2H) ppm.

Preparation 501-(4-Cyclopropylphenyl)propan-1-one

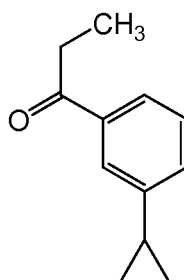
74

To a mixture of 1-(4-bromophenyl)propan-1-one (5.0g, 23.38mmol), cyclopropylboronic acid (3.9g, 35.07mmol), potassium phosphate (17.37g, 81.83mmol) and toluene (100mL) was added water (10mL), tricyclohexylphosphine (0.0653mg, 2.33mmol) and palladium(II) acetate (260mg, 1.16mmol) and the reaction mixture was heated at reflux under an argon atmosphere for 3 hours. The reaction was cooled, diluted with ethyl acetate, washed with water and brine, dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification by silica column chromatography eluting with 2% ethyl acetate in hexane gave the title compound (3.8g).

^1H NMR (400MHz, CDCl_3): δ = 0.74-0.82 (m, 2H), 0.90-1.00 (m, 2H), 1.10-1.20 (t, 3H), 1.80-1.90 (m, 1H), 2.92-2.97 (m, 2H), 7.00-7.10 (d, 2H), 7.83-7.85 (d, 2H) ppm.

Preparation 51

1-(3-Cyclopropylphenyl)propan-1-one

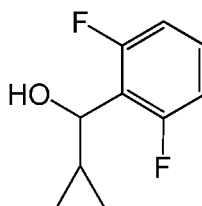


The title compound (1.9g) was prepared in an analogous fashion to Preparation 50 starting with 1-(3-bromophenyl)propan-1-one (3.0g, 17.24mmol).

^1H NMR (400MHz, $\text{DMSO}-d_6$): δ = 0.71-0.74 (m, 2H), 0.93-1.00 (m, 2H), 1.18-1.22 (t, 3H), 1.90-1.97 (m, 1H), 2.90-3.00 (m, 2H), 7.20 (d, 1H), 7.30 (t, 1H), 7.60 (s, 1H), 7.7 (d, 1H) ppm.

Preparation 52

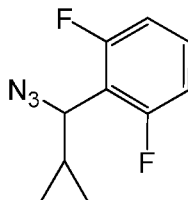
Cyclopropyl(2,6-difluorophenyl)methanol



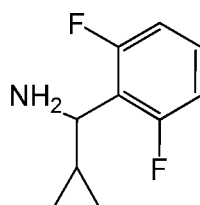
A solution of n-butyllithium (2.5M in hexanes, 350 mmol, 140 mL) was added dropwise to a solution 1,3-difluorobenzene (39.9 g, 350 mmol) in tetrahydrofuran (1000mL) at -78°C . After 1 hour, a solution of cyclopropylcarboxaldehyde (29.4 g, 420 mmol) in tetrahydrofuran (200 mL) was added to the reaction mixture, dropwise, at -78°C . After addition, the reaction mixture was warmed gradually to room temperature and stirred overnight. The reaction mixture was cooled to 0°C , and 60mL of saturated aqueous ammonium chloride was added. The aqueous layer was extracted by ethyl acetate (300mL) and the combined organic extracts were washed with brine,

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dried over anhydrous sodium sulfate and concentrated *in vacuo* to afford the title compound as a crude oil (65.3 g).

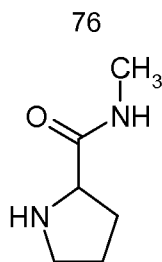
Preparation 532-[Azido(cyclopropyl)methyl]-1,3-difluorobenzene

Diphenyl phosphoryl azide (115.6 g, 420 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (63 mL, 420 mmol) were added to a solution of cyclopropyl(2,6-difluorophenyl)methanol (Preparation 52, 65 g, 350 mmol) in 280mL of toluene sequentially at 0°C. The reaction mixture was warmed to room temperature and then heated at 40°C overnight. The reaction mixture was cooled to 0°C and 100mL of brine was added. The layers were separated and the organic layer was dried over anhydrous sodium sulfate. Concentration followed by chromatography gave the title compound (62.5 g, 100 % based on 1,3-difluorobenzene).

Preparation 541-Cyclopropyl-1-(2,6-difluorophenyl) methylamine

Palladium (20% wt. % on activated carbon, 6.3g) was added to a solution of (2,6-difluorophenyl)(1-naphthyl)methyl azide (Preparation 53) (62.5g, 300 mmol) in ethanol (250mL) and ethyl acetate (250mL). The reaction mixture was stirred at room temperature under hydrogen (1 atmosphere) for 40 hours. The palladium was filtered off and the filtrate was concentrated *in vacuo*. Chromatography afforded the title compound (28.9 g, 53 %) as white solid.

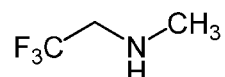
Preparation 55N-Methylpyrrolidine-2-carboxamide



The title compound was prepared from racemic proline as described by Shendage, D. M., et al. in *J. Am. Chem. Soc.*, **61**, 3675-3678.

Preparation 56

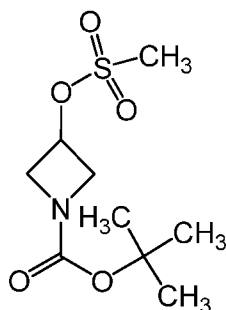
2,2,2-Trifluoro-N-methylethanamine hydrochloride



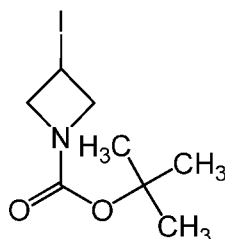
To a solution of lithium aluminiumhydride (69g, 1.8mol) in 1000mL of ether was added a solution of 2,2,2-trifluoro-N-methylacetamide (86g, 0.6mol) in ether at 0°C and the reaction mixture was stirred at room temperature overnight. Sodium sulfate decahydrate was added to the mixture at -10°C and the resulting suspension was filtered. Dry HCl gas was then bubbled into the filtrate to give a white solid. Isolation of the solid followed by recrystallization from methanol/ diethyl ether provided the title compound as a white solid (73g, 80.7% yield).

Preparation 57

tert-Butyl 3-(methylsulfonyloxy)azetidine-1-carboxylate

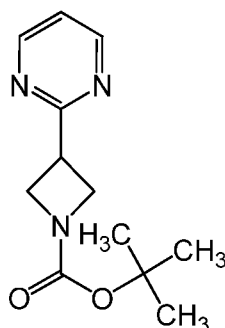


tert-Butyl 3-hydroxyazetidine-1-carboxylate (71g, 0.41 mol) was dissolved in dichloromethane (700mL). Triethylamine (114mL, 0.82 mol) was added and the solution was cooled in an ice bath before the addition of methanesulfonyl chloride (33.4mL, 0.43 mol) as a solution in dichloromethane (100mL). The reaction mixture was stirred at room temperature overnight and evaporated. The residue was dissolved in ether (500mL), triethylamine hydrochloride was filtered off, and the filtrate was evaporated. The residue was purified by column chromatography on silica gel eluting with hexane:ethyl acetate (3:1) to afford the title compound (80 g, 78%).
¹H NMR (400 MHz, DMSO-d₆): δ = 1.38 (s, 9H), 3.23 (s, 3H), 3.90–3.94 (m, 2H), 4.19–4.24 (m, 2H), 5.22–5.28 (m, 1H) ppm.

Preparation 58tert-Butyl 3-iodoazetidine-1-carboxylate

tert-Butyl 3-(methylsulfonyloxy)azetidine-1-carboxylate (Preparation 57, 80g, 0.318 mol) and potassium iodide (159g, 0.96 mol) were mixed in dimethylformamide (500 mL). The reaction mixture was stirred at 110°C for 7 hours. The solvent was evaporated and the resulting residue was suspended in water (1L). The product was extracted with ethyl acetate (800mL). The combined extracts were washed with water, dried using anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by column chromatography on silica gel eluting with ethyl acetate:hexane (1:4) to afford the title compound (64.6 g, 72%).

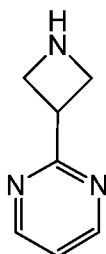
^1H NMR (400 MHz, DMSO- d_6): δ = 1.38 (s, 9H), 4.05–4.09 (m, 2H), 4.61–4.64 (m, 3H) ppm.

Preparation 59tert-Butyl 3-pyrimidin-5-ylazetidine-1-carboxylate

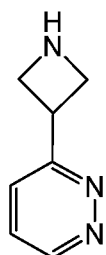
A 500mL three-necked flask equipped with a drop funnel and thermometer was charged with zinc dust (11.1 g, 0.17 mol). Dry tetrahydrofuran (150mL) was added. The mixture was degassed, and the flask was filled with argon. Dibromoethane (1 mL) was added in a flow of argon at room temperature. The mixture was kept at 60–65°C for 15 min and then cooled to room temperature. Trimethylsilyl chloride (1mL) was added, and the mixture was stirred for 1 hour. A solution of tert-butyl 3-iodoazetidine-1-carboxylate (Preparation 58, 28.3g, 0.1 mol) in dry tetrahydrofuran (75mL) was added dropwise and the reaction mixture was stirred for 1 hour and then degassed. $\text{Pd}(\text{PPh}_3)_4$ (1g) and a solution of 5-bromopyrimidine (19.1g, 0.12 mol) in THF (100 mL) were added. The mixture was degassed again, heated at reflux for 6 hours and filtered through Celite. After evaporation of the solvent, ethyl acetate (300mL) was added and

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the resulting mixture was washed with a solution of sodium hydrogencarbonate (50g) in water (500mL). The layers were separated, the aqueous layer was extracted with ethyl acetate and the combined organic extractions were dried with sodium sulfate and concentrated in vacuo. The residue was purified by column chromatography on silica gel, eluting with ethyl acetate to afford the title compound (15.1, 64%).

Preparation 602-(Azetidin-3-yl)pyrimidine hydrochloride

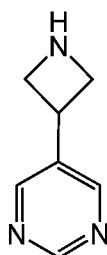
tert-Butyl 3-pyrimidin-5-ylazetidine-1-carboxylate (Preparation 59, 17.8 g, 0.078 mol) was dissolved in methanol (25mL) and 4M HCl in dioxane (90mL) was added at 20 °C. After 2 hours the precipitate which had formed was separated by filtration, washed with dioxane (100mL), THF (100mL), and ether (100mL) and dried to afford the title compound (12.5g, 79%).
¹H NMR (400 MHz, DMSO-d₆): δ = 4.16–4.32 (m, 5H), 7.48 (dd, 1H), 8.86 (d, 1H), 9.11 (s, 2H), 9.33 (s, 1H), 9.78 (s, 1H) ppm.

Preparation 613-(Azetidin-3-yl)pyridazine hydrochloride

The title compound was prepared from 3-chloropyridazine (see WO-2007/113232) and Preparation 58 using an analogous procedure to that described for Preparations 59 and 82 (3.7g, 54%).

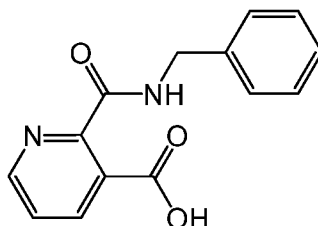
¹H NMR (400MHz, DMSO-d₆): δ = 4.13–4.22 (m, 2H), 4.26–4.36 (m, 3H), 8.00 (dd, 1H), 8.65 (d, 1H, 6 Hz), 8.81 (d, 1H, 6 Hz), 9.01 (s, 1H), 9.52 (br. s, 1H), 9.74 (br. s, 1H) ppm.

79

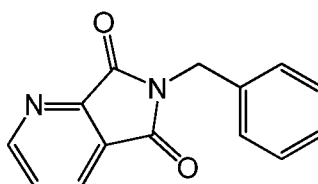
Preparation 625-(Azetidin-3-yl)pyrimidine hydrochloride

The title compound was prepared from 5-bromopyrimidine and Preparation 58 using an analogous procedure to that described for Preparations 59 and 82 (5.2 g, 39%).

¹H NMR: (400 MHz, DMSO- d₆): δ = 4.15–4.22 (m, 3H), 4.24–4.30 (m, 2H), 9.02 (s, 2H), 9.17 (s, 1H), 9.41–9.57 (s, 1H), 9.59–9.75 (s, 1H) ppm.

Preparation 632-(Benzylcarbamoyl)nicotinic acid

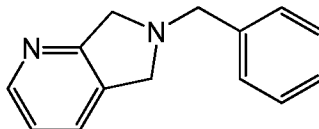
To a solution of furo[3,4-b]pyridine-5,7-dione (118 g, 0.789mol) in dry 1, 4-dioxane (60 mL) were added dropwise benzylamine (88.2mL, 0.824mol) and triethylamine (159.4g, 1.58mol) successively. Then the mixture was stirred at 30°C overnight. The solvents were removed by evaporation to give a syrup. The syrup was dried *in vacuo* at 60°C for 2 hours and used in subsequent reactions directly.

Preparation 646-Benzyl-5H-pyrrolo[3,4-b]pyridine-5,7(6H)-dione

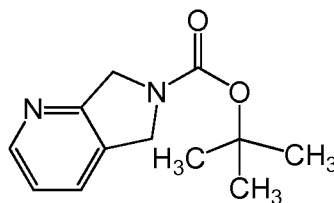
To 2-(benzylcarbamoyl)nicotinic acid (Preparation 63) (202.7 g, 0.789 mol) was added acetic anhydride (300mL), toluene (300mL) and trifluoro-acetic acid (30mL) successively. Then the mixture was heated to 100-110°C and stirred at this temperature overnight. Another portion of toluene (200mL) was added. Then the mixture was cooled to 0°C slowly. The solid formed in the

80

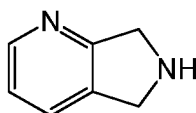
mixture was filtered, washed with toluene (150mL) and dried *in vacuo* to afford the title compound as an off-white solid (153.4 g 81%).

Preparation 656-Benzyl-6,7-dihydro-5H-pyrrolo[3,4-b]pyridine

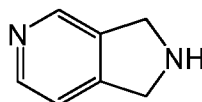
To a refluxing suspension of lithium aluminium hydride (24.5 g, 0.645 mol) in dry tetrahydrofuran (300mL) was added a suspension of 6-benzyl-5H-pyrrolo[3,4-b]pyridine-5,7(6H)-dione (Preparation 64, 76.8 g, 0.322 mol) in dry tetrahydrofuran (400mL) with vigorous stirring. After the addition of the 6-benzyl-5H-pyrrolo[3,4-b]pyridine-5,7(6H)-dione was complete, the mixture was stirred for another 20 minutes. The mixture was cooled to 0°C and quenched with 15% aqueous sodium hydroxide solution and stirred for 1 hour. The mixture was filtered, washed with ethyl acetate (120mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with dichloromethane:methanol (gradient elution 80:1 to 40:1) to afford the title compound as an orange liquid (13.8 g, 20%).

Preparation 66tert-Butyl 5H-pyrrolo[3,4-b]pyridine-6(7H)-carboxylate

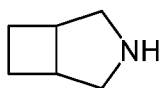
A mixture of 6-benzyl-6,7-dihydro-5H-pyrrolo[3,4-b]pyridine (Preparation 65, 27.5 g, 0.131 mol), di-tert-butyl dicarbonate (57 g, 0.262 mol), 20% Pd(OH)₂/C (2.0 g) and methanol (700mL) was stirred at 60°C in an autoclave under 15 atmospheres of hydrogen overnight. The catalyst was filtered off and the filtrate was concentrated. The residue was purified by column chromatography on silica gel eluting with petroleum ether:ethyl acetate (gradient elution 40:1 to 20:1) to afford the title compound as a colourless oil (3 g, 10 %).

Preparation 676,7-Dihydro-5H-pyrrolo[3,4-b]pyridine hydrochloride

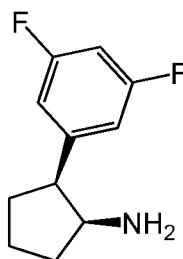
To a solution of tert-butyl-5H-pyrrolo[3,4-b]pyridine-6(7H)-carboxylate (Preparation 66, 4.9 g, 0.022 mol) in methanol (10mL) was added dropwise a saturated solution of hydrogen chloride in 1, 4-dioxane (50mL) at 0°C. The reaction mixture was stirred at room temperature for 3 hours. The solvent was concentrated *in vacuo* to afford the title compound as a grey solid (4.2 g, 98 %).

Preparation 682,3-Dihydro-1H-pyrrolo[3,4-c]pyridine hydrochloride

The title compound was prepared from furo[3,4-c]pyridine-1,3-dione using an analogous procedure to that described for Preparation 67.

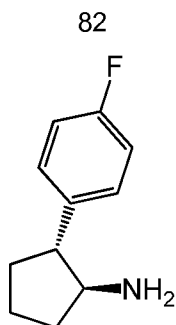
Preparation 693-Azabicyclo[3.2.0]heptane

The title compound was prepared by deprotection of benzyl 3-azabicyclo[3.2.0]heptane-3-carboxylate (see Salomon, R. G., et al., Tet. Lett., 1984, 30, 3167) by standard methods.

Preparation 70cis-2-(3,5-Difluorophenyl)cyclopentanamine

The title compound was prepared as described by Shepherd, T. A., et al., J. Med. Chem., 2002, 45, 2101.

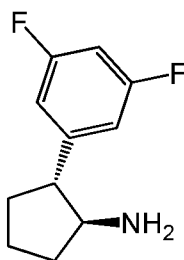
Preparation 71Trans-2-(4-fluorophenyl)cyclopentanamine



The title compound was prepared as described by Shepherd, T. A., et al., J. Med. Chem., 2002, 45, 2101 from 4-fluorophenyl magnesium bromide.

Preparation 72

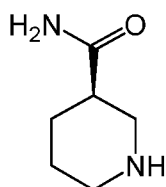
(1S,2R)-2-(3,5-Difluorophenyl)cyclopentanamine



The title compound was prepared as described by Shepherd, T. A., et al., J. Med. Chem., 2002, 45, 2101 from 3,5-fluorophenyl magnesium bromide.

Preparation 73

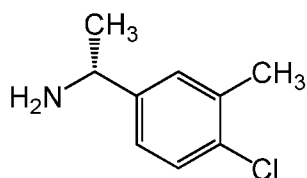
(R)-piperidine-3-carboxamide



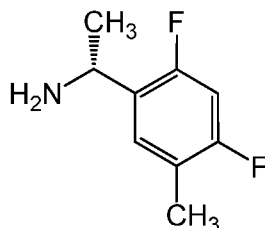
The title compound was prepared as described in WO-2006/123257, starting from (R)-3-carbamoyl-piperidine-1-carboxylic acid tert-butyl ester.

Preparation 74

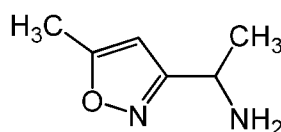
(R)-1-(4-Chloro-3-methylphenyl)ethanamine hydrochloride



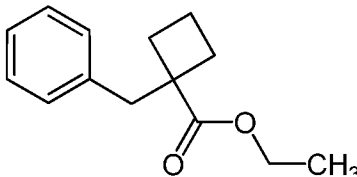
The title compound was prepared as described by Colyer, J. T., et al.; J. Org. Chem., 2006, 71, 6859 starting from 4-chloro-3-methylbenzaldehyde.

Preparation 75(R)-1-(2,4-Difluoro-5-methylphenyl)ethanamine hydrochloride

The title compound was prepared using the method of Colyer, J. T., et al., J. Org. Chem., 2006, 71, 6859 starting from 2,4-difluoro-5-methylbenzaldehyde.

Preparation 761-(5-Methylisoxazol-3-yl)ethanamine

The title compound was prepared using the method described by Ghosh, A. K., et al., J. Med. Chem., 2007, 50, 2399-2407 starting from ethyl 5-methylisoxazole-3-carboxylate.

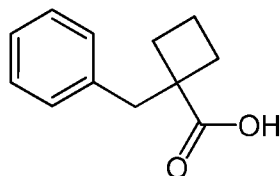
Preparation 77Ethyl 1-benzylcyclobutanecarboxylate

To a solution of lithium bis(trimethylsilyl)amide solution (287mL, 0.28 mol) in tetrahydrofuran (500mL) was added dropwise a solution of ethyl cyclobutanecarboxylate (35g, 0.273 mol) in tetrahydrofuran (50mL) while keeping the temperature between -60°C and -65°C. After the addition, the reaction mixture was stirred at -60°C to -65°C for 2 hours. A solution of benzyl bromide (49g, 0.287 mol) in tetrahydrofuran (50mL) was added dropwise and the resulting mixture was stirred at -60°C to -65°C for 1 hour and at room temperature for 3 hours. The reaction was quenched by the addition of saturated ammonium chloride aqueous solution (200mL) and the organic phase was separated. The aqueous layer was extracted with ethyl acetate (1.8L). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography

on silica gel eluting with petroleum ether:ethyl acetate (100:1) to afford the title compound as a yellow liquid (39 g, 63%).

Preparation 78

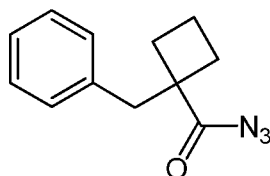
1-Benzylcyclobutanecarboxylic acid



To a solution of ethyl 1-benzylcyclobutanecarboxylate (Preparation 77, 56g, 0.26 mol) in methanol:tetrahydrofuran:water (250mL:125mL:63mL) was added lithium hydroxide hydrate (32.3g, 0.77mol), in portions, at 0°C. After the addition was complete, the reaction mixture was heated at 50°C for 8 hours. The volatiles were removed and water was added. The aqueous solution was washed with petroleum ether to remove impurities. The aqueous layer was acidified with conc. HCl until the solution was at pH 2 and then extracted with dichloromethane (600mL). The combined organic layers were washed with brine, dried using anhydrous sodium sulfate and concentrated *in vacuo* to afford the title compound as a white solid (46 g, 94%).

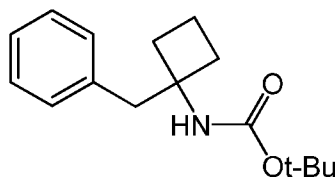
Preparation 79

1-Benzylcyclobutanecarbonyl azide

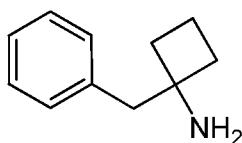


1-Benzylcyclobutanecarboxylic acid (Preparation 78, 30 g, 0.16 mol) was suspended in water (30mL) and acetone (450mL) was added. A solution of triethylamine (28.5 mL, 0.21mol) in acetone (50mL) was added dropwise at 0°C followed by a solution of ethyl chloroformate (20.1 mL, 0.21 mol) in acetone (50mL). The resulting mixture was stirred at 0°C for 30 min and a solution of sodium azide (15.6 g, 0.24 mol) in water (100mL) was added dropwise. The resulting mixture was stirred at 0°C for one hour. The reaction mixture was poured onto crushed ice and thoroughly extracted with ether. The combined ether extracts were washed with water, dried using anhydrous sodium sulfate and concentrated *in vacuo* to afford the title compound as a yellow liquid (27.6 g, 80%).

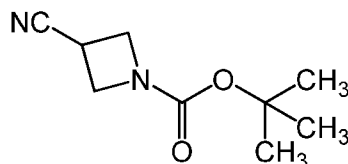
85

Preparation 80tert-Butyl 1-benzylcyclobutylcarbamate

A solution of 1-benzylcyclobutanecarbonyl azide (Preparation 79, 55.2 g, 0.26 mol) in toluene (500mL) was heated at reflux for 1 hour. After the reaction mixture was cooled to room temperature, t-butanol (120mL) was added in one portion. The resulting mixture was stirred at reflux overnight. The reaction mixture was concentrated *in vacuo* to dryness to afford the title compound (50 g, 73%) as a yellow liquid, which was used in further experiments without further purification.

Preparation 811-Benzylcyclobutanamine hydrochloride

tert-Butyl 1-benzylcyclobutylcarbamate (50 g, 0.19 mol) was added to 500mL of HCl in dioxane at 0°C. After the addition was complete, the reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated *in vacuo* to dryness. The residue was diluted with water and washed with ethyl acetate (450mL) to remove impurities. The aqueous solution was basified with solid potassium hydroxide until the solution was pH 12 and then extracted with dichloromethane (450mL). The combined organic layers were washed with brine, dried using anhydrous sodium sulfate and concentrated *in vacuo* to afford the title compound as a brown liquid (30 g, 100%).

Preparation 82tert-Butyl 3-cyanoazetidine-1-carboxylate

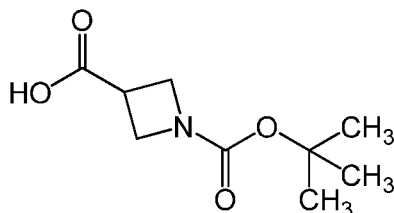
Sodium cyanide (47.3 g, 0.966 mol) was added to a stirred solution of tert-butyl 3-(methylsulfonyloxy)azetidine-1-carboxylate (Preparation 57, 121.4 g, 0.483 mol) in dimethylsulfoxide (170mL). The reaction mixture was heated to 100–105°C and stirred at this

temperature for 100 hours. The reaction mixture was diluted with water (1.5L) and extracted with ether (2.4L). The combined organic extracts were washed with water (1L) and brine (0.6L), dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by chromatography on silica gel eluting with hexane:ethyl acetate (3:1) to afford the title compound as a white crystalline solid (61.5 g, 70.0%).

^1H NMR (400 MHz, CDCl_3): δ = 4.20–4.10 (m, 4H), 3.40–3.32 (m, 1H), 1.41 (s, 9H) ppm.

Preparation 83

1-(tert-Butoxycarbonyl)azetidine-3-carboxylic acid

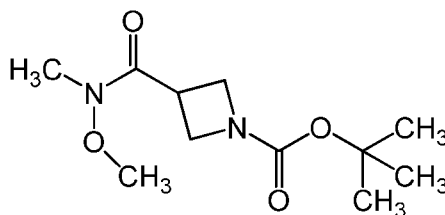


A solution of sodium hydroxide (27.5 g) in water (300mL) was added to solution of tert-butyl 3-cyanoazetidine-1-carboxylate (Preparation 82, 25.1 g, 0.138 mol) in methanol (300mL). The mixture was heated at reflux for 5 hours. The methanol was evaporated and the residuary aqueous solution was neutralized with 10% citric acid and extracted with dichloromethane (2.1L). The combined organic extracts were dried over magnesium sulfate and concentrated in vacuo to afford the title compound as a white crystalline solid (22.3 g, 80.8%).

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ = 4.01–3.97 (m, 2H), 3.87–3.84 (m, 2H), 3.36–3.28 (m, 1H), 1.37 (s, 9H) ppm.

Preparation 84

tert-Butyl 3-(methoxy(methyl)carbamoyl)azetidine-1-carboxylate



Carbonyldiimidazole (24.4 g, 0.150 mol) was added in portions to a solution of 1-(tert-butoxycarbonyl)azetidine-3-carboxylic acid (Preparation 83, 22.3 g, 0.111 mol) in tetrahydrofuran (250mL). The mixture was stirred at room temperature for 1.5 hours. A suspension of *N,O*-dimethylhydroxylamine hydrochloride (15.0 g, 0.154 mol) in a mixture of acetonitrile (300mL) and triethylamine (22.mL, 0.162 mol) was added. The resulting mixture was stirred at room temperature for 24 hours. The solvents were evaporated and water (300mL) and ethyl acetate (800mL) were added to the residue. The organic layer was separated, washed

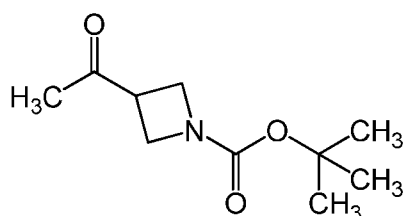
87

with a 5% aqueous citric acid (400mL), water (300mL) and brine (300mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford the title compound as a pale yellow oil (28.15 g, 100%).

^1H NMR (400 MHz, CDCl_3): δ = 4.12–4.09 (m, 2H), 4.03–3.99 (m, 2H), 3.64–3.56 (m, 1H), 3.63 (s, 3H), 3.17 (s, 3H), 1.40 (s, 9H) ppm.

Preparation 85

tert-Butyl 3-acetylazetidine-1-carboxylate

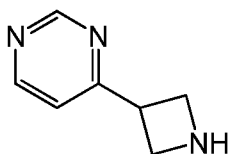


A solution of tert-butyl 3-(methoxy(methyl)carbamoyl)azetidine-1-carboxylate (Preparation 84, 27.1 g, 0.111 mol) in tetrahydrofuran (200mL) was added dropwise to a 1.4 M solution of methylmagnesium bromide in a 25:75 mixture of tetrahydrofuran and toluene (99.0 mL, 0.139 mol, 1.25 eq) over 40 minutes. The reaction temperature was kept at $\sim 0^\circ\text{C}$. After the addition, the mixture was stirred at $10\text{--}15^\circ\text{C}$ for 2 hours and then at room temperature for 1 hour. The mixture was cooled to 0°C and 10% aqueous citric acid (150mL) was added. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (600mL). The organic layers were combined, washed with brine (500mL) and dried using anhydrous sodium sulfate to give a residue which was purified by chromatography on silica gel, eluting with chloroform, to afford the title compound (20.6 g, 93.4%).

^1H NMR (400 MHz, CDCl_3): δ = 4.04–4.02 (m, 4H), 3.43–3.35 (m, 1H), 2.16 (s, 3H), 1.42 (s, 9H) ppm.

Preparation 86

4-(Azetidin-3-yl)pyrimidine



Step A: A solution of tert-butyl 3-acetylazetidine-1-carboxylate (Preparation 85, 20.6 g, 0.103 mol) in N-N-dimethylformamide dimethyl acetal was refluxed for 45 hours. The reaction mixture was evaporated and then co-evaporated with toluene (400mL) to leave a residue that was used in step B without further purification.

Step B: Formamidinium hydrochloride (4.96 g, 0.062 mol) and a solution of the product from Step A in methanol (75 mL) were added in series to a solution of sodium methylate (3.33 g, 0.062 mol) in absolute methanol (75 mL). The mixture was refluxed for 50 hours. The solvent was exchanged for dioxane and the mixture was refluxed for another 40 hours. The solvent was evaporated and water (150 mL) and ethyl acetate (250 mL) were added to the residue. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (500mL). The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated to give a residue that was purified by chromatography on silica gel, eluting with ethyl acetate, to afford tert-butyl 3-pyrimidin-4-ylazetidine-1-carboxylate (2.0 g, 20.6%).

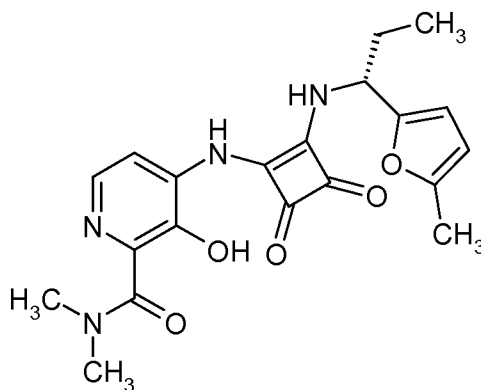
^1H NMR (400 MHz, DMSO- d_6): δ = 9.18 (d, 1H), 8.73 (d, 1H), 7.48 (dd, 1H), 4.21–4.17 (m, 2H), 4.02–3.98 (m, 2H), 3.96–3.88 (m, 1H), 1.39 (s, 9H) ppm.

Step C: Trifluoroacetic acid (9.9mL, 14.7 g, 0.13 mol) was added to a cooled solution of tert-butyl 3-pyrimidin-4-ylazetidine-1-carboxylate (product of Step B, 1.9 g, 0.008 mol) in dichloromethane (10mL) at 0–5°C. The mixture was stirred with cooling for 30 min and then stirred at room temperature for 1 hour. The solvent was removed in vacuo and the residue was azeotroped with dichloromethane (100mL) and methanol (100mL) to afford the title compound as a brown syrup (2.42 g, 99%).

^1H NMR (400 MHz, DMSO- d_6): δ = 9.33 (br. s, 1H), 9.00 (br. s, 1H), 9.24 (d, 1H), 8.78 (d, 1H), 7.52 (dd, 1H), 4.33–4.19 (m, 5H) ppm.

Example 1

3-Hydroxy-N,N-dimethyl-4-[(2-[(1R)-1-(5-methyl-2-furyl)propyl]amino)-3,4-dioxocyclobut-1-en-1-yl]amino]pyridine-2-carboxamide

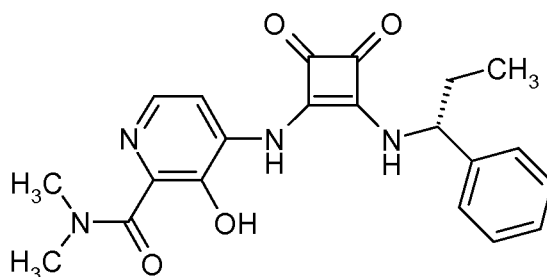


4-Amino-3-hydroxy-pyridine-2-carboxylic acid dimethylamide (Preparation 12, 77mg, 0.43mmol) was added in a single portion to a stirred solution of (R)-3-ethoxy-4-[1-(5-methyl-furan-2-yl)-propylamino]-cyclobut-3-ene-1,2-dione (prepared as described in WO-2002/083624, 56mg, 0.21mmol) and N,N-diisopropylethylamine (74 μL , 0.43 mmol) in absolute ethanol (1mL) and the

reaction mixture was stirred at 90°C overnight and then at room temperature for 24 hours. The resultant suspension was concentrated *in vacuo*. The crude residue was dissolved in 1mL of DMSO, and purified by HPLC chromatography (Preparative HPLC Method 1; Analytical HPLC Method E; RT 2.76mins; m/z 399.2 [MH]⁺) to give the desired product.

Example 2

(R)-4-(3,4-Dioxo-2-(1-phenylpropylamino)cyclobut-1-enylamino)-3-hydroxy-N,N-dimethylpicolinamide



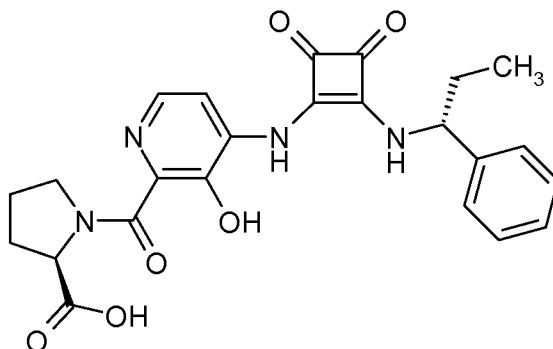
4-Amino-3-hydroxy-N,N-dimethylpicolinamide (Preparation 12, 315mg, 1.74mmol) and (R)-3-ethoxy-4-(1-phenylpropylamino)cyclobut-3-ene-1,2-dione (Preparation 17, 225mg, 0.868mmol) were dissolved in absolute ethanol (1mL) and the resulting solution was heated in a sealed tube at 90°C for 5 days. The reaction mixture was concentrated *in vacuo* and then partitioned between dichloromethane (100mL) and saturated aqueous ammonium chloride solution (25mL). The organic phase was dried over anhydrous sodium sulfate and concentrated *in vacuo* to give a yellow oil. Column chromatographic purification on silica gel eluting with a gradient of 100% dichloromethane to 90/10/1 dichloromethane/methanol/ammonia afforded the title compound as a yellow solid, 101mg.

¹H NMR (400MHz, DMSO-d₆): δ= 0.89 (3H, t), 1.90 (2H, m), 2.96-3.20 (6H, m), 5.09 (1H, m), 7.29 (1H, m), 7.33-7.43 (4H, m), 8.00 (2H, m), 8.90 (1H, m), 9.62 (1H, m), 11.66 (1H, m) ppm.

LRMS (ES): m/z 395 [M+H]⁺.

Example 3

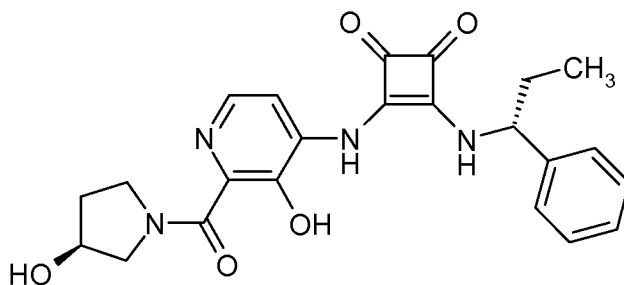
(R)-1-(4-(3,4-Dioxo-2-((R)-1-phenylpropylamino)cyclobut-1-enylamino)-3-hydroxypicolinoyl)pyrrolidine-2-carboxylic acid



A stirred solution of (R)-tert-butyl 1-(4-(3,4-dioxo-2-((R)-1-phenylpropylamino)cyclobut-1-enylamino)-3-methoxypicolinoyl)pyrrolidine-2-carboxylate (Preparation 24, 100mg, 0.187mmol) in dichloromethane (0.93ml) was treated with boron tribromide solution (1M in dichloromethane, 1.87mL, 1.87mmol) at 0°C and then stirred at room temperature for 6 hours. The reaction mixture was quenched with water (20mL), and the resulting solid was filtered, triturated with water (2 × 20mL), azeotroped with toluene (3 × 5mL), triturated with diethyl ether and dried under high vacuum. The crude residue was purified by HPLC (Preparative HPLC Method 1; Analytical HPLC Method E; RT 3.14 mins; m/z 465 [MH]⁺) to give the desired product.

Example 4

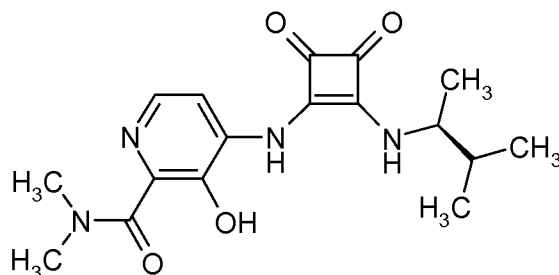
3-(3-Hydroxy-2-((S)-3-hydroxypyrrolidine-1-carbonyl)pyridin-4-ylamino)-4-((R)-1-phenylpropylamino)cyclobut-3-ene-1,2-dione



A stirred solution of 3-(2-((S)-3-hydroxypyrrolidine-1-carbonyl)-3-methoxypyridin-4-ylamino)-4-((R)-1-phenylpropylamino)cyclobut-3-ene-1,2-dione (Preparation 23, 150mg, 0.333mmol) in dichloromethane (1.5mL) was treated with boron tribromide solution (1M in dichloromethane, 3.33mL, 3.33mmol) at 0°C and then stirred at room temperature for 6 hours. The reaction mixture was quenched with ice-cold water and the resulting solid was filtered, triturated with water (2 × 5mL), azeotroped with toluene (3 × 10mL), triturated with diethyl ether (3 × 5mL) and dried under high vacuum. The crude residue was purified by HPLC (Preparative HPLC Method 1; Analytical HPLC Method E; RT 2.89 mins; m/z 437 [MH]⁺) to give the desired product.

Example 5

(S)-3-Hydroxy-N,N-dimethyl-4-(2-(3-methylbutan-2-ylamino)-3,4-dioxocyclobut-1-enylamino)picolinamide

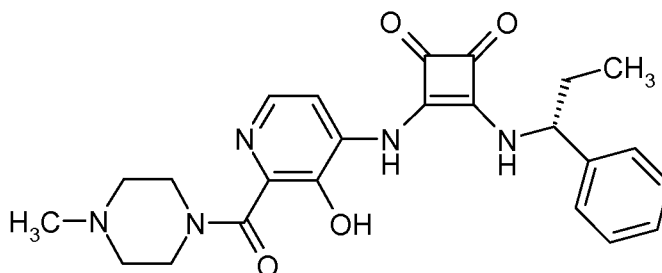


(S)-3-Methoxy-N,N-dimethyl-4-(2-(3-methylbutan-2-ylamino)-3,4-dioxocyclobut-1-enylamino)picolinamide (Preparation 15, 42mg, 0.117mmol) was dissolved in dichloromethane (10mL). The solution was cooled to 0°C and treated dropwise with boron tribromide solution (1M in dichloromethane, 0.936mL, 0.936mmol). The reaction mixture was stirred at 0°C for 1 hour. Saturated aqueous ammonium chloride aqueous solution (1mL) and aqueous ammonia solution (1mL) were added and the reaction mixture was stirred at 0°C for 30 minutes. Concentrated hydrochloric acid was added until pH 4 was reached. The product was extracted into dichloromethane which was then concentrated in vacuo to give a yellow oil. Column chromatographic purification on silica gel eluting with a gradient of 100% dichloromethane to 90/10/1 dichloromethane/methanol/ammonia afforded the title compound as an orange coloured gum, 8mg.

¹H NMR (400MHz, CD₃OD): δ= 0.99 (6H, d), 1.27 (3H, d), 1.81 (1H, m), 3.07-3.26 (6H, m), 4.15 (1H, m), 7.87 (1H, d), 8.24 (1H, d) ppm.

Example 6

(R)-3-(3-Hydroxy-2-(1-methylpiperazine-4-carbonyl)pyridin-4-ylamino)-4-(1-phenylpropylamino)cyclobut-3-ene-1,2-dione

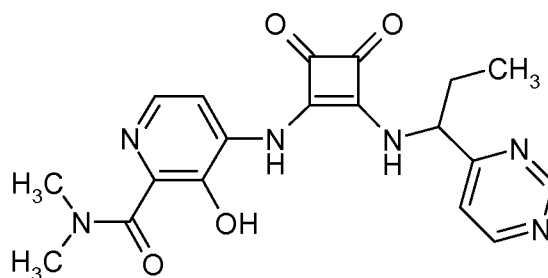


A stirred solution of (R)-3-(3-methoxy-2-(1-methylpiperazine-4-carbonyl)pyridin-4-ylamino)-4-(1-phenylpropylamino)cyclobut-3-ene-1,2-dione (Preparation 22, 100mg, 0.216mmol) in dichloromethane (1.08mL) was treated with boron tribromide solution (1M in dichloromethane,

1.72mL, 1.72mmol) at 0°C and then stirred at room temperature for 6 hours. The reaction mixture was quenched with water and then neutralised with saturated aqueous sodium hydrogen carbonate solution to obtain a pH of 7. The resulting solid was filtered, triturated with water (2 × 5mL), refiltered and azeotroped with toluene. The solid collected was then triturated with diethyl ether (3 × 10mL) and dried under high vacuum. The crude residue was purified by HPLC (Preparative HPLC Method 1; Analytical HPLC Method E; RT 2.24 mins; m/z 450 [MH]⁺) to give the desired product.

Example 7

4-(3,4-Dioxo-2-(1-(pyrimidin-4-yl)propylamino)cyclobut-1-enylamino)-3-hydroxy-*N,N*-dimethylpicolinamide



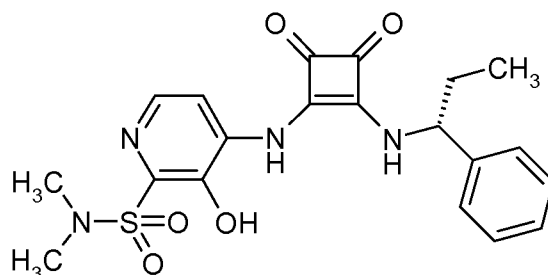
To a suspension of 4-(2-ethoxy-3,4-dioxocyclobut-1-enylamino)-3-hydroxy-*N,N*-dimethylpicolinamide (Preparation 16, 110 mg, 0.360mmol), in absolute ethanol (1.1mL) was added 1-(pyrimidine-4-yl)propan-1-amine (Preparation 31, 54.4mg, 0.396mmol) and the resulting mixture was stirred at room temperature overnight. The mixture was concentrated under reduced pressure and the crude compound was purified by column chromatography on silica gel eluting with 1-5% methanol in dichloromethane. The solid product was then recrystallised from a mixture of methanol and diethyl ether to give the title compound as a solid, 30mg.

¹H NMR (400MHz, DMSO-*d*₆): δ= 0.93 (3H, t), 1.83-2.01 (2H, m), 3.05 (3H, br s), 3.17 (3H, br s), 5.27 (1H, m), 7.60 (1H, d), 8.00 (2H, m), 8.82 (1H, d), 9.20-9.24 (2H, m), 9.85 (1H, br s), 11.64 (1H, br s) ppm.

LRMS (ES): m/z 397 [M+H]⁺.

Example 8

(R)-4-(3,4-Dioxo-2-(1-phenylpropylamino)cyclobut-1-enylamino)-3-hydroxy-N,N-dimethylpyridine-2-sulfonamide

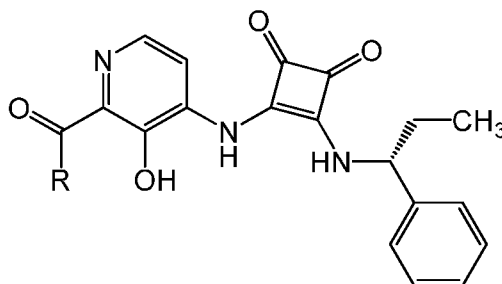


A stirred solution of (R)-4-(3,4-dioxo-2-(1-phenylpropylamino)cyclobut-1-enylamino)-3-methoxy-N,N-dimethylpyridine-2-sulfonamide (Preparation 27, 58mg, 0.13mmol) in dichloromethane (10mL) was treated with boron tribromide solution (1M in dichloromethane, 0.78mL, 0.78mmol) at 0°C and then stirred at room temperature for 1 hour. The reaction mixture was cooled to 0°C, quenched with saturated aqueous ammonium chloride:aqueous ammonia (10:1 by volume), stirred for 1 hour and then carefully acidified with aqueous hydrochloric acid solution to pH 4. The product was extracted twice into dichloromethane and the combined organic phases were washed with water and saturated aqueous sodium chloride solution, dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with dichloromethane:methanol:ammonia (gradient elution, 100:0:0 to 80:20:2 by volume) to furnish the title compound as a yellow solid, 10mg.

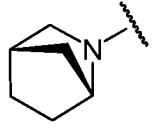
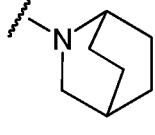
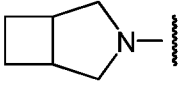
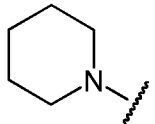
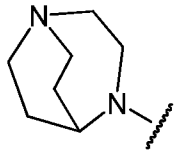
¹H NMR (400MHz, CD₃OD): δ = 0.99 (3H, t), 1.93-2.05 (2H, m), 2.92 (6H, s), 5.18 (1H, m), 7.30 (1H, m), 7.38 (4H, m), 7.82 (1H, m), 8.17 (1H, m) ppm.

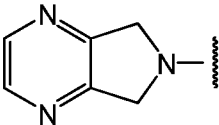
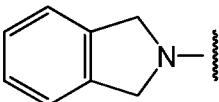
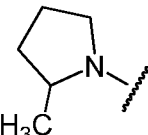
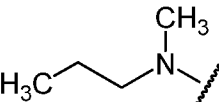
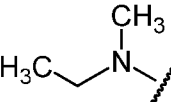
LRMS (ES): m/z 431 [M+H]⁺.

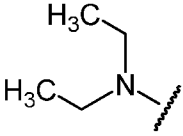
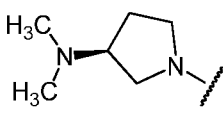
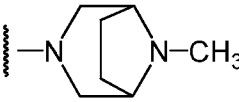
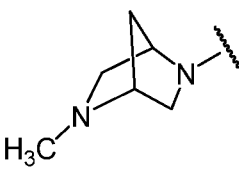
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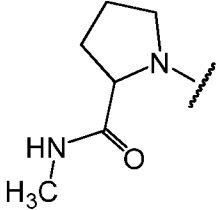
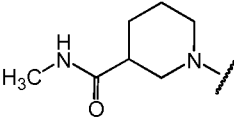
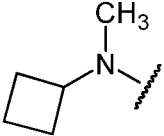
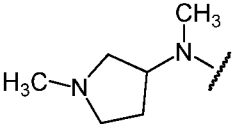
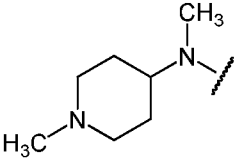


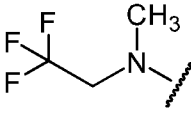
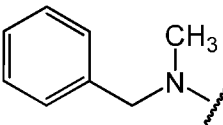
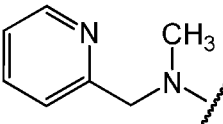
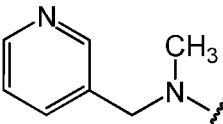
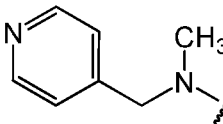
Ex.	R	Name	Experimental and Characterisation
9		3-(2-((1R,4S)-2-Azabicyclo[2.2.1]heptane-2-carbonyl)-3-	Compound prepared using Method (i) starting with Preparation 32 and (1R,4S)-2-azabicyclo[2.2.1]heptane (see WO-

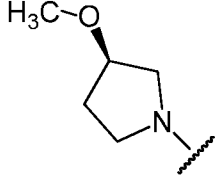
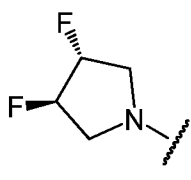
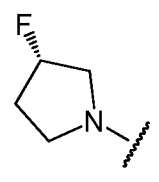
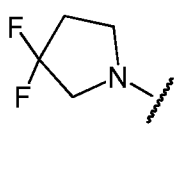
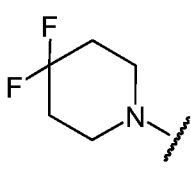
		hydroxypyridin-4-ylamino)-4-((R)-1-phenylpropylamino)cyclobut-3-ene-1,2-dione	2008/75006). The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.75 minutes. LRMS m/z [M+1] 447.26
10		(R)-3-(2-(2-Azabicyclo[2.2.2]octane-2-carbonyl)-3-hydroxypyridin-4-ylamino)-4-(1-phenylpropylamino)cyclobut-3-ene-1,2-dione	Compound prepared using Method (i) starting with Preparation 32 and 2-azabicyclo[2.2.2]octane (see Synthetic Communications 2002, 32(13), 1985). The title compound was purified using preparative HPLC Method 3 HPLC-MS (Method A): retention time 1.68 minutes. LRMS m/z [M+1] 461.49.
11		3-(2-(3-Azabicyclo[3.2.0]heptane-3-carbonyl)-3-hydroxypyridin-4-ylamino)-4-((R)-1-phenylpropylamino)cyclobut-3-ene-1,2-dione	Compound prepared using Method (i) starting with Preparation 32 and 3-azabicyclo[3.2.0]heptanes (Preparation 69) . The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.72 minutes. LRMS m/z [M+1] 447.44.
12		(R)-3-(3-Hydroxy-2-(piperidine-1-carbonyl)pyridin-4-ylamino)-4-(1-phenylpropylamino)cyclobut-3-ene-1,2-dione	Compound prepared using Method (i) starting with Preparation 32 and piperidine. The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.56 minutes. LRMS m/z [M+1] 435.26.
13		(R)-3-(2-(1,4-Diazabicyclo[3.2.2]nonane-4-carbonyl)-3-hydroxypyridin-4-ylamino)-4-(1-phenylpropylamino)cyclobut-3-ene-1,2-dione	Compound prepared using Method (i) starting with Preparation 32 and 1,4-diazabicyclo[3.2.2]nonane (see WO-2009/062987). The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.33 minutes. LRMS m/z [M+1] 476.46.
14		(R)-3-(2-(6,7-Dihydro-	Compound prepared using Method (i)

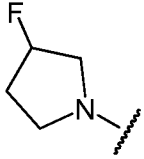
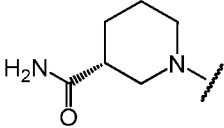
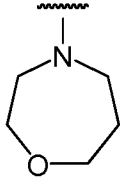
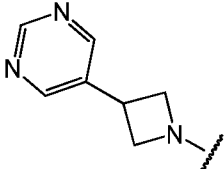
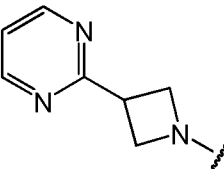
		5H-pyrrolo[3,4-b]pyrazine-6-carbonyl)-3-hydroxypyridin-4-ylamino)-4-(1-phenylpropylamino)cyclobut-3-ene-1,2-dione	starting with Preparation 32 and 6,7-dihydro-5H-pyrrolo[3,4-b]pyrazine (see WO-2009/014637). The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.63 minutes. LRMS m/z [M+1] 471.44
15		(R)-3-(3-Hydroxy-2-(isoindoline-2-carbonyl)pyridin-4-ylamino)-4-(1-phenylpropylamino)cyclobut-3-ene-1,2-dione	Compound prepared using Method (i) starting with Preparation 32 and isoindoline. The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.83 minutes. LRMS m/z [M+1] 469.39.
16		3-(3-Hydroxy-2-(2-methylpyrrolidine-1-carbonyl)pyridin-4-ylamino)-4-((R)-1-phenylpropylamino)cyclobut-3-ene-1,2-dione	Compound prepared using Method (i) starting with Preparation 32 and 2-methylpyrrolidine. The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.71 minutes. LRMS m/z [M+1] 435.26.
17		(R)-4-(3,4-Dioxo-2-(1-phenylpropylamino)cyclobut-1-enylamino)-3-hydroxy-N-methyl-N-propylpicolinamide	Compound prepared using Method (i) starting with Preparation 32 and N-methylpropan-1-amine. The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.57 minutes. LRMS m/z [M+1] 423.35.
18		(R)-4-(3,4-Dioxo-2-(1-phenylpropylamino)cyclobut-1-enylamino)-N-ethyl-3-hydroxy-N-methylpicolinamide	Compound prepared using Method (i) starting with Preparation 32 and N-methylethanamine. The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.53 minutes. LRMS m/z [M+1] 409.22.
19		(R)-4-(3,4-Dioxo-2-(1-	Compound prepared using Method (i)

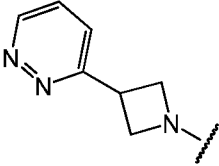
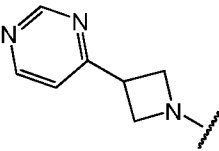
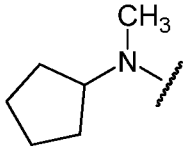
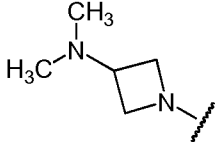
		Phenylpropylamino)cyclobut-1-enylamino)-N,N-diethyl-3-hydroxypicolinamide	starting with Preparation 32 and diethylamine. The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.58 minutes. LRMS m/z [M+1] 423.26.
20		3-(2-((S)-3-(Dimethylamino)pyrrolidin-1-carbonyl)-3-hydroxypyridin-4-ylamino)-4-((R)-1-phenylpropylamino)cyclobut-3-ene-1,2-dione	Compound prepared using Method (i) starting with Preparation 32 and (S)-N,N-dimethylpyrrolidin-3-amine. The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.35 minutes. LRMS m/z [M+1] 464.46.
21		3-(3-Hydroxy-2-(8-methyl-3,8-diazabicyclo[3.2.1]octane-3-carbonyl)pyridin-4-ylamino)-4-((R)-1-phenylpropylamino)cyclobut-3-ene-1,2-dione	Compound prepared using Method (i) starting with Preparation 32 and 8-methyl-3,8-diazabicyclo[3.2.1]octane (see Tetrahedron Letters, 2007, 48(4), 545). The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.34 minutes. LRMS m/z [M+1] 476.46.
22		3-(3-Hydroxy-2-((1R,4R)-5-methyl-2,5-diazabicyclo[2.2.1]heptane-2-carbonyl)pyridin-4-ylamino)-4-((R)-1-phenylpropylamino)cyclobut-3-ene-1,2-dione	Compound prepared using Method (i) starting with Preparation 32 and (1R,4R)-2-methyl-2,5-diazabicyclo[2.2.1]heptane. (see EP-A-397351). The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.37 minutes. LRMS m/z [M+1] 462.42.
23		1-(4-(3,4-Dioxo-2-((R)-1-phenylpropylamino)cyclobut-1-enylamino)-	Compound prepared using Method (i) starting with Preparation 32 and N-methylpyrrolidine-2-carboxamide (Preparation 55). The title compound was

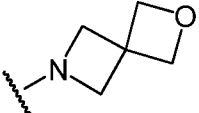
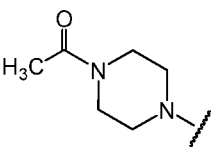
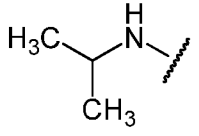
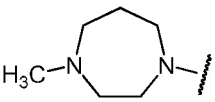
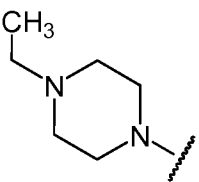
		3-hydroxypicolinoyl)- N-methylpyrrolidine- 2-carboxamide	purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.54 minutes. LRMS m/z [M+1] 478.32.
24		1-(4-(3,4-Dioxo-2- ((R)-1- phenylpropylamino)c yclobut-1-enylamino)- 3-hydroxypicolinoyl)- N-methylpiperidine-3- carboxamide	Compound prepared using Method (i) starting with Preparation 32 and N-methylpiperidine-3-carboxamide (see WO-2009/077844). The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.48 minutes. LRMS m/z [M+1] 492.37.
25		(R)-N-Cyclobutyl-4- (3,4-dioxo-2-(1- phenylpropylamino)c yclobut-1-enylamino)- 3-hydroxy-N- methylpicolinamide	Compound prepared using Method (i) starting with Preparation 32 and N-methylcyclobutanamine (see JP-2009/184933). The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.58 minutes. LRMS m/z [M+1] 435.26.
26		4-(3,4-Dioxo-2-((R)-1- phenylpropylamino)c yclobut-1-enylamino)- 3-hydroxy-N-methyl- N-(1-methylpyrrolidin- 3-yl)picolinamide	Compound prepared using Method (i) starting with Preparation 32 and N,1-dimethylpyrrolidin-3-amine. The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.34 minutes. LRMS m/z [M+1] 464.46.
27		(R)-4-(3,4-Dioxo-2-(1- phenylpropylamino)c yclobut-1-enylamino)- 3-hydroxy-N-methyl- N-(1-methylpiperidin- 4-yl)picolinamide	Compound prepared using Method (i) starting with Preparation 32 and N,1-dimethylpiperidin-4-amine (see US-2002/6423713). The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.33 minutes. LRMS m/z [M+1] 478.51.
28		(R)-4-(3,4-Dioxo-2-(1-	Compound prepared using Method (i)

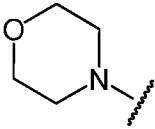
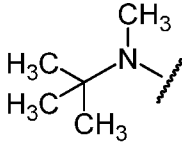
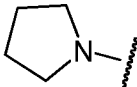
		phenylpropylamino)cyclobut-1-enylamino)-3-hydroxy-N-methyl-N-(2,2,2-trifluoroethyl)picolinamide	starting with Preparation 32 and 2,2,2-trifluoro-N-methylethanamine (Preparation 56). The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.60 minutes. LRMS m/z [M+1] 463.35.
29		(R)-N-Benzyl-4-(3,4-dioxo-2-(1-phenylpropylamino)cyclobut-1-enylamino)-3-hydroxy-N-methylpicolinamide	Compound prepared using Method (i) starting with Preparation 32 and N-methyl-1-phenylmethanamine. The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.65 minutes. LRMS m/z [M+1] 471.35.
30		(R)-4-(3,4-Dioxo-2-(1-phenylpropylamino)cyclobut-1-enylamino)-3-hydroxy-N-methyl-N-(pyridin-2-ylmethyl)picolinamide	Compound prepared using Method (i) starting with Preparation 32 and N-methyl-1-(pyridin-2-yl)methanamine. The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.48 minutes. LRMS m/z [M+1] 472.28.
31		(R)-4-(3,4-Dioxo-2-(1-phenylpropylamino)cyclobut-1-enylamino)-3-hydroxy-N-methyl-N-(pyridin-3-ylmethyl)picolinamide	Compound prepared using Method (i) starting with Preparation 32 and N-methyl-1-(pyridin-3-yl)methanamine. The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.42 minutes. LRMS m/z [M+1] 472.28.
32		(R)-4-(3,4-Dioxo-2-(1-phenylpropylamino)cyclobut-1-enylamino)-3-hydroxy-N-methyl-N-(pyridin-4-ylmethyl)picolinamide	Compound prepared using Method (i) starting with Preparation 32 and N-methyl-1-(pyridin-4-yl)methanamine. The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.39 minutes. LRMS m/z [M+1] 472.37.
33		3-(3-Hydroxy-2-((R)-3-methoxypyrrolidine-	Compound prepared using Method (i) starting with Preparation 32 and (R)-3-

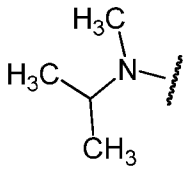
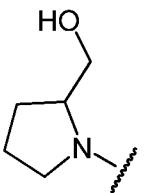
		1-carbonyl)pyridin-4-ylamino)-4-((R)-1-phenylpropylamino)cyclobut-3-ene-1,2-dione	methoxypyrrolidine (see EP-A-159679). The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.62 minutes. LRMS m/z [M+1] 451.35.
34		3-(2-((3R,4R)-3,4-Difluoropyrrolidine-1-carbonyl)-3-hydroxypyridin-4-ylamino)-4-((R)-1-phenylpropylamino)cyclobut-3-ene-1,2-dione	Compound prepared using Method (i) starting with Preparation 32 and (3R,4R)-3,4-difluoropyrrolidine (see Bioorganic and Medicinal Chemistry Letters, 2005, 15, 4770-4773). The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.67 minutes. LRMS m/z [M+1] 457.40.
35		3-(2-((S)-3-Fluoropyrrolidine-1-carbonyl)-3-hydroxypyridin-4-ylamino)-4-((R)-1-phenylpropylamino)cyclobut-3-ene-1,2-dione	Compound prepared using Method (i) starting with Preparation 32 and (S)-3-fluoropyrrolidine. The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.64 minutes. LRMS m/z [M+1] 439.45.
36		(R)-3-(2-(3,3-Difluoropyrrolidine-1-carbonyl)-3-hydroxypyridin-4-ylamino)-4-(1-phenylpropylamino)cyclobut-3-ene-1,2-dione	Compound prepared using Method (i) starting with Preparation 32 and 3,3-difluoropyrrolidine. The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.69 minutes. LRMS m/z [M+1] 457.40.
37		(R)-3-(2-(4,4-Difluoropiperidine-1-carbonyl)-3-hydroxypyridin-4-ylamino)-4-(1-phenylpropylamino)cyclobut-3-ene-1,2-dione	Compound prepared using Method (i) starting with Preparation 32 and 4,4-difluoropiperidine. The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.58 minutes. LRMS m/z [M+1] 471.35.

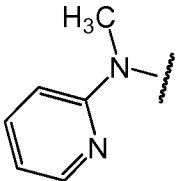
38		3-(2-(3-Fluoropyrrolidine-1-carbonyl)-3-hydroxypyridin-4-ylamino)-4-((R)-1-phenylpropylamino)cyclobut-3-ene-1,2-dione	Compound prepared using Method (i) starting with Preparation 32 and 3-fluoropyrrolidine. The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.65 minutes. LRMS m/z [M+1] 439.26.
39		(R)-1-(4-(3,4-Dioxo-2-((R)-1-phenylpropylamino)cyclobut-1-enylamino)-3-hydroxypicolinoyl)piperidine-3-carboxamide	Compound prepared using Method (i) starting with Preparation 32 and (R)-piperidine-3-carboxamide (Preparation 73). The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.44 minutes. LRMS m/z [M+1] 478.32
40		(R)-3-(3-Hydroxy-2-(1,4-oxazepane-4-carbonyl)pyridin-4-ylamino)-4-(1-phenylpropylamino)cyclobut-3-ene-1,2-dione	Compound prepared using Method (i) starting with Preparation 32 and 1,4-oxazepane (see WO-2000/40561). The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.51 minutes. LRMS m/z [M+1] 451.35.
41		(R)-3-(3-Hydroxy-2-(3-(pyrimidin-5-yl)azetidine-1-carbonyl)pyridin-4-ylamino)-4-(1-phenylpropylamino)cyclobut-3-ene-1,2-dione	Compound prepared using Method (i) starting with Preparation 32 and 5-(azetidin-3-yl)pyrimidine (Preparation 62). The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.62 minutes. LRMS m/z [M+1] 485.30.
42		(R)-3-(3-Hydroxy-2-(3-(pyrimidin-2-yl)azetidine-1-carbonyl)pyridin-4-ylamino)-4-(1-phenylpropylamino)cyclobut-3-ene-1,2-dione	Compound prepared using Method (i) starting with Preparation 32 and 2-(azetidin-3-yl)pyrimidine (Preparation 60). The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.68 minutes.

		yclobut-3-ene-1,2-dione	LRMS m/z [M+1] 485.48.
43		(R)-3-(3-Hydroxy-2-(3-(pyridazin-3-yl)azetidine-1-carbonyl)pyridin-4-ylamino)-4-(1-phenylpropylamino)cyclobut-3-ene-1,2-dione	Compound prepared using Method (i) starting with Preparation 32 and 3-(azetidin-3-yl)pyridazine (Preparation 61). The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.61 minutes. LRMS m/z [M+1] 485.30.
44		(R)-3-(3-Hydroxy-2-(3-(pyrimidin-4-yl)azetidine-1-carbonyl)pyridin-4-ylamino)-4-(1-phenylpropylamino)cyclobut-3-ene-1,2-dione	Compound prepared using Method (i) starting with Preparation 32 and 4-(azetidin-3-yl)pyrimidine (Preparation 86). The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.66 minutes. LRMS m/z [M+1] 485.30.
45		(R)-N-Cyclopentyl-4-(3,4-dioxo-2-(1-phenylpropylamino)cyclobut-1-enylamino)-3-hydroxy-N-methylpicolinamide	Compound prepared using Method (i) starting with Preparation 32 and N-methylcyclopentanamine. The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.61 minutes. LRMS m/z [M+1] 449.3.
46		(R)-3-(2-(3-(Dimethylamino)azetidine-1-carbonyl)-3-hydroxypyridin-4-ylamino)-4-(1-phenylpropylamino)cyclobut-3-ene-1,2-dione	Compound prepared using Method (i) starting with Preparation 32 and N,N-dimethylazetidin-3-amine (see WO-2007/115798). The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.39 minutes. LRMS m/z [M+1] 450.42.
47		3-(3-Hydroxy-2-(2-oxa-6-azaspiro[3.3]heptane-6-carbonyl)pyridin-4-	Compound prepared using Method (i) starting with Preparation 32 and 2-oxa-6-azaspiro[3.3]heptanes (see Angewandte Chemie International Edition, 2008,

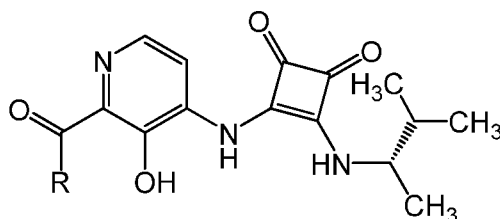
		ylamino)-4-((R)-1-phenylpropylamino)cyclobut-3-ene-1,2-dione	47(24), 4512). The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.62 minutes. LRMS m/z [M+1] 449.30.
48		(R)-3-(2-(4-Acetylpiperazine-1-carbonyl)-3-hydroxypyridin-4-ylamino)-4-(1-phenylpropylamino)cyclobut-3-ene-1,2-dione	Compound prepared using Method (i) starting with Preparation 32 and 1-(piperazin-1-yl)ethanone. The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.47 minutes. LRMS m/z [M+1] 478.32.
49		(R)-4-(3,4-Dioxo-2-(1-phenylpropylamino)cyclobut-1-enylamino)-3-hydroxy-N-isopropylpicolinamide	Compound prepared using Method (i) starting with Preparation 32 and propan-2-amine. The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.61 minutes. LRMS m/z [M+1] 409.40.
50		(R)-3-(3-Hydroxy-2-(4-methyl-1,4-diazepane-1-carbonyl)pyridin-4-ylamino)-4-(1-phenylpropylamino)cyclobut-3-ene-1,2-dione	Compound prepared using Method (i) starting with Preparation 32 and 1-methyl-1,4-diazepane. The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.34 minutes. LRMS m/z [M+1] 464.46.
51		(R)-3-(2-(4-Ethylpiperazine-1-carbonyl)-3-hydroxypyridin-4-ylamino)-4-(1-phenylpropylamino)cyclobut-3-ene-1,2-dione	Compound prepared using Method (i) starting with Preparation 32 and 1-ethylpiperazine. The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.34 minutes. LRMS m/z [M+1] 464.46.
52		(R)-3-(3-Hydroxy-2-(morpholine-4-carbonyl)pyridin-4-	Compound prepared using Method (i) starting with Preparation 32 and morpholine. The title compound was

		ylamino)-4-(1-phenylpropylamino)cyclobut-3-ene-1,2-dione	purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.48 minutes. LRMS m/z [M+1] 437.31.
53		(R)-N-tert-Butyl-4-(3,4-dioxo-2-(1-phenylpropylamino)cyclobut-1-enylamino)-3-hydroxy-N-methylpicolinamide	Compound prepared using Method (i) starting with Preparation 32 and N,2-dimethylpropan-2-amine. The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.58 minutes. LRMS m/z [M+1] 437.31.
54		(R)-3-(3-Hydroxy-2-(pyrrolidine-1-carbonyl)pyridin-4-ylamino)-4-(1-phenylpropylamino)cyclobut-3-ene-1,2-dione	Preparation 32 (50mg, 0.136mmol) was dissolved in dry THF and cooled to 0°C. 4-Methylmorpholine (27.8mg, 0.272mmol) was added followed by isobutylchloroformate (in 0.2mL THF) (372mg, 0.272mmol) dropwise. After 1 hour at room temperature pyrrolidine (19.34mg, 0.272mmol) was added and the reaction mixture was stirred overnight. Liquid liquid extraction using water (10mL) and dichloromethane (30mL) produced crude compound after drying (Na ₂ SO ₄). Column chromatographic purification on silica gel eluting with 1 to 2% methanol in dichloromethane afforded the title compound as a yellow solid. (6.0mg). ¹ HNMR (400MHz, DMSO- d ₆): δ = 0.91 (m, 3H), 1.83 (m, 2H), 1.91 (m, 4H), 3.60 (m, 2H), 4.05 (m, 2H), 5.10 (m, 1H), 7.33-7.41 (m, 5H), 8.06 (m, 2H), 8.89 (d, 1H), 9.66 (s, 1H), 14.03 (s, 1H) ppm. LRMS: m/z 421.2 [M+1].

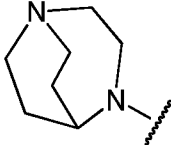
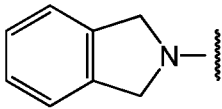
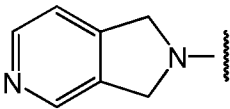
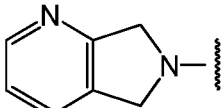
55		(R)-4-(3,4-Dioxo-2-(1-phenylpropylamino)cyclobut-1-enylamino)-3-hydroxy-N-isopropyl-N-methylpicolinamide	Preparation 32 (250mg, 0.681mmol) was dissolved in dry THF and cooled to 0°C. 4-Methylmorpholine (137.8mg, 1.362mmol) was added followed by isobutylchloroformate (in 0.2mL THF, 186.4mg, 0.136mmol) dropwise. After 1 hour at room temperature N-methylpropan-2-amine (19.34mg, 0.272mmol) was added dropwise and the reaction mixture was stirred overnight. Liquid liquid extraction using water (20mL) and dichloromethane (60mL) produced crude compound after drying (Na₂SO₄). Column chromatographic purification on silica gel eluting with 1 to 3% methanol in dichloromethane afforded the title compound as a yellow solid. (10.0mg). ¹HNMR (400MHz, DMSO- d₆): δ = 0.90(m, 3H), 1.13 (m, 6H), 1.90 (m, 2H), 2.87 (s, 3H), 4.13 (m, 1H), 4.78 (m, 1H), 5.10 (m, 1H), 7.30-7.39 (m, 5H), 7.97 (br m, 2H), 8.96 (br, 1H) ppm (one exchangeable not observed). LRMS: m/z 423.6 [M+1].
56		3-(3-Hydroxy-2-(2-(hydroxymethyl)pyrrolidine-1-carbonyl)pyridin-4-ylamino)-4-((R)-1-phenylpropylamino)cyclobut-3-ene-1,2-dione	Preparation 32 (100mg, 0.272mmol), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (62.7mg, 0.408mmol), 1-hydroxybenzotriazole (40.4mg, 0.299mmol) and dimethylformamide (1.36mL) were combined and cooled to 0°C. 4-Methylmorpholine (55.0mg, 0.544mmol) and pyrrolidin-2-ylmethanol (41.54mg, 0.408mmol) were added. The reaction mixture was allowed to warm to room temperature and was stirred overnight. Solvent was removed <i>in vacuo</i>. Liquid

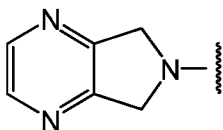
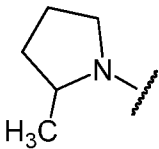
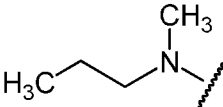
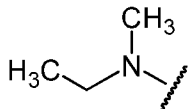
			liquid extraction using water and dichloromethane produced crude compound after drying (Na_2SO_4). The compound was purified by preparative HPLC Method 14 to afford the title compound as a brown solid (6.0mg.) $^1\text{HNMR}$ (400MHz, $\text{DMSO}-d_6$): δ = 0.90 (m, 3H), 1.70-2.15 (m, 6H), 3.50 (m, 1H) 3.61 (m, 1H), 4.04 (m, 1H), 4.30 (m, 1H), 4.84 (m, 1H), 5.10 (m, 2H), 7.31-7.41 (m, 5H), 7.60 (m, 1H), 8.07 (m, 1H), 8.90 (m, 1H), 9.67 (m, 1H), 13.81 (m, 1H) ppm. LRMS: m/z 451.6 [M+1].
57		(R)-4-(3,4-Dioxo-2-(1-phenylpropylamino)cyclobut-1-enylamino)-3-hydroxy-N-methyl-N-(pyridin-2-yl)picolinamide	Preparation 32 (150mg, 0.408mmol), HATU (465mg, 1.224mmol) and dimethylformamide (1.2mL) were combined. N-methylpyridin-2-amine (66.3mg, 0.613mmol) and DIPEA (210.9mg, 1.632mmol) were added and the reaction mixture was heated at 50°C overnight. The reaction mixture was concentrated and purified using preparative thin layer chromatography using 3% methanol in dichloromethane as the mobile phase to afford the title compound as a yellow solid (6mg). $^1\text{HNMR}$ (400MHz, $\text{DMSO}-d_6$): δ = 0.88 (t, 3H), 1.91 (m, 2H), 3.45 (s, 3H), 5.09 (m, 1H), 7.14 (m, 1H), 7.24 (m, 1H), 7.26-7.42 (m, 5H), 7.61 (m, 1H), 7.68 (m, 1H), 7.88 (m, 1H), 8.31 (m, 1H), 8.95 (br s, 1H), 9.72 (br, 1H), 10.98 (br, 1H) ppm. LRMS: m/z 451.6 [M+1].

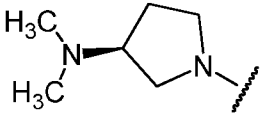
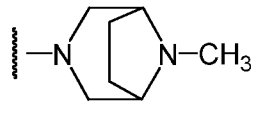
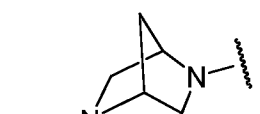
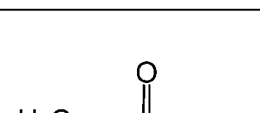
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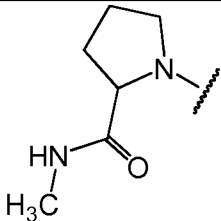
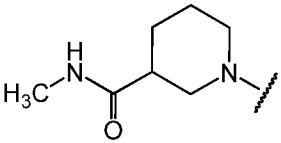
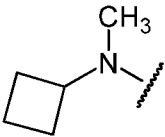
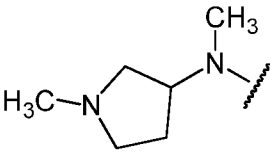
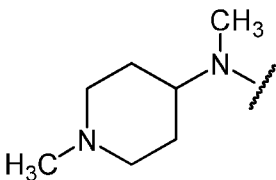


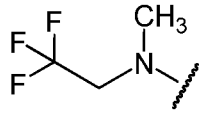
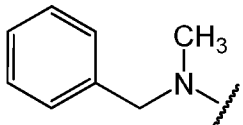
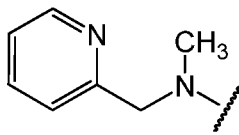
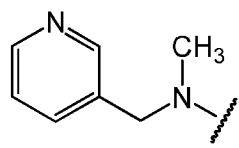
Ex.	R	Name	Experimental and Characterisation
58		3-(2-((1R,4S)-2-Azabicyclo[2.2.1]heptane-2-carbonyl)-3-hydroxypyridin-4-ylamino)-4-((S)-3-methylbutan-2-ylamino)cyclobut-3-ene-1,2-dione	Compound prepared using Method (i) starting with Preparation 35 and (1R,4S)-2-azabicyclo[2.2.1]heptane (see WO-2005/75006). The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.68 minutes. LRMS m/z [M+1] 399.45.
59		(S)-3-(2-(2-Azabicyclo[2.2.2]octane-2-carbonyl)-3-hydroxypyridin-4-ylamino)-4-(3-methylbutan-2-ylamino)cyclobut-3-ene-1,2-dione	Compound prepared using Method (i) starting with Preparation 35 and 2-azabicyclo[2.2.2]octane (see Synthetic Communications, 2002, 32(13), 1985). The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.60 minutes. LRMS m/z [M+1] 413.31.
60		3-(2-(3-Azabicyclo[3.2.0]heptane-3-carbonyl)-3-hydroxypyridin-4-ylamino)-4-((S)-3-methylbutan-2-ylamino)cyclobut-3-ene-1,2-dione	Compound prepared using Method (i) starting with Preparation 35 and 3-azabicyclo[3.2.0]heptanes (Preparation 69). The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.64 minutes. LRMS m/z [M+1] 399.45.
61		(S)-3-(3-Hydroxy-2-(piperidine-1-carbonyl)pyridin-4-ylamino)-4-(3-methylbutan-2-	Compound prepared using Method (i) starting with Preparation 35 and piperidine. The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A):

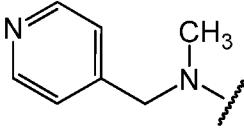
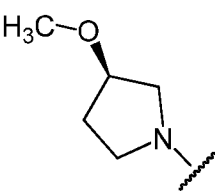
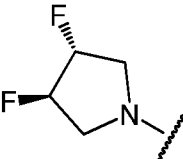
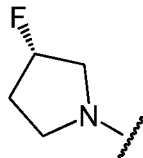
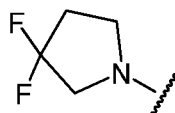
		ylamino)cyclobut-3-ene-1,2-dione	retention time 1.49 minutes. LRMS m/z [M+1] 387.27.
62		(S)-3-(2-(1,4-Diazabicyclo[3.2.2]nonane-4-carbonyl)-3-hydroxypyridin-4-ylamino)-4-(3-methylbutan-2-ylamino)cyclobut-3-ene-1,2-dione	Compound prepared using Method (i) starting with Preparation 35 and 1,4-diazabicyclo[3.2.2]nonane (see WO-2009/062987). The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.26 minutes. LRMS m/z [M+1] 428.47.
63		(S)-3-(3-Hydroxy-2-(isoindoline-2-carbonyl)pyridin-4-ylamino)-4-(3-methylbutan-2-ylamino)cyclobut-3-ene-1,2-dione	Compound prepared using Method (i) starting with Preparation 35 and isoindoline. The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.77 minutes. LRMS m/z [M+1] 421.40.
64		(S)-3-(2-(2,3-Dihydro-1H-pyrrolo[3,4-c]pyridine-2-carbonyl)-3-hydroxypyridin-4-ylamino)-4-(3-methylbutan-2-ylamino)cyclobut-3-ene-1,2-dione	Compound prepared using Method (i) starting with Preparation 35 and 2,3-dihydro-1H-pyrrolo[3,4-c]pyridine (Preparation 68). The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.44 minutes. LRMS m/z [M+1] 422.42.
65		(S)-3-(2-(6,7-Dihydro-5H-pyrrolo[3,4-b]pyridine-6-carbonyl)-3-hydroxypyridin-4-ylamino)-4-(3-methylbutan-2-ylamino)cyclobut-3-	Compound prepared using Method (i) starting with Preparation 35 and 6,7-dihydro-5H-pyrrolo[3,4-b]pyridine (Preparation 67). The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.61 minutes. LRMS m/z [M+1] 422.42.

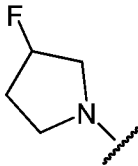
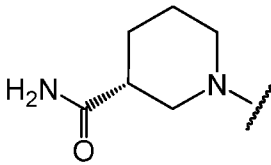
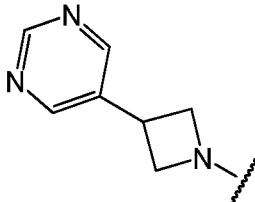
		ene-1,2-dione	
66		(S)-3-(2-(6,7-Dihydro-5H-pyrrolo[3,4-b]pyrazine-6-carbonyl)-3-hydroxypyridin-4-ylamino)-4-(3-methylbutan-2-ylamino)cyclobut-3-ene-1,2-dione	Compound prepared using Method (i) starting with Preparation 35 and 6,7-dihydro-5H-pyrrolo[3,4-b]pyrazine (see WO-2009/014637). The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.55 minutes. LRMS m/z [M+1] 423.45.
67		3-(3-Hydroxy-2-(2-methylpyrrolidine-1-carbonyl)pyridin-4-ylamino)-4-((S)-3-methylbutan-2-ylamino)cyclobut-3-ene-1,2-dione	Compound prepared using Method (i) starting with Preparation 35 and 2-methylpyrrolidine. The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.63 minutes. LRMS m/z [M+1] 387.45.
68		(S)-3-Hydroxy-N-methyl-4-(2-(3-methylbutan-2-ylamino)-3,4-dioxocyclobut-1-enylamino)-N-propylpicolinamide	Compound prepared using Method (i) starting with Preparation 35 and N-methylpropan-1-amine. The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.49 minutes. LRMS m/z [M+1] 375.27.
69		(S)-N-Ethyl-3-hydroxy-N-methyl-4-(2-(3-methylbutan-2-ylamino)-3,4-dioxocyclobut-1-enylamino)picolinamide	Compound prepared using Method (i) starting with Preparation 35 and N-methylethanamine. The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.43 minutes. LRMS m/z [M+1] 361.22.
70		3-(2-((S)-3-(Dimethylamino)pyrrolidine-1-carbonyl)-3-	Compound prepared using Method (i) starting with Preparation 35 and (S)-N,N-dimethylpyrrolidin-3-amine. The title compound was purified using

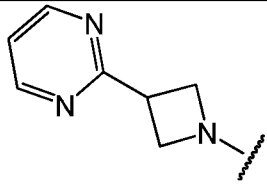
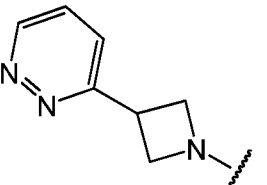
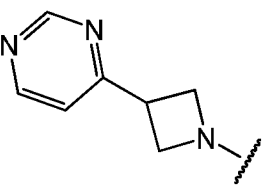
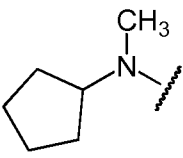
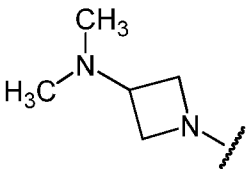
		hydroxypyridin-4-ylamino)-4-((S)-3-methylbutan-2-ylamino)cyclobut-3-ene-1,2-dione	preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.29 minutes. LRMS m/z [M+1] 416.47.
71		3-(3-Hydroxy-2-(8-methyl-3,8-diazabicyclo[3.2.1]octane-3-carbonyl)pyridin-4-ylamino)-4-((S)-3-methylbutan-2-ylamino)cyclobut-3-ene-1,2-dione	Compound prepared using Method (i) starting with Preparation 35 and 8-methyl-3,8-diazabicyclo[3.2.1]octane. The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.27 minutes. LRMS m/z [M+1] 428.47.
72		3-(3-Hydroxy-2-((1R,4R)-5-methyl-2,5-diazabicyclo[2.2.1]heptane-2-carbonyl)pyridin-4-ylamino)-4-((S)-3-methylbutan-2-ylamino)cyclobut-3-ene-1,2-dione	Compound prepared using Method (i) starting with Preparation 35 and (1R,4R)-2-methyl-2,5-diazabicyclo[2.2.1]heptanes (see EP-A-397351). The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.30 minutes. LRMS m/z [M+1] 414.43.
73		(S)-3-(3-Hydroxy-2-(4-methyl-3-oxopiperazine-1-carbonyl)pyridin-4-ylamino)-4-(3-methylbutan-2-ylamino)cyclobut-3-ene-1,2-dione	Compound prepared using Method (i) starting with Preparation 35 and 1-methylpiperazin-2-one. The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.40 minutes. LRMS m/z [M+1] 416.29.
74		1-(3-Hydroxy-4-(2-((S)-3-methylbutan-2-ylamino)-3,4-dioxocyclobut-1-enylamino)picolino	Compound prepared using Method (i) starting with Preparation 35 and N-methylpyrrolidine-2-carboxamide (Preparation 55). The title compound was purified using preparative HPLC

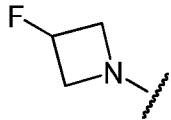
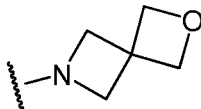
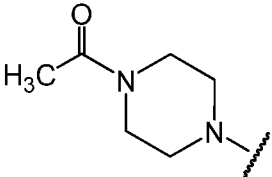
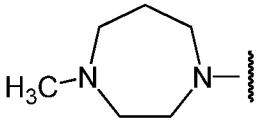
		yl)-N-methylpyrrolidine-2-carboxamide	Method 3. HPLC-MS (Method A): retention time 1.46 minutes. LRMS m/z [M+1] 430.42.
75		1-(3-Hydroxy-4-(2-((S)-3-methylbutan-2-ylamino)-3,4-dioxocyclobut-1-enylamino)picolinoyl)-N-methylpiperidine-3-carboxamide	Compound prepared using Method (i) starting with Preparation 35 and N-methylpiperidine-3-carboxamide (see WO-2009/077844). The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.4 minutes. LRMS m/z [M+1] 444.28.
76		(S)-N-Cyclobutyl-3-hydroxy-N-methyl-4-(2-(3-methylbutan-2-ylamino)-3,4-dioxocyclobut-1-enylamino)picolinamide	Compound prepared using Method (i) starting with Preparation 35 and N-methylcyclobutanamine (see JP2009184933). The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.50 minutes. LRMS m/z [M+1] 387.27.
77		3-Hydroxy-N-methyl-4-(2-((S)-3-methylbutan-2-ylamino)-3,4-dioxocyclobut-1-enylamino)-N-(1-methylpyrrolidin-3-yl)picolinamide	Compound prepared using Method (i) starting with Preparation 35 and N,1-dimethylpyrrolidin-3-amine. The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.28 minutes. LRMS m/z [M+1] 416.47
78		(S)-3-Hydroxy-N-methyl-4-(2-(3-methylbutan-2-ylamino)-3,4-dioxocyclobut-1-enylamino)-N-(1-methylpiperidin-4-yl)picolinamide	Compound prepared using Method (i) starting with Preparation 35 and N,1-dimethylpiperidin-4-amine (see US-2002/6423813). The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.26 minutes. LRMS m/z [M+1] 430.42.

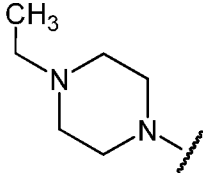
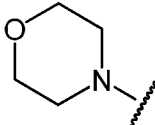
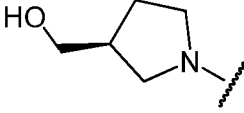
79		(S)-3-Hydroxy-N-methyl-4-(2-(3-methylbutan-2-ylamino)-3,4-dioxocyclobut-1-enylamino)-N-(2,2,2-trifluoroethyl)picolinamide	Compound prepared using Method (i) starting with Preparation 35 and 2,2,2-trifluoro-N-methylethanamine (Preparation 56.). The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.53 minutes. LRMS m/z [M+1] 415.36.
80		(S)-N-Benzyl-3-hydroxy-N-methyl-4-(2-(3-methylbutan-2-ylamino)-3,4-dioxocyclobut-1-enylamino)picolinamide	Compound prepared using Method (i) starting with Preparation 35 and N-methyl-1-phenylmethanamine. The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.59 minutes. LRMS m/z [M+1] 423.26.
81		(S)-3-Hydroxy-N-methyl-4-(2-(3-methylbutan-2-ylamino)-3,4-dioxocyclobut-1-enylamino)-N-(pyridin-2-ylmethyl)picolinamide	Compound prepared using Method (i) starting with Preparation 35 and N-methyl-1-(pyridin-2-yl)methanamine. The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.39 minutes. LRMS m/z [M+1] 424.28.
82		(S)-3-Hydroxy-N-methyl-4-(2-(3-methylbutan-2-ylamino)-3,4-dioxocyclobut-1-enylamino)-N-(pyridin-3-ylmethyl)picolinamide	Compound prepared using Method (i) starting with Preparation 35 and N-methyl-1-(pyridin-3-yl)methanamine. The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.34 minutes. LRMS m/z [M+1] 424.28.
83		(S)-3-Hydroxy-N-methyl-4-(2-(3-	Compound prepared using Method (i) starting with Preparation 35 and N-

		methylbutan-2-ylamino)-3,4-dioxocyclobut-1-enylamino)-N-(pyridin-4-ylmethyl)picolinamide	methyl-1-(pyridin-4-yl)methanamine. The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.31 minutes. LRMS m/z [M+1] 424.47.
84		3-(3-Hydroxy-2-((R)-3-methoxypyrrolidine-1-carbonyl)pyridin-4-ylamino)-4-((S)-3-methylbutan-2-ylamino)cyclobut-3-ene-1,2-dione	Compound prepared using Method (i) starting with Preparation 35 and (R)-3-methoxypyrrolidine. The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.54 minutes. LRMS m/z [M+1] 403.36.
85		3-(2-((3R,4R)-3,4-Difluoropyrrolidine-1-carbonyl)-3-hydroxypyridin-4-ylamino)-4-((S)-3-methylbutan-2-ylamino)cyclobut-3-ene-1,2-dione	Compound prepared using Method (i) starting with Preparation 35 and (3R,4R)-3,4-difluoropyrrolidine (see Bioorganic and Medicinal Chemistry Letters, 2005, 15, 4770-4773). The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.60 minutes. LRMS m/z [M+1] 409.40.
86		3-(2-((S)-3-Fluoropyrrolidine-1-carbonyl)-3-hydroxypyridin-4-ylamino)-4-((S)-3-methylbutan-2-ylamino)cyclobut-3-ene-1,2-dione	Compound prepared using Method (i) starting with Preparation 35 and (S)-3-fluoropyrrolidine. The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.57 minutes. LRMS m/z [M+1] 391.36.
87		(S)-3-(2-(3,3-Difluoropyrrolidine-1-carbonyl)-3-hydroxypyridin-4-ylamino)-4-(3-methylbutan-2-ylamino)cyclobut-3-ene-1,2-dione	Compound prepared using Method (i) starting with Preparation 35 and 3,3-difluoropyrrolidine. The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A):

		methylbutan-2-ylamino)cyclobut-3-ene-1,2-dione	retention time 1.63 minutes. LRMS m/z [M+1] 409.4.
88		(S)-3-(2-(4,4-Difluoropiperidin-1-carbonyl)-3-hydroxypyridin-4-ylamino)-4-(3-methylbutan-2-ylamino)cyclobut-3-ene-1,2-dione	Compound prepared using Method (i) starting with Preparation 35 and 4,4-difluoropiperidine. The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.51 minutes. LRMS m/z [M+1] 423.45.
89		3-(2-(3-Fluoropyrrolidin-1-carbonyl)-3-hydroxypyridin-4-ylamino)-4-((S)-3-methylbutan-2-ylamino)cyclobut-3-ene-1,2-dione	Compound prepared using Method (i) starting with Preparation 35 and 3-fluoropyrrolidine. The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.56 minutes. LRMS m/z [M+1] 391.54.
90		(R)-1-(3-Hydroxy-4-(2-((S)-3-methylbutan-2-ylamino)-3,4-dioxocyclobut-1-enylamino)picolinoyl)piperidine-3-carboxamide	Compound prepared using Method (i) starting with Preparation 35 and (R)-piperidine-3-carboxamide (Preparation 73.) The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.38 minutes. LRMS m/z [M+1] 430.33.
91		(S)-3-(3-Hydroxy-2-(3-(pyrimidin-5-yl)azetidine-1-carbonyl)pyridin-4-ylamino)-4-(3-methylbutan-2-ylamino)cyclobut-3-ene-1,2-dione	Compound prepared using Method (i) starting with Preparation 35 and 5-(azetidin-3-yl)pyrimidine (Preparation 62). The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.55 minutes. LRMS m/z [M+1] 437.44.
92		(S)-3-(3-Hydroxy-2-(3-(pyrimidin-2-	Compound prepared using Method (i) starting with Preparation 35 and 2-

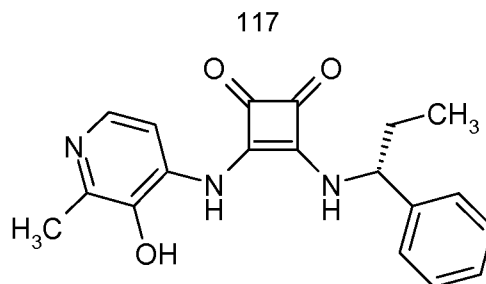
		yl)azetidine-1-carbonyl)pyridin-4-ylamino)-4-(3-methylbutan-2-ylamino)cyclobut-3-ene-1,2-dione	(azetidin-3-yl)pyrimidine (Preparation 60). The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.61 minutes. LRMS m/z [M+1] 437.40.
93		(S)-3-(3-Hydroxy-2-(3-(pyridazin-3-yl)azetidine-1-carbonyl)pyridin-4-ylamino)-4-(3-methylbutan-2-ylamino)cyclobut-3-ene-1,2-dione	Compound prepared using Method (i) starting with Preparation 35 and 3-(azetidin-3-yl)pyridazine (Preparation 61). The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.55 minutes. LRMS m/z [M+1] 437.40.
94		(S)-3-(3-Hydroxy-2-(3-(pyrimidin-4-yl)azetidine-1-carbonyl)pyridin-4-ylamino)-4-(3-methylbutan-2-ylamino)cyclobut-3-ene-1,2-dione	Compound prepared using Method (i) starting with Preparation 35 and 4-(azetidin-3-yl)pyrimidine (Preparation 86). The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.59 minutes. LRMS m/z [M+1] 437.40.
95		(S)-N-Cyclopentyl-3-hydroxy-N-methyl-4-(2-(3-methylbutan-2-ylamino)-3,4-dioxocyclobut-1-enylamino)picolinamide	Compound prepared using Method (i) starting with Preparation 35 and N-methylcyclopentanamine. The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.53 minutes. LRMS m/z [M+1] 401.5.
96		(S)-3-(2-(3-(Dimethylamino)azetidine-1-carbonyl)-3-hydroxypyridin-4-ylamino)-4-(3-methylbutan-2-ylamino)cyclobut-3-ene-1,2-dione	Compound prepared using Method (i) starting with Preparation 35 and N,N-dimethylazetidin-3-amine. The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.33 minutes. LRMS m/z [M+1] 402.43.

		ene-1,2-dione	
97		(S)-3-(2-(3-Fluoroazetidine-1-carbonyl)-3-hydroxypyridin-4-ylamino)-4-(3-methylbutan-2-ylamino)cyclobut-3-ene-1,2-dione	Compound prepared using Method (i) starting with Preparation 35 and 3-fluoroazetidine (see WO-2004/043940). The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.61 minutes. LRMS m/z [M+1] 377.41.
98		(S)-3-(2-(Azetidine-1-carbonyl)-3-hydroxypyridin-4-ylamino)-4-(3-methylbutan-2-ylamino)cyclobut-3-ene-1,2-dione	Compound prepared using Method (i) starting with Preparation 35 and azetidine. The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.62 minutes. LRMS m/z [M+1] 359.36.
99		3-(3-Hydroxy-2-(2-oxa-6-azaspiro[3.3]heptan-6-carbonyl)pyridin-4-ylamino)-4-((S)-3-methylbutan-2-ylamino)cyclobut-3-ene-1,2-dione	Compound prepared using Method (i) starting with Preparation 35 and 2-oxa-6-azaspiro[3.3]heptanes (see Angewandte Chemie International Edition, 2008, 47(24), 4512). The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.55 minutes. LRMS m/z [M+1] 401.4.
100		(S)-3-(2-(4-Acetylpiperazine-1-carbonyl)-3-hydroxypyridin-4-ylamino)-4-(3-methylbutan-2-ylamino)cyclobut-3-ene-1,2-dione	Compound prepared using Method (i) starting with Preparation 35 and 1-(piperazin-1-yl)ethanone. The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.39 minutes. LRMS m/z [M+1] 430.42.
101		(S)-3-(3-Hydroxy-2-(4-methyl-1,4-diazepane-1-carbonyl)pyridin-4-ylamino)-4-(3-methylbutan-2-ylamino)cyclobut-3-ene-1,2-dione	Compound prepared using Method (i) starting with Preparation 35 and 1-methyl-1,4-diazepane. The title compound was purified using

		ylamino)-4-(3-methylbutan-2-ylamino)cyclobut-3-ene-1,2-dione	preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.26 minutes. LRMS m/z [M+1] 416.47.
102		(S)-3-(2-(4-Ethylpiperazine-1-carbonyl)-3-hydroxypyridin-4-ylamino)-4-(3-methylbutan-2-ylamino)cyclobut-3-ene-1,2-dione	Compound prepared using Method (i) starting with Preparation 35 and 1-ethylpiperazine. The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.26 minutes. LRMS m/z [M+1] 416.47.
103		(S)-3-(3-Hydroxy-2-(morpholine-4-carbonyl)pyridin-4-ylamino)-4-(3-methylbutan-2-ylamino)cyclobut-3-ene-1,2-dione	Compound prepared using Method (i) starting with Preparation 35 and morpholine. The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.40 minutes. LRMS m/z [M+1] 389.31.
104		3-(3-Hydroxy-2-((S)-3-(hydroxymethyl)pyrrolidine-1-carbonyl)pyridin-4-ylamino)-4-((S)-3-methylbutan-2-ylamino)cyclobut-3-ene-1,2-dione	Compound prepared using Method (i) starting with Preparation 35 and (S)-pyrrolidin-3-ylmethanol. The title compound was purified using preparative HPLC Method 3. HPLC-MS (Method A): retention time 1.44 minutes. LRMS m/z [M+1] 403.26.

Example 105

3-(2-Methyl-3-oxo-3,4-dihydropyridin-4-ylamino)-4-((R)-1-phenylpropylamino)cyclobut-3-ene-1,2-dione

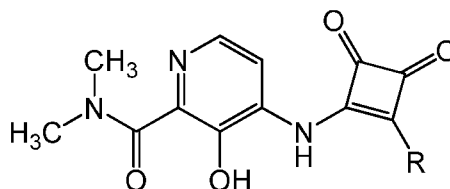


(R)-3-(3-Methoxy-2-methylpyridin-4-ylamino)-4-(1-phenylpropylamino)cyclobut-3-ene-1,2-dione (Preparation 36, 350mg, 0.997mmol) was dissolved in dichloromethane (15mL). Tert-butylammonium iodide (400mg) was added and the solution was cooled to 0°C. Boron tribromide (1M solution in dichloromethane, 5.98mL, 5.98mmol) was added dropwise and the reaction mixture was stirred at room temperature for 5 hours. The reaction was quenched with the addition of saturated sodium hydrogen carbonate aqueous solution and dichloromethane was used to extract the product. The dichloromethane was dried over anhydrous sodium sulfate and concentrated *in vacuo* to give crude product that was purified by preparative HPLC (Method 1).

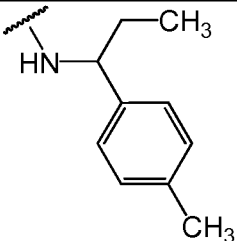
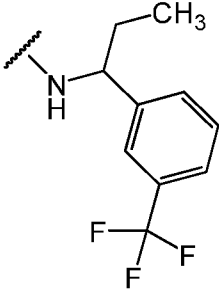
HPLC MS Method E: retention time 2.98 minutes.

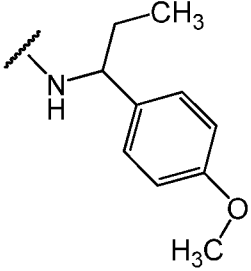
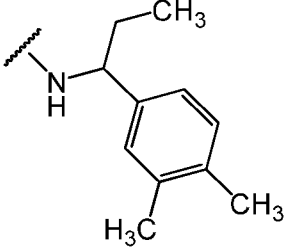
LRMS(ES): m/z 338.14 $[M+H]^+$.

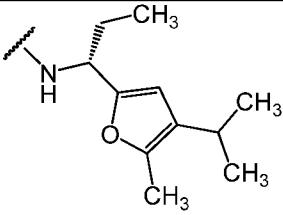
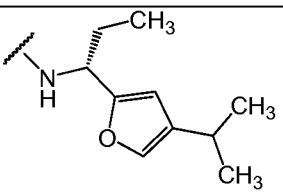
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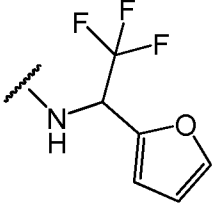
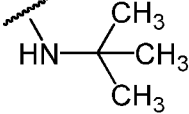
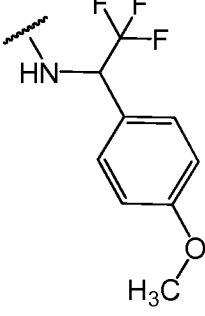


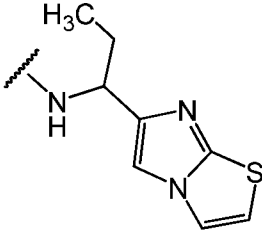
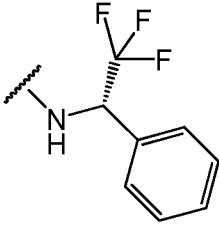
Ex.	R	Name	Experimental and characterisation
106		(S)-4-(3,4-Dioxo-2-(1-phenylpropylamino)cyclobut-1-enylamino)-3-hydroxy-N,N-dimethylpicolinamide	(S)-3-Ethoxy-4-(1-phenylpropylamino)cyclobut-3-ene-1,2-dione (Preparation 37, 37.9g, 0.292mmol), 4-amino-3-hydroxy-N,N-dimethylpicolinamide (Preparation 12, 53mg, 0.293mmol) and DIPEA (37.7mg, 0.292mmol) were combined and heated to 90°C for 5 days. The reaction was concentrated <i>in vacuo</i> and partitioned between dichloromethane (20mL) and saturated aqueous ammonium chloride (10mL). The organic phase was concentrated and the crude

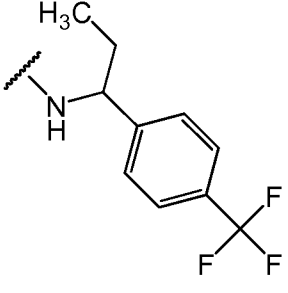
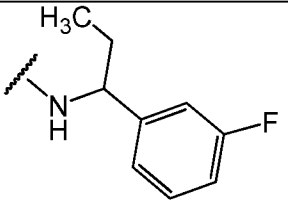
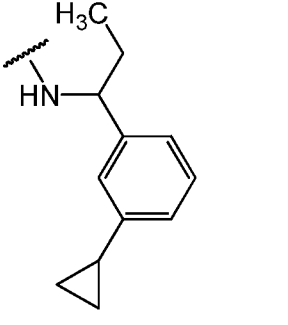
			product was purified using column chromatography on silica gel eluting with 95/5/0.5 dichloromethane/methanol/ammonia to afford the title compound as a yellow oil (13mg, 58%). ¹ H NMR (400MHz, CD ₃ OD): δ = 0.98 (t, 3H), 1.94-2.06 (m, 2H), 3.11-3.23 (br d, 6H), 5.14-5.21 (m, 1H), 7.23-7.45 (m, 5H), 7.84 (m, 1H), 8.20 (m, 1H) ppm. 3 exchangeables not observed. LRMS(ES): m/z 395 [M+H] ⁺ .
107		4-(3,4-Dioxo-2-(1-p-tolylpropylamino)cyclobut-1-enylamino)-3-hydroxy-N,N-dimethylpicolinamide	Compound prepared by heating Preparation 16 (23mg, 0.075mmol) and 1-p-tolylpropan-1-amine (20.7mg, 0.11mmol) in ethanol (1mL) with DIPEA (65uL, 0.37mmol) at 60°C for 1.5 hours. Solvent removed <i>in vacuo</i> and residue purified by column chromatography on silica gel eluting with 0 to 30% methanol in dichloromethane to afford title compound as a yellow solid (18mg, 59%). ¹ H NMR (400MHz, CD ₃ OD): δ = 0.97 (t, 3H), 1.92-2.03 (m, 2H), 2.32 (s, 3H), 3.11-3.25 (br d, 6H), 5.15 (m, 1H), 7.20 (d, 2H), 7.24 (d, 2H), 7.84 (m, 1H), 8.21 (m, 1H) ppm. 3 exchangeables not observed. LRMS(ES): m/z 409 [M+H] ⁺ .
108		4-(3,4-Dioxo-2-(1-(3-(trifluoromethyl)phenyl)propylamino)cyclobut-1-enylamino)-3-hydroxy-N,N-dimethylpicolinamide	Compound prepared by heating Preparation 16 (25mg, 0.082mmol) and 1-(3-(trifluoromethyl)phenyl)propan-1-amine (25.0mg, 0.12mmol) in ethanol (1mL) with DIPEA (43 μ L, 0.24mmol) at 60°C for 2 hours. Solvent was removed <i>in vacuo</i> and the residue was partitioned between saturated aqueous ammonium chloride solution (10mL) and dichloromethane (10mL). The organic

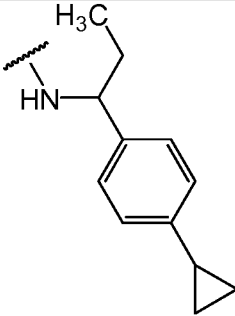
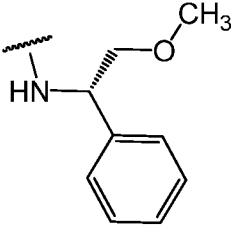
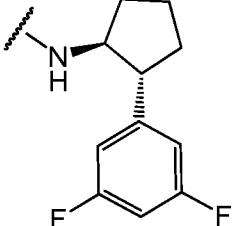
			phase was concentrated <i>in vacuo</i> and purified by preparative HPLC Method 2. HPLC MS method E: Retention time 2.99 minutes. LRMS(ES): m/z 463.15 M+H] ⁺ .
109		3-Hydroxy-4-(2-(1-(4-methoxyphenyl)propylamino)-3,4-dioxocyclobut-1-enylamino)-N,N-dimethylpicolinamide	Compound prepared by heating Preparation 16 (25mg, 0.082mmol) and 1-(4-methoxyphenyl)propan-1-amine (20.0mg, 0.12mmol) in ethanol (1mL) with DIPEA (43 μ L, 0.24mmol) at 60°C for 2 hours. Solvent was removed <i>in vacuo</i> and the residue was partitioned between saturated aqueous ammonium chloride solution (10mL) and dichloromethane (10mL). The organic phase was concentrated and the residue was purified by column chromatography on silica gel eluting with 0 to 40% methanol in dichloromethane to afford the title compound as a yellow solid. ¹ H NMR (400MHz, CD ₃ OD): δ = 0.98 (t, 3H), 1.95-2.03 (m, 2H), 3.03-3.23 (br d, 6H), 3.78 (s, 3H), 5.08 (m, 1H), 6.93 (d, 2H), 7.30 (d, 2H), 7.85 (m, 1H), 8.21 (m, 1H) ppm. 3 exchangeables not observed. LRMS(ES): m/z 423 [M-H].
110		4-(2-(1-(3,4-Dimethylphenyl)propylamino)-3,4-dioxocyclobut-1-enylamino)-3-hydroxy-N,N-dimethylpicolinamide	Compound prepared by heating Preparation 16 (25mg, 0.082mmol) and 1-(3,4-dimethylphenyl)propan-1-amine (20.1mg, 0.12mmol) in ethanol (1mL) with DIPEA (43 μ L, 0.24mmol) at 60°C for 2 hours. Solvent was removed <i>in vacuo</i> and the residue was partitioned between saturated aqueous ammonium chloride solution (10mL) and dichloromethane. The organic phase was concentrated <i>in vacuo</i> and purified by preparative HPLC Method 1. HPLC MS method E.

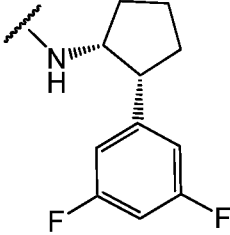
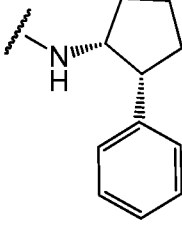
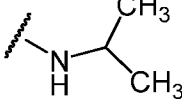
			Retention time 3.00 minutes. LRMS(ES): m/z 423.2 M+H ⁺ .
111		(R)-3-Hydroxy-4-(2-(1-(4-isopropyl-5-methylfuran-2-yl)propylamino)-3,4-dioxocyclobut-1-enylamino)-N,N-dimethylpicolinamide	Compound prepared by reacting Preparation 16 (100mg, 0.327mmol) and (R)-1-(4-isopropyl-5-methylfuran-2-yl)propan-1-amine (see WO-2008/005570, 65.0mg, 0.359mmol) in ethanol (5mL) at room temperature for 18 hours. Solvent was removed <i>in vacuo</i> and the residue was purified by column chromatography on silica gel eluting with 1 to 5% methanol in dichloromethane. The product was triturated with hexane to afford a yellow solid (80.0mg, 24%). ¹ H NMR (400MHz, DMSO- <i>d</i> ₆): δ = 0.91 (m, 3H), 1.09 (d, 6H), 1.81-1.97 (m, 2H), 2.19 (s, 3H), 2.72-2.76 (m, 1H), 3.04 (br s, 3H), 3.16 (br s, 3H), 5.10 (m, 1H), 6.29 (s, 1H), 8.03 (s, 2H), 8.88 (br s, 1H), 9.62 (br s, 1H), 11.60 (br s, 1H) ppm. LRMS(ES): m/z 441.4 [M+H] ⁺ .
112		(R)-3-Hydroxy-4-(2-(1-(4-isopropylfuran-2-yl)propylamino)-3,4-dioxocyclobut-1-enylamino)-N,N-dimethylpicolinamide	Compound prepared by reacting Preparation 16 (240mg, 0.786mmol) and (R)-1-(4-isopropylfuran-2-yl)propan-1-amine (see WO-2005/068460, 145.0mg, 0.866mmol) in ethanol (5mL) at room temperature for 12 hours. Solvent was removed <i>in vacuo</i> and the residue was purified by column chromatography on silica gel eluting with 3% methanol in dichloromethane to afford the title compound as a yellow solid (80.0mg, 24%). ¹ H NMR (400MHz, DMSO- <i>d</i> ₆): δ = 0.90-0.92 (m, 3H), 1.13 (d, 6H), 1.84-1.99 (m, 2H), 2.67-2.72 (m, 1H), 3.03 (s, 3H), 3.13 (s, 3H), 5.12 (m, 1H), 6.39 (s, 1H), 7.42 (s, 1H), 7.93-8.03 (m, 2H), 8.93

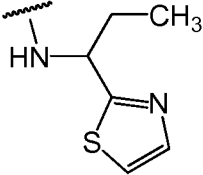
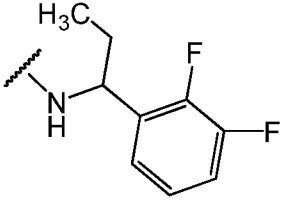
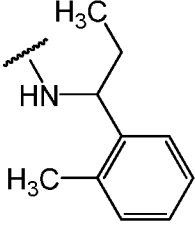
			(m, 1H) ppm. 2 exchangeables not observed. LRMS(ES):m/z 427.4 [M+H] ⁺ .
113		4-(3,4-Dioxo-2-(2,2,2-trifluoro-1-(furan-2-yl)ethylamino)cyclobut-1-enylamino)-3-hydroxy-N,N-dimethylpicolinamide	Compound prepared using Method (ix) starting with Preparation 16 and 2,2,2-trifluoro-1-(furan-2-yl)ethanamine (see Tetrahedron Asymmetry, 12(16), 2309). The product was purified using preparative HPLC Method 15 to afford the title compound as a yellow solid (38.0mg). ¹ H NMR (400MHz, DMSO-d ₆): δ = 3.04 (br s, 3H), 3.14 (br s, 3H), 6.15 (m, 1H), 6.60 (s, 1H), 6.81 (s, 1H), 7.90 (s, 1H), 7.92-8.03 (m, 2H) ppm. 3 exchangeables not observed. LRMS: m/z 425.2 [M+H] ⁺ .
114		4-(2-(tert-Butylamino)-3,4-dioxocyclobut-1-enylamino)-3-hydroxy-N,N-dimethylpicolinamide	Compound prepared using Method (ix) starting with Preparation 16 (150mg, 0.491mmol) and 2-methylpropan-2-amine (425mg, 1.473mmol) and purified by preparative thin layer chromatography on silica using 5% methanol in dichloromethane as mobile phase to afford the title compound as a yellow solid (54.0mg). ¹ H NMR (400MHz, CD ₃ OD): δ = 1.50 (s, 9H), 3.13 (s, 6H), 7.79 (m, 1H), 8.14 (m, 1H) ppm. 3 exchangeables not observed. LRMS: m/z 333.4 [M+H] ⁺ .
115		4-(3,4-Dioxo-2-(2,2,2-trifluoro-1-(4-methoxyphenyl)ethylamino)cyclobut-1-enylamino)-3-hydroxy-N,N-dimethylpicolinamide	Compound prepared using method (ix) starting with Preparation 16 (110mg, 0.364mmol) and 2,2,2-trifluoro-1-(4-methoxyphenyl)ethanamine (see Journal of the American Chemical Society, 1996, 118, 7134, 104mg, 1.437mmol). The reaction was purified by preparative HPLC Method 13 to afford the title compound as a yellow solid (51.0mg). ¹ H

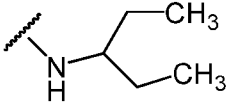
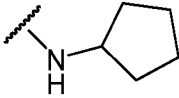
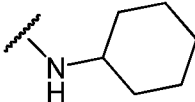
			NMR (400MHz, DMSO- <i>d</i> ₆): δ = 2.95-3.20 (br d, 6H), 3.79 (s, 3H), 5.95 (m, 1H), 7.07 (d, 2H), 7.46 (d, 2H), 7.91-8.00 (br m, 2H), 9.44 (br s, 1H), 9.75 (br s, 1H), 11.71 (br s, 1H) ppm. LRMS: m/z 465.6 [M+H] ⁺ .
116		3-Hydroxy-4-(2-(1-(imidazo[2,1-b]thiazol-6-yl)propylamino)-3,4-dioxocyclobut-1-enylamino)-N,N-dimethylpicolinamide	Compound prepared using Method (ix) starting with Preparation 16 (150mg, 0.491mmol) and 1-(imidazo[2,1-b]thiazol-6-yl)propan-1-amine (Preparation 7) (149mg, 0.589mmol) and purified by trituration with diethyl ether to afford the title compound as a yellow solid (60.0mg). ¹ H NMR (400MHz, DMSO <i>d</i> ₆): δ = 0.85-0.93 (m, 3H), 1.82-2.01 (m, 2H), 3.05 (s, 3H), 3.18 (s, 3H), 5.18 (m, 1H), 7.25 (d, 1H), 7.72 (s, 1H), 7.88 (d, 1H), 8.01 (m, 1H), 9.03 (m, 1H), 9.73 (m, 1H), 11.58 (m, 1H) ppm (one exchangeable not observed). LRMS: m/z 441.2 [M+H] ⁺ .
117		(S)-4-(3,4-Dioxo-2-(2,2,2-trifluoro-1-phenylethylamino)cyclobut-1-enylamino)-3-hydroxy-N,N-dimethylpicolinamide	Compound prepared using Method (ix) starting with Preparation 16 (150mg, 0.491mmol) and (S)-2,2,2-trifluoro-1-phenylethanamine (see Journal of Fluorine Chemistry, 2005, 126(3) 377, 125mg, 0.589mmol) and purified by preparative HPLC Method 13 to afford the title compound as a yellow solid (52.0mg). ¹ H NMR (400MHz, DMSO- <i>d</i> ₆): δ = 3.04 (s, 3H), 3.12 (s, 3H), 6.02 (m, 1H), 7.48-7.54 (m, 5H), 7.90-8.00 (m, 2H) ppm. 3 exchangeables not observed. LRMS: m/z 435.6 [M+H] ⁺ .

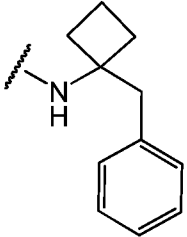
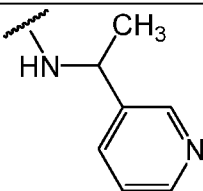
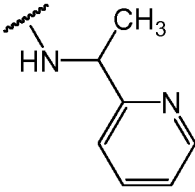
118		4-(3,4-Dioxo-2-(1-(4-(trifluoromethyl)phenyl)propylamino)cyclobut-1-enylamino)-3-hydroxy-N,N-dimethylpicolinamide	Compound prepared using Method (ix) starting with Preparation 16 and 1-(4-(trifluoromethyl)phenyl)propan-1-amine and purified by trituration with diethyl ether to afford the title compound as a yellow solid (80.0mg). ¹ H NMR (400MHz, DMSO- <i>d</i> ₆): δ = 0.92 (m, 3H), 1.92 (m, 2H), 3.04 (br s, 3H), 3.15 (br s, 3H), 5.19 (m, 1H), 7.60 (m, 2H), 7.77 (m, 2H), 7.92 (m, 1H), 7.99 (m, 1H), 9.03 (m, 1H) ppm. 2 exchangeables not observed. LRMS: m/z 463.0 [M+H] ⁺ .
119		4-(2-(1-(3-Fluorophenyl)propylamino)-3,4-dioxocyclobut-1-enylamino)-3-hydroxy-N,N-dimethylpicolinamide	Compound prepared using Method (ix) starting with Preparation 16 and 1-(3-fluorophenyl)propan-1-amine and purified by trituration with diethyl ether to afford the title compound as a yellow solid (75.0mg). ¹ H NMR (400MHz, DMSO- <i>d</i> ₆): δ = 0.91 (m, 3H), 1.92 (m, 2H), 3.05 (br s, 3H), 3.17 (br s, 3H), 5.12 (m, 1H), 7.14-7.23 (m, 3H), 7.46 (m, 1H), 8.00 (s, 2H), 8.89 (br s, 1H), 9.62 (br s, 1H) ppm. 1 exchangeable not observed. LRMS: m/z 413.0 [M+H] ⁺ .
120		4-(2-(1-(3-Cyclopropylphenyl)propylamino)-3,4-dioxocyclobut-1-enylamino)-3-hydroxy-N,N-dimethylpicolinamide	Compound prepared using Method (ix) starting with Preparation 16 and 1-(3-cyclopropylphenyl)propan-1-amine (Preparation 47). The reaction was purified by preparative HPLC Method 12 to afford the title compound as a yellow solid (40.0mg). ¹ H NMR (400MHz, DMSO- <i>d</i> ₆): δ = 0.67 (m, 2H), 0.90 (t, 3H), 0.96 (d, 2H), 1.88-1.98 (m, 3H), 3.04 (br s, 3H), 3.16 (br s, 3H), 5.04 (m, 1H), 6.96 (m, 1H), 7.10 (m, 2H), 7.27 (m, 1H), 7.90-8.10 (m, 2H), 8.80-8.95 (m, 1H), 9.55-9.75 (br m, 1H), 11.50-11.80 (m,

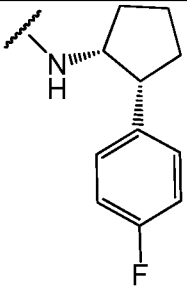
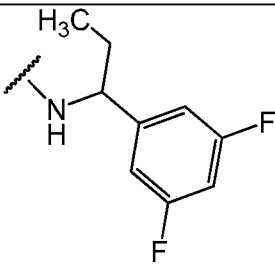
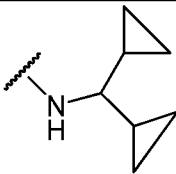
			1H) ppm. LRMS: m/z 435.0 [M+H] ⁺ .
121		4-(2-(1-(4-Cyclopropylphenyl)propylamino)-3,4-dioxocyclobut-1-enylamino)-3-hydroxy-N,N-dimethylpicolinamide	Compound prepared using Method (ix) starting with Preparation 16 and 1-(4-cyclopropylphenyl) propylamine (Preparation 46). The reaction was purified by preparative HPLC Method 12 to afford the title compound as a yellow solid (45.0mg). ¹ H NMR (400MHz, DMSO- <i>d</i> ₆): δ = 0.65 (m, 2H), 0.80-1.00 (m, 5H), 1.85-1.90 (m, 3H), 3.04 (br s, 3H), 3.15 (br s, 3H), 5.04 (m, 1H), 7.10 (d, 2H), 7.23 (d, 2H), 7.85-7.95 (m, 1H), 7.99 (m, 1H), 8.85-9.01 (br m, 1H) ppm. 2 exchangeables not observed. LRMS: m/z 434.8 [M+H] ⁺ .
122		(S)-3-Hydroxy-4-(2-(2-methoxy-1-phenylethylamino)-3,4-dioxocyclobut-1-enylamino)-N,N-dimethylpicolinamide	Compound prepared using Method (ix) starting with Preparation 16 and (S)-2-methoxy-1-phenylethylamine. The reaction was purified by preparative HPLC Method 16 to afford the title compound as a yellow solid (50.0mg). ¹ H NMR (400MHz, CD ₃ OD): δ = 3.14-3.19 (br d, 6H), 3.40 (s, 3H), 3.75 (m, 2H), 5.51 (m, 1H), 7.31-7.39 (m, 5H), 7.86 (m, 1H), 8.20 (m, 1H) ppm. 3 exchangeables not observed. LRMS(ES):m/z 411.0 [M+H] ⁺ .
123		4-(2-((1S,2R)-2-(3,5-Difluorophenyl)cyclopentylamino)-3,4-dioxocyclobut-1-enylamino)-3-hydroxy-N,N-dimethylpicolinamide	Compound prepared using Method (ix) starting with Preparation 16 and (1S,2R)-2-(3,5-difluorophenyl)cyclopentylamine (see Journal of Medicinal Chemistry, 2002, 45, 2101). Product purified by trituration with diethyl ether to afford the title compound as a yellow solid (70.0mg). ¹ H NMR (400MHz, DMSO- <i>d</i> ₆): δ = 1.70-1.80 (m, 5H), 2.05-2.25 (m, 3H), 3.02 (br s, 3H), 3.10 (br s, 3H), 4.47

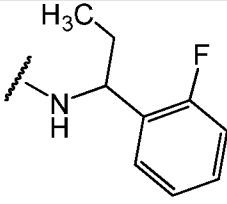
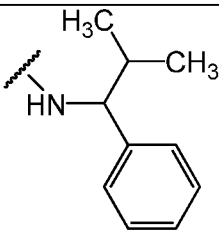
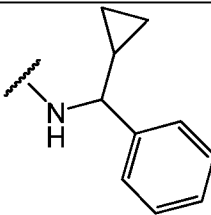
			(m, 1H), 7.04 (m, 4H), 7.87 (m, 1H), 7.94 (m, 1H), 8.75 (m, 1H) ppm. LRMS: m/z 457.6 [M+H] ⁺ .
124		4-(2-((1R,2R)-2-(3,5-Difluorophenyl)cyclopentylamino)-3,4-dioxocyclobut-1-enylamino)-3-hydroxy-N,N-dimethylpicolinamide	Compound prepared using Method (ix) starting with Preparation 16 and (1R,2R)-2-(3,5-difluorophenyl)cyclopentanamine (see Journal of Medicinal Chemistry, 2002, 45, 2101). Product purified by trituration with diethyl ether to afford the title compound as a yellow solid (63.0mg). ¹ H NMR (400MHz, DMSO- <i>d</i> ₆): δ = 1.70-1.85 (m, 5H), 2.11-2.25 (m, 3H), 3.02 (br s, 3H), 3.10 (br s, 3H), 4.47 (m, 1H), 7.04 (m, 4H), 7.86 (m, 1H), 7.93 (m, 1H), 8.75 (m, 1H) ppm. LRMS: m/z 457.6 [M+H] ⁺ .
125		4-(3,4-Dioxo-2-((1R,2R)-2-phenylcyclopentylamino)cyclobut-1-enylamino)-3-hydroxy-N,N-dimethylpicolinamide	Compound prepared using Method (ix) starting with Preparation 16 and (1R,2R)-2-phenylcyclopentanamine (see Journal of Medicinal Chemistry, 2002, 45, 2101). Product purified by trituration with diethyl ether to afford the title compound as a yellow solid (115.0 mg). ¹ H NMR (400MHz, DMSO- <i>d</i> ₆): δ = 1.78 (m, 2H), 1.90-2.12 (m, 3H), 2.22 (m, 1H), 3.04-3.21 (m, 7H), 4.83 (m, 1H), 7.14-7.21 (m, 5H), 7.87 (m, 1H), 7.95 (m, 1H), 8.28 (m, 1H), 9.39 (br m, 1H), 11.60-11.78 (m, 1H) ppm. LRMS: m/z 421.4 [M+H] ⁺ .
126		3-Hydroxy-4-(2-(isopropylamino)-3,4-dioxocyclobut-1-enylamino)-N,N-dimethylpicolinamide	Compound prepared using Method (ix) starting with Preparation 16 (150mg, 0.491mmol) and propan-2-amine (34.9mg, 0.590mmol). Product purified by trituration with diethyl ether to afford the title compound as a yellow solid (105.0mg). ¹ H NMR (400MHz, CD ₃ OD): δ = 1.32 (d, 6H), 3.13-3.20 (br d, 6H),

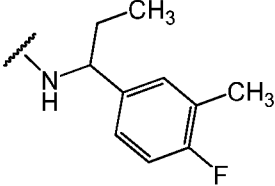
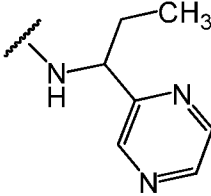
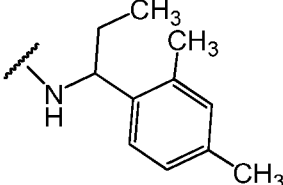
			4.35 (m, 1H), 7.88 (m, 1H), 8.22 (m, 1H) ppm. 3 exchangeables not observed. LRMS: m/z 319.4 [M+H] ⁺ .
127		4-(3,4-Dioxo-2-(1-(thiazol-2-yl)propylamino)cyclobut-1-enylamino)-3-hydroxy-N,N-dimethylpicolinamide	Compound prepared using Method (ix) starting with Preparation 16 and 1-(thiazol-2-yl)propan-1-amine (see WO-2005/068460) and purified by trituration with diethyl ether to afford the title compound as a yellow solid (55.0mg). ¹ H NMR (400MHz, DMSO-d ₆): δ = 0.97 (m, 3H), 1.98 (m, 1H), 2.13 (m, 1H), 3.05 (br s, 3H), 3.15 (br s, 3H), 5.50 (m, 1H), 7.75 (s, 1H), 7.85 (s, 1H), 7.95-8.05 (m, 2H), 9.24 (m, 1H) ppm. 2 exchangeables not observed. LRMS: m/z 402.2 [M+H] ⁺ .
128		4-(2-(1-(2,3-Difluorophenyl)propylamino)-3,4-dioxocyclobut-1-enylamino)-3-hydroxy-N,N-dimethylpicolinamide	Compound prepared using Method (ix) starting with Preparation 16 and 1-(2,3-difluorophenyl)propan-1-amine (Preparation 45) and purified by trituration with diethyl ether to afford the title compound as a yellow solid (50.0mg). ¹ H NMR (400MHz, DMSO-d ₆): δ = 0.94 (m, 3H), 1.92 (m, 2H), 3.04 (br s, 3H), 3.15 (br s, 3H), 5.38 (m, 1), 7.24 (m, 2H), 7.39 (m, 1H), 7.94 (m, 1H), 7.98 (m, 1H), 9.02 (m, 1H) ppm. 2 exchangeables not observed. LRMS: m/z 431.2 [M+H] ⁺ .
129		4-(3,4-Dioxo-2-(1-o-tolylpropylamino)cyclobut-1-enylamino)-3-hydroxy-N,N-dimethylpicolinamide	Compound prepared using Method (ix) starting with Preparation 16 (150mg, 0.491mmol) and 1-o-tolylpropan-1-amine (see WO-2005/068460, 109mg, 0.589 mmol). The reaction was purified by preparative HPLC Method 17 to afford the title compound as a yellow solid. (50.0mg). ¹ H NMR (400MHz, DMSO-d ₆): δ = 0.86 (m, 3H), 1.85 (m, 2H) 2.36 (s,

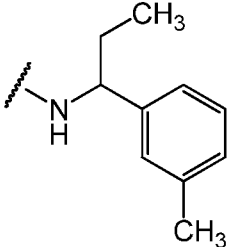
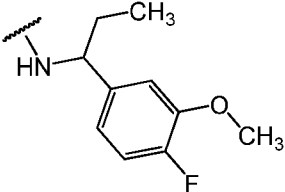
			3H), 3.04 (br s, 3H), 3.15 (br s, 3H), 5.34 (m, 1H), 7.20 (m, 2H), 7.27 (m, 1H), 7.33 (m, 1H), 7.90-8.10 (m, 2H), 8.91 (br m, 1H) ppm (2 exchangeables not observed). LRMS: m/z 409.0 [M+H] ⁺ .
130		4-(3,4-Dioxo-2-(pentan-3-ylamino)cyclobut-1-enylamino)-3-hydroxy-N,N-dimethylpicolinamide	Compound prepared using Method (ix) starting with Preparation 16 and pentan-3-amine and purified by trituration with diethyl ether to afford the title compound as a yellow solid (85.0mg). ¹ H NMR (400MHz, CD ₃ OD): δ = 1.00 (m, 6H), 1.50-1.61 (m, 2H), 1.69-1.72 (m, 2H), 3.13 (s, 6H), 4.01 (m, 1H), 7.77 (m, 1H), 8.16 (m, 1H) ppm. 3 exchangeables not observed. LRMS: m/z 346.8 [M+H] ⁺ .
131		4-(2-(Cyclopentylamino)-3,4-dioxocyclobut-1-enylamino)-3-hydroxy-N,N-dimethylpicolinamide	Compound prepared using Method (ix) starting with Preparation 16 and cyclopentanamine and purified by trituration with diethyl ether to afford the title compound as a yellow solid (65.0mg). ¹ H NMR (400MHz, DMSO-d ₆): δ = 1.42-1.94 (m, 8H + evidence of impurity), 2.97-2.99 (br d, 6H), 4.40 (m, 1H), 7.67 (m, 1H), 7.88 (m, 1H), 8.70 (m, 1H) ppm (1 exchangeable not observed). LRMS: m/z 344.8 [M+H] ⁺ .
132		4-(2-(Cyclohexylamino)-3,4-dioxocyclobut-1-enylamino)-3-hydroxy-N,N-dimethylpicolinamide	Compound prepared using Method (ix) starting with Preparation 16 and cyclohexanamine and purified by trituration with diethyl ether to afford the title compound as a yellow solid (85.0mg). ¹ H NMR (400MHz, CD ₃ OD): δ = 1.19-1.45 (m, 6H), 1.65 (m, 1H), 1.81 (m, 2H), 2.02 (m, 2H), 3.01 (s, 6H), 4.01 (m, 1H), 7.70 (m, 1H), 8.10 (m, 1H) ppm (2 exchangeables not observed). LRMS: m/z 359.3 [M+H] ⁺ .

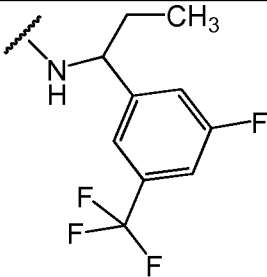
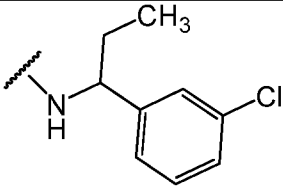
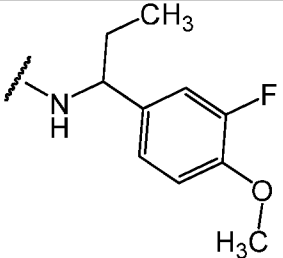
133		4-(2-(1-Benzylcyclobutylamino)-3,4-dioxocyclobut-1-enylamino)-3-hydroxy-N,N-dimethylpicolinamide	Compound prepared using Method (ix) starting with Preparation 16 and 1-benzylcyclobutanamine (Preparation 81) and purified by trituration with diethyl ether to afford the title compound as a yellow solid (85.0mg). ¹ H NMR (400MHz, DMSO- <i>d</i> ₆): δ = 1.86 (m, 2H), 2.11 (m, 2H), 2.30 (m, 2H), 3.03 (s, 3H), 3.13-3.17 (m, 5H), 7.14 (m, 2H), 7.23 (m, 1H), 7.32 (m, 2H), 8.02 (m, 1H), 8.10 (m, 1H), 8.85 (m, 1H) ppm (2 exchangeables not observed). LRMS: m/z 421.0 [M+H] ⁺ .
134		4-(3,4-Dioxo-2-(1-(pyridin-3-yl)ethylamino)cyclobut-1-enylamino)-3-hydroxy-N,N-dimethylpicolinamide	Compound prepared using Method (ix) starting with Preparation 16 and 1-(pyridin-3-yl)ethanamine and purified by trituration with diethyl ether to afford the title compound as a yellow solid (95.0mg). ¹ H NMR (400MHz, DMSO- <i>d</i> ₆): δ = 1.62 (d, 3H), 3.05 (s, 3H), 3.16 (s, 3H), 5.37 (m, 1H), 7.43 (m, 1H), 7.84 (m, 1H), 8.00 (m, 2H), 8.52 (m, 1H), 8.65 (m, 1H), 9.13 (m, 1H), 9.61 (m, 1H), 11.74 (m, 1H) ppm. LRMS: m/z 382.2 [M+H] ⁺ .
135		4-(3,4-Dioxo-2-(1-(pyridin-2-yl)ethylamino)cyclobut-1-enylamino)-3-hydroxy-N,N-dimethylpicolinamide	Compound prepared using Method (ix) starting with Preparation 16 and 1-(pyridin-2-yl)ethanamine and purified by trituration with diethyl ether to afford the title compound as a yellow solid (88.0mg). ¹ H NMR (400MHz, DMSO- <i>d</i> ₆): δ = 1.56 (d, 3H), 3.05 (s, 3H), 3.17 (s, 3H), 5.47 (m, 1H), 7.36 (m, 1H), 7.44 (m, 1H), 7.86 (m, 1H), 8.00 (m, 2H), 8.63 (m, 1H), 9.23 (m, 1H), 9.83 (m, 1H) ppm (1 exchangeable not observed). LRMS: m/z 382.2 [M+H] ⁺ .

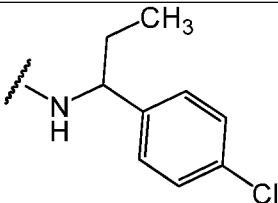
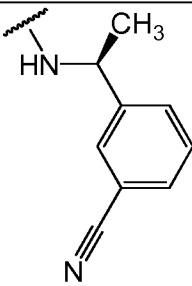
136		4-(2-((1R,2R)-2-(4-Fluorophenyl)cyclopentylamino)-3,4-dioxocyclobut-1-enylamino)-3-hydroxy-N,N-dimethylpicolinamide	Compound prepared using Method (ix) starting with Preparation 16 and (1R,2R)-2-(4-fluorophenyl)cyclopentanamine (see Journal of Medicinal Chemistry, 2002, 45 2101) and purified by trituration with diethyl ether to afford the title compound as a yellow solid (115.0mg). ^1H NMR (400MHz, $\text{DMSO}-d_6$): δ = 1.77 (m, 2H), 1.96 (m, 2H), 2.05 (m, 1H), 2.22 (m, 1H), 3.04 (s, 3H), 3.18 (s, 3H), 4.78 (m, 1H), 7.05 (m, 2H), 7.21 (m, 2H), 7.88 (m, 1H), 7.97 (m, 1H), 8.26 (br m, 1H), 9.38 (br m, 1H), 11.69 (br m, 1H) ppm. LRMS: m/z 439.0 $[\text{M}+\text{H}]^+$.
137		4-(2-(1-(3,5-Difluorophenyl)propylamino)-3,4-dioxocyclobut-1-enylamino)-3-hydroxy-N,N-dimethylpicolinamide	Compound prepared using Method (ix) starting with Preparation 16 and (1-(3,5-difluorophenyl)propan-1-amine (see WO-2005/068460) and purified by trituration with diethyl ether to afford the title compound as a yellow solid (50.0mg). ^1H NMR (400MHz, $\text{DMSO}-d_6$): δ = 0.92 (m, 3H), 1.91 (m, 2H), 3.05 (s, 3H), 3.17 (s, 3H), 5.12 (m, 1H), 7.12-7.20 (m, 3H), 8.00 (s, 2H), 8.85 (br m, 1H), 9.62 (br m, 1H), 11.5-11.75 (br m, 1H) ppm. LRMS: m/z 431.0 $[\text{M}+\text{H}]^+$.
138		4-(2-(Dicyclopropylmethylamino)-3,4-dioxocyclobut-1-enylamino)-3-hydroxy-N,N-dimethylpicolinamide	Compound prepared using Method (ix) starting with Preparation 16 and dicyclopropylmethanamine. The reaction was purified by preparative HPLC Method 11 to afford the title compound as a yellow solid (53.0mg). ^1H NMR (400MHz, $\text{DMSO}-d_6$): δ = 0.35 (m, 4H), 0.45 (m, 2H), 0.56 (m, 2H), 1.07 (m, 2H), 3.05 (s, 3H), 3.09- 3.17 (m, 4H), 8.02-8.03 (m, 2H), 8.74 (m, 1H) ppm. 2 exchangeables not observed. LRMS: m/z

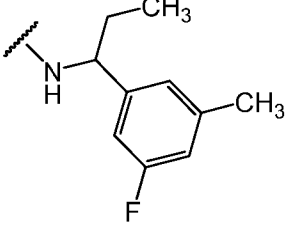
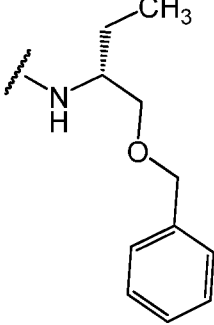
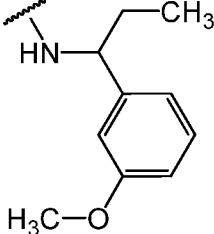
			370.8 [M+H] ⁺ .
139		4-(2-(1-(2-Fluorophenyl)propylamino)-3,4-dioxocyclobut-1-enylamino)-3-hydroxy-N,N-dimethylpicolinamide	Compound prepared using Method (ix) starting with Preparation 16 and (1-(2-fluorophenyl)propan-1-amine and purified by trituration with diethyl ether to afford the title compound as a yellow solid (52.0mg). ¹ H NMR (400MHz, DMSO-d ₆): δ = 0.93 (m, 3H), 1.92 (m, 2H), 3.05 (s, 3H), 3.17 (m, 3H), 5.36 (m, 1H), 7.26 (m, 2H), 7.37-7.43 (m, 2H), 7.99 (br m, 2H), 8.97 (br m, 1H) ppm (2 exchangeables not observed). LRMS: m/z 413.0 [M+H] ⁺ .
140		3-Hydroxy-N,N-dimethyl-4-(2-(2-methyl-1-phenylpropylamino)-3,4-dioxocyclobut-1-enylamino)picolinamide	Compound prepared using Method (ix) starting with Preparation 16 and 2-methyl-1-phenylpropan-1-amine (see WO-2006/81332) and purified by trituration with diethyl ether to afford the title compound as a yellow solid (85.0mg). ¹ H NMR (400MHz, DMSO-d ₆): δ = 0.82 (d, 3H), 0.97 (d, 3H), 2.17 (m, 1H), 3.05 (s, 3H), 3.17 (s, 3H), 5.01 (m, 1H), 7.30-7.42 (m, 5H), 8.00 (m, 2H), 8.90 (br m, 1H), 9.69 (br m, 1H), 11.72 (br m, 1H) ppm. LRMS: m/z 409.6 [M+H] ⁺ .
141		4-(2-(Cyclopropyl(phenyl)methylamino)-3,4-dioxocyclobut-1-enylamino)-3-hydroxy-N,N-dimethylpicolinamide	Compound prepared using Method (ix) starting with Preparation 16 (50.02mg, 0.164mmol) and cyclopropyl(phenyl)methanamine (24.15mg, 0.164mmol) and purified by preparative thin layer chromatography on silica using 3% methanol in dichloromethane as mobile phase to afford the title compound as a yellow solid (30.0mg). ¹ H NMR (400MHz, DMSO-d ₆): δ = 0.36 (m, 1H), 0.47 (m, 1H), 0.58 (m, 2H), 1.34 (m, 1H), 2.98 (s, 6H), 4.60 (1H), 7.29-7.40 (m, 5H), 7.70

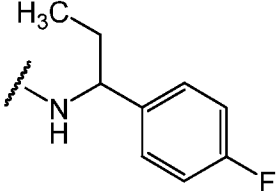
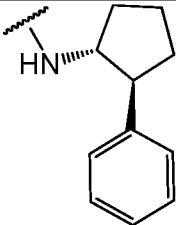
			(m, 1H), 7.89 (m, 1H), 9.13 (m, 1H) ppm (2 exchangeables not observed). LRMS: m/z 407.2 [M+H] ⁺ .
142		4-(2-(1-(4-Fluoro-3-methylphenyl)propylamino)-3,4-dioxocyclobut-1-enylamino)-3-hydroxy-N,N-dimethylpicolinamide	Compound prepared using Method (ix) starting with Preparation 16 (51.26mg, 0.168mmol) and 1-(4-fluoro-3-methylphenyl)propan-1-amine (Preparation 44, 28.07mg, 0.168mmol) and purified by preparative thin layer chromatography on silica using 3% methanol in dichloromethane as mobile phase to afford the title compound as a yellow solid (15.0mg). ¹ H NMR (400MHz, DMSO-d ₆): δ = 0.88 (m, 3H), 1.89 (m, 2H), 2.32 (s, 3H), 3.05 (s, 3H), 3.18 (s, 3H), 5.06 (m, 1H) 7.15-7.21 (m, 3H), 7.27 (m, 1H), 8.00 (m, 2H), 8.86 (m, 1H), 11.67 (br m, 1H). LRMS: m/z 427.4 [M+H] ⁺ .
143		4-(3,4-Dioxo-2-(1-(pyrazin-2-yl)propylamino)cyclobut-1-enylamino)-3-hydroxy-N,N-dimethylpicolinamide	Compound prepared using Method (ix) starting with Preparation 16 (53.26mg, 0.174mmol) and 1-(pyrazin-2-yl)propan-amine hydrochloride (Preparation 48) (30.3mg, 0.174mmol). The reaction was purified by preparative HPLC Method 10 to afford the title compound as a yellow solid (15.0mg). ¹ H NMR (400MHz, CD ₃ OD): δ = 1.00 (m, 3H), 2.04 (m, 2H), 3.14-3.21 (br d, 6H), 5.45 (m, 1H), 7.88 (m, 1H), 8.21 (m, 1H), 8.54 (s, 1H), 8.67 (m, 2H) ppm (3 exchangeables not observed). LRMS: m/z 397.4 [M+H] ⁺ .
144		4-(2-(1-(2,4-Dimethylphenyl)propylamino)-3,4-dioxocyclobut-1-enylamino)-3-hydroxy-N,N-dimethylpicolinamide	Compound prepared using Method (ix) starting with Preparation 16 (63.61mg, 0.208mmol) and 1-(2,4-dimethylphenyl)propan-1-amine (34.0mg, 0.208mmol) and purified by preparative

		hydroxy-N,N-dimethylpicolinamide	thin layer chromatography on silica using 3% methanol in dichloromethane as mobile phase to afford the title compound as a yellow solid (15.0mg). ¹ H NMR (400MHz, CD ₃ OD): δ = 1.00 (m, 3H), 1.91 (m, 2H), 2.27 (s, 3H), 2.38 (s, 3H), 3.11 (s, 6H), 5.45 (m, 1H), 7.00-7.05 (m, 2H), 7.21 (m, 1H), 7.71 (m, 1H), 8.11 (m, 1H) ppm (3 exchangeables not observed). LRMS: m/z 423.5 [M+H] ⁺ .
145		4-(3,4-Dioxo-2-(1-m-tolylpropylamino)cyclobut-1-enylamino)-3-hydroxy-N,N-dimethylpicolinamide	Compound prepared using Method (ix) starting with Preparation 16 (52.4mg, 0.171mmol) and 1-(3-methylphenyl)propylamine (Preparation 43, 31.88mg, 0.171mmol) and purified by preparative thin layer chromatography on silica to afford the title compound as a yellow solid (23.0mg). ¹ H NMR (400MHz, DMSO-d ₆): δ = 0.87 (m, 3H), 1.84 (m, 2H), 2.28 (s, 3H), 3.07 (s, 6H), 5.04 (m, 1H), 7.07-7.13 (m, 3H), 7.21 (m, 1H), 7.74 (m, 1H), 7.91 (m, 1H), 9.00 (m, 1H) ppm (2 exchangeables not observed). LRMS: m/z 409.2 [M+H] ⁺ .
146		4-(2-(1-(4-Fluoro-3-methoxyphenyl)propylamino)-3,4-dioxocyclobut-1-enylamino)-3-hydroxy-N,N-dimethylpicolinamide	Compound prepared using Method (ix) starting with Preparation 16 (37.81mg, 0.123mmol) and 1-(4-fluoro-3-methoxyphenyl)propan-1-amine (Preparation 42, 22.69mg, 0.123mmol) and purified by preparative thin layer chromatography on silica using 3% methanol in dichloromethane as mobile phase to afford the title compound as a yellow solid (30.0mg). ¹ H NMR (400MHz, DMSO-d ₆): δ = 0.87 (m, 3H), 1.86 (m, 2H), 2.91 (m, 6H) 3.81 (s, 3H), 5.02 (m, 1H), 7.10-7.21 (m, 4H), 7.61 (m, 1H),

			7.81 (m, 1H) ppm (2 exchangeables not observed). LRMS: m/z 433.4 [M+H] ⁺ .
147		4-(2-(1-(3-Fluoro-5-(trifluoromethyl)phenyl)propylamino)-3,4-dioxocyclobut-1-enylamino)-3-hydroxy-N,N-dimethylpicolinamide	Compound prepared using Method (ix) starting with Preparation 16 (41.0mg, 0.136mmol) and 1-(3-fluoro-5-(trifluoromethyl)phenyl)propanamine (Preparation 41, 30.0mg, 0.1357mmol) and purified by preparative thin layer chromatography on silica to afford the title compound as a yellow solid (18.0mg). ¹ H NMR (400MHz, CD ₃ OD): δ = 1.01 (m, 3H), 1.98 (m, 2H), 3.14-3.20 (br d, 6H), 5.27 (m, 1H), 7.39-7.46 (m, 2H), 7.54 (s, 1H), 7.87 (br s, 1H), 8.21 (m, 1H) ppm (3 exchangeables not observed). LRMS: m/z 481.6 [M+H] ⁺ .
148		4-(2-(1-(3-Chlorophenyl)propylamino)-3,4-dioxocyclobut-1-enylamino)-3-hydroxy-N,N-dimethylpicolinamide	Compound prepared using Method (ix) starting with Preparation 16 (54.14mg, 0.177mmol) and 1-(3-chlorophenyl)propanamine (see WO-2005/068460, 30.0mg, 0.177mmol) and purified by preparative thin layer chromatography on silica to afford the title compound as a yellow solid (23.5mg). ¹ H NMR (400MHz, DMSO- <i>d</i> ₆): δ = 0.90 (m, 3H), 1.89 (m, 2H), 3.02-3.09 (br d, 6H), 5.10 (m, 1H), 7.31-7.42 (m, 2H), 7.40-7.42 (m, 2H), 7.85 (m, 1H), 7.95 (m, 1H), 8.96 (br m, 1H) ppm (2 exchangeables not observed). LRMS: m/z 429.4 [M+H] ⁺ .
149		4-(2-(1-(3-Fluoro-4-methoxyphenyl)propylamino)-3,4-dioxocyclobut-1-enylamino)-3-hydroxy-N,N-dimethylpicolinamide	Compound prepared using Method (ix) starting with Preparation 16 (39.18mg, 0.128mmol) and 1-(3-fluoro-4-methoxyphenyl)propan-1-amine (Preparation 40, 28.20mg, 0.128mmol) and purified by preparative thin layer

		hydroxy-N,N-dimethylpicolinamide	chromatography on silica to afford the title compounds as a yellow solid (18.2mg). ¹ H NMR (400MHz, DMSO- <i>d</i> ₆): δ = 0.89 (m, 3H), 1.89 (m, 2H), 3.05 (s, 3H), 3.18 (s, 3H), 3.83 (s, 3H), 5.03 (m, 1H), 7.12-7.24 (m, 3H), 8.00 (s, 2H), 8.82 (m, 1H), 9.59 (m, 1H), 11.67 (m, 1H) ppm. LRMS: m/z 443.6 [M+H] ⁺ .
150		4-(2-(1-(4-Chlorophenyl)propylamino)-3,4-dioxocyclobut-1-enylamino)-3-hydroxy-N,N-dimethylpicolinamide	Compound prepared using Method (ix) starting with Preparation 16 (54.14mg, 0.177mmol) and 1-(4-chlorophenyl)propanamine (Preparation 39, 30.0mg, 0.177mmol) and purified by preparative thin layer chromatography on silica using 3% methanol in dichloromethane as mobile phase to afford the title compound as a yellow solid (20.0mg). ¹ H NMR (400MHz, DMSO- <i>d</i> ₆): δ = 0.89 (t, 3H), 1.88 (m, 2H), 3.03 (s, 3H), 3.12 (s, 3H), 5.09 (m, 1H), 7.38 (d, 2H), 7.45 (d, 2H), 7.85-7.97 (m, 2H), 8.97 (m, 1H) ppm (2 exchangeables not observed). LRMS: m/z 429.2 [M+H] ⁺ .
151		(S)-4-(2-(1-(3-Cyanophenyl)ethylamino)-3,4-dioxocyclobut-1-enylamino)-3-hydroxy-N,N-dimethylpicolinamide	Compound prepared using Method (ix) starting with Preparation 16 (62.67mg, 0.208mmol) and (S)-3-(1-aminoethyl)benzonitrile (see WO-2005/082859, 30.0mg, 0.205mmol) and purified by preparative thin layer chromatography on silica using 3% methanol in dichloromethane as mobile phase to afford the title compound as a yellow solid (23.0mg). ¹ H NMR (400MHz, DMSO- <i>d</i> ₆): δ = 1.59 (d, 3H), 3.02-3.12 (br d, 6H), 5.38 (m, 1H), 7.61 (m, 1H), 7.77 (m, 2H), 7.89 (m, 2H), 7.96 (m, 1H), 9.01 (m, 1H) ppm (2 exchangeables not

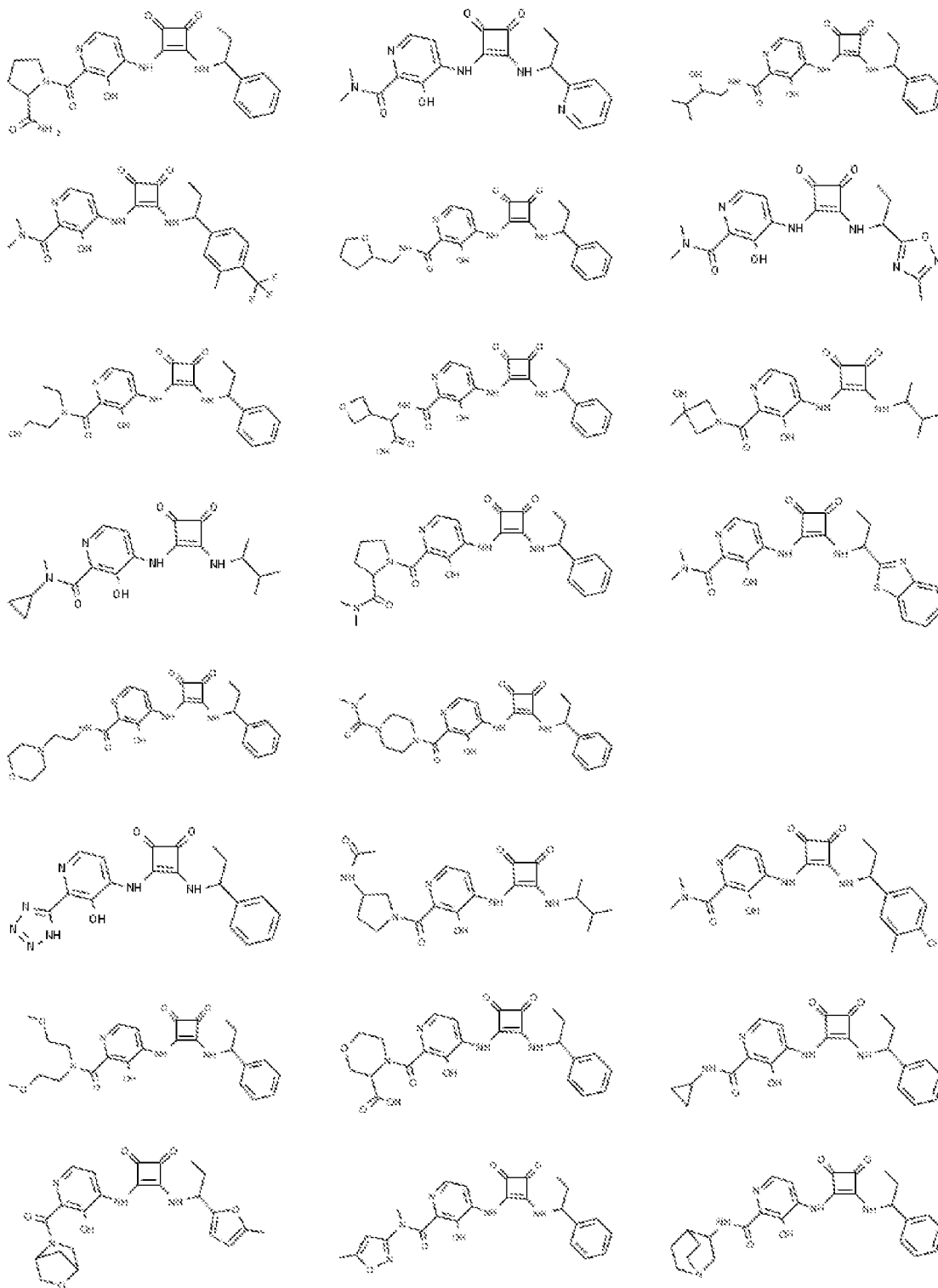
			observed). LRMS: m/z 406.4 [M+H] ⁺ .
152		4-(2-(1-(3-Fluoro-5-methylphenyl)propylamino)-3,4-dioxocyclobut-1-enylamino)-3-hydroxy-N,N-dimethylpicolinamide	Compound prepared using Method (ix) starting with Preparation 16 (47.88mg, 0.157mmol) and 1-(3-fluoro-5-methylphenyl)propan-1-amine (Preparation 38, 26.3mg, 0.157mmol) and purified by preparative thin layer chromatography on silica using 3% methanol in dichloromethane to afford the title compound as a yellow solid (30.0mg). ¹ H NMR (400MHz, DMSO- <i>d</i> ₆): δ = 0.88 (m, 3H), 1.85 (m, 2H), 2.30 (s, 3H), 2.96 (s, 6H), 5.06 (m, 1H), 6.91-7.00 (m, 3H), 7.66 (m, 1H), 7.84 (m, 1H), 9.05 (m, 1H) ppm. LRMS: m/z 427.2 [M+H] ⁺ .
153		(R)-4-(2-(1-(Benzyloxy)butan-2-ylamino)-3,4-dioxocyclobut-1-enylamino)-3-hydroxy-N,N-dimethylpicolinamide	Compound prepared using Method (ix) starting with Preparation 16 (53.84mg, 0.176mmol) and (R)-1-(benzyloxy)butan-2-amine (31.6mg, 0.176mmol) and purified by preparative thin layer chromatography on silica using 3% methanol in dichloromethane to afford the title compound as a yellow solid (22.0mg). ¹ H NMR (400MHz, DMSO- <i>d</i> ₆): δ = 0.91 (m, 3H), 1.55 (m, 1H), 1.70 (m, 1H), 3.05 (m, 3H), 3.17 (m, 3H), 3.56 (m, 2H), 4.19 (m, 1H), 4.53 (m, 2H), 7.32 (m, 5H), 8.01 (br m, 2H), 8.64 (m, 1H), 9.62 (m, 1H), 11.62 (br m, 1H) ppm. LRMS: m/z 439.6 [M+H] ⁺ .
154		3-Hydroxy-4-(2-(1-(3-methoxyphenyl)propylamino)-3,4-dioxocyclobut-1-enylamino)-N,N-dimethylpicolinamide	Compound prepared using Method (ix) starting with Preparation 16 (44.83mg, 0.147mmol) and 1-(3-methoxyphenyl)propan-1-amine (see WO-2005/066194, 24.32mg, 0.147mmol) and purified by preparative thin layer chromatography on silica using 3%

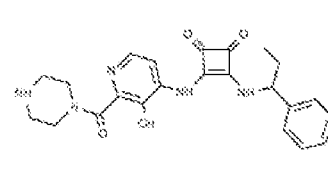
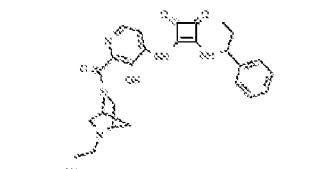
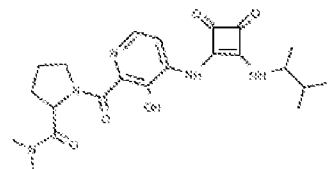
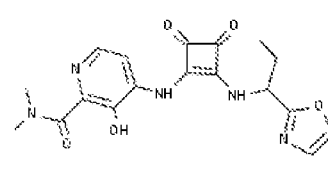
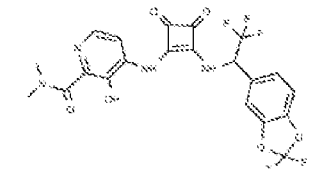
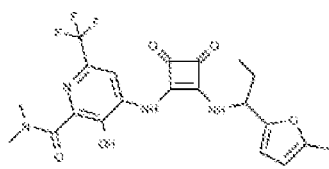
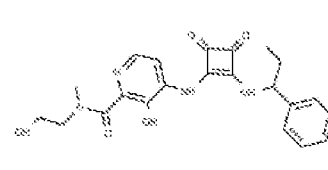
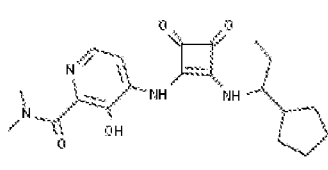
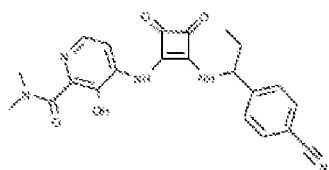
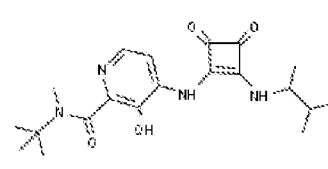
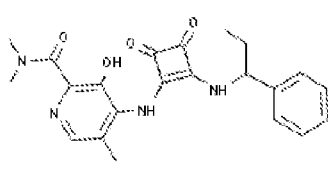
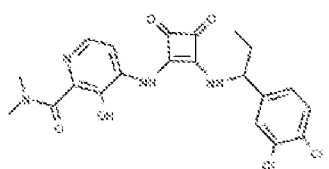
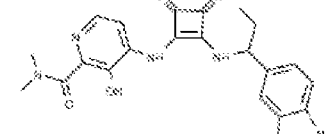
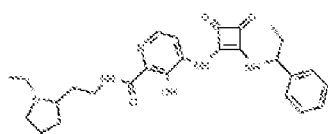
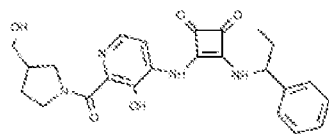
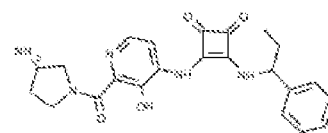
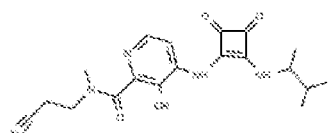
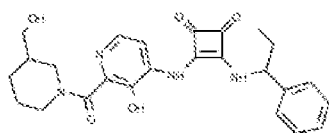
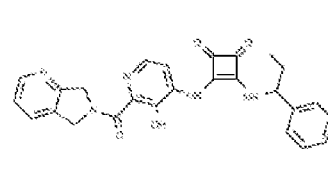
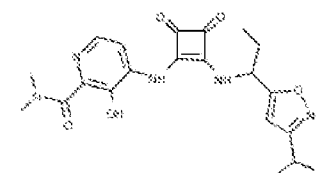
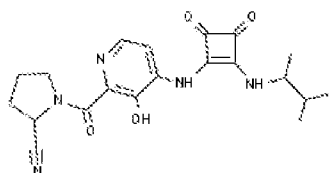
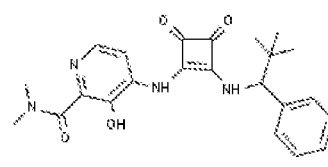
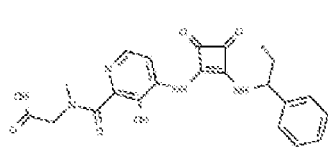
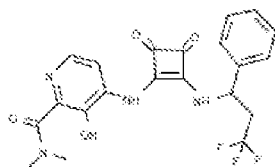
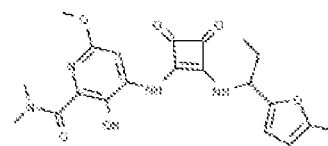
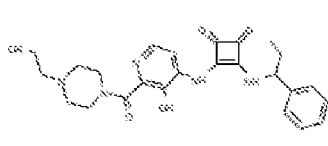
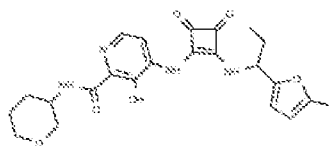
		ide	methanol in dichloromethane to afford the title compound as a yellow oil (30.0mg). ^1H NMR (400MHz, DMSO- d_6): δ = 0.87 (m, 3H), 1.85 (m, 2H), 2.90 (s, 6H), 3.74 (s, 3H), 5.05 (m, 1H), 6.82-6.89 (m, 3H), 7.27 (m, 1H), 7.68 (m, 1H), 7.87 (m, 1H), 8.98 (m, 1H) ppm (2 exchangeables not observed). LRMS: m/z 425.2 $[\text{M}+\text{H}]^+$.
155		4-(2-(1-(4-Fluorophenyl)propylamino)-3,4-dioxocyclobut-1-enylamino)-3-hydroxy-N,N-dimethylpicolinamide	Compound prepared using Method (ix) starting with Preparation 16 and 1-(4-fluorophenyl)propan-1-amine and purified by trituration with diethyl ether to afford the title compound as a yellow solid (52.0mg). ^1H NMR (400MHz, DMSO- d_6): δ = 0.90 (m, 3H), 1.90 (m, 2H), 3.04 (s, 3H), 3.16 (m, 3H), 5.10 (m, 1H), 7.22 (m, 2H), 7.40 (m, 2H), 8.00 (s, 2H), 8.93 (m, 1H), 9.62 (m, 1H) ppm. 1 exchangeable not observed. LRMS: m/z 413.2 $[\text{M}+\text{H}]^+$.
156		4-(3,4-Dioxo-2-((1R,2S)-2-phenylcyclopentylamino)cyclobut-1-enylamino)-3-hydroxy-N,N-dimethylpicolinamide	Compound prepared using Method (ix) starting with Preparation 16 and (1R,2S)-2-phenylcyclopentanamine (see Journal of Medicinal Chemistry, 2002, 45, 2101) and purified by trituration with diethyl ether to afford the title compound as a yellow solid (75.0mg). ^1H NMR (400MHz, DMSO- d_6): δ = 1.69-1.83 (m, 4H), 2.13-2.21 (m, 2H), 2.94-3.02 (m, 4H), 3.13 (s, 3H), 4.48 (m, 1H), 7.19-7.30 (m, 5H), 7.89-7.94 (m, 2H), 8.75 (m, 1H) ppm (2 exchangeables not observed). LRMS: m/z 421.4 $[\text{M}+\text{H}]^+$.

The following further Examples can be prepared analogously, substituting appropriate starting materials where necessary and making appropriate changes to experimental conditions informed by common general knowledge.

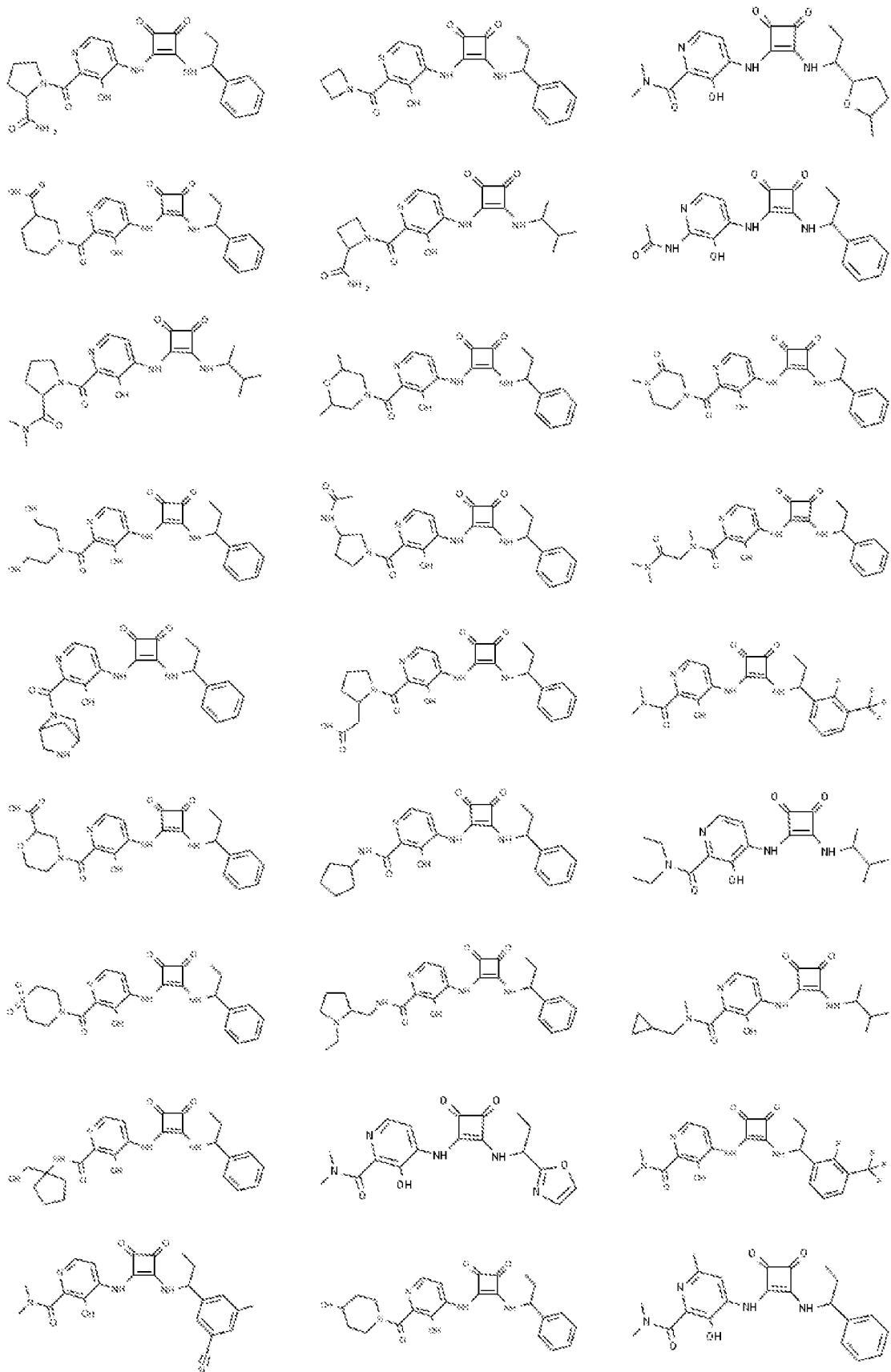
Example 157	4-[(3,4-dioxo-2-[(1R)-1-phenylpropyl]amino)cyclobut-1-en-1-yl]amino]-3-hydroxy-N-methylpyridine-2-carboxamide
Example 158	4-[(2-[(1S)-1,2-dimethylpropyl]amino)-3,4-dioxocyclobut-1-en-1-yl]amino]-3-hydroxy-N-isopropylpyridine-2-carboxamide
Example 159	4-[(3,4-dioxo-2-[(1R)-1-phenylpropyl]amino)cyclobut-1-en-1-yl]amino]-3-hydroxy-N-oxetan-3-ylpyridine-2-carboxamide
Example 160	4-[(2-[(1S)-1,2-dimethylpropyl]amino)-3,4-dioxocyclobut-1-en-1-yl]amino]-3-hydroxy-N-oxetan-3-ylpyridine-2-carboxamide
Example 161	3-hydroxy-4-[(2-[(1-(2-methoxyphenyl)propyl]amino)-3,4-dioxocyclobut-1-en-1-yl]amino]-N,N-dimethylpyridine-2-carboxamide
Example 162	4-[(2-[(1-(2-cyclopropylphenyl)propyl]amino)-3,4-dioxocyclobut-1-en-1-yl]amino]-3-hydroxy-N,N-dimethylpyridine-2-carboxamide
Example 163	4-[(3,4-dioxo-2-[(1-pyridin-4-ylethyl)amino]cyclobut-1-en-1-yl]amino)-3-hydroxy-N,N-dimethylpyridine-2-carboxamide
Example 164	3-hydroxy-4-[(2-[(3-methoxypyridin-2-yl)amino]-3,4-dioxocyclobut-1-en-1-yl]amino)-N,N-dimethylpyridine-2-carboxamide
Example 165	4-[(2-[(1-(4-cyanophenyl)ethyl]amino)-3,4-dioxocyclobut-1-en-1-yl]amino)-3-hydroxy-N,N-dimethylpyridine-2-carboxamide
Example 166	4-[(3,4-dioxo-2-[(1-[2-(trifluoromethyl)phenyl]propyl]amino)cyclobut-1-en-1-yl]amino)-3-hydroxy-N,N-dimethylpyridine-2-carboxamide
Example 167	3-hydroxy-4-[(2-[(2-methoxyphenyl)amino]-3,4-dioxocyclobut-1-en-1-yl]amino)-N,N-dimethylpyridine-2-carboxamide

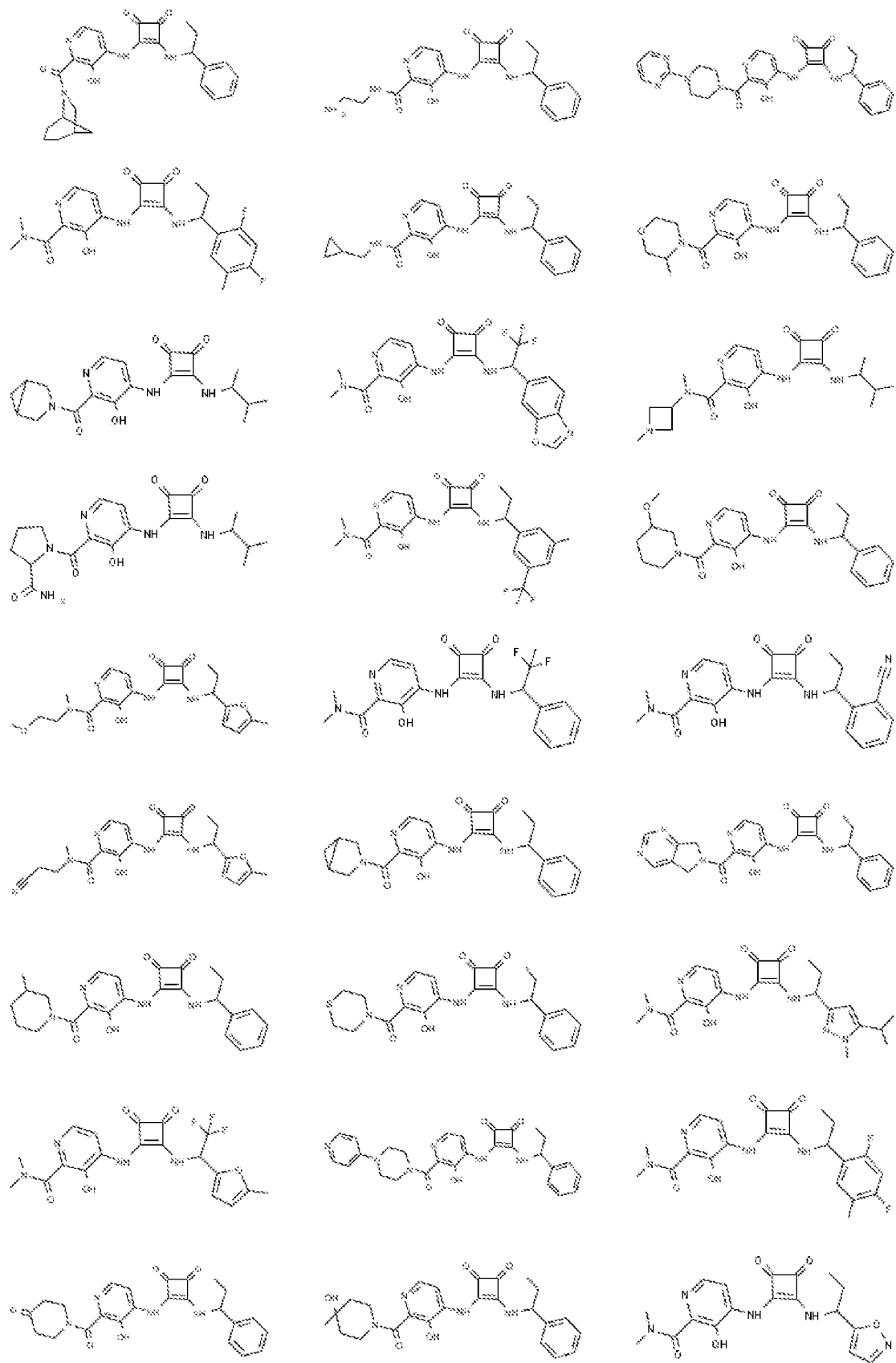
The following compounds are also examples of compounds of formula (I):



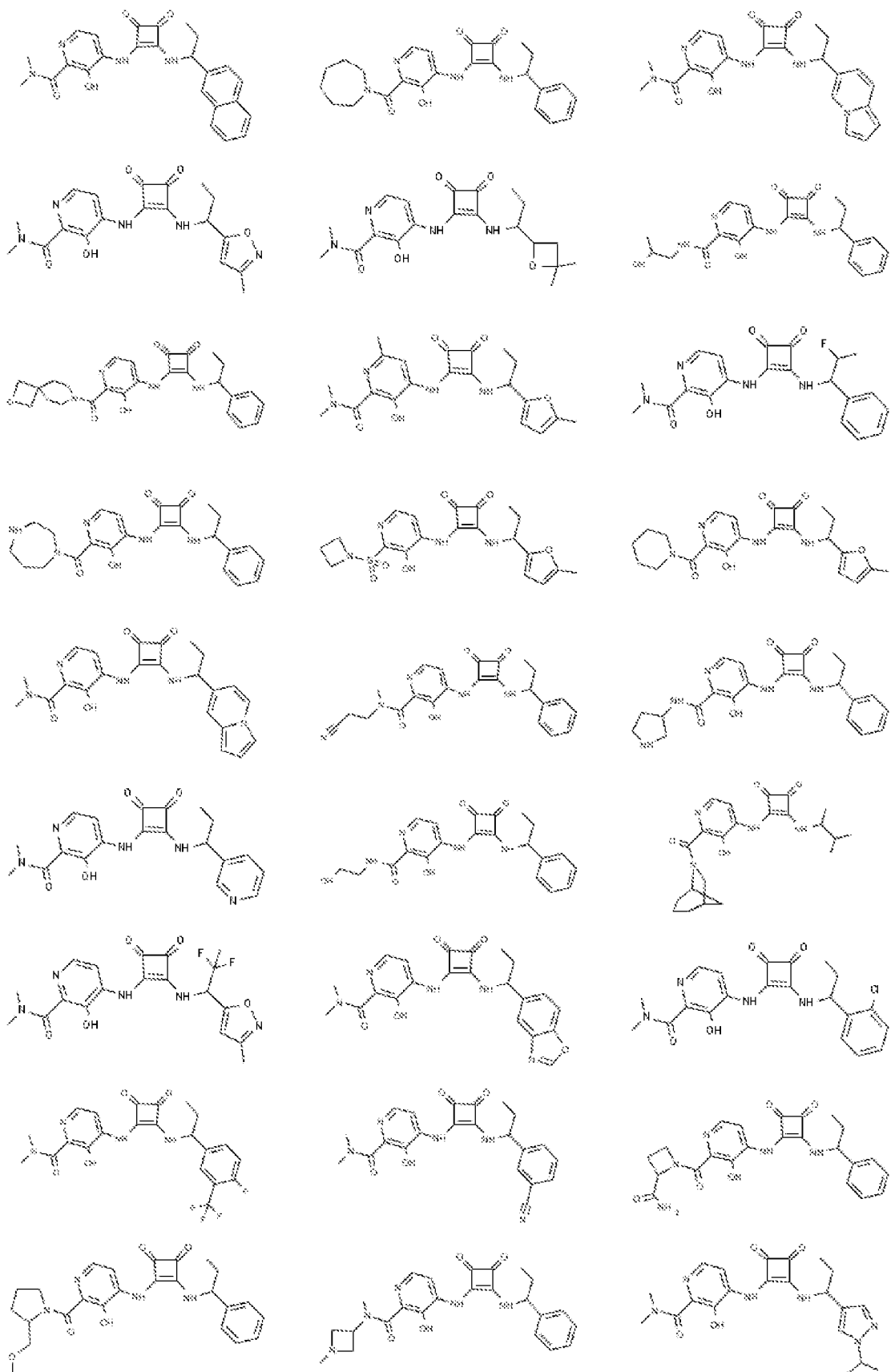


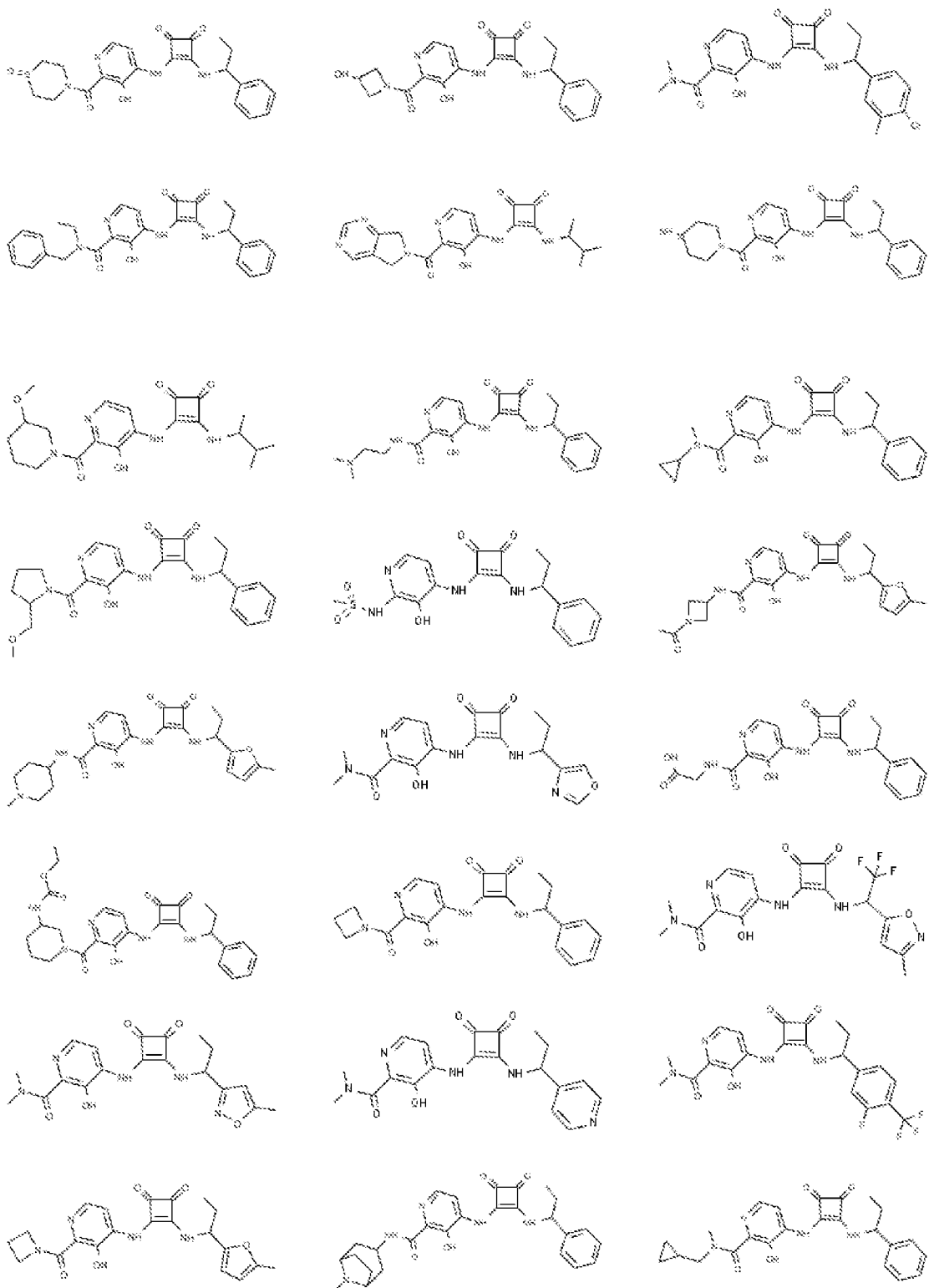
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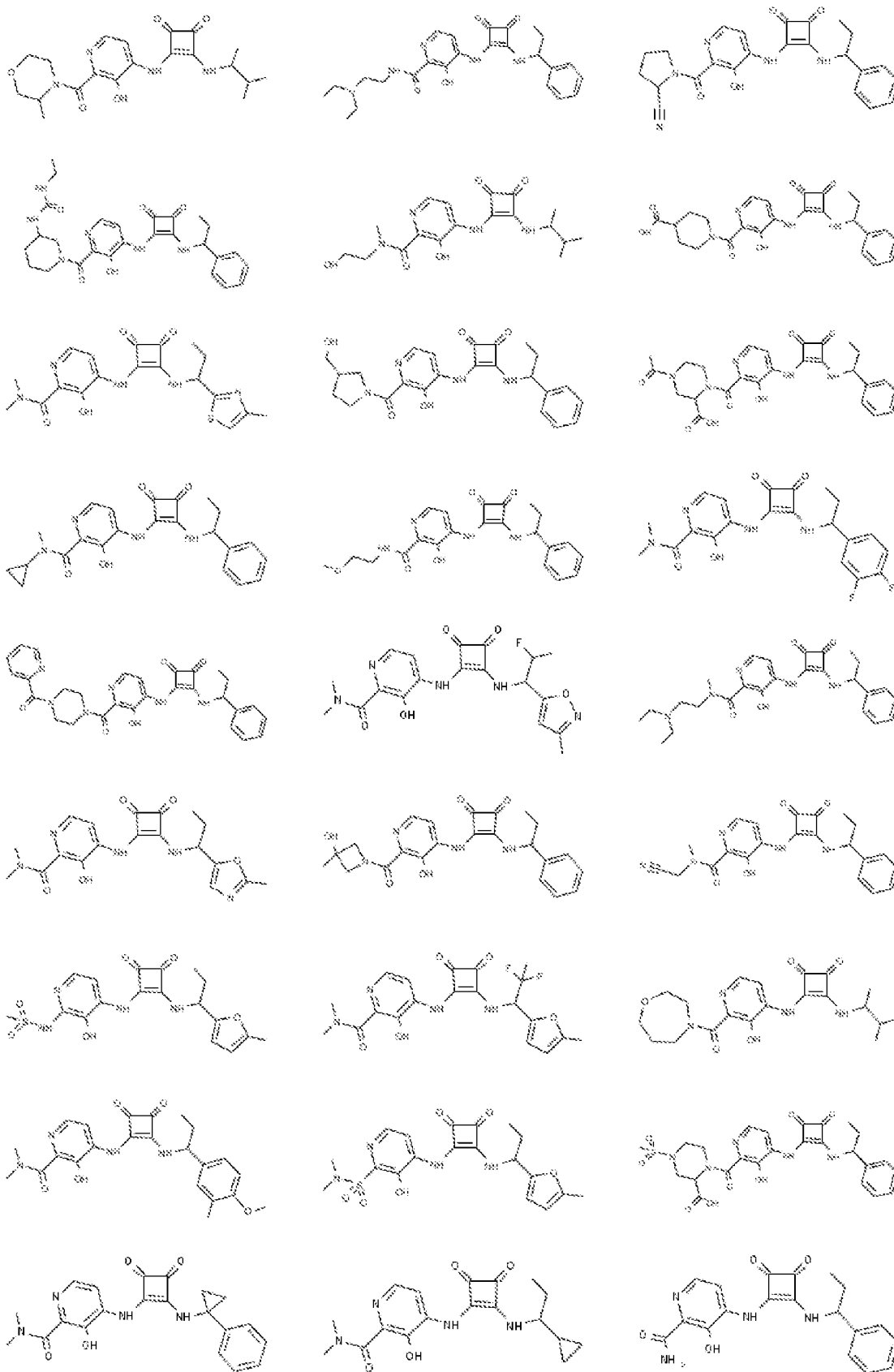




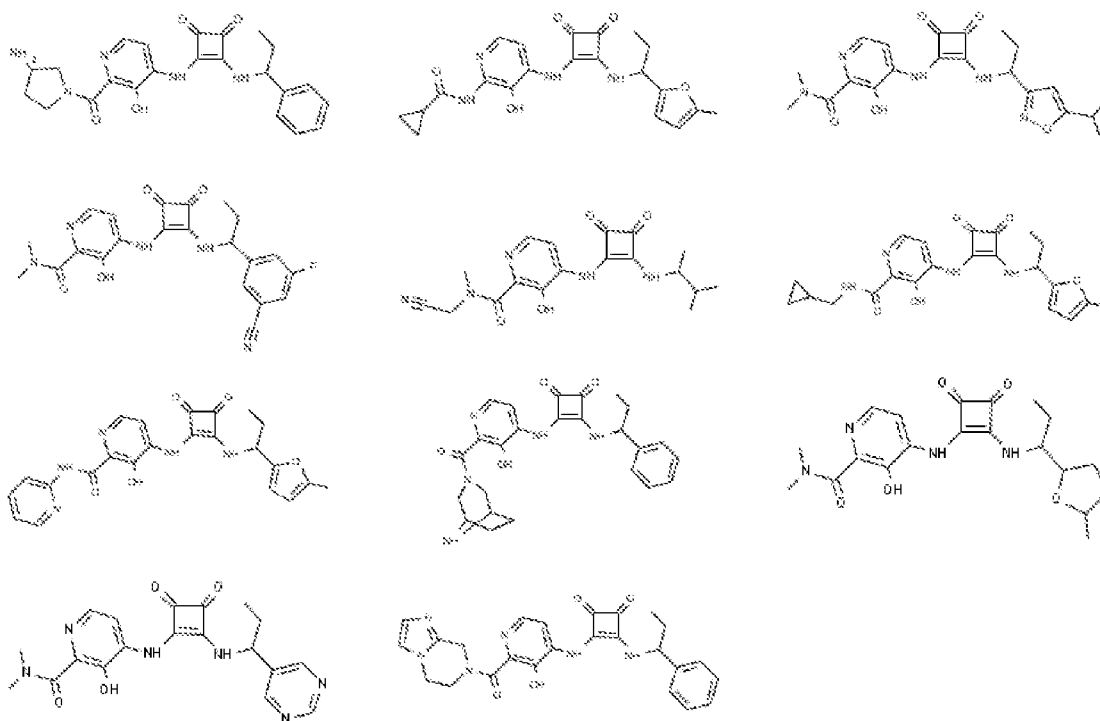
142







145



Biological Data

CXCR2 membrane binding filtration assay

100x stock solutions of test compounds were first prepared in 100% DMSO then diluted 10-fold with CXCR2 assay buffer (50mM Hepes, pH 7.4, 5mM MgCl₂, 1mM CaCl₂, 0.2% BSA, solution filter sterilized prior to use). A 1nM stock of [¹²⁵I] IL-8 (Perkin Elmer) is prepared in CXCR2 assay buffer. Frozen stock aliquots of hCXCR2-CHO over-expressing membranes are thawed on ice before diluting in assay buffer to a concentration of 31.25 µg/ml in room temperature assay buffer, immediately prior to use. Total Binding of [¹²⁵I] IL-8 is defined in the presence of test compound vehicle (10% DMSO in assay buffer).

Assays are performed in 96 well 1ml polypropylene deep well plates. Total assay volume is 200µl. Test compounds are profiled as 10-point, half-log increment IC₅₀ curves in singlicate to a maximum final assay concentration of 10µM. The final assay concentration of [¹²⁵I] IL-8 is 0.1nM in all wells. The final assay concentration of DMSO is 1% in all wells. All wells contain 0.5ug of hCXCR2-CHO membrane suspension. Test compound or vehicle are added to the plate first (20ul/well). 20µl of 1nM [¹²⁵I] IL-8 is added to all wells. Finally, 160 µl of membrane suspension (3.125 µg/ml) is added to all wells in the plate. Assay plates are sealed and shaken for 22.5

hours at room temperature. Separation of free and receptor bound [125 I] IL-8 is achieved by vacuum filtration, followed by 3 x 1ml with wash buffer (50mM Hepes, pH 7.4, 500mM NaCl, 0.1% BSA), onto 96-well GF/C filter plates (Perkin Elmer), using a Packard filtermate harvester. Filter plates are pre-soaked for 2 hours with 0.33% PEI and primed with 50mM Hepes, pH 7.4, 0.5% BSA, before filtration of the assay. Following filtration, the GF/C plates are dried for 2 hours at 45°C. Before the addition of 50µl/well of 'Microscint 0' scintillation cocktail (Perkin Elmer). CPM/well are determined by reading on a Packard Topcount NXT counter. [125 I] IL-8 binding (cpm) in the presence of test compound is plotted versus compound concentration (on a Log scale) to determine an IC₅₀ from the resultant sigmoid curve.

IC₅₀ values are corrected to K_i values by applying the Cheng Prusoff equation:

Cheng-Prusoff equation:
$$K_i = \frac{IC_{50}}{1 + [L]/K_d}$$

Where IC₅₀ is the concentration of test compound, inhibiting specific radioligand binding by 50%. [L] is the free radioligand concentration and K_D and K_i are the equilibrium dissociation constants of [125 I]-IL-8 and test compound respectively.

CXCR2 membrane binding scintillation proximity assay

100X stock solutions of test compounds are first prepared in 100% DMSO then diluted 10-fold with CXCR2 assay buffer (50mM Hepes, pH 7.4, 5mM MgCl₂, 1mM CaCl₂, 0.2% BSA, 0.05% pluronic F127, solution filter sterilised prior to use). A 1nM stock of [125 I] IL-8 (Perkin Elmer) is prepared in CXCR2 assay buffer. WGA PVT SPA beads are resuspended in CXCR2 assay buffer at 50mg/ml. Frozen stock aliquots of hCXCR2-CHO over-expressing membranes are thawed on ice and precoupled at 20ug protein/mg bead in 0.5x final volume CXCR2 assay buffer for 2 hours at 4°C. Precoupled bead/membrane mix is centrifuged at 2000rpm for 3 minutes and resuspended in final volume of CXCR2 assay buffer. Total Binding of [125 I] IL-8 is defined in the presence of test compound vehicle (10% DMSO in assay buffer). Non-specific binding of [125 I] IL-8 is defined in the presence of a final assay concentration of 4µM PF-05058078. PF-05058078 is prepared as a 400uM stock solution in 100% DMSO before diluting to a 10X stock of 40µM in CXCR2 assay buffer.

Assays are performed in 96 well non binding surface polystyrene plates. Total assay volume is 100µl. Test compounds are profiled as 10-point, half-log increment IC₅₀ curves in singlicate to a maximum final assay concentration of 40µM. The final assay concentration of [125 I] IL-8 is 0.1nM

in all wells. The final assay concentration of DMSO is 1% in all wells. All wells contain 10ug of hCXCR2-HEK membrane precoupled with WGA PVT SPA bead. Test compound, vehicle or PF-05058078 are added to the plate first (10ul/well). 10 μ l of 1nM [¹²⁵I] IL-8 is added to all wells. Finally, 80 μ l of membrane/bead suspension is added to all wells in the plate. Assay plates are sealed and shaken for 1 hour at room temperature. Plates are incubated for a further 9 hours. CPM/well are determined by reading on a Packard Topcount NXT counter. Specific binding of [¹²⁵I]-IL-8 is calculated by subtracting non-specific binding from total binding values. Test compound data are expressed as a percentage of specific binding. Percentage specific binding in the presence of test compound is plotted versus compound concentration (on a Log scale) to determine an IC₅₀ from the resultant sigmoid curve.

Human neutrophil chemotaxis assay 1

Human neutrophil isolation: Peripheral blood from healthy donors is collected by venipuncture in 4% (w/v) EDTA (9 parts blood:1 part EDTA). The red blood cells are removed by sedimentation on 6% (w/v) Dextran (Sigma) for 40 minutes. The granulocytes in the supernatant are separated from the peripheral blood mononuclear cells using Ficoll-Paque PLUS (Amersham Biosciences) density gradient centrifugation at 400xg for 35 minutes. Contaminating red blood cells are removed using hypotonic shock lysis with ice-cold sterile water for 30 seconds followed by restoration of osmolarity with double strength PBS and the final granulocyte pellet is resuspended in ice cold assay buffer (RPMI + 20mM Hepes + 2mM L-Glutamine + 0.1% (w/v) BSA). The isolated leukocyte preparations are typically 85-95% neutrophils.

Human neutrophils are diluted in assay buffer to 8x10⁴ cells/well and added along with compound (or 1% DMSO – final assay concentration) to the top chamber of a 96-well Multiscreen migration plate (Millipore, containing a 3 μ m polycarbonate filter). Chemo-attractant (1nM IL-8 or 3nM GRO α) in assay buffer is added along with compound (or 1% DMSO) to the bottom chamber. Both halves are pre-incubated at 37°C for 60 minutes prior to sandwiching the plate together. The chemotaxis assay is run for a further 60 minutes at 37°C. The number of cells that migrate into the bottom chamber are determined using cell lysis in the presence of a fluorescent DNA dye (CyQuant Picogreen, Invitrogen). The samples are transferred onto a black clear-bottom 96-well plate and the fluorescence read using a Fusion plate reader (Packard, excitation filter 485nm, emission filter 535nm). The raw relative fluorescence units are converted into % of max stimulation using Basal (absence of chemo-attractant) and max (1nM IL-8 or 3nM GRO α) control wells on every plate.

Human neutrophil chemotaxis assay 2

Human neutrophil isolation: Peripheral blood from healthy donors is collected by venipuncture in 4% (w/v) EDTA/HBSS(-) (9 parts blood:1 part EDTA). The red blood cells are removed by sedimentation on 4% (w/v) Dextran/HBSS(-) (Pharmacosmos) for 40 minutes. The granulocytes in the supernatant are separated from the peripheral blood mononuclear cells using Ficoll-Paque PLUS (Amersham Biosciences) density gradient centrifugation at 400xg for 35 minutes. Contaminating red blood cells are removed using hypotonic shock lysis with ice-cold sterile water for 30 seconds followed by restoration of osmolarity with double strength PBS and the final granulocyte pellet is re-suspended in ice cold assay buffer (HBSS(+)) +10mM D-Glucose + 0.1% (w/v) BSA). The isolated leukocyte preparations are typically 85-95% neutrophils.

Human neutrophils are diluted in assay buffer to 8×10^6 cells/well and added along with compound (or 1% DMSO - final assay concentration) to the top chamber of a 96-well Multiscreen migration plate (Millipore, containing a $3\mu\text{m}$ polycarbonate filter). Chemoattractant (1nM IL-8 or 3nM GRO α) in assay buffer is added along with compound (or 1% DMSO) to the bottom chamber. Both halves are pre-incubated at 37°C for 60 minutes prior to sandwiching the plate together. The chemotaxis assay is run for a further 60 minutes at 37°C. The number of cells that migrate into the bottom chamber are determined using cell lysis in the presence of a fluorescent DNA dye (CyQuant Picogreen, Invitrogen). The samples are transferred onto a black clear-bottom 96-well plate and the fluorescence read using a Fusion plate reader (Packard, excitation filter 485nm, emission filter 535nm). The raw relative fluorescence units are converted into % of max stimulation using Basal (absence of chemoattractant) and max (1nM IL-8 or 3nM GRO α) control wells on every plate.

Results

Example	CXCR2 membrane binding filtration assay (K _i vs IL-8, nM)	Human neutrophil chemotaxis assay 1 (IC ₅₀ vs GRO α , nM)	Human neutrophil chemotaxis assay 1 (IC ₅₀ vs IL-8, nM)
1	5.3	8.4	21.6

Example	CXCR2 membrane binding scintillation proximity assay (IC ₅₀ vs IL-8, nM)	Human neutrophil chemotaxis assay 2 (IC ₅₀ vs IL-8, nM)	Human neutrophil chemotaxis assay 2 (IC ₅₀ vs GRO α , nM)
1	16.5	3.66	0.912
2	28.3	7.15	2.11

3	51.8	2490	>3000
4	24.5	57.5	15.8
5	97.0	59.4	5.74
6	47.2	199	43.4
7	96.6	499	83.6
8	475		
9	35.0		
10	20.8		
11	26.4		
12	16.8		
13	87.6		
14	19.4		
15	128		
16	33.6		
17	26.4		
18	20.5		
19	63.2		
20	30.5		
21	171		
22	59.2		
23	71.8		
24	27.4		
25	12.6		
26	119		
27	82.5		
28	14.2		
29	36.0		
30	34.5		
31	52.3		
32	75.9		
33	13.2		
34	12.0		
35	15.3		
36	21.1		
37	39.5		
38	16.1		

150

39	87.9		
40	25.2		
41	38.1		
42	26.2		
43	24.0		
44	30.4		
45	18.9		
46	26.7		
47	28.1		
48	69.7		
49	663		
50	86.6		
51	36.1		
52	34.6		
53	58.9		
54	34.5	30.7	1.31
55	13.7	22.2	3.11
56	47.0		
57	12.5		
58	23.0		
59	25.8		
60	38.7		
61	22.2		
62	258		
63	28.6		
64			
65	30.2		
66			
67	24.6		
68	21.4		
69	19.6		
70	70.0		
71	129		
72	58.7		
73	52.1	435	110
74	134		

75	57.0		
76	16.8		
77	246		
78	253		
79	12.6		
80	64.7		
81	31.6		
82	46.7		
83	96.6		
84	10.5		
85	9.78		
86	18.5		
87	12.2		
88	48.1		
89	12.0		
90	46.4		
91	38.6		
92	36.9		
93	26.1		
94	41.6		
95	16.1		
96	77.8		
97	28.2		
98	22.7		
99	65.2		
100	61.7		
101	138		
102	143		
103	32.4		
104	19.4		
105	319		
106	365	245	53.1
107	424	19.9	2.58
108	512	77.4	86.7
109	83.7		
110	48.3	7.25	1.61

152

111	55.8	6.57	4.73
112	34.7	2.94	2.41
113	24.1	6.80	2.42
114	49.1		
115	42.2		
116	407		
117	31.2	5.17	0.836
118	391		
119	22.9		
120	260	29.1	1.97
121	82.2	100	2.10
122	35.2	32.9	4.79
123	36.9	138	2.64
124	102		
125	744	1190	15.9
126	55.0		
127	48.8	47.2	13.8
128	79.5		
129	441		
130	38.7	37.2	4.07
131	51.6	156	20.7
132	23.1		
133	>122	121	0.644
134	358		
135	37.7	5510	72.5
136	227		
137	83.8	15.9	2.03
138	33.5	23.6	2.63
139	45.1		
140	17.9		
141	43.5		
142	47.4		
143	32.0		
144	218		
145	19.3		
146	39.2		

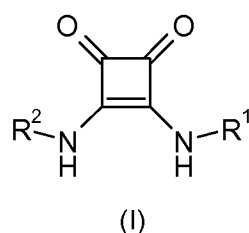
153

147	>334		
148	44.9		
149	50.1		
150	80.6		
151	163		
152	51.0		
153	10.3		
154	40.9		
155	31.3		
156	12.9		
157	1480		
158	1690		
159	2640		
160	4760		
161	>4650		
162	2100		
163	>2590		
164	15600		
165	774		
166	>2380		
167	27.4	6.12	3.64

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Claims

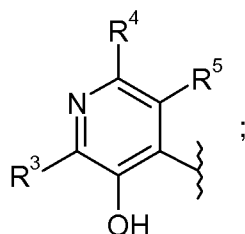
1. A compound of formula (I):



or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of said compound or salt, wherein:

R^1 is C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, C_6 - C_{12} bicycloalkyl, Aryl¹, Aryl², Het¹, Het², Het³ or Het⁴, said C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl and C_6 - C_{12} bicycloalkyl being optionally substituted by 1 to 3 substituents independently selected from -CN, halo, -NH₂, -SH, -SO₂NH₂, -OCONH₂ and -X-R^a, with the proviso that the R^1 moiety may not be attached through a methylene (-CH₂-) group;

R^2 is



X is a bond, C_1 - C_6 alkylene, -CO-, -O-, -O-(C_1 - C_6 alkylene)-, -NR⁶-, -S-, -SO-, -SO₂-, -COO-, -OCO-, -NR⁶SO₂-, -SO₂NR⁶-, -NR⁶CONR⁶-, -NR⁶COO- or -OCONR⁶-;

R^a is C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, Aryl¹, Aryl², Het¹, Het², Het³ or Het⁴, said C_3 - C_8 cycloalkyl and C_6 - C_{12} bicycloalkyl being optionally substituted by one or more C_1 - C_6 alkyl, -OH or C_1 - C_6 alkoxy groups;

R^3 and R^4 are each independently H, -CN, halo, -OH, -NH₂, -SH, -CONH₂, -SO₂NH₂, -NR⁶CONH₂, -OCONH₂ or -Y-R^b;

or, alternatively, where R^3 and R^4 are attached to adjacent carbon atoms, R^3 and R^4 , taken together with the carbon atoms to which they are attached, form a 5 or 6-membered ring which

may be aromatic or partially saturated and which may be carbocyclic or contain up to two heteroatoms selected from N, S and O, said ring being optionally substituted by 1-3 substituents selected from C₁-C₆ alkyl, C₃-C₈ cycloalkyl, halo, -CN, -OR⁶, -NR⁷R⁸, -SR⁶, -SOR⁹, -SO₂R⁹, -COR⁶, -OCOR⁶, -COOR⁶, -NR⁶COR⁶, -CONR⁷R⁸, -NR⁶SO₂R⁹, -SO₂NR⁷R⁸, -NR⁶CONR⁷R⁸, -NR⁶COOR⁹ and -NR⁶SO₂NR⁷R⁸;

R⁵ is H, -CN, halo, -OH, -NH₂, -SH, -CONH₂, -SO₂NH₂, -NR⁶CONH₂, -OCONH₂ or -Y-R^b;

Y is a bond, C₁-C₆ alkylene, -CO-, -O-, -NR⁶-, -S-, -SO-, -SO₂-, -CONR⁶-, -COO-, -OCO-, -NR⁶CO-, -NR⁶SO₂-, -SO₂NR⁶-, -NR⁶CONR⁶-, -NR⁶COO- or -OCONR⁶-;

R^b is C₁-C₆ alkyl, C₃-C₈ cycloalkyl, C₆-C₁₂ bicycloalkyl, Aryl¹, Aryl², Het¹, Het², Het³ or Het⁴, said C₁-C₆ alkyl, C₃-C₈ cycloalkyl and C₆-C₁₂ bicycloalkyl being optionally substituted by 1-5 substituents selected from R⁹, -CN, -OR⁶, -NR⁷R⁸, -SR⁶, -SOR⁹, -SO₂R⁹, -COR⁶, -OCOR⁶, -COOR⁶, -NR⁶COR⁶, -CONR⁷R⁸, -NR⁶SO₂R⁹, -SO₂NR⁷R⁸, -NR⁶CONR⁷R⁸, -NR⁶COOR⁹ and -NR⁶SO₂NR⁷R⁸ and optionally substituted by 1 substituent R^d;

Aryl¹ is phenyl or naphthyl, said phenyl and naphthyl being optionally substituted by 1 substituent -Z-R^d and 1-4 substituents each independently selected from -Z-R^e;

Aryl² is a 3 to 8-membered monocyclic or 6 to 12-membered bicyclic carbocycle which is partially unsaturated, said carbocycle being optionally substituted by 1 substituent -Z-R^d and 1-4 substituents each independently selected from -Z-R^f;

Het¹ is a 3 to 8-membered saturated or partially unsaturated monocyclic heterocycle, containing 1 or 2 heteroatoms selected from O and N, said heterocycle being optionally substituted by 1 substituent -Z-R^d and 1-4 substituents each independently selected from -Z-R^f;

Het² is a 6 to 12-membered saturated or partially unsaturated multicyclic heterocycle containing 1-3 heteroatoms selected from O, S and N, said heterocycle being optionally substituted by 1 substituent -Z-R^d and 1-4 substituents each independently selected from -Z-R^f;

Het³ is (i) a 6-membered aromatic heterocycle containing 1-3 N atoms or (ii) a 5-membered aromatic heterocycle containing either (a) 1-4 N atoms or (b) 1 O or S atom and 0-3 N atoms, said heterocycle being optionally substituted by 1 substituent -Z-R^d and 1-4 substituents each independently selected from -Z-R^e;

Het⁴ is (i) a 10-membered bicyclic aromatic heterocycle containing 1-4 N atoms or (ii) a 9-membered bicyclic aromatic heterocycle containing either (a) 1-4 N atoms or (b) 1 O or S atom and 0-3 N atoms or (iii) an 8-membered bicyclic aromatic heterocycle containing (a) 1-4 N atoms or (b) 1 O or S atom and 1-3 N atoms or (c) 2 O or S atoms and 0-2 N atoms, said heterocycle being optionally substituted by 1 substituent -Z-R^d and 1-4 substituents each independently selected from -Z-R^e;

Z is a bond, -CO- or C₁-C₆ alkylene;

R^d is Aryl³, Aryl⁴, Het⁵, Het⁶, Het⁷ or Het⁸;

R^e is C₁-C₆ alkyl, C₃-C₈ cycloalkyl, halo, -CN, -OR⁶, -NR⁷R⁸, -SR⁶, -SOR⁹, -SO₂R⁹, -COR⁶, -OCOR⁶, -COOR⁶, -NR⁶COR⁶, -CONR⁷R⁸, -NR⁶SO₂R⁹, -SO₂NR⁷R⁸, -NR⁶CONR⁷R⁸, -NR⁶COOR⁹ or -NR⁶SO₂NR⁷R⁸;

R^f is C₁-C₆ alkyl, C₃-C₈ cycloalkyl, halo, oxo, -OR⁶, -NR⁷R⁸, -SR⁶, -SOR⁹, -SO₂R⁹, -COR⁶, -OCOR⁶, -COOR⁶, -NR⁶COR⁶, -CONR⁷R⁸, -NR⁶SO₂R⁹, -SO₂NR⁷R⁸, -NR⁶CONR⁷R⁸, -NR⁶COOR⁹ or -NR⁶SO₂NR⁷R⁸;

Aryl³ is phenyl or naphthyl, said phenyl and naphthyl being optionally substituted with 1-5 substituents selected from C₁-C₆ alkyl, C₃-C₈ cycloalkyl, halo, -CN, -OR⁶, -NR⁷R⁸, -SR⁶, -SOR⁹, -SO₂R⁹, -COR⁶, -OCOR⁶, -COOR⁶, -NR⁶COR⁶, -CONR⁷R⁸, -NR⁶SO₂R⁹, -SO₂NR⁷R⁸, -NR⁶CONR⁷R⁸, -NR⁶COOR⁹ and -NR⁶SO₂NR⁷R⁸;

Aryl⁴ is a 3 to 8-membered monocyclic or 6 to 12-membered bicyclic carbocycle which is partially unsaturated, said carbocycle being optionally substituted by 1-5 substituents selected from C₁-C₆ alkyl, C₃-C₈ cycloalkyl, halo, oxo, -OR⁶, -NR⁷R⁸, -SR⁶, -SOR⁹, -SO₂R⁹, -COR⁶, -OCOR⁶, -COOR⁶, -NR⁶COR⁶, -CONR⁷R⁸, -NR⁶SO₂R⁹, -SO₂NR⁷R⁸, -NR⁶CONR⁷R⁸, -NR⁶COOR⁹ and -NR⁶SO₂NR⁷R⁸;

Het⁵ is a 3 to 8-membered saturated or partially unsaturated monocyclic heterocycle, containing 1 or 2 heteroatoms selected from O and N, said heterocycle being optionally substituted by 1-5 substituents selected from C₁-C₆ alkyl, C₃-C₈ cycloalkyl, halo, oxo, -OR⁶, -NR⁷R⁸, -SR⁶, -SOR⁹, -SO₂R⁹, -COR⁶, -OCOR⁶, -COOR⁶, -NR⁶COR⁶, -CONR⁷R⁸, -NR⁶SO₂R⁹, -SO₂NR⁷R⁸, -NR⁶CONR⁷R⁸, -NR⁶COOR⁹ and -NR⁶SO₂NR⁷R⁸;

Het⁶ is a 6 to 12-membered saturated or partially unsaturated multicyclic heterocycle containing 1-3 heteroatoms selected from O, S and N, said heterocycle being optionally substituted by 1-5 substituents selected from C₁-C₆ alkyl, C₃-C₈ cycloalkyl, halo, oxo, -OR⁶, -NR⁷R⁸, -SR⁶, -SOR⁹, -SO₂R⁹, -COR⁶, -OCOR⁶, -COOR⁶, -NR⁶COR⁶, -CONR⁷R⁸, -NR⁶SO₂R⁹, -SO₂NR⁷R⁸, -NR⁶CONR⁷R⁸, -NR⁶COOR⁹ and -NR⁶SO₂NR⁷R⁸;

Het⁷ is (i) a 6-membered aromatic heterocycle containing 1-3 N atoms or (ii) a 5-membered aromatic heterocycle containing either (a) 1-4 N atoms or (b) 1 O or S atom and 0-3 N atoms, said heterocycle being optionally substituted with 1-4 substituents selected from C₁-C₆ alkyl, C₃-C₈ cycloalkyl, halo, -CN, -OR⁶, -NR⁷R⁸, -SR⁶, -SOR⁹, -SO₂R⁹, -COR⁶, -OCOR⁶, -COOR⁶, -NR⁶COR⁶, -CONR⁷R⁸, -NR⁶SO₂R⁹, -SO₂NR⁷R⁸, -NR⁶CONR⁷R⁸, -NR⁶COOR⁹ and -NR⁶SO₂NR⁷R⁸;

Het⁸ is (i) a 10-membered bicyclic aromatic heterocycle containing 1-4 N atoms or (ii) a 9-membered bicyclic aromatic heterocycle containing either (a) 1-4 N atoms or (b) 1 O or S atom and 0-3 N atoms, or (iii) an 8-membered bicyclic aromatic heterocycle containing (a) 1-4 N atoms or (b) 1 O or S atom and 1-3 N atoms or (c) 2 O or S atoms and 0-2 N atoms, said heterocycle being optionally substituted with 1-5 substituents selected from C₁-C₆ alkyl, C₃-C₈ cycloalkyl, halo, -CN, -OR⁶, -NR⁷R⁸, -SR⁶, -SOR⁹, -SO₂R⁹, -COR⁶, -OCOR⁶, -COOR⁶, -NR⁶COR⁶, -CONR⁷R⁸, -NR⁶SO₂R⁹, -SO₂NR⁷R⁸, -NR⁶CONR⁷R⁸, -NR⁶COOR⁹ and -NR⁶SO₂NR⁷R⁸;

R⁶ is H, C₁-C₆ alkyl or C₃-C₈ cycloalkyl, said C₁-C₆ alkyl and C₃-C₈ cycloalkyl being optionally substituted by -OH or C₁-C₆ alkoxy;

R⁷ and R⁸ are each independently H, C₁-C₆ alkyl or C₃-C₈ cycloalkyl or are taken together with the nitrogen atom to which they are attached to form a 4-, 5- or 6-membered saturated heterocyclic ring containing 1-2 nitrogen atoms or 1 nitrogen and 1 oxygen atom, said heterocyclic ring being optionally substituted by one or more C₁-C₆ alkyl or C₃-C₈ cycloalkyl groups; and

R⁹ is C₁-C₆ alkyl or C₃-C₈ cycloalkyl, said C₁-C₆ alkyl and C₃-C₈ cycloalkyl being optionally substituted by -OH or C₁-C₆ alkoxy;

wherein, in each instance, said C₁-C₆ alkyl, C₁-C₆ alkylene, C₃-C₈ cycloalkyl and C₆-C₁₂ bicycloalkyl may have one or more hydrogen atoms replaced with a fluorine atom.

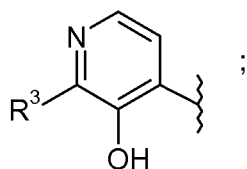
2. A compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of said compound or salt, as claimed in claim 1, wherein R¹ is (a) -CHR^xR^y, wherein R^x is C₁-C₅ alkyl or C₃-C₈ cycloalkyl, said C₁-C₅ alkyl being optionally substituted by methoxy and R^y is Het³, Het⁴, phenyl, -CH₂OCH₂Ph or C₃-C₈ cycloalkyl, said Het³, Het⁴ and phenyl being optionally substituted by C₁-C₆ alkyl, halo, C₁-C₆ alkoxy, -CN or C₃-C₈ cycloalkyl; or (b) C₃-C₈ cycloalkyl optionally substituted by phenyl or benzyl, said phenyl or benzyl being optionally substituted by halo; or (c) t-butyl, 3-methylbut-2-yl, isopropyl or pent-3-yl; wherein, in each instance, said C₁-C₅ alkyl, C₁-C₆ alkyl and C₃-C₈ cycloalkyl may have one or more hydrogen atoms replaced with a fluorine atom.

3. A compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of said compound or salt, as claimed in claim 1, wherein R¹ is (a) -CHR^xR^y, wherein R^x is methyl, ethyl, isopropyl, methoxymethyl or cyclopropyl and R^y is -CH₂OCH₂Ph, cyclopropyl, phenyl, pyrimidinyl, furanyl, imidazo[2,1-b]thiazolyl, thiazolyl, pyridyl or pyrimidinyl, said phenyl, pyrimidinyl, furanyl, imidazo[2,1-b]thiazolyl, thiazolyl, pyridyl and pyrimidinyl being optionally substituted by C₁-C₆ alkyl, halo, C₁-C₆ alkoxy, -CN or C₃-C₈ cycloalkyl; or (b) cyclobutyl, cyclopentyl or cyclohexyl, each being optionally substituted by phenyl, fluorophenyl or benzyl; or (c) t-butyl, 3-methylbut-2-yl, isopropyl or pent-3-yl; wherein said C₁-C₆ alkyl, C₃-C₈ cycloalkyl, methyl, ethyl, isopropyl, methoxymethyl and cyclopropyl may have one or more hydrogen atoms replaced with a fluorine atom.

4. A compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of said compound or salt, as claimed in claims 1, wherein R¹ is 1-phenylprop-1-yl, 1-pyridylprop-1-yl, 1-pyrazinylprop-1-yl, 3-methylbut-2-yl, 1-pyrimidinylprop-1-yl, 1-(methylphenyl)prop-1-yl, 1-(trifluoromethylphenyl)prop-1-yl, 1-(methoxyphenyl)prop-1-yl, 1-(dimethylphenyl)prop-1-yl, 1-(methylfuranyl)prop-1-yl, 1-((methyl)(isopropyl)furanyl)prop-1-yl, 1-phenylbut-1-yl, 1-(isopropylfuranyl)prop-1-yl, (fluorophenyl)(isopropyl)methyl, (trifluoromethyl)(furanyl)methyl, ter-butyl, (trifluoromethyl)(methoxyphenyl)methyl, 1-phenylbutan-1-yl, (chloromethyl)(methyl)methyl, (chlorophenylmethyl)cyclopropyl, 1-(imidazo[2,1-b]thiazolyl)prop-1-yl, (trifluoromethyl)(phenyl)methyl, 1-(trifluoromethylphenyl)prop-1-yl, 1-(fluorophenyl)prop-1-yl, 1-(cyclopropylphenyl)prop-1-yl, 1-phenyl-2-methoxyprop-1-yl, difluorophenylcyclopentyl, phenylcyclopentyl, isopropyl, 1-thiazolylprop-1-yl, 1-(difluorophenyl)prop-1-yl, pent-3-yl, cyclopentyl, cyclohexyl, benzylcyclobutyl, 1-thiazolylprop-1-yl (phenyl)(isopropyl)methyl, (methyl)(methylisoxazolyl)methyl, (isopropyl)(triazolyl)methyl, phenylcyclopentyl, (methyl)((difluoro)(methyl)phenyl)methyl, (methyl)(pyridyl)methyl, fluorophenylcyclopentyl, 1-(difluorophenyl)prop-1-yl, dicyclopropylmethyl, 1-(fluorophenyl)prop-1-yl, 2-methyl-3-phenylprop-

3-yl, (phenyl)(cyclopropyl)methyl, (methyl)((difluoro)(methyl)phenyl)methyl, 1-((fluoro)(methyl)phenyl)prop-1-yl, (isopropyl)(methoxyphenyl)methyl, 1-pyrimidinylprop-1-yl, 1-(dimethylphenyl)prop-1-yl, 1-(methylphenyl)prop-1-yl, 1-((fluoro)(methoxy)phenyl)prop-1-yl, 1-((fluoro)(trifluoromethyl)prop-1-yl, (cyclopropyl)(difluorophenyl)methyl, 1-chlorophenylprop-1-yl, 1-cyanophenylprop-1-yl, 1-(benzyloxymethyl)prop-1-yl, ((methyl)(chloro)phenyl)(methyl)methyl or 1-methoxyphenylprop-1-yl.

5. A compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of said compound or salt, as claimed in any one of claims 1 to 4, wherein R^2 is:



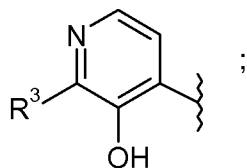
R^3 is $-\text{CONR}^6-\text{R}^b$, $-\text{COR}^b$, $-\text{SO}_2\text{NR}^5-\text{R}^b$ or C_1-C_6 alkyl;

R^6 is H, C_1-C_6 alkyl or C_3-C_8 cycloalkyl; and

R^b is C_1-C_6 alkyl, C_3-C_8 cycloalkyl, Het^1 , Het^2 or Het^3 , said C_1-C_6 alkyl being optionally substituted by 1 substituent Aryl^3 or Het^7 ;

wherein, in each instance, said C_1-C_6 alkyl and C_3-C_8 cycloalkyl may have one or more hydrogen atoms replaced with a fluorine atom.

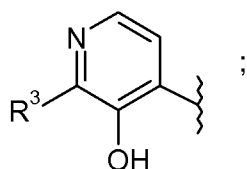
6. A compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of said compound or salt, as claimed in any one of claims 1 to 4, wherein R^2 is:



wherein R^3 is $-\text{CONH}(\text{C}_1-\text{C}_6 \text{ alkyl})$, $-\text{CONH}(\text{C}_3-\text{C}_8 \text{ cycloalkyl})$, $-\text{CON}(\text{C}_1-\text{C}_6 \text{ alkyl})(\text{C}_1-\text{C}_6 \text{ alkyl})$, $-\text{CON}(\text{C}_1-\text{C}_6 \text{ alkyl})(\text{C}_3-\text{C}_8 \text{ cycloalkyl})$, $-\text{CON}(\text{C}_3-\text{C}_8 \text{ cycloalkyl})(\text{C}_3-\text{C}_8 \text{ cycloalkyl})$, $-\text{CON}(\text{C}_1-\text{C}_6 \text{ alkyl})(\text{Het}^1)$, $-\text{CON}(\text{C}_1-\text{C}_6 \text{ alkyl})(\text{Het}^3)$, $-\text{CON}(\text{C}_1-\text{C}_6 \text{ alkyl})(\text{CH}_2\text{Ph})$, $-\text{CON}(\text{C}_1-\text{C}_6 \text{ alkyl})(\text{CH}_2\text{Het}^3)$, $\text{C}_1-\text{C}_6 \text{ alkyl}$, $-\text{SO}_2\text{N}(\text{C}_1-\text{C}_6 \text{ alkyl})(\text{C}_1-\text{C}_6 \text{ alkyl})$, $-\text{COHet}^1$ or $-\text{COHet}^2$; wherein, in each instance,

said C₁-C₆ alkyl and C₃-C₈ cycloalkyl may have one or more hydrogen atoms replaced with a fluorine atom.

7. A compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of said compound or salt, as claimed in any one of claims 1 to 4, wherein R² is:



wherein R³ is -CON(CH₃)₂, -CO(carboxypyrrolidinyl), -CO(hydroxypyrrolidinyl), -CO(methylpiperazinyl), -SO₂N(CH₃)₂, -CO(pyrrolo[3,4-b]pyrazinyl), -CO(isoindolinyl), -CO(methylpyrrolidinyl), -CON(CH₃)(CH₂CH₂CH₃), -CON(CH₃)(CH₂CH₃), -CON(CH₂CH₃)(CH₂CH₃), -CO(dimethylaminopyrrolidinyl), -CO(methyl-3,8-diazabicyclo[3.2.1]octanyl), -CO(methyl-2,5-diazabicyclo[2.2.1]heptanyl), -CO(methylaminocarbonylpyrrolidinyl), -CO(methylaminocarbonylpiperidinyl), -CON(CH₃)(cyclobutyl), -CON(CH₃)(methylpyrrolidinyl), -CON(CH₃)(methylpiperidinyl), -CON(CH₃)(CH₂CF₃), -CON(CH₃)(CH₂Ph), -CON(CH₃)(pyridylmethyl), -CO(methoxypyrrolidinyl), -CO(difluoropyrrolidinyl), -CO(fluoropyrrolidinyl), -CO(difluoropiperidinyl), -CO(aminocarbonylpiperidinyl), -CO(1,4-oxazepanyl), -CO(pyrimidinylazetidiny), -CO(pyridazinylazetidiny), -CON(CH₃)(cyclopentyl), -CO(dimethylaminoazetidiny), -CO(2-oxa-6-azaspiro[3.3]heptanyl), -CO(acetyl piperazinyl), -CONH(isopropyl), -CO(methyl-1,4-diazepanyl), -CO(ethylpiperazinyl), -CO(morpholinyl), -CON(CH₃)(t-butyl), -CO(pyrrolidinyl), -CON(CH₃)(isopropyl), -CO(hydroxymethylpyrrolidinyl), -CON(CH₃)(pyridyl), -CO(2-azabicyclo[2.2.1]heptanyl), -CO(2-azabicyclo[2.2.2]octanyl), -CO(3-azabicyclo[3.2.0]heptanyl), -CO(piperidinyl), -CO(1,4-diazabicyclo[3.2.2]nonanyl), -CO(2,3-dihydro-1H-pyrrolo[3,4-c]pyridinyl), -CO(6,7-dihydro-5H-pyrrolo[3,4-b]pyridinyl), -CO(6,7-dihydro-5H-pyrrolo[3,4-b]pyrazinyl), -CO(methylpyrrolidinyl), -CO(methyl-3-oxopiperazinyl), -CO(azetidiny), -CO(fluoroazetidiny) or methyl.

8. A pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as defined in any preceding claim, and a pharmaceutically acceptable excipient.

9. A method of treating a disease or condition mediated at least in part by activation of the CXCR-2 receptor, in a subject in need of such treatment, comprising administering to the subject a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as defined in any one of claims 1 to 7.
10. The method of claim 9 wherein the disease or condition is asthma or COPD.
11. The use a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as defined in any one of claims 1 to 7, for the manufacture of a medicament for the treatment of a disease or condition mediated at least in part by activation of the CXCR-2 receptor.
12. The use of claim 11 wherein the disease or condition is asthma or COPD.
13. A combination comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as defined in any one of claims 1 to 7, and a second pharmacologically active agent.

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2010/051876

A. CLASSIFICATION OF SUBJECT MATTER INV. C07D213/71 C07D213/81 C07D401/14 C07D453/06 C07D471/04 C07D487/04 C07D491/107 A61K31/50 A61K31/501 A61K31/443 A61K31/4412 A61P11/06		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) C07D A61K A61P Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2004/053953 A1 (TAVERAS ARTHUR G [US] ET AL) 18 March 2004 (2004-03-18) claims 1,11-13	1-13
X	US 2003/097004 A1 (TAVERAS ARTHUR G [US] ET AL) 22 May 2003 (2003-05-22) claims 1,23,24; examples 1-125	1-13
A	BUTERA, JOHN A. ET AL: "Design and SAR of Novel Potassium Channel Openers Targeted for Urge Urinary Incontinence. 1. N-Cyanoguanidine Bioisosteres Possessing in Vivo Bladder Selectivity" JOURNAL OF MEDICINAL CHEMISTRY, 43(6), 1187-1202 CODEN: JMCMAR; ISSN: 0022-2623, 2000, XP002592171 compound 16	1-13
☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents : *A* document defining the general state of the art which is not considered to be of particular relevance *E* earlier document but published on or after the international filing date *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) *O* document referring to an oral disclosure, use, exhibition or other means *P* document published prior to the international filing date but later than the priority date claimed *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. *G* document member of the same patent family		
Date of the actual completion of the international search 15 July 2010		Date of mailing of the international search report 27/07/2010
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Matés Valdivielso, J

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